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REVIEW

Gastroesophageal reflux in children: an updated review

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Abstract

Background: Gastroesophageal reflux is a common disorder in pediatrics. Clinicians should be familiar with the proper evaluation and management of this condition.

Objective: To provide an update on the current understanding, evaluation, and management of gastroesophageal reflux in children.

Methods: A PubMed search was performed with Clinical Queries using the key term 'gastroesophageal reflux'. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews. The search was restricted to the English literature and the pediatric age group.

Results: Regurgitation is the most frequent symptom of gastroesophageal reflux and is present in nearly all cases. Gastroesophageal reflux occurs normally in infants, is often physiological, peaks at 4 months of age, and tends to resolve with time. Gastroesophageal reflux disease occurs when gastric contents reflux into the esophagus or oropharynx and produce troublesome symptom(s) and/or complication(s). A thorough clinical history and a thorough physical examination are usually adequate for diagnosis. When the diagnosis is ambiguous, diagnostic studies may be warranted. A combined esophageal pH monitoring and multichannel intraluminal esophageal electrical impedance device is the gold standard for the diagnosis of gastroesophageal reflux disease if the diagnosis is in doubt. In the majority of cases, no treatment is necessary for gastroesophageal reflux apart from reassurance of the benign nature of the condition. Treatment options for gastroesophageal reflux disease are discussed.

Conclusion: In most cases, no treatment is necessary for gastroesophageal reflux apart from reassurance because the condition is benign and self-limiting. Thickened feedings, postural therapy, and lifestyle changes should be considered if the regurgitation is frequent and problematic. Pharmacotherapy should be considered in the treatment of more severe gastroesophageal reflux disease for patients who do not respond to conservative measures. Proton pump inhibitors are favored over H_2-receptor antagonists because of their superior efficacy. Antireflux surgery is indicated for patients with significant gastroesophageal reflux disease who are resistant to medical therapy.

Keywords: antireflux surgery, H_2-receptor antagonists, postural therapy, proton pump inhibitors, regurgitation, thickened feedings.

Citation

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Introduction

Gastroesophageal reflux is generally defined as retrograde passage of gastric contents into the esophagus with or without regurgitation/vomiting.[1–6] Infrequent episodes of reflux are often physiological and occur particularly in infants.[3,7] Most episodes are brief and do not cause symptoms or complications.[8] Gastroesophageal reflux disease occurs when gastric contents reflux into the esophagus or oropharynx and produce troublesome symptom(s) and/or complication(s).[7–11] The diagnosis is being suspected and confirmed with increasing frequency because of the heightened awareness of the symptoms peculiar to infants and children.

To provide an update on the current understanding, evaluation, and management of gastroesophageal reflux, a narrative review was conducted based on a Pubmed search using the key term 'gastroesophageal reflux'. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observation studies, and reviews. The search was restricted to the English literature and the pediatric age group.

Epidemiology

Epidemiological studies suggest that gastroesophageal reflux occurs in approximately 50% of infants younger than 2 months of age, 60–70% of infants 3–4 months of age, and 5% of infants by 12 months of age.[12,13] The male-to-female ratio is approximately 2:1.[14] Infrequent episodes of regurgitation are often physiological and tend to resolve with time. Preterm infants are at risk for gastroesophageal reflux because of physiological immaturity of the lower esophageal sphincter, impaired esophageal peristalsis, relatively abundant milk intake, and slower gastric emptying.[14–17] The estimated incidence of gastroesophageal reflux in infants born less than 34-week gestation is approximately 22%.[16]

Several studies have shown that there is a subgroup of infants with cow's milk protein allergy who present with regurgitation and vomiting: symptoms that are indistinguishable from gastroesophageal reflux.[18–21] Some authors suggest that the two conditions may be causally related.[18–21] On the other hand, breastfed infants are less likely to have gastroesophageal reflux than formula-fed infants.[9,22–24] Breastfeeding is also associated with more rapid resolution of gastroesophageal reflux.[25]

Data on the incidence of gastroesophageal reflux disease in the pediatric age group beyond infancy are scarce. Ruigómez and colleagues, using data extracted from The Health Improvement Network (THIN) UK primary care database between January 1, 2000 and December 31, 2005, identified 1700 children of 1–17 years of age with a first diagnosis of gastroesophageal reflux disease.[26] The overall incidence of gastroesophageal reflux disease was determined to be 0.84 per 1000 person-years (95% confidence interval (CI): 0.80–0.89).[26] The incidence decreased with age from 1.48 per 1000 person-years (95% CI: 1.27–1.73) among 1-year-old children until the age of 12 years, whereupon it increased to a maximum at 16–17 years of 2.26 per 1000 person-years for girls and 1.75 per 1000 person-years for boys.

Gastroesophageal reflux disease is more prevalent in children with obesity, neurological impairment, congenital heart disease, abnormalities of the gastrointestinal tract, congenital diaphragmatic hernia, and chromosomal abnormalities.[27–35] Obesity is an important predisposing factor. It has been shown that obesity is associated with increased transient relaxation of the lower esophageal sphincter and higher intragastric pressure.

Gastroesophageal reflux disease occurs more frequently in patients with cystic fibrosis and interstitial lung disease.[36–38] The mechanical influence of a depressed diaphragm caused by hyperinflation, along with increased abdominal pressure with chronic coughing, might be responsible.[1,2] A 2018 meta-analysis of six studies (n=548) showed a strong correlation between gastroesophageal reflux disease and adenoid hypertrophy.[39] Other risk factors include greasy, highly acidic food, caffeine, alcohol, smoking, overeating, increase in intraabdominal pressure, delayed gastric emptying, supine position, and medications (e.g. calcium channel blockers, methylxanthines, diazepam, theophylline).[28]

There is an increased concordance of gastroesophageal reflux in monozygotic twins compared with dizygotic twins, suggesting genetic factors might have a role to play in the etiology. A gene for infantile gastroesophageal reflux has been mapped to 9q22-9q31.[40]

Pathophysiology

The lower esophageal sphincter is the major component of the antireflux barrier.[3] The crural ligament, the angle of His, and the phrenoesophageal ligament contribute to the antireflux barrier.[10,41] The normal lower esophageal sphincter pressure is 5–20 mm Hg and is 4 mm Hg or more above intragastric pressure.[7,42] The sphincter relaxes briefly during peristalsis. Transient relaxation of the lower esophageal sphincter to the level of gastric pressure or a pressure of 0–2 mm Hg may result in retrograde passage of gastric contents into the esophagus.[4,43] As a matter of fact, most gastroesophageal reflux episodes are caused by transient relaxation of the lower esophageal sphincter triggered by postprandial gastric distension.[44] However, gastroesophageal reflux may also occur with normal lower esophageal sphincter pressure if there is increased intraabdominal pressure or if there is delayed gastric emptying.[45,46]

Clinical manifestations

Clinical presentations vary with age. Regurgitation is the most frequent symptom and is present in nearly all cases.[1,2] Although gastroesophageal reflux is often present at birth, regurgitation may not be pronounced until the 2nd or 3rd week of life when the oral intake is increased with a peak at 4 months of age.[12,13] The regurgitation is usually effortless and is worse after feeding and when the infant is in a recumbent position or when pressure is applied to the abdomen.[1,2,4,17] Approximately 25% of infants regurgitate four or more times a day.[5,13] In some infants, regurgitation may occur more than six times a day.[14] Infants with gastroesophageal reflux feed and thrive well and have no other symptoms; they are described as 'happy spitters'.[45]

In addition to regurgitation, infants and young children with gastroesophageal reflux disease may present with irritability, excessive crying, poor appetite, feeding refusal, gagging, failure to thrive, sleep disturbance, chronic cough, wheezing, stridor, grimacing, opisthotonus, and torticollis.[10,17,47,48] Sandifer syndrome, characterized by spasmodic torsional dystonia with arching of the back, torsion of neck, and lifting up of the chin, is highly specific of gastroesophageal reflux disease.[10,45,49] It is hypothesized that in Sandifer syndrome, the arching of the back and rigid opisthotonic posturing provide relief from the discomfort caused by the acid reflux.[4,50]

Older children and adolescents with gastroesophageal reflux disease may experience chronic regurgitation,

nausea, dysphagia, heartburn, retrosternal or epigastric pain, chronic cough, hoarseness, halitosis, and dental erosions.[43,44,47–51]

Differential diagnosis

Differential diagnosis of gastroesophageal reflux/gastroesophageal reflux disease is broad and includes antral/duodenal web, pyloric stenosis, duodenal atresia, hiatal hernia, intestinal malrotation, intussusception, food allergy (in particular, cow's milk protein allergy), food intolerance, achalasia, gastritis, gastroparesis, eosinophilic esophagitis, peptic ulcer disease, sepsis, congenital adrenal hyperplasia, adrenal crisis, increased intracranial pressure, rumination syndrome, self-induced vomiting, cyclic vomiting syndrome, lead poisoning, metabolic acidosis, and inborn error of metabolism.[43,47,48,51–57] Sandifer syndrome is often misdiagnosed as spastic torticollis.[2]

Onset of regurgitation/vomiting after 6 months of age, increasing/persisting regurgitation/vomiting beyond 1 year of age, consistently forceful vomiting, bilious vomiting, fever, lethargy, significant weight loss, excessive irritability, hematemesis, difficulty swallowing, abdominal distension/tenderness, constipation, melena, hematochezia, chronic diarrhea, dysuria, seizures, hypo- or hypertonia, bulging fontanelle, micro/macrocephaly, abnormal neurologic findings, and hepatosplenomegaly suggest a diagnosis other than gastroesophageal reflux disease.[3,5,17,24,48,57]

Complications

Gastroesophageal reflux and gastroesophageal reflux disease may cause heightened parental anxiety and stress and may have an adverse effect on quality of life of the child as well as the parents.[43,57] A relationship between frequency and duration of gastroesophageal reflux and later development of gastroesophageal reflux disease has been noted by many investigators.[7,11,49]

Complications of gastroesophageal reflux disease vary with age of the child. Regurgitation may be so severe and voluminous that there is a great loss of ingested calories with resultant failure to thrive.[1,7] Gastroesophageal reflux disease has also been reported to be associated with rumination and protein-losing enteropathy with digital clubbing.[2]

Reflux of acidic gastric contents into the esophagus can cause peptic esophagitis with bleeding into the gastrointestinal tract.[58] This may present as hematemesis, melena, and iron deficiency anemia.[59] Older children may complain of heartburn, water-brash, and dysphagia.[4,60] Sleep interruptions and arousals are more common in children with gastroesophageal reflux disease, possibly due to greater nocturnal acid reflux in a lying down position.[61,62] Peptic esophagitis may lead to stricture formation, shortening of the esophagus, esophageal mucosal dysplasia, and Barrett esophagus.[57,58,63]

Respiratory complications include reactive airway disease, sinusitis, laryngitis, obstructive bronchitis, recurrent aspiration pneumonia, and apparent life-threatening events.[10,14,57,63,64] It is known that stimulation of laryngeal chemoreceptors by acidic fluids can cause apnea.[2] The mechanism for the respiratory arrest seems to be either laryngospasm or reflex central apnea. Unrelieved, this respiratory arrest may lead to cardiac arrest.[65] It is conceivable that this may be the cause of death in some patients with sudden infant death syndrome.[65] Patients with gastroesophageal reflux disease are at risk of cardiac autonomic dysfunction.[65]

Gastroesophageal reflux may also lead to recurrent otitis media.[4,66] Patients with gastroesophageal reflux are more prone to chronic tubotympanic disorders and conductive hearing impairment.[67]

In severe cases of gastroesophageal reflux disease, refluxate may reach the oral cavity.[68,69] The refluxate can be strongly detrimental to the oral health by causing dental caries, dental erosion, and oral mucosal lesions.[68–72] The acidic oral environment induced by gastroesophageal reflux disease may encourage the growth of acidophilic *Streptococcus mutans* and *Candida albicans*.[57,70]

Diagnostic studies

A thorough clinical history and a complete physical examination remain the cornerstone of diagnosis.[45,46,57,73] When the diagnosis is ambiguous or when complications are suspected, further investigations may be warranted.[57]

Barium contrast radiography

An upper gastrointestinal (GI) series is not recommended to diagnose gastroesophageal reflux in infants and children.[5,48,74] The test is neither sensitive nor specific.[3,49,74] An upper GI barium contrast study does not reflect the frequency of gastroesophageal reflux under physiological condition.[48] The test, however, can be used to detect anatomic abnormalities such as esophageal stricture, esophageal extrinsic compression, achalasia, antral web, pyloric stenosis, duodenal web, duodenal stenosis, hiatal hernia, malrotation, and annular pancreas which may cause vomiting.[5,48,49] The disadvantages of an upper GI series are total dependence upon the radiologist for interpretation and choice of spot films and insensitivity to subtle abnormalities. Also, the test does not provide any information about the physiological function of the esophagus.[4]

Esophagogastric ultrasonography

There is no evidence to support esophagogastric ultrasonography as a diagnostic tool for gastroesophageal reflux disease in infants and children.[5,73] Compared with 24-hour esophageal pH monitoring as a standard test for gastroesophageal reflux disease, color Doppler sonography has a sensitivity of 95.5%

and a specificity of 11%, with a positive predictive value of 84.3% and a negative predictive value of 33.3%.[75] Esophagogastric ultrasonography can be used to detect conditions such as pyloric stenosis, which may mimic gastroesophageal reflux disease.[73]

Esophageal manometry

Esophageal manometric pressure studies of the lower esophageal sphincter function have been used to rule out esophageal motility disorders such as rumination syndrome and esophageal achalasia, the symptom of which may mimic gastroesophageal reflux.[5,48] There is insufficient evidence to support the use of esophageal manometry for the diagnosis of gastroesophageal reflux.[5]

Esophageal pH monitoring

Esophageal pH monitoring has proved both sensitive and specific in detecting gastroesophageal reflux.[2,12] A pH probe consists of a pH-sensing electrode that is built into the distal end of a transnasally placed catheter.[12] The catheter is placed so that the pH sensor is positioned just proximal to the lower esophageal sphincter.[12] A wireless esophageal pH capsule can also be used to monitor the esophageal pH. In the absence of gastroesophageal reflux, the pH of the esophageal lumen is in the range of 4–7.[3] A reflux index reflects the percentage of time in a 24-hour period where the esophageal pH is less than 4.[45,76] Generally, a reflux index >11% in infants or >7% in older children is considered abnormal.[45,76] The test is useful to diagnose gastroesophageal reflux, determine its severity, assess whether gastroesophageal reflux contributes to any extraesophageal pathology, and gauge the adequacy of acid suppression therapy.[48,77] The main limitation of esophageal pH monitoring is that it does not detect reflux episodes other than acidic ones.[57,73]

Multichannel intraluminal esophageal electrical impedance

Multichannel intraluminal esophageal electrical impedance detects both acid and nonacid reflux by capturing changes in the electrical impedance during the movement of a liquid, solid, and/or gas bolus between measuring electrodes at different esophageal levels, regardless of physical or chemical characteristics of the bolus.[17,66,73,78] It is the most sensitive tool to evaluate gastroesophageal reflux disease in patients with both atypical and typical symptoms.[79] Multichannel intraluminal esophageal electrical impedance detects gastroesophageal reflux if there is a sequential drop in impedance to less than 50% of baseline values, starting distally above the lower esophageal sphincter and propagating retrograde to at least the next two or more proximal measuring segments.[17] Whereas 24-hour esophageal pH monitoring detects only acid reflux, multichannel intraluminal esophageal electrical impedance detects reflux events.[48,80] The combined esophageal pH monitoring and multichannel intraluminal esophageal electrical impedance device can detect gastroesophageal reflux regardless of the pH of the refluxate.[48,49,79,80] It has been shown that the combined device has a higher detection rate of gastroesophageal reflux compared with esophageal pH and multichannel intraluminal esophageal electrical impedance device when used alone and is superior to other investigations to assess the temporal relationship between specific symptoms and the reflux of both acid and nonacid gastric contents.[25,47,63,66,73,81,82] The combined device is the cornerstone of modern assessment of gastroesophageal reflux.[25,47,63,66,73,81,82]

Upper gastrointestinal endoscopy and biopsy

It has been shown that a normal upper GI endoscopy does not necessarily rule out the possibility of gastroesophageal reflux disease.[5,83] The negative predictive value of a macroscopically and microscopically normal endoscopy is low.[83] The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) do not recommend the use of upper GI endoscopy to diagnose gastroesophageal reflux disease in infants and children.[5] Upper GI endoscopy should be considered in selected cases to exclude other conditions (e.g. eosinophilic esophagitis, peptic ulcer) that mimic gastroesophageal reflux and to assess complications of gastroesophageal reflux disease (e.g. esophagitis, stricture formation, Barrett esophagitis).[49,73,84] The esophageal biopsy may show changes indicative of esophagitis, namely, presence of polymorphic leucocytes infiltrating the mucosa, increased numbers of intraepithelial eosinophils, basal zone hyperplasia, and elongation of epithelial papillae.[10,49] The absence of histological changes, however, does not rule out gastroesophageal reflux disease.[63] The NASPGHAN and ESPGHAN suggest upper GI endoscopy with biopsy to assess complications of gastroesophageal reflux disease, in case an underlying mucosal disease is suspected before escalation of therapy.[5]

Diagnosis

In the majority of cases, diagnostic studies are not necessary to diagnose gastroesophageal reflux and gastroesophageal reflux disease.[24,57] The diagnosis is primarily clinical.[24,57,73] The combined esophageal pH monitoring and multichannel intraluminal esophageal electrical impedance device is the gold standard for the diagnosis of gastroesophageal reflux disease if the diagnosis is in doubt.[3,48,49,78,80] When the combined esophageal pH monitoring and multichannel intraluminal esophageal electrical impedance device is not available, the NASPGHAN and ESPGHAN suggest to consider esophageal pH monitoring to correlate persistent troublesome symptoms with acid gastroesophageal reflux events.[5] Current recommendations do not support an empiric trial of proton pump inhibitors as a diagnostic test for gastroesophageal reflux disease in infants and young children because symptoms suggestive of gastroesophageal reflux disease are not/less specific in children

of this age group.[5,10,73,84] The NASPGHAN and ESPGHAN suggest a 4–8-week trial of proton pump inhibitors in older children with typical symptoms of gastroesophageal reflux disease (such as heartburn retrosternal or epigastric pain) as a diagnostic test for gastroesophageal reflux disease.[5]

Management

Conservative measures

In the majority of cases, no treatment is necessary for gastroesophageal reflux apart from reassurance of the benign nature of the condition. Thickened feedings, postural therapy, and lifestyle changes should be considered if the regurgitation is frequent and problematic.[7,85,86]

Thickened feedings

In infants, thickening the formula or expressed breast milk with cereal is reasonable because it is more difficult to bring up a thickened formula or expressed breast milk. Also, the intake of milk is bound to decrease with the introduction of solid as the infant is getting enough calories from the solid food. A rough guide is to add one tablespoon of cereal to every ounce of formula or expressed breast milk.[2,47] Commercial thickened formulas are available for this purpose. Smaller and more frequent thickened feeds are recommended, especially for premature infants.[2,5,15,43] A 2017 meta-analysis of eight randomized controlled trials (n=637 infants) showed that thickened feeds were moderately effective in the reduction of the frequency of regurgitation in infants with gastroesophageal reflux.[87] The use of thickened formula is associated with increased weight gain and is superior to postural therapy in reducing episodes of regurgitation.[88,89] Overfeeding should be avoided, as this may aggravate the reflux.

Postural therapy

Maintaining an infant in an upright position for 20–30 minutes after feeding helps to reduce episodes of regurgitation.[14,48] Positional therapy (e.g. head elevation, lateral, and prone position) is not recommended to treat symptoms of gastroesophageal reflux in sleeping infants, due to the risk of sudden infant death syndrome, but may be considered for the treatment of gastroesophageal reflux in children.[5,74]

Lifestyle changes

As breastfed infants are less likely to have gastroesophageal reflux than formula-fed infants, breastfeeding should be encouraged.[9,22–24] A subset of infants with cow's milk allergy presents with regurgitation and vomiting, which may mimic gastroesophageal reflux.[45] After all, the two conditions may be causally related, and they may coexist.[18–21,45] The NASPGHAN and ESPGHAN suggest a 2–4-week trial of an extensively hydrolyzed hypoallergenic formula or amino acid-based formula in formula-fed infants suspected to have gastroesophageal reflux not responding to thickened feedings and postural therapy.[5,43,47] In breastfed infants, mothers should consider eliminating cow's milk and potentially allergenic substances (e.g. nuts, eggs, chocolate) from their diet.[5,43,47]

Other nonpharmacologic measures include weight reduction for individuals who are overweight, avoidance of overfeeding, avoidance of active/passive smoking, avoidance of alcohol, avoidance of food before bedtime, and avoidance of certain food items.[8,14,44,47,48,90–93] Spicy and greasy foods may slow gastric emptying and therefore should be avoided.[25,47,90] Caffeinated beverages, peppermint, and chocolate may lower esophageal sphincter pressure and should also be avoided.[8,25,47] Some of these measures are age specific or age restricted. In general, the earlier measures are all that is necessary in the treatment of children/adolescents with mild or infrequent symptoms of gastroesophageal reflux/gastroesophageal reflux disease.[8,11,63]

Pharmacotherapy

In general, pharmacotherapy is not indicated in the treatment of uncomplicated gastroesophageal reflux in infants as symptoms tend to resolve with time.[2,17] Pharmacotherapy should be considered in the treatment of gastroesophageal reflux disease in patients who do not respond to conservative measures such as thickened feedings, postural therapy, and lifestyle changes.[2] Both H_2-receptor antagonists and proton pump inhibitors have been proven safe and effective for infants and children in reducing their gastric acid output.[4,94] A 2017 systematic review of 23 randomized placebo-controlled trials (n=1598 children) showed that H_2-receptor antagonists and proton pump inhibitors were efficacious in the treatment of pediatric gastroesophageal reflux disease, especially in those children with reflux esophagitis.[94] The duration of treatment varies from a few weeks to a few months. Patients with gastroesophageal reflux disease should be re-evaluated on a regular basis to determine if ongoing treatment is necessary.

H_2-receptor antagonists

H_2-receptor antagonists that have been used for the treatment of gastroesophageal reflux disease include cimetidine (children: 30–40 mg/kg/day divided into four doses; adults: 400–800 mg twice a day), ranitidine (children: 5–10 mg/kg/day divided into two to three doses; adults: 150 mg twice a day), famotidine (children: 1 mg/kg/day divided into two doses; adults: 20 mg twice a day), and nizatidine (children: 10–20 mg/kg/day divided into two doses; adults: 150 mg twice a day or 300 mg once a day).[5,8] These medications reduce gastric acid secretion by competitive inhibition of the interaction between histamine and H_2-receptor located on the gastric parietal cells.[42,45] In addition, H_2-receptor antagonists reduce output of pepsin and gastric acid volume.[42] They do not, however, reduce the frequency of the gastroesophageal reflux. They are less effective than proton pump inhibitors but are more effective than placebo in reducing gastric acid secretion.[47,48] They have a relatively rapid onset of action.[8] Their long-term use is limited by tachyphylaxis (tolerance), which can develop within 14 days,

and hypochlorhydria.[42,5,47] The latter may lead to gastric bacterial colonization.[42] There is also increased risk of community-acquired pneumonia and enteric infection, in particular, *Clostridium difficile*.[95–98] Common adverse events include somnolence, dizziness, headache, abdominal pain, and diarrhea.[8] Cimetidine is a moderate inhibitor of cytochrome P450 and can increase levels of some coadministered medications such as selective serotonin reuptake inhibitors, theophylline, cisapride, and warfarin.[8,99] In addition, cimetidine has weak antiandrogenic activity, and its chronic use may lead to gynecomastia.[100,101]

Proton pump inhibitors

Proton pump inhibitors that have been used for the treatment of gastroesophageal reflux disease include omeprazole (infants: 3 to <5 kg, 2.5 mg/day, 5 to <10 kg, 5 mg/day, ≥10 kg, 10 mg/day; children: 1 mg/kg/day [maximum 20 mg/day]; adults: 20–40 mg/day), esomeprazole (infants: 3 to <5 kg, 2.5 mg/day, 5 to <10 kg, 5 mg/day, ≥10 kg, 10 mg/day; children: <20 kg, 10 mg/day, >20 kg, 10–20 mg/day; adults: 20–40 mg/day), lansoprazole (infants and children: 1 mg/kg/day [maximum 15 mg/day]; adults: 15–30 mg/day; dexlansoprazole (children ≥12 years and adults: 30 mg/day), pantoprazole (children: 15 to <40 kg, 20 mg/day, ≥40 kg, 40 mg/day; adults: 40 mg/day), rabeprazole (children ≥12 years and adults: 20 mg/day).[8] Generally, proton pump inhibitors are given once daily, ideally 30 minutes before meal.[8,43,47] Some children, however, may require twice daily dosing to achieve optimal gastric acid suppression.[8] Infants and younger children require a relative higher dose of proton pump inhibitors per kilogram because of enhanced drug metabolic activities during infancy and early childhood.[4,8] These medications selectively inhibit acid secretion by blocking the hydrogen–potassium–adenosine triphosphatase (H^+–K^+–ATPase) pumps that reside on the gastric parietal cell membrane.[42,45,102] Similar to H_2-receptor antagonists, proton pump inhibitors do not, however, reduce the frequency of the gastroesophageal reflux.[3,103] Proton pump inhibitors help to ameliorate dyspepsia, prevent acid-induced esophageal injury, and accelerate healing of esophagitis.[104,105] In children, proton pump inhibitors are favored over H_2-receptor antagonists because of their superior efficacy.[8,11,47] These medications are safe and well tolerated.[45,104,105] Proton pump inhibitors are the drugs of choice for the treatment of gastroesophageal reflux disease, especially if there is evidence of esophagitis.[8] Tachyphylaxis does not occur with proton pump inhibitors. Common adverse events associated with the use of proton pump inhibitors include somnolence, dizziness, headaches, rash, nausea, abdominal pain, diarrhea, and constipation.[8,45,47] Patients on proton pump inhibitors are also at increased risk of hypochlorhydria, gastric bacterial colonization, community-acquired pneumonia, and enteric infection, in particular, *Clostridium difficile*.[10,42,48,102]

Antacids

Antacids such as aluminum hydroxide, calcium carbonate, and magnesium hydroxide are not useful in the treatment of gastroesophageal reflux disease in infants, but may be considered for short-term use in older children and adults for relief of heartburn.[5,48] Antacids work by neutralizing gastric acid, thereby decreasing the exposure of the esophageal mucosa to gastric acidity during episodes of gastroesophageal reflux.[8,45] Their chronic use may lead to milk-alkali syndrome, hypophosphatemic rickets, or aluminum toxicity (e.g. osteopenia, neurotoxicity, microcytic anemia).[5,45,47,48] As such, chronic antacid therapy is generally not recommended.[5,45,47,48]

Prokinetic agents

Prokinetic agents such as metoclopramide (0.1–0.3 mg/kg/dose three to four times a day), cisapride (0.8–1 mg/kg/day), domperidone (0.3–0.6 mg/kg/dose three times a day), and baclofen (0.5–1.5 mg/kg/day) promote gastric emptying and theoretically might be of use for the treatment of gastroesophageal reflux disease.[45] However, the use of prokinetic agents has not been found to be helpful in the treatment of gastroesophageal reflux in large cohort studies.[3,106] These agents are not recommended for use in children because of significant side effects (e.g. dizziness, drowsiness, restlessness, extrapyramidal effects, prolactinemia, galactorrhea, ventricular arrhythmias, QT prolongation), and uncertain benefit in the treatment of gastroesophageal reflux disease.[5,8,17,24,73,107,108]

Surface barrier agents

Surface barrier agents work by acting as a physical barrier to prevent damage to the esophageal mucosa by refluxed gastric acid.[8] Sodium alginate, a polysaccharide derived from brown seaweed, has been used in the treatment of gastroesophageal reflux disease.[90,109] In the presence of gastric acid in the stomach, alginate precipitates and forms a viscous gel, thereby increasing the viscosity of feeds and reducing gastroesophageal reflux.[42,45,90,110,111] A 2017 meta-analysis of 15 studies (n=2095) showed that alginates were less effective than H_2-receptor antagonists and proton pump inhibitors but more effective than placebo in the treatment of gastroesophageal reflux disease.[112] The NASPGHAN and ESPGHAN do not recommend the use of alginates for chronic treatment of gastroesophageal reflux disease.[5]

Sucralfate is a sucrose–sulfate–aluminum compound that forms a gel in the presence of gastric acid.[45,90] The compound adheres to the esophageal mucosal surface and protects the mucosa from injury caused by gastric acid.[8,45,113] Side effects include dizziness, light-headedness, and constipation.[44] The use of sucralfate in the treatment of gastroesophageal reflux disease is not recommended because of the short duration of action, limited efficacy, and potential for aluminium toxicity.[5]

Surgical treatment

Absolute indications for antireflux surgery, usually laparoscopic fundoplication, are life-threatening events such

as cardiopulmonary failure, apnea, and near miss sudden infant death syndrome attributable to gastroesophageal reflux disease.[2] Those children with failure to thrive, esophagitis, esophageal strictures, intractable emesis, or chronic problems (e.g. neurological impairment, cystic fibrosis) with a significant risk of gastroesophageal reflux disease-related complications who do not respond to medical treatment should also be considered for antireflux surgery.[3,5,28,41] The success rate of fundoplication ranges from 60 to 90%.[5] Complications of surgical treatment include infection at the surgical site, hemorrhage, perforation of bowel, pneumothorax, breakdown of the wrap, hiatal hernia, esophageal stricture, gas bloat syndrome, inability to vomit, choking on some solids, slow eating habit, injury to the vagus nerve, heartburn, dumping syndrome, and intestinal obstruction.[2,5,25,58,84] Familiarity with these complications is important to the presurgical counseling as well as long-term follow-up of these patients.

Prognosis

Approximately 95% of infants outgrow the gastroesophageal reflux by 12 months of age, with the greatest improvement at about 8–10 months of age when the infant starts to sit upright.[22] Children with neurodevelopmental disabilities and a strong family history of gastroesophageal reflux disease have a poorer prognosis compared with infants with physiological gastroesophageal reflux.[2] Children in whom reflux symptoms persist beyond 18 months of age are more likely to experience chronic gastroesophageal reflux disease.[114]

Conclusion

Gastroesophageal reflux is extremely common during the first few months of life and often physiological. Physiological gastroesophageal reflux does not affect growth, does not cause symptoms, and typically resolves on its own by 12 months of age. Thickened feedings, postural therapy, and lifestyle changes should be considered if the regurgitation is frequent and problematic. On the other hand, gastroesophageal reflux disease is much less frequent. Pharmacotherapy should be considered in the treatment of more severe gastroesophageal reflux disease for patients who do not respond to conservative measures. Both H_2-receptor antagonists and proton pump inhibitors have been proven safe and effective for infants and children in reducing their gastric acid output. They do not, however, reduce the frequency of the gastroesophageal reflux. Proton pump inhibitors are more effective than H_2-receptor antagonists in reducing gastric acid secretion and are therefore the drugs of choice. The duration of treatment varies from a few weeks to a few months. Patients with gastroesophageal reflux disease should be re-evaluated on a regular basis to determine if ongoing treatment is necessary. Antireflux surgery should be considered for those with esophageal strictures, life-threatening complications, and intractable emesis not responding to medical treatment.

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