

GASTROESOPHAGEAL REFLUX DISEASE DIAGNOSIS AND TREATMENT

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Abstract

It remains a challenge to diagnose and treat gastro-esophageal reflux (GER) and GER disease (GERD) in infants and children. Together with Embase, MEDLINE, and the Cochrane Database, the published guidelines and position papers were reviewed and summarized in order to suggest a realistic GER and GERD strategy and management for healthcare providers and to standardize and enhance the quality of care for infants and children. Two algorithms were developed for this purpose, 1 for infants <12 months of age and the other for older children. None of the signs and symptoms of GER and GERD are unique and there is no screening test or tool for a gold standard. As a first-line approach, nutritional management is recommended in babies, while for early management, a clinical trial with antacid medication is recommended in children. The aim of the realistic recommendations of this review is to optimize GER management in infants and older children and to minimize the number of investigations and the improper use of medication.

Keywords: Gastro-esophageal reflux, Gastroesophageal reflux disease, Esophagitis, Endoscopy, Impedance, Proton pump inhibitors, pH.

Introduction:

Guidelines on gastroesophageal reflux (GER) and GER disease (GERD) were published in 2009 and 2018 by the joint committees of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[1,2]. This analysis is an update to these guidelines and a personal opinion. From June 2015 (end date of the search for the NASPGHAN-ESPGHAN guidelines) to September 2019, a systematic literature search was conducted, including Embase, MEDLINE, PubMed, and the Cochrane Database. GER is the passage with or without regurgitation and/or vomiting of gastric contents into the esophagus. When reflux causes problematic symptoms and/or complications, GER becomes GERD (Table 1) [3]. In older children, GERD is evident in the presence of regurgitation, heartburn, reflux esophagitis, or esophageal stenosis, and is strongly suspected in cases of hematemesis and inability to thrive in children who vomit. None of the symptoms and signs of GERD are unique, however. Fortunately, in just a minority of infants, severe

esophageal mucosal problems and hematemesis occur. The symptoms are mild to moderate in most cases, primarily reducing the normal quality of life or nocturnal sleep. Nevertheless it is difficult to identify the "troublesome" nature of the symptoms and can vary between infants, their ability to explain them, their caregivers, and healthcare professionals. As a result, the concept of GERD depends, for the most part, on the subjective perception of symptoms as they affect the quality of life. In addition, in infants and children, the range of potential GERD symptoms varies widely by age and is non-specific [1,4]. This can lead to both over- and under-diagnosis and care that is not required. It is often difficult to decide, particularly in children, what is problematic, what is pathological, and what is physiological. Many GERD infants cry excessively, but GERD infants who cry excessively but do not regurgitate or vomit rarely suffer. The degree of parental anxiety is in addition, the motivating force for diagnosis and management. The lack of a gold standard diagnostic instrument further hampers GERD diagnosis in infants and children. However in children with underlying medical disorders, such as esophageal atresia, developmental dysfunction and respiratory issues, including cystic fibrosis,

GERD is a prominent occurrence. According to the NASPGHAN-ESPGHAN guidelines, refractory GERD is a GERD that after 8 weeks, does not respond or does not respond adequately to optimal care.

In order to recognize warning symptoms and signs, clinical history and physical examination are necessary and separate GERD from other disorders. Regurgitation is described as the passage into the pharynx, mouth, or out of the mouth of refluxed contents [1,2]. Other words are deemed similar to regurgitation, such as spitting-up, possessing, and pouring. Vomiting is a synchronized autonomic and voluntary motor reaction that causes gastric material to be forcefully expelled through the mouth. With subsequent chewing and re-swallowing, rumination is the effortless regurgitation of recently swallowed food into the mouth. Rumination syndrome is not addressed further and is a different clinical entity in which rumination occurs within minutes of a meal, does not occur during sleep, and does not lead to normal GER care. Repetitive contractions of the muscles of the abdominal wall, diaphragm, and tongue are involved in rumination [5,6]. Regurgitation and vomiting episodes in infants are frequent. Infections, anatomical abnormalities, and metabolic disorders can be ruled out if repetitive regurgitation or vomiting is still present within the first 1 to 2 weeks of life. Diagnoses other than infant GER or GERD should be considered when the onset of regurgitation is after the age of 6 months and when symptoms continue after the age of 12 months. Particular attention should be paid to dietary history, since cow's milk protein allergy may perfectly mimic the symptoms of GERD.

Hypersensitivity to reflux occurs in patients with esophageal symptoms (heartburn or chest pain) who do not have endoscopic and/or multiple intraluminal impedance (MII) and/or pH metric proof of GERD, but who do have clinical evidence that reflux is temporally associated with symptoms [1,2]. In patients with esophageal symptoms (heartburn or chest pain) who often lack clinical proof of reflux and do not have evidence that symptoms are caused by episodes of reflux, functional heartburn occurs. Non-erosive reflux disease (NERD) identifies patients with esophageal symptoms that lack evidence of endoscopic esophagitis but have an excessive acid load based on evidence given by acid reflux results of MII-pH and/or pH metric results that may or may not cause symptoms.

The signs and symptoms are described in Tables 1 and 2. An increased prevalence of GERD is associated with excessive body weight.

A special category of patients are anxious children. Many children with overt GERD are upset and cry a lot because it can cause inflammation and pain, not only esophagitis but also esophageal dilatation caused by reflux (regurgitated milk). Unconsolable screaming and overt regurgitation or vomiting are frequently present in infants with GERD. Crying may however, be triggered by several conditions other than GERD and is not always the reference symptom in GERD infants. Occult GERD, or GERD, is very rare in infants who do not regurgitate or vomit. Further assessment is needed of the role of occult GERD in children with chronic respiratory symptoms. In an infant, the length of the esophagus is about 10 cm and can hold just about 5 ml of blood. And, in other words, it is hard to understand how so much discomfort and pain can be caused by a minimum amount of reflux that limits itself to a few centimeters.

Table 2

'Red flag' symptoms and signs that may be associated with disorders other than GERD

Symptoms	Signs
Regurgitation started <2 weeks of life or >6 months or persistent after 18 months of life	Abnormal (general or abdominal, neurological, respiratory) physical examination
Bilious, nocturnal or persistent vomiting	Abdominal distension
Chronic or bloody diarrhea	Fever
Hematemesis	Failure to thrive/weight loss
Dysuria	Lethargy or excessive irritability
Seizures	Abnormal muscle tone
Dysphagia	Bulging fontanel or excessive increase of head circumference or micro/macrocephaly
Recurrent pneumonia	Abnormal psychomotor development

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GERD: gastro-esophageal reflux disease.

Material and Methods

Barium contrast, Ultrasound, and Scintigraphy

For a very limited time and mostly during the postprandial phase, these techniques may examine reflux. Regardless of symptoms, one or more reflux episodes can be observed in up to 50 percent of children receiving radiological imaging. For the diagnosis of hiatal hernia, malrotation, pyloric stenosis, duodenal web, duodenal stenosis, antral web, esophageal narrowing, Schatzki's ring, achalasia, esophageal stricture, and esophageal extrinsic compression, the upper gastrointestinal (GI) barium contrast analysis is primarily helpful in detecting GI malformations. Another sign is recurrent symptoms after anti-reflux surgery [7,8]. For GERD diagnosis, ultrasonography is not indicated, as the results are obviously investigator-dependent. Ultrasound sensitivity is around 95 percent in the 15 minutes postprandial, but the accuracy is just 11 percent compared to pH-metry [9,10]. The correlation between the thickness of the esophageal wall and esophagitis is also weak.

Table 1

Symptoms and signs associated with GERD in infants and children

Symptoms	Signs
Heartburn/chest pain	Esophageal mucosal complications (esophagitis, esophageal stricture, Barrett's esophagus)
Epigastric pain	Recurrent/chronic desaturations
Regurgitation/vomiting	Recurrent aspiration pneumonia
Recurrent inconsolable crying/irritability	Laryngitis
Hematemesis	Recurrent otitis media
Feeding refusal	Abnormal posturing/Sandifer syndrome
Odyno/dysphagia, hoarseness	Failure to thrive/weight loss
Recurrent/chronic dry cough, wheezing/ALTE/BRUE	Dental erosions
Disturbed sleep	-
Seizure episodes	-

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GERD: gastro-esophageal reflux disease, ALTE: apparent life-threatening event, BRUE: brief resolved unexplained event.

Sensitivity and specificity are only modest, at 69% and 78% respectively, with regard to scintigraphy[11]. In addition to showing tracer refluxing into the esophagus, scintigraphy assesses gastric emptying and may also illustrate pulmonary aspiration[12].

Esophagogastroduodenoscopy with biopsies

The existence of eosinophils, papillary lengthening, and/or basal cell hyperplasia is known as microscopic esophagitis. In the esophageal mucosa, erosive esophagitis is characterized as noticeable breaks. Esophagitis is not a particular symptom. The sensitivity of erosive esophagitis was reported to range from 15 percent to 71 percent in diagnosing GERD and the sensitivity of microscopic esophagitis was between 83 percent and 88 percent in diagnosing GERD. The authors found that histologic esophagitis had a 62 percent and 73 percent negative predictive value (NPV) [13,14]. When attention was also given to the endoscopic presence of the mucosa in control patients, the upper endoscopy NPV decreased to only 33%[15]. These results suggest that the presence of GERD does not rule out a biopsy without the hallmarks of esophagitis or the absence of macroscopic lesions. Histology and macroscopic appearance were common in the control group in all 3 studies, if specified, which automatically resulted in 100 percent reported specificity and NPV [13,14,15]. There is also insufficient evidence to justify the use of endoscopy for the diagnosis of GERD in infants and children, with or without a biopsy. Upper GI tract endoscopy, however is useful for evaluating the mucosa in the presence of signs or symptoms of alarm, such as hematemesis, dysphagia, or failure to thrive or anemia; for detecting GERD complications, such as erosive esophagitis, stiffness, and Barrett's esophagus; or for diagnosing GERD-like disorders, such as eosinophilic esophagitis. Despite the usual endoscopic appearance of the esophageal mucosa and the lack of histological anomalies, GERD may occur. Especially in infants, the association between esophagitis and acid exposure time on pH monitoring is very low. The region under the curve is a pH-metry parameter that takes into account the acidity of the episodes of reflux and has been shown to correlate with esophagitis, but has lost appeal in recent years and is no longer mentioned in commercially available pH-metry reports [16].

Results

TREATMENT OF PHARMACOLOGICALS

Acid is neutralized by antacids and alginates and contains sodium/potassium bicarbonate, or aluminum, magnesium, or calcium salts. It is recorded that alginates minimize the symptoms of reflux and the number of regurgitation and vomiting episodes. It has also been shown that alginate decreases the number of reflux episodes calculated by pH-MII. The reduction of symptoms was verified by the same research. Some trials have not shown the effectiveness of alginate. This may be due to the nature of such studies,

alternating without and with alginate feeding. Alginates are recommended by the recommendations of the National Institute for Health and Care Excellence as an alternative treatment for feeding thickening agents in breastfed infants or as a trial in infants whose symptoms continue despite conservative measures. There are no major adverse effects from on-demand or short-term administration of alginate. In infants and children with renal failure, aluminum-containing antacids should not be used. The efficacy of various PPIs, including lansoprazole, esomeprazole, rabeprazole, pantoprazole, and omeprazole, has been assessed over the past decade, although no studies have compared different PPIs. Both infant research failed to demonstrate that PPIs were effective at minimizing screaming, fussiness, cough, arching back, regurgitation, and vomiting than placebos. Recently, PPI adverse effects gained a lot of attention as about 25 percent of patient's experienced bacterial overgrowth of the small intestinal bowel. There were records of a rise in upper and lower respiratory tract infections, GI infections, and eczema. A risk factor for infections with *Clostridium difficile* is PPIs [17]. PPIs are the first alternative, since histamine 2 receptor antagonists (H2RAs), such as ranitidine, are less effective than PPIs in reducing gastric acidity. However, obviously, H2RAs can still be used to treat acid-related diseases when PPIs are not available. The ease of administration and prescription costs should also be taken into account in the option of administering PPIs versus H2RAs, as credible evidence of their effectiveness is limited. In contrast with a drug from the same class, there is no evidence for the superiority of either PPI or H2RAs. Lansoprazole improved symptoms at 7.5 or 15 mg twice daily for 2 weeks, described as a decrease in more than extensively hydrolyzed scores in the Updated Infant Gastroesophageal Reflux Questionnaire.

Prokinetics

Baclofen has been reported to decrease transient lower esophageal sphincter (LES) relaxation, episodes of reflux, and to accelerate gastric emptying, but no randomized GERD studies have been reported in children. Due to the recorded side effects, including dyspeptic symptoms, drowsiness, dizziness, weakness, and a decreased threshold for seizures, Baclofen can be used for GERD control, but not as a first-choice medication. There is no proof that domperidone or metoclopramide, as opposed to placebo, decreases visible regurgitation or vomiting, but induces more adverse effects. Extrapyramidal symptoms (9%), diarrhea (6%), and sedation (6%) are the most popular adverse effects. The most significant adverse effect of domperidone is the prolongation of the corrected QT interval. In the U.S., Domperidone is not accessible. Cisapride, a mixed serotonergic agent promoting the release of acetylcholine at myenteric plexus synapses, has increased the risk of sudden death, resulting in restricted access programs. There is no support for the effectiveness of a high incidence of side effects of bethanechol [16,17]. In patients with gastroparesis, erythromycin and

azithromycin, agonists of motilin, may be of benefit. These medications, however, have not been shown to minimize GER.

Discussion

After other options have failed [1], anti-reflux surgery is typically proposed. Fundoplication reduces GER because during swallow-induced relaxation, it increases LES baseline pressure, decreases the amount of transient LES relaxations and nadir pressure, increases the duration of the intra-abdominal esophagus, accentuates the His angle and if present, decreases the hiatal hernia. The open Nissen fundoplication has been replaced by laparoscopic surgery. The use of robot-assisted Nissen funds does not give a major advantage. In children with confirmed GERD who have failed or are not adherent to optimal medical therapy or who have life-threatening presentations of GERD, anti-reflux surgery may be indicated.

There has been an interest in developing less invasive and equally successful endoscopic therapies for GERD, considering the effectiveness of fundoplication for the treatment of refractory GERD for medical treatment. In infants and children with GERD, there is no evidence to support regular radiofrequency ablation (Stretta procedure). However in selected situations, and if executed by experienced experts, the technique can be of use. Regarding endoluminal endoscopic gastroplication, the same can be said. Today, because of the scale of the devices, this procedure should not be used in infants and toddlers.

The suggested realistic solution, which is different for infants and young children (Fig. 1) and older children (Fig. 2), is summarized by two algorithms (Fig. 2). However, due to inadequate evidence-based information, there is no suggested realistic solution based on evidence. In addition, both diagnostic and therapeutic opportunities vary from region to region. Last but not least, management would also be decided by the organization of healthcare systems.

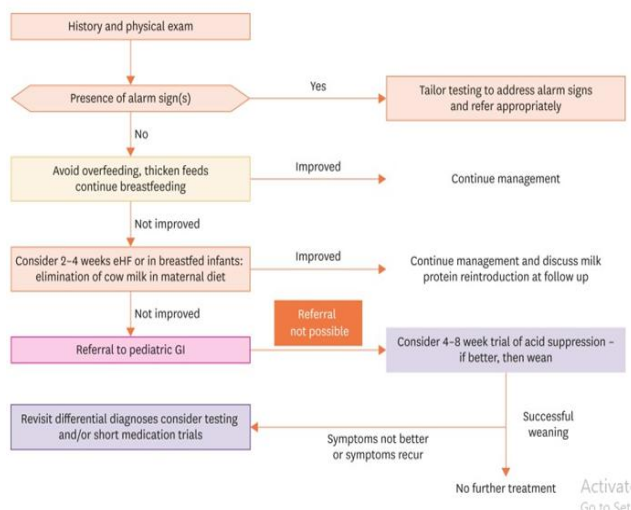


Figure 1:

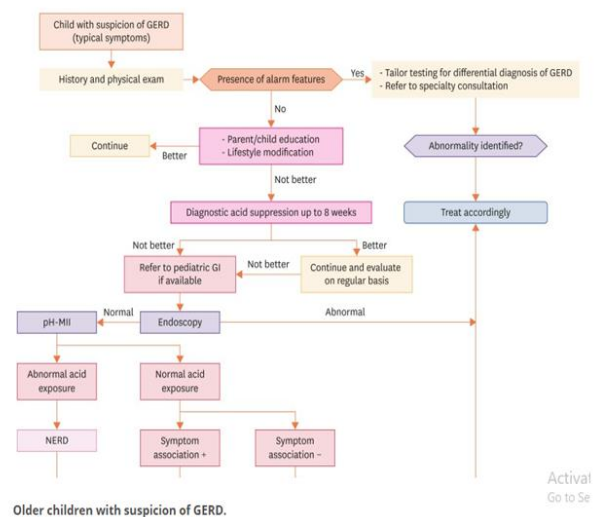


Figure 2:

As always, a full history and a complete physical examination begin with optimal diagnosis and management. The "red flags" or "alarm signs" and the most common differential diagnoses that may present similar histories, symptoms and signs should be known to the healthcare provider. One instance is the differential diagnosis of GER, GERD, and cow's milk protein allergy in children.

If dietary control still remains ineffective, referral is recommended to a pediatric gastroenterologist. A 2 to 4 week trial of antacid medication (PPI and H2RA) is appropriate in cases where referral is not feasible, but as stated, it is not recommended without an objective diagnosis of GERD. However a suitable referral is recommended if the trial of antacid treatment also fails. Diagnostic investigations are not recommended in the absence of warning signs at the primary healthcare level.

The older the infant, the closer the suggested solution is to adult management. Of course, the suggested method begins with a full history and physical examination at any age. The healthcare professional should be informed and act appropriately of the warning signs and most important differential diagnoses (Tables 2). In the absence of red flags, the suggested first interventions are parent and child education and lifestyle changes. A screening trial with antacid treatment for 2 to 4 weeks is recommended for children who are old enough to express themselves in a consistent manner (>8-12 years) if there is inadequate progress. Again, if no change begins after 1 month, it is very unlikely that change will occur later on. If there is adequate progress, the antacid prescription should be continued and periodically reviewed for the necessity of continuation, e.g. every 3 to 6 months. The patient should be referred for a diagnostic upper GI tract endoscopy with biopsies in case of inadequate progress. Suitable management should be initiated in the case of anomalies. A pH-MII recording is recommended if the endoscopy and histology are normal. A diagnosis of NERD is defined if the

outcome is abnormal and management should be decided accordingly. If the pH-MII test is normal but there is a positive correlation of symptoms, the patient suffers from a hypersensitive esophagus. The inference is that the patient suffers from a functional GI condition in the event that there is also a negative symptom correlation [19].

Conclusion

GER and GERD diagnosis and management have remained difficult for years. According to current facts and consensus by key opinion figures, evaluations and recommendations aim to suggest the best approach. In certain cases, however, management decisions based on medical investigations must be taken by the clinician with little assurance as to the outcome and thus the findings are always inconclusive.

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