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Abstract

Despite the existence of internationally approved guidelines, the diagnosis of gastroesophageal reflux (GER)-*disease* remains difficult (Rosen et al. *J Pediatr Gastroenterol Nutr.* 66:516-54, 2018). GER-disease is generally considered a clinical diagnosis. However, differentiation between physiologic GER, functional regurgitation, and GER-disease in infants and between functional heartburn, hypersensitive esophagus, rumination syndrome, symptoms of esophageal dysfunction, and GER-disease in older children can be difficult based on clinical grounds alone. In addition, some patients present with extra-esophageal problems such as chronic respiratory disease, chronic cough, or ENT problems.

Many diagnostic tests have been proposed, but none of them can truly be seen as a gold standard. Upper gastrointestinal endoscopy with biopsies can show erosive esophagitis and Barrett's esophagus and is able to differentiate between reflux esophagitis and eosinophilic esophagitis, but cannot show or exclude non-erosive GER-disease. In theory, 24-h pH-impedance testing allows for detecting all GER events and establishing a temporal association between individual GER events and symptoms. However, no true normative data are available and its analysis can be difficult, especially in severe cases with low impedance baselines. Additionally, the statistical calculation of an association between GER and symptoms is dependent on sufficient symptoms and their adequate objective monitoring. A trial with acid suppression can be helpful to diagnose acid-related disease in older children, but not in patients where weakly acidic GER is predominant. The placebo effect of such a trial carries the risk of chronic over-

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treatment in functional heartburn. Several less invasive tests have been studied, but their diagnostic value is, as yet, limited.

Keywords

Gastroesophageal reflux · Gastroesophageal reflux disease · Esophagus · Motility · Eosinophilic esophagitis · Rumination · Diagnostics

Introduction

Gastroesophageal reflux (GER), defined as the effortless retrograde flow of gastric contents into the esophagus, is a normal physiologic process occurring multiple times a day in children of all ages. It usually does not lead to symptoms or complications. GER can be liquid and gaseous (belch) and can vary from alkaline (pH > 7) to acid (pH < 4). If GER leads to flow of gastric contents into the oropharynx or above, it is referred to as *regurgitation*. *Vomiting* has a different underlying mechanism and leads to forceful expulsion of gastric contents out of the mouth.

GER-*disease* is defined as GER leading to troublesome symptoms that affect daily functioning or complications [1]. In the pediatric age range, complications include, but are not limited to, esophagitis, Barret's esophagus, anemia, growth retardation, and extra-esophageal problems (e.g., recurrent pneumonia, dental erosions, cardiorespiratory events in infants and ENT problems).

Diagnosis of GER-*disease* is primarily based on clinical presentation. A thorough history and physical examination is essential in all patients, not only to differentiate between GER and GER-*disease*, GER-*disease* and rumination, and GER-*disease* and vomiting, but also to rule out other underlying diseases. If there is uncertainty about the diagnosis or a suspicion of complicated disease, additional testing may be necessary. Several diagnostic and therapeutic algorithms are available [1, 2]. The available diagnostic tests are outlined below.

History, Physical Exam, and Questionnaires**Typical Symptoms****Infants**

GER-related symptoms, especially regurgitation and crying, are very common in infancy and not necessarily suggestive of or specific for any disease [3–5]. Regurgitation occurs at least regularly in 70% of 4 month old infants and at least daily in 13.8% of healthy children ranging from 0–12 months [6–8]. If excessive, it may simply be the result of overfeeding, which can be easily corrected [1]. Infants that regurgitate more than once daily for more than 3 weeks (without alarm symptoms) fulfil criteria for *infant regurgitation* as per Rome IV criteria for functional diseases, but do not suffer from GER-*disease* [8]. In physiologic GER and infant regurgitation, the regurgitation episodes resolve with age without treatment [3, 6, 9].

On the other hand, GER-disease can cause severe symptoms and complications, while infants may initially present with similar non-specific symptoms like regurgitation and crying.

To discern between physiological GER, infant regurgitation, and GER-disease, it is important to thoroughly evaluate the severity of symptoms as objective as possible and to investigate the presence of more signs and symptoms that may suggest pathology (Table 16.1) or alternative diagnoses. Alarm symptoms as shown in Table 16.2 should prompt for specific diagnostic workup and/or treatment, depending on the suspected disorder.

In addition, information about feeding type, volumes, frequency and associated problems is essential. Feeding problems may be the result of oropharyngeal dysphagia or eosinophilic esophagitis rather than GER-disease. Non-IgE mediated cow's milk allergy may also present with atypical regurgitation and irritability. Other symptoms of allergy should be asked for and eczema should be specifically looked for during the physical exam. Note that true mono-symptomatic presentation of cow's milk allergy is rare and, if present, involves dermatitis and not gastrointestinal

Table 16.1 Symptoms and complications of physiological GER and GER-disease in infants

<i>Symptoms associated with physiological GER and/or infant regurgitation</i>	
	Regurgitation
	Crying
	Irritability
<i>Symptoms associated with GER-disease</i>	
<i>Esophageal symptoms</i>	
Typical symptoms	Excessive regurgitation
Atypical symptoms	Excessive crying/irritability
	Feed refusal
	Choking
	Back arching
	Anemia
<i>Extra-esophageal symptoms and complications</i>	
General	Growth retardation/failure to thrive
	Anemia
	Hematemesis
	Sleep disturbance
	Sandifer's syndrome
	BRUE
Lungs/ENT	Recurrent pneumonia
	Laryngitis
	Stridor
	Chronic cough
	Apnea
	Desaturations
Heart	Bradycardia
Mouth	Halitosis

Symptoms of physiologic GER and GER-disease in infants. From: van Wijk MP. Pediatric gastroesophageal reflux and upper gastrointestinal tract motility. Amsterdam: University of Amsterdam; 2010. With permission from the author

Table 16.2 “Red flag” symptoms and signs that suggest disorders other than gastroesophageal reflux disease

Symptoms and signs	Remarks
General	Suggesting a variety of conditions, including systemic infections
Weight loss	
Lethargy	
Fever	
Excessive irritability/pain	
Dysuria	May suggest urinary tract infection, especially in infants and young children
Onset of regurgitation/vomiting >6 months or increasing/persisting >12–18 months of age	Late onset as well as symptoms increasing or persisting after infancy, based on natural course of the disease, may indicate a diagnosis other than GERD
Neurological	
Bulging fontanel/rapidly increasing head circumference	May suggest raised intracranial pressure, for example, due to meningitis, brain tumor or hydrocephalus
Seizures	
Macro/microcephaly	
Gastrointestinal	
Persistent forceful vomiting	Indicative of hypertrophic pyloric stenosis (infants up to 2 months old)
Nocturnal vomiting	May suggest increased intracranial pressure
Bilious vomiting	Regarded as symptom of intestinal obstruction. Possible causes include Hirschsprung’s disease, intestinal atresia or mid-gut volvulus or intussusception
Hematemesis	Suggests a potentially serious bleed from the esophagus, stomach or upper gut, possibly GERD-associated, occurring from acid-peptic disease ^a , Mallory–Weiss tear ^b or reflux esophagitis
Chronic diarrhea	May suggest food protein-induced gastroenteropathy ^b
Rectal bleeding	Indicative of multiple conditions, including bacterial gastroenteritis, inflammatory bowel disease, as well as acute surgical conditions and food protein-induced gastroenteropathy rectal bleeding ^b (bleeding caused by proctocolitis)
Abdominal distension	Indicative of obstruction, dysmotility, or anatomic abnormalities

GERD gastroesophageal reflux disease, *NSAID* non-steroidal anti-inflammatory drugs

Alarm symptoms that should prompt further investigation. From: Rosen R, Vandenas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;66(3):516–54, with permission from Wolters Kluwer Health, Inc

^aEspecially with NSAID use

^bMore likely in infants with eczema and/or a strong family history of atopic disease

^cAssociated with vomiting

symptoms [10]. It is, however, not uncommon for parents of patients with cow's milk allergy to report only symptoms suggestive of GER-disease [11].

Finally, maternal depressive symptoms have been shown to be associated with a threefold higher risk of gastroesophageal reflux symptoms in the infant as compared to infants of mothers without depressive symptoms, so maternal mental health deserves attention during history taking [12, 13].

Several questionnaires have been developed to more objectively score GER-related symptoms in infants [14–20]. Although the IGERQ-R is most commonly used, was validated for symptom tracking over time [15] and a clinically meaningful difference in its total score was determined [21], it was not validated for the diagnosis of GER-disease, nor was any one of the other questionnaires. Its limited diagnostic value is likely related to the symptoms overlapping between GER-disease and pharyngeal dysphagia [22].

Older Children and Adolescents

New-onset regurgitation or increase thereof after the age of 12 months, should raise the suspicion GER-disease or other diseases that provoke GER. In infants with regurgitation, which persists after the age of 18 months, true GER-disease should also be considered.

For other symptoms than regurgitation, it is hard to objectify a relation with GER. In toddlers and young children no data exist on the specificity or sensitivity of symptoms. A validated questionnaire exists for children up to 4 years of age, but robust testing of its sensitivity and specificity as compared to an objective reference test is lacking [20]. The same questionnaire was also adapted for, but not validated in children from 5–11 years [23].

With age, symptoms of GER-diseases tend to become more specific and they resemble adult symptomatology in adolescence. A history and physical exam by an expert gastroenterologist has a sensitivity of only 67% and a specificity of 70% for diagnosing GER-disease in adults, indicating that even with increased specificity, the clinical diagnosis of GER-disease remains similarly difficult in adolescents [24].

No diagnostic questionnaires are available for adolescents, but the Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire (PGSQ) is available for validated symptom assessment in patients from 2 to 17 years old [25]. Some studies in adolescents have used the Reflux Disease Questionnaire, which was purposely developed to separate GER-disease from other causes of upper abdominal and lower retrosternal symptoms in adults, and was thoroughly validated [26]. Its test characteristics approach those of an expert gastroenterologist in adults, but were not tested in adolescents [26, 27].

Extra-Esophageal Symptoms

Many extra-esophageal symptoms have been linked to GER (Table 16.1).

In (premature) infants brief resolved unexplained events (BRUEs) are commonly thought to be GER related. Most studies, however, do not provide evidence for such

a relation and oropharyngeal dysphagia seems to be a larger contributing factor in the majority of these children [28–30]. Other presentations at different ages, like chronic cough, laryngitis, and wheezing, can be GER related [31, 32] but more common causes should be excluded first, especially when no typical GER-related symptoms are present. If still suspected to be GER related, history should focus on the presence of additional typical GER symptoms and on a possible temporal relation between the symptoms and feeding times. This is similarly true for older children and adolescents [31, 32].

Diagnostic Tests

Proton Pump Inhibitor (PPI) Trial

In infants, the use of PPI as an empiric diagnostic trial is not recommended. In this age group, PPI has been shown to lack additional efficacy as compared to placebo [33]. Because of the very high placebo effect observed in most clinical trials, a PPI-trial as diagnostic test additionally carries a large risk of over-diagnosing GER-disease and subsequent prolonged unnecessary treatment.

In adolescents, it seems reasonable to use a PPI-trial for 4–8 weeks as per adult guidelines, i.e., in treatment naïve patients with typical symptoms of heartburn and/or regurgitation and this test is now incorporated in pediatric guidelines too [1, 34]. Clinical improvement during such a trial has, however, poor test characteristics in adults (sensitivity 54%, specificity 65%, PPV 75% and NPV 41%) and the results should therefore be interpreted with caution, especially in younger children [24]. Unnecessary treatment of patients who respond based on a placebo effect remains a matter of concern in this age group and therapy based on the results of a PPI-trial should therefore be reconsidered regularly.

Endoscopy and Esophageal Biopsies

Endoscopy, albeit considered a relatively safe procedure, is invasive and requires sedation in children. Although clear macroscopic abnormalities during endoscopy confirm GER, negative predictive value is very low, and a normal-looking mucosa does not exclude GER-disease [35, 36]. In patients with GER-diseases, endoscopy can differentiate between erosive and non-erosive disease. Barrett's esophagus (BE) as a complication of GER-disease, is very rare in children and can be demonstrated only in 0.13% of all children and adolescents undergoing endoscopy with biopsies [37]. Approximately 70% of children with BE have an underlying disorder that predisposes to severe GER-disease [38]. Endoscopy thus has limited clinical consequences when used as a first-line diagnostic test; both erosive esophagitis and non-erosive GER-disease need treatment with acid suppression.

Endoscopy should thus be reserved for patients with therapy-resistant GER-disease, alarm symptoms such as hematemesis, or those in whom another cause of

their symptoms is suspected (eosinophilic esophagitis, Crohn's disease or infectious esophagitis). If an endoscopy is performed, biopsies should be taken to rule out eosinophilic esophagitis and examine microscopic esophagitis, even if no macroscopic abnormalities are seen [1].

Function Tests

High-Resolution Manometry

High-resolution manometry (HRM) cannot be seen as a standard diagnostic test for GER-disease and should be reserved for specific indications in refractory cases. In these children, HRM can have an important role in the diagnostic process. First, many PPI-refractory patients in fact do not have GER-disease, and HRM can help to diagnose motility disorders as described by the Chicago classification, or, when combined with impedance rumination syndrome and supragastric belching [39, 40].

Second, all patients considered for anti-reflux surgery should have a manometry test to exclude rumination syndrome and disorders of esophagogastric junction outflow obstruction (such as achalasia) [41–43], accurately show and subtype the presence of a hiatus hernia (HH) [44] and evaluate esophageal peristalsis. Although debated, patients with severe forms of hypomotility may have more post-fundoplication dysphagia, especially when a Nissen fundoplication is performed [45–48]. In children HRM in combination with impedance has shown promising results in predicting post-fundoplication dysphagia [49, 50].

HRM can accurately localize the position of the lower esophageal sphincter, which can be used to position a 24-hour pH(–impedance) catheter.

Finally, high-resolution *impedance* manometry can evaluate impedance baseline at the moment of maximal esophageal contraction (contractile segment impedance), which shows promise in augmenting the diagnosis of GER-disease [51, 52]. This metric, however, needs further validation in adults and children, before its role in the diagnostic process can be determined.

24-Hour Esophageal pH—Monitoring

24-Hour esophageal pH monitoring is able to detect pH changes at a single level in the esophagus and thus indirectly measures acid GER. Although esophageal acid exposure is an important factor in symptom generation and the development of complications, especially in older children, this test has some drawbacks, which should be considered when results are interpreted [53].

First, the cut-off value for the amount of acid exposure that is pathological is still a matter of debate, because true normal values are not available with currently used pH-sensors [1]. Early pH-metry studies that used glass electrodes, were validated using other reference standards that have severe limitations [36, 54, 55]. In addition, the most commonly used parameter, the reflux index or acid exposure time (AET), does not answer the essential question whether symptoms are related to GER.

Second, adult pH monitoring results have shown a significant day-to-day variability, which complicates its interpretation [56]. The use of Bravo wireless

capsules allows for 48–72 hours of pH recording and was used to show that the variability may be less in children [57]. Nevertheless, Bravo capsules are not widely available and seldomly used in children as they require endoscopy for their placement.

Third, pH monitoring also possesses intrinsic qualities, which limit sensitivity and specificity. First of all, GER episodes are indirectly detected by acidification of the lumen surrounding the pH sensor, which is normally positioned at 3 or 5 cm proximal to the lower esophageal sphincter. Observations have shown marked regional differences in pH levels throughout the esophagus and it is as yet unclear what position of the pH sensor gives best diagnostic results [58]. Second, for standard automated recognition of a GER episode, pH must drop by at least 1 point and to a value lower than 4. As a result, weakly acidic ($4 < \text{pH} \leq 7$) and alkaline ($\text{pH} > 7$) GER episodes are per definition not detected by standardized esophageal pH monitoring. This is especially problematic in infants, in whom frequent feeding and subsequent buffering of stomach contents causes gastric pH to be only weakly acidic during most of the day [59]. Because most GER episodes occur in the early postprandial period, when pH in the stomach is highest, it is not surprising that in infants, the majority of GER episodes is weakly acidic and therefore not detected by standardized esophageal pH monitoring [60]. Another consequence of the indirect measurement of GER is that acid re-reflux or “superimposed” acid GER (i.e., acid GER during the period in which the acid of a previous GER episode is still being cleared) is not detected. Finally, the results of pH monitoring are influenced by dietary intake during the test, because acidic food and drinks will also cause a drop in pH in the surroundings of the pH sensor. Dietary restrictions are, therefore, commonly imposed on patients, resulting in test conditions that do not necessarily reflect daily routine. Despite its limitations, esophageal pH monitoring is still performed in many centers worldwide due to the fact that it is readily available, analysis is automated and it is relatively inexpensive. A 24 h pH-metry can be considered in the suspicion of acid-related disease with/without symptom correlation (see below) and to evaluate the efficacy of acid-suppressive therapy in patients with already proven GER-disease [1].

24-Hour Esophageal pH-Impedance Monitoring

With the introduction of pH-impedance monitoring, some disadvantages of pH monitoring seem to have been overcome. Because pH-impedance detects esophageal flow directly, it is possible to detect all GER episodes and classify these into acidic, weakly acidic, and weakly alkaline GER [53]. Due to the multiple measuring sites, the direction of flow can be determined. Hence, GER can be discerned from swallowed material, making dietary restrictions unnecessary. Furthermore, this makes it possible to study the mechanisms of bolus and acid clearance and provides information on the proximal extent of a GER episode which can be helpful for determining a relation between GER and extra-esophageal symptoms [61].

pH-impedance has its limitations, too. Again, normal values do not exist in the pediatric age range, and although efforts to establish these have been made (Fig. 16.1), it is unlikely that truly normative data will ever become available

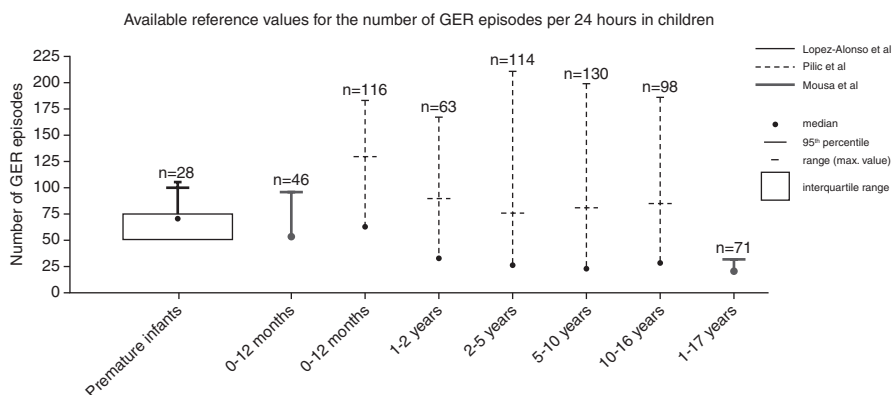


Fig. 16.1 Available reference data for the number of GER events per 24 hour and their distribution. From: Singendonk MMJ, Benninga MA, van Wijk MP. Reflux Monitoring in Children. *Neurogastroenterol Motil.* 2016; 28(10): 1452–9. With permission from John Wiley and Sons

because of ethical considerations preventing the study of healthy children with invasive techniques [60, 62, 63]. Although available and continuously improving, the sensitivity and specificity of the software currently used for automated recognition of MII GER patterns require further optimization and is unlikely to obviate the need for some degree of manual review of the tracing, which makes analysis time-consuming.

A clear statistical association between GER episodes and symptoms theoretically provides convincing evidence of causality. Multiple statistical measures of association have been described: the symptom index (SI), and the symptom association probability score (SAP) are the most commonly used. The SI is the percentage of symptoms related to a GER episode and is considered positive when above 50% [64]. The SI does not take the total number of GER events into account and, by chance, leaves room for a false positive result when many GER events are present. The SAP was developed to overcome these problems. It is a statistical means (Fisher exact test) of calculating the probability that the symptoms and GER episodes found are unrelated. The p-value of this test is then subtracted from 100% to reveal the SAP [65].

With the ability of pH-impedance to detect all GER episodes, symptom association scores are indeed valuable in the diagnosis of GER-disease. However, several difficulties arise. First, not all patients experience symptoms during a 24-h study period and if they do, reporting is not always accurate [66]. Second, clear criteria defining a temporal association are lacking and are a matter of debate [67].

Apart from detecting GER episodes, pH-impedance tests can be used to evaluate other parameters. Baseline impedance is a marker for mucosal integrity and was shown to be low in infants and children with esophagitis [68, 69]. Its calculation is time-consuming and there is no consensus on which method should be used. Mean nocturnal baseline impedance is a simplified means of calculating baseline impedance and was shown to correlate with AET and esophagitis in adults [70] and with AET in children and could be supportive of a diagnosis of GER-disease [34]. Where the MNBI measures mucosal integrity, another novel metric, the post-reflux

swallow-induced peristaltic wave (PSPW) index, is a measure of esophageal clearance. Although not studied in children yet, it was also included in adult guidelines as a measure that can support the diagnosis of GER-disease [34].

In clinics, pH-impedance testing can be used to correlate symptoms with GER episodes in all age groups; to discriminate between the different phenotypes in patients with typical GER symptoms and without esophagitis [71]:

(1) patients with abnormal esophageal acid exposure (non-erosive reflux disease (NERD)); (2) those with a positive symptom association to acid or non-acid reflux but without abnormal AET (reflux hypersensitivity), and (3) patients with normal esophageal acid exposure and a negative symptom association (functional heartburn).

In addition, it can also be used in a patient with persistent symptoms despite acid suppression. Both the efficacy of the medication can be checked and a relation between GER and the persisting symptoms can be found, if present [72].

The role of pH-impedance in confirming supragastric belching, aerophagia, and rumination is beyond the scope of this chapter.

Function Testing in Extra-Esophageal Symptoms

If infants or children present with atypical or extra-esophageal symptoms, other, more common causes of these symptoms should be excluded, before any diagnostic tests for GER-disease are performed. To identify GER as a cause of such symptoms, very few diagnostic tests are available. If a temporal relation between single GER episodes and symptoms can be shown, a causative relation is likely. This can be done using pH monitoring when symptoms are related to acid GER. However, it is likely that especially these symptoms can be related to weakly acidic GER, so symptom association scores using pH-impedance tests can be helpful.

It should be noted that, especially in infants with atypical GER symptoms, functional testing is only appropriate when symptoms are thought to be directly related to bolus GER episodes, and not so much to the cumulative effect of excessive GER. Furthermore every effort should be made to obtain symptoms as objective as possible [66].

Other Tests

Imaging

Barium contrast studies, ultrasound and real-time MRI can be used to show single reflux events. Because reflux episodes in itself are not pathologic, study time is short and it is unlikely that a patient has typical symptoms during the investigation, their diagnostic value is very limited.

However, barium contrast studies and ultrasound have a important role in ruling out anatomical abnormalities and other diseases [1].

Non-invasive Tests

The non-invasive test that is most thoroughly studied, is the presence of pepsin in different body secretions (tracheal fluid, ear effusion, exhaled breath and saliva). Pepsin is the main human digestive protease and is excreted by gastric chief cells as a zymogen, pepsinogen. Salivary pepsin was proposed to be a potential biomarker of GERD in adults and children [73–76]. Although some adult studies report promising sensitivity and specificity of a salivary pepsin assay as compared to pH-metry or pH-MII [73], it was shown that current test characteristics limit its clinical use [77].

Conclusion

GER-disease is primarily a clinical, yet difficult diagnosis. A PPI-trial may be considered in older children but its limited sensitivity and specificity should be considered when interpreting improvement. If additional testing is required, endoscopy and pH-impedance are the most useful tests and together allow for excluding GER-disease or phenotyping it.

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