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Clinical Picture of Gastroesophageal Reflux Disease in Children

Paolo Quitadamo and Annamaria Staiano

Abstract

Gastroesophageal reflux (GER), defined as the passage of gastric contents into the esophagus, is a normal physiologic process occurring several times per day in healthy infants, children, and adults. The majority of GER episodes occur in the postprandial period, last in <3 min, and cause few or no symptoms. Conversely, when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications, we talk about “gastroesophageal reflux disease (GERD).” Distinguishing physiologic GER from GERD may often be tricky for clinicians, especially in infants. The typical presentation of GERD includes the following symptoms: recurrent regurgitation, vomiting, weight loss or poor weight gain, excessive crying and irritability in infants, heartburn or chest pain, ruminative behavior, hematemesis, and dysphagia. Besides these esophageal symptoms, there is a set of extra-esophageal symptoms, mainly respiratory, which may occur along with typical symptoms or may represent the only clinical picture of GERD: odynophagia, wheezing, stridor, cough, hoarseness, dental erosions, and apnea/apparent life-threatening events (ALTEs). While infantile GER tends to resolve spontaneously and does not deserve pharmacological treatment, GERD management includes lifestyle changes, pharmacologic therapy, and surgery. Therefore, a proper diagnosis of these two conditions, besides other possible conditions mimicking reflux, is crucial in order to target the treatment, avoiding the overuse of antacid drugs that currently represents a major source of concern.

Keywords: gastroesophageal reflux, gastroesophageal reflux disease, vomiting, regurgitation, heartburn, irritability, chest pain, respiratory symptoms, typical GERD presentation, atypical GERD presentation

1. Introduction

Gastroesophageal reflux (GER) is a normal physiologic process occurring several times per day in healthy infants, children, and adults. Most episodes of GER in healthy individuals occur in the postprandial period, last in <3 min, and cause few or no symptoms [1]. In contrast, according to the clinical practice guidelines for the diagnosis and management of reflux in the pediatric population, published by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), gastroesophageal reflux disease (GERD) is present when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications [2]. Reflux symptoms may vary widely according to age. Therefore, distinguishing physiologic GER from GERD may often be tricky, especially in infants. A proper diagnosis of these two conditions, besides other

possible conditions mimicking reflux, is crucial in order to target the treatment, avoiding the overuse of antacid drugs which currently represents a major source of concern. The clinical picture alone is frequently nonspecific and does not allow, except in older children and adolescents, to detect the actual need for acid suppressive medications. Therefore, instrumental diagnostic testing, such as esophageal combined multiple intraluminal impedance and pH monitoring and upper gastro-intestinal endoscopy, are often requested [3].

The typical presentation of GERD includes the following symptoms: recurrent regurgitation, vomiting, weight loss or poor weight gain, excessive crying and irritability in infants, heartburn or chest pain, ruminative behavior, hematemesis, and dysphagia. Besides these esophageal symptoms, there is a set of extra-esophageal symptoms, mainly respiratory, which may occur along with typical symptoms or may represent the only clinical picture of GERD: odynophagia, wheezing, stridor, cough, hoarseness, dental erosions, and apnea/apparent life-threatening events (ALTEs). Moreover, GERD may underlie other signs or conditions, such as impaired quality of life, food refusal, persisting hiccups, abnormal posturing/Sandifer's syndrome, anemia, and bradycardia. Finally, esophagitis, Barrett's esophagus, and esophageal adenocarcinoma are possible acknowledged and worrisome long-term outcomes, especially when GERD is undiagnosed or untreated [3].

As already reported, all the above-mentioned signs and symptoms are variously prevalent and relevant in the different pediatric age groups. Therefore, GERD clinical pictures of infants, children, and adolescents will be treated in separate paragraphs.

2. Clinical picture of physiologic GER and GERD in infants

Regurgitation and vomiting are very frequent in healthy infants, mostly during the first months of life. About 70% of healthy infants physiologically regurgitate several times per day, and in about 95% of them, symptoms disappear without intervention by 12–14 months of age [4, 5]. The term “happy spitter” has been used to identify these patients, in order to highlight the benignity of such condition. Infants regurgitate more frequently than adults due to the large liquid volume intake, the prolonged horizontal position of infants, and the limited capacity of both the stomach and esophagus [6]. Irritability and excessive crying are also very frequent in infants and may present along with regurgitation and vomiting. Therefore, neither regurgitation and vomiting nor irritability and excessive crying, regardless of their severity extent and their extent, are sufficient to diagnose GERD. GERD should be suspected in infants with these symptoms, but none of the symptoms are specific to GERD alone. The major role of history and physical examination in the evaluation of purported GERD is to rule out other more worrisome disorders that present with similar symptoms (especially vomiting) and to identify possible complications of GERD. The vast majority of spitting and crying infants suffer from physiologic GER (also called infant regurgitation), a benign condition with an excellent prognosis, needing no intervention except for parental education and anticipatory guidance, and possible changes on feeding composition. Overfeeding exacerbates recurrent regurgitation [6]. Thickened or anti-regurgitation formulas decrease overt regurgitation [7].

Although reflux does occur physiologically in most infants, clinicians should be aware that there is a continuum between physiologic GER and GERD leading to significant symptoms, signs, and complications. Therefore, a small proportion of symptomatic infants may deserve an instrumental diagnostic assessment for GERD or other GERD-mimicking diseases. To help identify this subgroup of infants, the latest international GER guidelines drafted a list of warning signals requiring investigations in infants with regurgitation or vomiting (**Table 1**).

Gastrointestinal bleeding
Hematemesis
Hematochezia
Bilious vomiting
Consistently forceful vomiting
Onset of vomiting after 6 months of life
Failure to thrive
Diarrhea
Constipation
Fever
Lethargy
Hepatosplenomegaly
Bulging fontanelle
Seizures
Macro/microcephaly
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome

Table 1.
Warning signals requiring investigation in infants with regurgitation or vomiting.

3. Clinical picture of GERD in young children

Whether persisting from infancy or of new onset, regurgitation and vomiting are less common in children older than 18 months of age and deserve an instrumental evaluation to diagnose possible GERD or to rule out alternative diagnosis [2]. Besides regurgitation and vomiting, GERD may present in children with many

Gastrointestinal obstruction
Pyloric stenosis
Malrotation with intermittent volvulus
Intestinal duplication
Hirschsprung disease
Antral/duodenal web
Foreign body
Incarcerated hernia
Other gastrointestinal disorders
Achalasia
Gastroparesis
Gastroenteritis
Peptic ulcer
Eosinophilic esophagitis/gastroenteritis
Food allergy
Inflammatory bowel disease
Pancreatitis
Appendicitis

Infectious
Sepsis
Meningitis
Urinary tract infection
Pneumonia
Otitis media
Hepatitis
Metabolic/endocrine
Galactosemia
Hereditary fructose intolerance
Urea cycle defects
Amino and organic acidemias
Congenital adrenal hyperplasia
Renal
Obstructive uropathy
Renal insufficiency
Toxic
Lead
Iron
Vitamins A and D
Medications— <i>ippecac</i> , <i>digoxin</i> , <i>theophylline</i> , etc.
Cardiac
Congestive heart failure
Vascular ring
Others
Pediatric falsification disorder (<i>Munchausen syndrome by proxy</i>)
Child neglect or abuse
Self-induced vomiting
Cyclic vomiting syndrome
Autonomic dysfunction

Table 2.
Differential diagnosis of vomiting in infants and children.

other signs or symptoms, the most frequent of which are heartburn, food refusal, dysphagia, feeding or sleeping disturbances, failure to thrive, persisting hiccups, impaired quality of life, and dental erosions. Respiratory symptoms, such as chronic cough, wheezing, hoarseness, laryngitis, chronic asthma, aspiration pneumonia, ear problems, and sinusitis, are atypical symptoms possibly associated with GERD. Nevertheless, the paucity of clinical studies, varying disease definitions, and small sample sizes do not allow to draw firm conclusions about their association with reflux [8].

According to the latest international pediatric guidelines, subjective reflux symptom description is unreliable in children younger than 8 to 12 years of age, and many of the purported symptoms of GERD in children are nonspecific [9–11].

Therefore, a clinical diagnosis based on a history of heartburn cannot be inferred since these individuals cannot reliably communicate the quality and quantity of their symptoms [12–16]. GERD testing mainly include esophageal pH/MII, upper GI endoscopy, and barium upper GI series. The diagnosis of GERD has to be inferred when tests show excessive frequency or duration of reflux episodes, esophagitis, or a clear association of symptoms and signs with reflux episodes in the absence of alternative diagnose (**Table 2**).

4. Clinical picture of GERD in older children and adolescents

In older children and adolescents' heartburn, regurgitation and chest pain are the specific symptoms of GERD. According to experts' opinions, in this age group, the description and localization of these symptoms are a reliable indicator for GERD, and an acid suppressive trial may be empirically started, regardless of an objective evaluation of reflux. This approach is mainly driven from adult studies [17, 18]. Along with heartburn and chest pain, other symptoms and signs may occur in older children and adolescents, such as regurgitation, epigastric pain, food refusal, dysphagia, impaired quality of life, sleeping disturbances, anorexia, and dental erosions. Moreover, likewise infants and younger children, even older children and adolescents, may experience respiratory symptoms as the only manifestation of GERD [3].

Several studies report a significant degree of overlap between GERD and functional dyspepsia (FD) [19, 20]. According to the Rome diagnostic criteria for pediatric functional gastrointestinal disorders, FD is defined as a "persistent or recurrent pain or discomfort in the upper abdomen, most often aggravated by meal ingestion, not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome) when no physical or organic cause for the symptom is identified with conventional testing" [21].

Clinicians should careful approach upper GI symptoms, being aware that the current literature on the overlap between GERD and FD is affected by considerable heterogeneity in terms of the criteria and diagnostic procedures used to assess both conditions. To exclude GERD, patients must undergo upper digestive endoscopy, pH monitoring, and/or an empiric acid-suppressive trial. A lack of correspondence between symptoms and reflux episodes, together with normal acid exposure in the distal esophagus, would suggest a diagnosis of FD. Finally, clinicians should also be aware that other causes of heartburn-like chest pain including respiratory, cardiac, musculoskeletal, medication-induced, or infectious etiologies should be considered besides GERD.

5. Overview on GERD and respiratory symptoms

As abovementioned, GERD may also underlie respiratory symptoms, such as chronic cough, wheezing, stridor, odynophagia, and hoarseness. Although the role of GERD in the pathogenesis of respiratory symptoms in adults is widely accepted [22], in children there is less evidence to support this relationship [23, 24]. Several pathogenetic mechanisms have been proposed to explain the link between GERD and respiratory symptoms, including aspiration of acid gastric contents into the upper airways, vagal reflex induced by the presence of acid in the esophageal lumen, and sensitization of the central cough reflex [2, 25].

Recent advances in the pathogenesis of reflux-induced respiratory symptoms have followed the introduction in clinical practice of MII-pH, which is available for pediatric use since 2002 [26]. Combined esophageal pH and impedance monitoring offer several advantages over a standard pH assessment, including the ability

of detecting non-acid reflux events, determining the height and composition of the refluxate (liquid, gas, or mixed), recognizing swallows from authentic reflux episodes, assessing the bolus clearance time, and measuring symptom association with reflux (symptom association probability, SAP) even while the patient is assuming acid-suppressive medications [27]. Thanks to pH-impedance studies, several authors have recently highlighted the role of weakly acid and non-acid reflux [28–35]. Furthermore, a recent review reported that a significant percentage of patients with GERD-related respiratory symptoms do not improve despite an aggressive acid-suppressive therapy [36], thus supporting the hypothesis that respiratory symptoms are less related to acidity than GI symptoms.

In conclusion, the analysis of the medical literature concerning the relationship between GERD and respiratory symptoms highlights a large body of evidence often discordant or conflicting, rarely allowing to draw firm conclusions to be used in clinical practice. Over the next years, the use of pH-impedance, combined with manometry or with cardiorespiratory monitoring, in longitudinal, placebo-controlled, double-blind clinical trials, will help in clarifying the main pathophysiological aspects that link GER and respiratory system, providing the clinician with fundamental scientific basis for diagnostic and therapeutic choices.

6. Management of physiologic GER

In newborns and infants, TLESRs are physiological events. Further considering the physiologic poorer tone of the lower esophageal sphincter, the frequency of GER events is commonly much higher compared to the other ages of life. Thus, uncomplicated GER in otherwise healthy infants is classified as physiologic or functional GER. This condition tends to resolve spontaneously in 95% of infants within 12–14 months of life [37, 38]. According to the current international guidelines, infants with functional GER should not receive pharmacological treatment, despite symptoms may cause significant distress to both infants and parents [2]. The most common symptoms associated with GER in the first year of life are regurgitation, vomiting, irritability, cough, and food refusal [39–42]. When physiologic GER is clinically suspected in healthy, thriving infants, parental education, reassurance, and anticipatory guidance are always required and usually sufficient [2].

6.1 Feeding changes in infants

Cow's milk allergy: Infants with cow's milk protein allergy may present with vomiting and regurgitation as well as infants with GER. In order to avoid possible misdiagnoses, formula-fed infants with regurgitation and vomiting could benefit of a 4-week trial with hydrolyzed milk or amino acid formula [43, 44]. Breast-fed infants as well may be affected by cow's milk protein allergy since a few proteins pass into the human breast milk. Therefore, an exclusion of cow's milk proteins from maternal diet should be considered [45–47].

Overfeeding: Although exact numbers are unknown, overfeeding has recently been thought to be a prominent cause of GER because the ingested volume is relatively large compared to the size of the stomach in infants. Large-volume feeds can promote regurgitation in infants due to gastric distention and increase in TLESR frequency [48]. Restricting volume, however, can result in insufficient energy intake. Thus, increasing the caloric concentration of the feedings while decreasing the total volume of the feedings may decrease GER [2].

Thickening feeds: Several studies have demonstrated the efficacy of thickened formula in reduction of reflux events in infants with GER. A thickened formula

was recently tested in premature neonates with apnea. The primary outcome was assessed through multichannel intraluminal impedance, reporting a significant decrease of only acid reflux episodes, while apneic episodes and non-acid GER indexes were not significantly altered [49–51]. The efficacy of thickened formula was demonstrated both on typical and atypical reflux symptoms [52–55]. Despite thickened feeds are currently increasingly being used to treat infants with GER [56], it has been debated that thickened formula increases the caloric intake, thus predisposing infants to later obesity [51, 53, 56–58]. Conversely, infants fed with formula thickened with carob bean gum were reported having a comparable weight increase to the control group [54]. Similar results were with a soy fiber-thickened formula [58]. Furthermore, the fermentation of thickening agents has been reported to cause side effects such as abdominal pain and diarrhea [42]. Further, well-designed clinical trial on these possible side effects are needed in order to evaluate their true relevance.

6.2 Positioning therapy for infants

Positioning of the body may have an impact on the incidence of GER episodes. Therefore, among the conservative measures to manage infantile GER, the current NASPGHAN-ESPGHAN guidelines include positioning strategies. Different positionings have been so far evaluated: semisupine, prone, supine and flat, supine with head elevated, and left-side down and right-side down position [59–66]. Infants with GER were shown having a longer exposure to gastroesophageal reflux in semisupine position, with an infant seat, than in prone position. Therefore, semisupine position is strongly discouraged, especially for infants younger than 6 months of age. The prone position reduces the reflux episodes significantly more than the other positions. However, the increased risk of a sudden infant death syndrome (SIDS) shifts the prone position in a negative cost/benefit ratio. Currently, the prone position is advisable only in infants with demonstrated airway disorders, in which the risk of death from GERD is higher than that from SIDS. Conversely, the prone position may be suggested for all infants in the early postprandial period when they are still awake or in children older than 1 year of age [2].

6.3 PPI abuse in infants

The number of PPI prescriptions for infants has increased manifold over the last years, despite the absence of evidence for acid-related disorders in the majority [66, 67]. This dramatic increase in PPIs' prescribing patterns has raised concerns related to their appropriate use and associated costs [68]. Although irritable infants are frequently empirically treated with PPIs as the reflux esophagitis is believed to be the cause of crying, there is no evidence supporting the usefulness of PPIs, neither as a diagnostic test nor as a treatment strategy in this age group. Double-blind randomized placebo-controlled trials of PPI efficacy in infants with GER symptoms showed that PPIs and placebo produced similar improvement in crying, despite the finding that acid suppression occurred only in the PPI group [6, 69]. In the largest double-blind randomized placebo-controlled trial of PPIs in infants with symptoms purported to be GERD-related, response rates in those treated with lansoprazole or placebo for 4 weeks were identical (54%) [70]. Therefore, no placebo-controlled treatment trial, in which enrollment was based on "typical" GERD symptoms, has demonstrated symptom improvement in infants. Thus, in accordance to the ESPGHAN-NASPGHAN international guidelines, we believe that a serious effort to curtail PPI empiric use in infant is firmly required.

7. Treatment options for GERD

GERD management in children includes lifestyle changes, pharmacologic therapy, and surgery. Lifestyle changes which may contribute to prevent and improve reflux symptoms in infants have already been discussed in the previous sections. In children and adolescents, lifestyle changes include modification of diet and sleeping position, weight reduction, and smoking cessation [2, 71]. Although usually sufficient to manage physiologic GER, lifestyle changes alone are not effective in the treatment of GERD, which must include pharmacologic therapies and possible surgical intervention for severe, unresponsive cases.

The major pharmacologic agents currently used for treating GERD in children are gastric acid-buffering agents, mucosal surface barriers, and gastric antisecretory agents. Since the withdrawal of cisapride from commercial availability in most countries, prokinetic agents have been less frequently used, although domperidone is commercially available in Canada and Europe. Pediatric studies comparing pharmacologic agents for GERD have been impaired by small sample size, absence of controls, and use of unreliable endpoints. Therefore, most studies investigating effectiveness and safety of GERD drugs have been performed in adults, and their applicability to children of all ages is uncertain.

7.1 Histamine-2 receptor antagonists

Histamine-2 receptor antagonists (H^2 RAs) inhibit histamine-2 receptors on gastric parietal cells, thus decreasing acid secretion. H^2 RAs currently available in most countries are cimetidine, ranitidine, famotidine, and nizatidine. These four drugs have similar spectra of activity, side effects, and clinical indications and are extremely well tolerated by patients [72–79]. However, the efficacy of H^2 RAs in achieving mucosal healing is much greater in mild than in severe esophagitis [80]. Extrapolation of the results of a large number of adult studies to older children and adolescents suggests that H^2 RAs may be used in these patients for the treatment of GERD symptoms and for healing esophagitis, although H^2 RAs are less effective than PPIs for both symptom relief and healing of esophagitis [77, 81, 82]. The fairly rapid tachyphylaxis that develops with H^2 RAs is a major drawback to their chronic use. The occurrence of tachyphylaxis, or a decrease of the response, to intravenous ranitidine and the escape from its acid-suppressive effect have been observed after 6 weeks [83], and tolerance to oral H^2 RAs in adults is well recognized [84, 85]. In some infants, H^2 RA therapy causes irritability, head banging, headache, somnolence, and other side effects that, if interpreted as persistent symptoms of GERD, could result in an inappropriate increase in dosage [79]. H^2 RAs, particularly cimetidine, are associated with an increased risk of liver disease [86, 87] and cimetidine with gynecomastia [88].

7.2 Proton pump inhibitors

PPIs act by blocking $Na^+-K^+-ATPase$, the final common pathway of parietal cell acid secretion, often called the proton pump, thus inhibiting acid secretion. Studies in adults have shown that PPIs produce higher and faster healing rates for erosive esophagitis than H^2 Ras, largely because of their ability to maintain intragastric pH at or above 4 for longer periods and to inhibit meal-induced acid secretion [89]. Moreover, the strong suppression of acid secretion by PPIs also results in decrease of 24-h intragastric volumes, thereby facilitating gastric emptying and decreasing volume reflux [90]. To date, PPIs approved for use in children in North America are omeprazole, lansoprazole, esomeprazole, pantoprazole, and rabeprazole. No

PPI has been approved for use in infants younger than 1 year of age. Most studies of PPIs in children are open-label and uncontrolled [91, 92]. In children, as in adults, PPIs are highly efficacious for the treatment of GERD symptoms and the healing of erosive disease. PPIs have greater efficacy than H²RAs. Young children may require higher per kilogram doses to obtain the same acid-blocking effect [93–96].

7.3 Prokinetic agents

Although the role of delayed gastric emptying in the pathogenesis of GERD has never been clarified and remains controversial, prokinetic agents have been used as first-choice treatment for reflux symptoms in children for many years. The most well-known prokinetic drug is cisapride, widely prescribed until 2000, when it was withdrawn due to cardiac toxicity which increased the risk of sudden death [97]. Currently, other prokinetics such as domperidone and metoclopramide are still commonly prescribed. Nevertheless, neither have robust evidence to support their use in children with GERD [98–100]. Baclofen is a gamma-amino-butyric-acid (GABA) receptor agonist which has been shown to reduce both acid and non-acid refluxes in adults, probably by inhibiting the transient relaxations of the lower esophageal sphincters (TLESRs) [101]. In children, baclofen was shown to accelerate gastric emptying for 2 h after administration, decreasing the frequency of emesis [102, 103]. Despite its promising effects, many side effects, such as dyspeptic symptoms, drowsiness, dizziness, and seizures, preclude its routine use [104]. In conclusion, there is insufficient evidence to justify the routine use of cisapride, metoclopramide, domperidone, or baclofen for GERD.

7.4 Alginates and antacids

Alginates and antacids are commonly combined in the same product and are widely used by adult patients to treat reflux symptoms. Antacids act by directly buffering gastric contents, thereby reducing heartburn. There is little evidence for the use of antacids in pediatric age [105, 106]. Conversely, alginates have been studied to a greater extent in children. Alginates precipitate in the stomach to form a low-density but viscous gel that forms a foam that floats on the surface of gastric content and can preferentially enter the esophagus instead of gastric content during reflux episodes [107]. Studies performed both in infants and children showed a significant reduction in the height of reflux episodes, along with an improvement of symptomatic scores [108–113]. On-demand use of antacids and alginates may provide prompt relief from reflux symptoms in children and adolescents [114]. Nevertheless, although alginates seem to have a good safety profile, antacids have possible adverse effects, such as increased serum levels of aluminum, magnesium, or calcium, which represent a major drawback to their long-term use [113, 115, 116].

7.5 Surgical therapy

Surgical treatment represents the last option for GERD management. When and which children could likely benefit from anti-reflux surgery (ARS) has never yet been elucidated. Currently, surgery should be considered for children with confirmed GERD who have failed optimal medical therapy, who are dependent on medical therapy over a long period of time, who are significantly nonadherent with medical therapy, or who have life-threatening complications [2]. Medical literature on surgical therapy in children with GERD mainly consists of retrospective case series in which details on GERD diagnosis and on previous medical therapy are partially lacking, making it difficult to evaluate the indications for and the outcomes of

surgery [117–119]. Moreover, most surgical series include children with underlying conditions predisposing to the most severe GERD, such as neurological impairment, thereby confounding efforts to determine the benefits versus risks of surgical anti-reflux procedures in specific patient populations. Nevertheless, according to the available data, ARS in children shows a good overall success rate (median 86%) in terms of complete relief of symptoms, and its outcome does not seem to be significantly influenced by different surgical techniques [120]. Gastric fundoplication is the most commonly performed intervention. Different types of fundoplication have been developed, according to Nissen (360° fundic wrap around the esophagus) and Thal and Toupet (both partial wraps). Traditionally, these procedures were performed open, whereas in most centers, laparoscopic fundoplications are now preferred. Nevertheless, a recent pediatric trial showed that open and laparoscopic fundoplications provide similar control of reflux and quality of life at follow-up, although the latter is associated with reduced incidence of retching persisting over a 4-year period [120–122].

Author details

Paolo Quitadamo^{1,2} and Annamaria Staiano^{1*}

1 Department of Translational Medical Science, Section of Pediatrics, “Federico II” University of Naples, Italy

2 Department of Pediatrics, AORN Santobono-Pausilipon, Naples, Italy

*Address all correspondence to: staiano@unina.it

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