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SPECIAL ISSUE

'Gastroenterology in Pediatrics: Current knowledge about some common disorders'

Editor

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Gastro-esophageal reflux in children: Symptoms, diagnosis and treatment

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REVIEW ARTICLE

Gastro-esophageal reflux in children: Symptoms, diagnosis and treatment

Yvan Vandenplas, Bruno Hauser, Thierry Devreker, Tania Mahler, Elisabeth Degreef, Gigi Veereman-Wauters

Abstract:
Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus and is a normal physiologic process occurring several times per day in healthy individuals. In infants and toddlers, no symptoms allow to diagnose GERD or to predict response to therapy. In older children and adolescents, history and physical examination may be sufficient to diagnose GERD.
Endoscopically visible breaks in the distal esophageal mucosa are the most reliable evidence of reflux esophagitis. Esophageal pH monitoring quantitatively measures esophageal acid exposure. The severity of pathologic acid reflux does not predict symptom severity or treatment outcome. Combined multiple intraluminal impedance and pH monitoring (MII-pH) measures both acid, weakly acid, non-acid and gas reflux episodes. MII-pH is superior to pH monitoring alone for evaluation of the temporal relationship between symptoms and GER. Barium contrast radiography is not useful for the diagnosis of GERD, but is useful to detect anatomic abnormalities. Tests on ear, lung and esophageal fluids for lactose, pepsin or lipid laden macrophages have all been proposed without convincing evidence. An empiric trial of acid suppression as a diagnostic test can be used in older children (> 10 years).
Parental education, guidance and support are always required and usually sufficient to manage healthy, thriving infants with symptoms likely due to physiologic GER. Use of a thickened feed, by preference commercially available anti-regurgitation formula, decrease visible regurgitation. Positional therapy brings additional benefit. Prone (beyond the age of sudden infant death syndrome) or left side sleeping position, and/or elevation of the head of the bed decrease GER.
Chronic use of buffering agents or sodium alginate is not recommended for GERD since some have absorbable components that may have adverse effects with long-term use. Potential adverse effects of currently available prokinetic agents outweigh the potential benefits of these medications for treatment of GERD. Proton pump inhibitors (PPIs) are superior to histamine-2 receptor antagonists (H2RAs). Administration of long-term acid suppression without a diagnosis is not recommended. No PPI has been approved for use in infants < 1 year of age. The potential adverse effects of acid suppression, including increased risk of community-acquired pneumonias and gastrointestinal infections, need to be balanced against the benefits of therapy. Anti-reflux surgery is of benefit in selected children with chronic, relapsing GERD. Indications include failure of optimized medical therapy; dependence on long-term medical therapy; significant non-adherence with medical therapy; or pulmonary aspiration of refluxate.

Key words: *Gastroesophageal reflux, children*
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Introduction

Healthy and sick individuals do not differ in the presence or absence of reflux, but in the frequency and/or intensity of reflux episodes, and/or in symptoms associated with reflux episodes (1). In young infants, regurgitation is the most frequent clinical manifestation of GER. More than half of the 3 to 6 months old infants regurgitate at least once a day, and the decreases during the second semester of the 1st year of life (2). Almost 25% of the parents consider the frequency and/or volume of regurgitation as a concern serious enough to consult a physician (3). After the age of one year, regurgitation becomes relatively seldom. The great majority of the regurgitating infants are happy, healthy and thriving. Regurgitation is defined as the passage of refluxed contents into the pharynx, mouth or from the mouth (4). GER-disease is present when reflux of gastric contents is the cause of troublesome symptoms and/or complications (4).

Few longitudinal follow-up studies have been performed to evaluate whether infants with significant GER are more likely to have persistent symptoms through childhood and/or adulthood. Although scientifically convincing evidence is missing, most studies indicate a relation between reflux symptoms during early and later life. Nelson et al. followed 6-12 month infants with frequent regurgitation and compared them to a control group. One year later, regurgitation had stopped in all, but eating and meals were still considered as unpleasant moments (5). There was no difference in ear, sinus, upper respiratory infections, or in "children's eating behaviour inventory" (5). These findings suggest that infant regurgitation may result in a "negative eating experience" that persists for a significant longer period than the regurgitation itself. Only one study looked at the prevalence of symptoms in older children and adolescents: according to parents symptoms were less frequent than according to the adolescents (6). In a small series on 37 children with abnormal pH metry or esophagitis (age 3 - 19 years) reported that 6 had "severe" esophagitis, one Barrett esophagus (7). Age and pH metry results were related to the severity of esophagitis. More than 10 % of these children needed a Nissen intervention because of refractory GERD (7). Almost 20 years ago, Johnston et al reported on the long term follow-up of children with hiatal hernia (8). The series consisted of 118 patients that were for more than 20 years known with a hiatal hernia, which was diagnosed during childhood. 94 of these patients were not operated, and there was persistence of the hiatal hernia in 53 % of the non-surgically treated patients, of which only few were symptomatic (46 % heartburn monthly, but only 3/96 "severe"). Also, an "effective" treatment in childhood was associated with a significant reduction antacid consumption as adult (8). (Of course, it is not clear if this can be attributed to efficacy of the treatment or to less severe hernia or reflux.) Adults with GER-disease, had more frequently "at least 1 GER-symptom during childhood" than adults without GER (9).

In a group of 69 children with a median age of 16 months, referred to a teriary care reference center, the major reflux-symptoms at referral were: vomiting (72%), epigastric and abdominal pain (36%), feeding difficulties (29%), failure to thrive (28%), irritability (19%) (10). Esophagitis was present in 62%. These children were treated with "standard medical therapy",that could be stopped successfully in 63 % one year later. Only 4 (6 %) of these children required a Nissen intervention (10).

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Carre described autosomal dominant inheritance of hiatal hernia by discovering familial hiatal hernia in five generations of a large family, but without demonstrating the link to GERD (11). Barrett's esophagus is partially genetically determined (12).

The genetic influence on GERD is supported by increased GER-symptoms in relatives of GERD patients (13). Moreover, the concordance for GER is higher in monozygotic than dizygotic twins (14). Genes in question have been localized to chromosomes 9 and 13. A locus on chromosome 13q, between microsatellite D13S171 and D13S263, has been linked with severe GERD in 5 multiple affected families (15). This could not be confirmed in another 5 families, probably due to genetic heterogeneity of GERD and different clinical presentation of patients (16). The relevance of these findings for the general population remains unclear.

It is not clear to which extent life style has an influence in reflux during infancy and childhood. In adults, race, sex, body mass index and age are independently associated with hiatus hernia and esophagitis, race being the most important risk factor (17). In adults, GERD affects Caucasians more often than African Americans or Native Americans (18). In adults, alcohol, smoking, drugs, food components, intake and weight are among many factors influencing the incidence of GER.

Table 1. Symptoms and signs that may be associated with gastroesophageal reflux (According to Ref 1)

Symptoms
Recurrent regurgitation with/without vomiting
Weight loss or poor weight gain
Irritability in infants
Ruminative behavior
Heartburn or chest pain
Hematemesis
Dysphagia, odynophagia
Wheezing
Stridor
Cough
Hoarseness
Signs
Esophagitis
Esophageal stricture
Barrett esophagus
Laryngeal/pharyngeal inflammation
Recurrent pneumonia
Anemia
Dental erosion
Feeding refusal
Dystonic neck posturing (Sandifer syndrome)
Apnea spells
Apparent life threatening events (ALTE)

Still in adults, over-the-counter use of low-dose aspirin and non-steroidal anti-inflammatory drugs has a major impact on the incidence of severe GER (19). The true natural history of GER and GERD is difficult to evaluate since most infants and children get in some way or another treatment. There are anecdotic data suggesting that severe complications such as esophageal stricture are more frequent in populations with a more limited access to health care, eg. in North Africa, than in the same population living in Western Europe. 1887(2,3,4).

Diagnosis

Many of the symptoms and signs that may be associated in infants and children are non-specific. The diagnosis of GERD is often made clinically based upon troublesome symptoms (Table 1)(20). Subjective symptoms are unreliable in children less than 8 to12 years of age. GERD is diagnosed when tests show excessive frequency or duration of reflux events, esophagitis, or a clear association of symptoms and signs with reflux events in the absence of an alternative diagnosis.

It is not known whether symptoms and/or test-results can predict an individual patient's response to therapy and long term outcome. The severity of symptoms does not correlate to the degree of abnormality of reflux investigations (20,21). Tests differ in the information provide: while endoscopy is helpful in demonstrating esophagitis, others are helpful in establishing a causal relationship between reflux and symptoms, or evaluate therapy response or exclude other conditions. Since there is not one test that can address all these questions, tests must be carefully selected according to the information sought, and the limitations of each test must be recognized.

Although the cornerstone of all diagnostic tests is history and physical examination, history is of limited interest in children less than 8-12 years old. Diagnostic tests can be subdivided in those measuring only postprandial reflux (barium meal, nuclear scintigraphy, ultrasonography), those measuring reflux over prolonged periods (pH monitoring for aci reflux, impedance-pH measurement for acid, weakly acid and non-acid reflux and bilirubin for bile reflux), and endoscopy evaluating mainly the histological consequence of reflux. Finally, there are do data in children on using a therapeutic trial as diagnostic test, the standard in adults.

History and physical examination

The major role of history and physical examination is to contribute to the exclusion of

other disorders that also present with vomiting and to identify complications of GERD (4). Despite that the underlying pathophysiology of GERD is similar at all ages, reflux symptoms vary with age (20,22). Regurgitation, irritability, and vomiting are common in both infants with physiologic GER and GERD and are indistinguishable from regurgitation, irritability and vomiting caused by other conditions such as food allergy, colic and other disorders (23,24).
In adults, GERD is often diagnosed based on a history of heartburn defined as substernal, burning chest pain, with or without regurgitation. Recent adult and pediatric consensus guidelines have applied the terms "typical reflux syndrome" or "reflux chest pain syndrome" to this presentation. Based on expert opinion, the diagnosis of GERD can be made in adolescents presenting with typical heartburn symptoms. However, a clinical diagnosis based on a history of heartburn cannot be used in infants, children or non-verbal adolescents (e.g., those with neurologic impairment) as these individuals cannot reliably communicate the quality and quantity of their symptoms. The verbal child can communicate pain, but descriptions of quality, intensity, location and severity generally are unreliable until at least 8 and possibly 12 years of age (25).

Parent or patient-reported questionnaires based on clusters of symptoms have been developed because symptoms do not consistently correlate with objective findings or response to medical treatment, Orenstein et al developed a diagnostic questionnaire for infants with a score of >7 (of 25 possible) having a sensitivity of 0.74 and specificity of 0.94 during primary validation (26). The questionnaire has undergone several revisions (27). However, when applied to another population, it had a sensitivity and specificity of only 43% and 79%. According to Salvatore et al., the questionnaire had a sensitivity and specificity of 47% and 81% for a RI >10% and 65% and 63% for a reflux index >5%, and failed to identify 26% of infants with GERD. No single symptom was significantly associated with esophagitis (21). Diagnostic questionnaires such as the GERD Symptom Questionnaire have not been compared to objective standards like endoscopy, pH monitoring or esophageal MII monitoring. In infants and young children, no symptom or cluster of symptoms has been shown to reliably predict complications of reflux or to predict those infants likely to respond to therapy (4).

Barium contrast radiography
Barium meal or upper gastrointestinal (GI) series is neither sensitive nor specific for diagnosing GERD. The brief duration of the upper GI series produces false negative results, while the frequent occurrence of non-pathological reflux during the examination produces false positive results. Therefore, routine performance of upper GI series to diagnose reflux or GERD is not justified. However, the upper GI series is useful to detect anatomic abnormalities.

Nuclear scintigraphy
The 99Technetium nuclear scan evaluates postprandial reflux and demonstrates reflux independent of the gastric pH. Scintigraphy can also measure gastric emptying (although specific gastric emptying studies provide more accurate information), which may be delayed in children with GERD (28). A lack of standardized techniques and the absence of age-specific norms limit the value of this test. Gastroesophageal scintigraphy scanning can detect reflux episodes and aspiration occurring during or shortly after meals, but its reported sensitivity for microaspiration is relatively low (although one study reported a higher incidence (29)). Not finding aspiration does not exclude aspiration may occur at other moment. But also the finding of aspiration is not necessarily pathologic, since aspiration of gastric contents and saliva occurs in healthy adults during deep sleep (30). Nuclear scintigraphy is not recommended in the routine diagnosis and management of GERD in infants and children (4).

Esophageal and gastric ultrasonography
Ultrasound is not recommended as a routine test to measure GER but the technique provides some specific information as it measures fluid movements over short periods of time. It can also detect hiatus hernia, length and position of the LES relative to the diaphragm and magnitude of the gastro-esophageal angle of His (4). Barium upper gastrointestinal series can provide the same

information, but cause a lot of irradiation. Compared to esophageal pH metry, the sensitivity of color Doppler ultrasound performed for 15 minutes post-prandially is about 95% with a specificity of only 11%, and there is no correlation between reflux frequency detected by ultrasound and pH metry reflux (31). At present, there is no role for ultrasound as a routine diagnostic tool for GERD in children (4).

Motility studies

GERD cannot be diagnosed by esophageal manometry. Esophageal manometry measures esophageal peristalsis, upper and lower esophageal sphincter pressures and the coordinated function of these structures during swallowing. Manometric studies were critical to identify transient relaxations of the LES (TLESR). Esophageal motor abnormalities are common in patients with esophagitis. Manometry is critical to diagnose achalasia or other motor disorders of the esophagus which may mimic GERD, but not for the diagnosis of GER(-disease). Recent studies indicate there is no role for manometry in predicting outcome of fundoplication (32).

Endoscopy and biopsy

EGD with biopsies is the only method to reliably diagnose esophageal manifestations of GERD, such as erosive esophagitis or Barrett esophagus. Upper GI endoscopy allows direct visual examination of the esophageal mucosa. Mucosal biopsies enable evaluation of the microscopic anatomy. Macroscopic lesions associated with GERD include esophagitis, erosions, exudate, ulcers, strictures, hiatal hernia, areas of possible esophageal metaplasia, and polyps. While endoscopy can detect strictures, subtle degrees of narrowing may be better shown on barium contrast study. Malrotation and achalasia cannot be diagnosed by endoscopy.

Recent Global Consensus guidelines define reflux esophagitis as the presence of endoscopically visible breaks in the esophageal mucosa at or immediately above the GE junction (4). Evidence from adult studies indicates that visible breaks in the esophageal mucosa are the endoscopic sign of greatest interobserver reliability (33). However, it can be debated if experience in adults can be extrapolated to children. Mucosal erythema or an irregular Z-line are not reliable signs of reflux esophagitis (33). Grading the severity of esophagitis, using a recognized endoscopic classification system is useful for evaluation of the severity of esophagitis and response to treatment. The Hetzel-Dent classification has been used in several pediatric studies, while the Los Angeles classification is generally used for adults, but is suitable also for children (4). The diagnostic yield of endoscopy is generally greater if multiple samples of good size and orientation are obtained from biopsy sites that are identified relative to major esophageal landmarks. Eosinophilia, elongation of papillae (rete pegs), basal hyperplasia, and dilated intercellular spaces (spongiosis) are nonspecific reactive changes that may be found in esophagitis of other causes, or in healthy volunteers (4). The presence of endoscopically normal esophageal mucosa does not exclude a diagnosis of non-erosive reflux disease or esophagitis of other etiologies. Recent studies have shown considerable overlap between the histology of reflux esophagitis and eosinophilic esophagitis (34,35).

Although GERD is likely the most common cause of esophagitis, other disorders such as eosinophilic esophagitis (EE), Crohn disease, and infections also cause esophagitis. EE and GERD have very similar symptoms and signs, and can be best distinguished by endoscopy with biopsy. A key difference endoscopically is that EE is not generally an erosive disease, but has its own typical endoscopic features such as speckled exudates, trachealization of the esophagus, or linear furrowing. In up to 30% of cases, however, the esophageal mucosal appearance is normal (34). When eosinophilic esophagitis is considered as part of the differential diagnosis, it is advisable to take esophageal biopsies from the proximal and distal esophagus. Mucosal eosinophilia may be present in the esophageal mucosa in asymptomatic infants <1 year of age (36), and in symptomatic infants eosinophilic infiltrate may be due to milk protein allergy (37). The major role for esophageal histology is to rule out other conditions in the differential diagnosis, such as eosinophilic esophagitis, Crohn disease, Barrett esophagus, infection, and others. When biopsies

from ESEM show columnar epithelium, the term Barrett esophagus (BE) should be applied and the presence or absence of intestinal metaplasia specified.

Esophageal pH monitoring

Esophageal pH monitoring measures the frequency and duration of acid reflux episodes. Wireless capsule sensors that can be clipped to the esophageal mucosa during endoscopy have allowed pH monitoring without a nasal probe. A new technique measuring pharyngeal pH (Restec®) has been developed, but still needs evaluation in children.

By convention, a drop in pH below 4.0 is considered an acid reflux episode. This cut-off was initially chosen because heartburn induced by acid perfusion of the esophagus in adults generally occurs at pH <4.0 (38). Although pH monitoring data analysis is performed automatically by computer programs, visual inspection of the tracing is required to detect artifacts and for interpretation. The RI (percentage of the entire record that esophageal pH is <4.0) is the commonly used summary score. Common other parameters obtained from pH monitoring include the total number of reflux episodes, the number of reflux episodes lasting >5 minutes, the duration of the longest reflux episode. Several scoring systems for pH monitoring studies have been developed but no system is clearly superior to the RI. The calculated area under the pH 4.0 curve has been associated with erosive esophagitis in children (39). However, this parameter has not entered routine use. Normal pediatric ranges are different for glass or for antimony electrodes (40). Most of the data above pertains to infants, in whom frequency, volume and type of feeding may have different buffering effects. "Cut-off" values that discriminate between physiologic GER and pathologic GERD are misleading because there is a continuum between both. Normal ranges should be regarded as guidelines rather than absolutes. Insufficient attention has been given to the demonstration of a relation in time between symptoms and (acid) reflux. Esophageal pH monitoring is insensitive to weakly acid and non-acid reflux events. The degree of abnormality of pH monitoring has not been shown to correlate with symptom severity (21). Although the RI is often abnormal in children with difficult-to-control asthma and in infants with daily wheezing, there is a lack of data during or after treatment to demonstrate a causal relation (20). Esophageal pH monitoring is useful for evaluating the efficacy of anti-secretory therapy.

Esophageal pH monitoring results may help correlate symptoms with acid reflux by applying various analytic methods, including the symptom index (SI), symptom sensitivity index (SSI) and symptom association probability (SAP). The optimal cut-offs of these parameters and thus the clinical utility of pH studies to determine a causal relationship between specific symptoms (pain, cough, etc) and reflux have been insufficiently studies in pediatric patients. Esophageal pH monitoring provides a quantitative measure of esophageal acid exposure, with established normal ranges but the severity of pathologic acid reflux does not correlate consistently with symptom severity or demonstrable complications (4,20,21).

Combined multiple intraluminal impedance (MII) and pH monitoring

Multiple intraluminal impedance (MII) is a pH-independent procedure for measuring the movement of fluids, solids and air in the esophagus (41). MII measures changes in the electrical impedance (i.e., resistance) between multiple electrodes located along an esophageal catheter. Esophageal impedance tracings are analyzed for the typical changes in impedance caused by the passage of volume or gas (or mixed) boluses. The direction and velocity of a bolus can be calculated using the defined distance between electrodes and the time between alterations in the impedance pattern of sequential electrode pairs. Although MII can detect very small bolus volumes, pH-only reflux (acid reflux without bolus movement) exists as well (mainly in young infants) (42). Therefore, impedance measurement should always be combined with pH detection in a single catheter. The combined measurement of pH and impedance (pH/MII) provides additional information as to whether refluxed material is acid, weakly acidic or non-acidic. Limited studies have found variable reproducibility (43,44). Evaluation of MII

recordings is aided by automated analysis tools but (1) the automatic analysis software stills needs validation in children, and (2) a visual reading will remain required. Although normal values for all age groups have not yet been established, these are likely to be not detrimental because the main advantage and indication of the technique is demonstration of symptom-reflux association in time.

The combination of pH/MII with simultaneous monitoring of symptoms using video-polysomnography or manometry has proven useful for the evaluation of symptom correlations between reflux episodes and apnea, cough, other respiratory symptoms and behavioral symptoms (45). However, the nasal presence of a probe alters the quality of sleep.

One of the classic arguments in favor of MII-pH measurement is the measurement of reflux during the postprandial period or at other times when gastric contents are non-acid. But, among the arguments to not recommend ultrasound, nuclear scintigraphy and barium meal in the diagnosis features the consideration that measuring reflux in the postprandial period is not recommended because of the overlap with physiologic reflux. Measurement of other parameters such as symptom index (SI) or symptom association probability (SAP) may be of additional value to prove symptom association with reflux, especially when combined with MII (46). However, as for pH metry, cut-off values for these parameters in children are not known.

Bilirubin detection

Continuous monitoring of biluribin in the esophagus has been suggested as a means of detecting esophageal reflux of duodenal juice or duodeno-gastroesophageal reflux (DGER). One study indicated that therapy with PPI decreased the esophageal damage caused by DGER (47). The role of bile reflux in children resistant to PPI treatment has not been established.

Tests on ear, lung and esophageal fluids

Recent studies reported the finding of pepsin, a gastric enzyme, in middle ear effusions of children with chronic otitis media (48,49). This relation has not been validated in controlled treatment trials. Also, many infants with acute otitis media do vomit. As a consequence, the finding of pepsin can be a consequence and not causal. The presence of lactose, glucose, pepsin, or lipid filled macrophages in bronchoalveolar lavage fluid has been proposed to implicate aspiration secondary to reflux as a cause of chronic pulmonary conditions (50). But, randomized controlled therapeutic trials are here as well missing.

Empiric trial of acid suppression as a diagnostic test

Empiric treatment with acid-suppression as diagnostic test has been studied in adults in many clinical situations. However, empiric therapy has only modest sensitivity and specificity as a diagnostic test for GERD depending upon the comparative reference standard used (endoscopy, pH monitoring, symptom questionnaires) (51), and the appropriate duration of a "diagnostic trial" of acid suppression has not been determined. The treatment period required to achieve uniform therapeutic responses with PPI therapy probably varies with disease severity, treatment dose and specific symptoms or complications (52). The 2-week "PPI test" lacks adequate specificity and sensitivity for use in clinical practice.

As long as there are no data in infants, children and adolescents, the utility of a (2 week) therapeutic trial will be debated and will find defenders and opponents. Additionally, it must be accepted that there is no "golden standard" diagnostic test. Although endoscopy with histology is probably the best for esophagitis, and although impedance-pH measurement is probably the best for GER-disease, it is broadly accepted that these techniques have their shortcomings and are likely to miss the diagnosis of GERD in some patients. Also, it seems not realistic to recommend these investigations as minimal diagnostic approach in each individual child. Therefore, although not sustained by evidence from literature, a short therapeutic trial seems reasonably defendable in some situations. However, insufficient or no response should by preference lead to the conclusion of reflux being unlikely the cause of the symptoms and not to

change of reflux medication or increasing dosage as is now frequently the case.

Symptoms and signs

Determination of the exact prevalence of GER (and GERD) at any age is virtually impossible for many reasons: most reflux episodes are asymptomatic, symptoms and signs are nonspecific and self-treatment is common. Only impedance-pH recording seems an appropriate technique to quantify the incidence, duration,

volume and height of physiologic reflux. However, for ethical reasons this information seems impossible to obtain. While reflux occurs physiologically at all ages, there is at all ages also a continuum between GER and GERD (Table 1 and 2). GERD is a spectrum of a disease that can best be defined as manifestations of esophageal or adjacent organ injury secondary to the reflux of gastric contents into the esophagus or, beyond, into the oral cavity or airways. Less than 10 % of infants and children have (acid and troublesome) GERD (53). The presenting symptoms of GERD differ according to age (Table 3).

Belching or eructation occurs during transient relaxation of the LES, and is an important method of venting air from the stomach. The upper esophageal sphincter relaxes in response to esophageal body distention by gas, in contract to its contractile response to esophageal body distension by fluid. Since we know from impedance that many reflux episodes are "mixed" with air-reflux before volume-reflux, a better in-depth study of the physiologic functioning of the upper esophageal sphincter is needed. Hiccups are

involuntary reflex contractions of the diaphragm followed by laryngeal closure. In some cases, hiccups cause GER.

The clinician needs to be aware that not all regurgitation and vomiting in infants and young children is GER(-disease). Bilious vomiting, gastrointestinal bleeding, consistently forceful vomiting, weight loss or failure to thrive, bulging fontanelle, macro- and/or microcephaly, seizures, diarrhea, constipation, fever, lethargy, hepatosplenomegaly, abdominal tenderness or distension should raise the possibility of an alternate diagnoses such as anatomic abdominal problems, genetic and/or metabolic syndromes (Table 2). The physician's challenge is to separate regurgitation and vomiting caused by reflux from numerous other disorders provoking the same manifestations.

Table 2. Warning signals requiring investigation in infants with regurgitation or vomiting (According to ref 1).

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

GER and uncomplicated regurgitation

Regurgitation is a characteristic symptom of reflux in infants, but is neither necessary nor sufficient for a diagnosis of GERD, because regurgitation is not sensitive or specific. Regurgitation with occasional projectile vomiting is the most common presentation of infantile GER. Up to 70 % of healthy 3-4 month old infants regurgitate. Regurgitation resolves in 95% of individuals by 12–14 months of age (2). Frequent

regurgitation, defined as >3 times per day, occurs in about 25 % of infants during the first months of life.

Although a prospective follow-up reported disappearance of regurgitation before 12 months in all, an increased prevalence of feeding refusal, duration of meals, parental feeding related distress and impaired quality of life was noticed (30). In fact, many infants get some intervention (reassurance, position, dietary treatment).

Although most studies report a comparable incidence of regurgitation in unselected populations of formula versus breastfed infants, Hegar et al. reported a higher incidence in formula-fed infants (2). This observation fits with the knowledge that GER and symptoms of GERD may be indistinguishable from those of food allergy (4,20). The incidence of cow milk protein allergy is 3 – 5 %, and is 5 to 10 times higher in formula fed than in breastfed infants (54).

Although the "happy spitter" certainly exists (and is not rare), many regurgitating infants have symptoms of distress and discomfort. Irritability is not, in the absence of other warning symptoms, an indication for extensive testing (20). But in fact, parental coping-capacity or anxiousness will determine if a physician has to intervene or not. Infant regurgitation is a benign condition with a good prognosis, needing no other intervention than parental education and anticipatory guidance. Overfeeding exacerbates recurrent regurgitation. Thickened or anti-regurgitation formula decreases overt regurgitation (20,55,56).

GER(D) and recurrent regurgitation and poor weight gain

If poor weight gain is documented, it is obvious that the infant cannot be considered as a happy spitter. Poor weight gain is a crucial warning sign that necessitates clinical management. These infants need a complete diagnostic workup. Hospitalisation may be needed. There may be abnormal sucking and swallowing. These infants may not have apparent malformations, and may be diagnosed as suffering "non-organic failure to thrive" ("NOFTT"), a "disorder" that sometimes is attributed to social/sensory deprivation, socio-economic or primary maternal-child problems. GERD is only one of the many etiologies of "feeding problems" in infancy. Primary GER without associated anatomic malformations is only seldom a cause of failure to thrive (20).

GER(D) and distressed behaviour

This group of patients is much more difficult to deal with than the infant with poor weight gain. The same amount of distress and crying may be evaluated by parents as acceptable while the same amount of crying will be unbearable for other parents. Many factors, some of them infant related (eg. cow's milk protein allergy), others not infant related (eg. tobacco smoke), may cause infant irritability. There is substantial individual variability and healthy infants may cry up to 6 hours a day.

In infants, there are only limited data that causally related irritability and sleep disturbances to GER. The esophageal nervous system exposed to acid, seems susceptible to pain hypersensitivity despite the absence of tissue damage. In adults, "non-erosive reflux disease" ("NERD") is a well accepted entity. Again in adults, impaired quality-of-life, notably regarding pain, mental health and social function has been demonstrated in patients with GERD, regardless the presence of esophagitis (57). Despite that, only half of the adult complainers of heartburn seek medical help, although 60% takes medications. Thus, some adults "learn to live with their symptoms", and acquire tolerance to long-lasting symptoms, while others accept to live with an impaired quality-of-life. In infancy and young children, persistent crying, irritability, back-arching, feeding and sleeping difficulties have been proposed as possible equivalents of adult heartburn. Esophageal pain and behaviors perceived by the caregiver (usually the mother) to represent pain (e.g., crying and retching) potentially affect the response of the infant to visceral stimuli and the ability to cope with these sensations, both painful and non-painful. Two controlled studies with PPI in distressed infants have been performed, showing an equal decrease in distressed behaviour in the treatment and the placebo group (58,59). There is no evidence that acid suppressive therapy is effective in infants who present only with inconsolable crying. In infants and toddlers, there is no symptom or group of symptoms that can

Table 3. Symptoms according to age (According to ref. 1)

Manifestations	Infants	Children	Adults
Impaired quality of life	+++	+++	+++
Regurgitation	++++	+	+
Excessive crying / Irritability	+++	+	-
Vomiting	++	++	+
Food refusal / Feeding disturbancies / Anorexia	++	+	+
Persisting hiccups	++	+	+
Failure to thrive	++	+	-
Abnormal posturing / Sandifer's syndrome	++	+	-
Esophagitis	+	++	+++
Persistant cough / Aspiration pneumonia	+	++	+
Wheezing / Laryngitis / Ear problems	+	++	+
Laryngomalacia / Stridor / Croup	+	++	-
Sleeping disturbancies	+	+	+
Anemia / Melena / Hematemesis	+	+	+
Apnea/ ALTE / Desaturation	+	-	-
Bradycardia	+	?	?
Heartburn / Pyrosis	?	++	+++
Epigastric pain	?	+	++
Chest pain	?	+	++
Dysphagia	?	+	++
Dental erosions / Water brush	?	+	+
Hoarseness / Globus pharyngeus	?	+	+
Chronic asthma / sinusitis	-	++	+
Laryngostenosis / Vocal nodules problems	-	+	+
Stenosis	-	(+)	+
Barrett's / Esophageal adenocarcinoma	-	(+)	+

Legend: +++ very common; ++ common; + possible; (+) rare; - absent; ? unknown

reliably diagnose GERD or predict treatment response.

Cow's milk protein allergy (CMPA) overlaps with many symptoms of GER disease, and may coexist or complicate GERD (1,4,20,54). Treatment of CMPA implies the use of hydrolysates or amino acid formula. A decrease of GER(-like) symptoms with a hydrolysate is not a proof for an underlying immunological mechanism such as allergy. Gastric emptying of a hydrolysate is more rapid than that of regular formula; a rapid gastric emptying decreases regurgitation. Infants presenting with regurgitation and vomiting may suffer CMPA, GER-disease, both conditions or none of both. A commercial thickened extensive hydrolysate may be welcome in distressed infants presenting with symptoms matching both with troublesome regurgitation and/or CMPA.

GER(D) and heartburn

Descriptions of intensity, location and severity of pain (caused by reflux) may be unreliable until the age of 8 to 12 years (1,4,20). In adults, adolescents and older children, heartburn is the most characteristic symptom of GERD. Diagnosis and management of GERD in older children (> 12 years) and adolescents follows the recommendations for adults (1,4,20). A symptom-based diagnosis of GERD in infants and young children remains difficult.

GERD and esophagitis

Esophagitis is defined as visible breaks of the esophageal mucosa (4,20). Esophagitis is present in 15 up to 62 % of children with GER symptoms. Histology is recommended to rule out complications (Barrett esophagus) or other causes of esophagitis (eosinophilic esophagitis). Erosive esophagitis in 0-17 year old children with GER-symptoms is 12.4 %, and increases with age (60). The median age of the group with erosive esophagitis was 12.7 + 4.9 years, versus 10.0 + 5.1 years in those without erosive esophagitis (61). The incidence of erosive esophagitis was only 5.5 % in those younger than one year (62). This finding is in sharp contrast with the extremely high incidence (24.8 %) of anti-reflux medication prescribed in extremely low birth weight infants at the moment of discharge (60). Hiatal hernia is more frequent in children with erosive esophagitis than without (7.7 % versus 2.5 %) (59).

Typical substernal burning pain ("heartburn", pyrosis) occurs in many children suffering from esophagitis. Odynophagia, which is pain on swallowing, usually represents esophageal inflammation. Esophagitis typically presents with pain, but it can also be asymptomatic. The group with asymptomatic esophagitis is in some ways the most problematic. Even severe esophagitis may remain asymptomatic as demonstrated by children who present with peptic strictures without having experienced any discomfort attributable to esophagitis.

In nonverbal infants, behaviors suggesting esophagitis include crying, irritability, sleep disturbance, "colic". Infants frequent also appear very hungry for the bottle until their first swallows and then become irritable and refuse to drink. But all these symptoms are aspecific. Although these signs and symptoms are frequent in infants with esophagitis, their predictive value for the presence of esophagitis is low.

The reason(s) for the impressive rise in prevalence of EoE is still not well understood and difficulties in separating EoE from reflux esophagitis may be encountered. The mucosa may appear pale, granular, furrowed and occasionally rings may be seen during endoscopy (4,20,34). In reflux esophagitis, the distal and lower eosinophilic infiltrate is mostly limited to less than 5/per high power field (HPF) with 85% positive response to GER treatment. In primary eosinophilic esophagitis, there are >20 eosinophils per HPF. More recent, failure of PPI treatment as a condition to diagnose EoE brought reflux esophagitis back in the picture of EoE (34). EoE necessitates proper hypo- or anti-allergic treatment (hypo-allergenic feeding, corticoids, montelukast, etc.). Atopic features are reported in more than 90% and peripheral eosinophilia in 50% of patients.

GER(D) and dysphagia, odynophagia and food refusal

Dysphagia is the difficulty of swallowing; odynophagia is pain caused by swallowing. Although GERD is frequently mentioned as a

cause of dysphagia or odynophagia, there are no pediatric data showing this relation. Dysphagia is a prominent symptom in patients with eosinophilic esophagitis. Feeding difficulty and/or refusal are often used to describe uncoordinated sucking and swallowing, gagging, vomiting and irritability during feeding. A relation between GER, GERD and feeding refusal has not been established. In case of feeding difficulties, achalasia and foreign body should be among the list of possible differential diagnoses.

GER(D) and extraesophageal manifestations

GER(D) and reactive airway disease and recurrent pneumonia

Reactive airway disease and recurrent pneumonia may be caused by direct aspiration, or by vagal mediated bronchial and laryngeal spasm, or by neurally mediated inflammation. Esophageal acidification in adults with asthma can produce airway hyperresponsiveness and airflow obstruction (62). Few studies tempted to evaluate the opposite: the impact of asthma on the severity of GERD. Chronic hyperinflation as occurs in asthma favors many GER-mechanisms. An association between wheezing, especially if nocturnal, and reflux measured by pH or impedance probe has been frequently reported. However, a correlation between pH-metry results and pulmonary function tests was not found (63). There are no criteria on which patients in whom reflux treatment may result in a reduction of asthma medication can be selected. Today, it is not yet clear if recording in the upper esophagus or pharynx will help in making therapeutic decisions in patients with chronic respiratory problems (64,65). A new technique to record pharyngeal reflux has been developed (Restech□), with promising results needing confirmation (65). A "negative symptom association probability" does not exclude a causal role for GER since a certain "amount" of reflux may be necessary to start airway inflammation. The sensitivity and specificity of lipid-laden macrophages has been shown to be poor. The measurement of pepsin in broncho-alveolar lavage may be more promising, although substantial overlap between patients and controls has been shown (50). One study evaluating nuclear scintigraphy with late imaging reported that 50% of patients with a variety of respiratory symptoms had pulmonary aspiration after 24 hours (29). But aspiration also occurs in healthy subjects, especially during sleep (1,4,20). And later studies failed to reproduce these findings (66). There is no convincing literature that reflux treatment improves respiratory symptoms or lung function parameters. More data are needed in these patients.

The majority of the cystic fibrosis (CF) patients have pathological acid reflux (1,4,20). A high prevalence of acid GER was reported in very young CF-infants, before respiratory symptoms developed. Early reflux treatment seems to slow down the respiratory deterioration. In children with CF, a better weight gain was reported during PPI treatment (whether this is due a reduction of acid reflux or better buffering of acid gastric content in the intestine is not clear).

GER(D) and apnea, ALTE and SIDS

Literature can best be summarized as follows: most series fail to show a temporal association between pathologic apnea and GER, apparent life threatening events (ALTE) and GER and bradycardia and GER (1,20). However, impedance in combination with poly-somnographic recording has shown a relation between GER and short, physiologic apnea (45). There are well selected cases or small series that demonstrate that pathologic apnea can occur as well as consequence of GER. However, reflux causing pathologic apnea and/or ALTE remains seldom.

Treatment

Anticipatory guidance

Parental education, guidance and support are always required and usually sufficient to manage healthy, thriving infants presenting with regurgitation or other signs and symptoms likely due to physiologic GER. Whether regurgitation is considered "troublesome" or not depends largely on the coping capacity of the parents. Therefore, reassurance is essential in the management of regurgitation. However, frequently, parents will expect (going from "demand" to "require") some therapeutic intervention. In these circumstances, it

is important that therapeutic advice should be without risk for adverse effects. As a consequence, medication is not recommended.

Feeding changes in infants

Although about 50% of normal 3-4 month old infants regurgitate at least once a day, up to 20% of caregivers in the United States seek medical help for this reason (3). A subset of infants with allergy to cow's milk protein experience regurgitation and vomiting indistinguishable from that associated with physiologic GER (4,20,53). Elimination of cow's milk protein from the diet is followed by a rapid decrease (usually within 2 weeks) of episodes of vomiting and regurgitation, and re-introduction causes recurrence of symptoms (54).

Overfeeding is a well known cause of regurgitation. Reduced feeding volume decreases reflux frequency (67). But, feeding should remain within normal volume and frequency in order to allow normal development. Infants with inadequate weight gain due to losses by regurgitation may benefit from increasing the caloric density of formula when volume or frequency of feedings is decreased as part of therapy.

In the United States, rice cereal is the most commonly used thickening agent for formula. Rice cereal-thickened formula decreases the volume of regurgitation but may increase coughing during feedings (20). Formula with added rice cereal may require a nipple with an enlarged hole to allow adequate flow. Excessive caloric intake is a potential problem with long-term use of feedings thickened at home with rice cereal or cornstarch. Thickening a 20 kcal/oz infant formula with one tablespoon of rice cereal per ounce increases the caloric density to ~34 kcal/oz (~1.1 kcal/ml). Thickening with one tablespoon per two ounces of formula increases the caloric density to ~27 kcal/oz (~0.95 kcal/ml). Commercial anti-regurgitation (AR) formulas containing processed rice, corn or potato starch, guar gum or locust bean gum are available in Europe, Asia and the United States. These formulas decrease overt regurgitation and vomiting frequency and volume compared with non-thickened formulas or formulas thickened with rice cereal (68-70). The caloric density, osmolarity, protein, calcium, and fatty acid content of commercialized AR formulas is appropriate to an infant's nutritional needs when taken in normal volume, whereas a formula with added thickener has a higher caloric density and in normal ingested volumes may provide more calories than needed. Most commercialized AR formulae do not require a substantially increased sucking effort. In vitro studies have shown a decrease in the absorption of minerals and micronutrients from formulas commercially thickened with indigestible but not digestible carbohydrates. The clinical significance of these findings is unclear since a 3-month follow-up study of children on formula thickened with bean gum showed normal growth and nutritional parameters (71).

A recent meta-analysis confirmed that commercialized AR-formula reduced the frequency and severity of regurgitation and vomiting (55). The number of infants without regurgitation was decreased significantly (55). Overall, there was no effect on the incidence of acid reflux episodes as measured by pH monitoring. However, results were different for rice (increase of reflux), bean gum (neutral), corn starch (reduction) (55). Although) the number of esophageal reflux episodes may not decrease, the reduction in regurgitation may be a welcomed improvement in quality of life for the caregivers and the infant. The allergenicity of commercial thickening agents is uncertain and the possible nutritional risks of long-term use require further study.

Insufficient weight gain excludes physiologic reflux. There are rare infants with GERD who are unable to gain weight despite conservative measures in whom nasogastric or nasojejunal feeding may be beneficial (72). Similarly, nasojejunal feeding is occassionally useful in infants with recurrent reflux-related pneumonia to prevent recurrent aspiration. Although these approaches to therapy are widely utilized, there are no controlled studies comparing them to pharmacologic or surgical treatments.

Positioning therapy for infants

There is substantial evidence from literature that GER is less frequent in prone than in supine position. Although evidence is somehow conflicting, most data suggest that prone head-elevated position further reduces GER (1,4,20). Prone sleep positioning is associated with longer uninterrupted sleep periods, and supine sleep positioning with more frequent arousals and crying (73). However, concerns regarding the association between prone positioning and sudden infant death syndrome (SIDS) required a reassessment of the benefits and risks of prone positioning for reflux management. The Nordic epidemiological SIDS study demonstrated that the odds ratio of mortality from SIDS was over 10 times higher in prone-sleeping infants and 3 times higher in side-sleeping infants than in supine infants (74,75). Therefore, prone positioning is acceptable if the infant is observed and awake, particularly in the postprandial period but prone positioning during sleep can only be considered in infants with certain upper airway disorders where the risk of death from GERD might outweigh the risk of SIDS. Prone positioning may be beneficial in children over 1 year of age with GER or GERD whose risk of SIDS is negligible.

Esophageal pH and combined pH/MII monitoring show that reflux is quantitatively similar in the left-side-down and prone positions. Measured reflux in these two positions is less than in the right-side-down and supine positions (76,75). Two impedance studies in preterm infants found that postprandial reflux was greater in the right-side than in the left-side position (76,77). Based upon these findings, one study recommended that infants be placed right-side for the first hour after feeding to promote gastric emptying and thereafter be switched to left-side to decrease reflux (77). These findings notwithstanding, it is important to note that side-lying is an unstable position for an infant who may slip unobserved into the prone position. Bolstering an infant with pillows to maintain a side lying position is not recommended.

The semi-supine positioning as attained in an infant car-seat exacerbates GER (78). Reflux in supine infants with head elevated is equal or greater than in infants supine and flat. However, a recently published pilot-study evaluating the Multicare-AR Bed® showed that a 40°-supine position in a specially developed bed reduced regurgitation, reflux and crying (79).

Lifestyle changes in children and adolescents

Most studies investigating recommendations such as dietary modification, avoidance of alcohol, weight loss, positioning changes, and cessation of smoking have been performed in adults, thus their applicability to children of all ages is uncertain. A review of lifestyle changes in adults with GERD concluded that only weight loss was effective (80). One uncontrolled study found that a very low-carbohydrate diet reduced distal esophageal acid exposure and improved symptoms in obese individuals with GERD (81). There is more overnight reflux in adults eating a late evening meal than in adults eating an earlier evening meal. The difference was especially obvious in overweight adults (82).

Current evidence generally does not support or refute the use of specific dietary changes to treat reflux beyond infancy. Expert opinion suggests that children and adolescents with GERD should avoid caffeine, chocolate, alcohol and spicy foods if they provoke symptoms. Smoking should be avoided in those with GERD. Three studies have shown that chewing sugarless gum after a meal decreases reflux (83-85). It is not known whether any lifestyle changes have an additive benefit in children or adolescents receiving pharmacological therapy.

The effectiveness of positioning for treatment of GER and GERD in children over 1 year of age has not been studied. Adults who sleep with the head of the bed elevated have fewer, shorter episodes of reflux, and fewer reflux symptoms. Other studies in adults have shown that reflux increases in the right lateral decubitus position (86). It is likely therefore that adolescents, like adults, may benefit from the left lateral decubitus sleeping position with elevation of the head of the bed.

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