Gastroesophageal reflux: natural evolution, diagnostic approach and treatment

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Gastroesophageal reflux (GER) is a normal physiologic process occurring several times per day in healthy infants. Regurgitation is defined as the passage of refluxed gastric contents into the pharynx or mouth, sometimes with expulsion out of the mouth. There are only a few studies that have been performed to determine the prevalence of regurgitation and its natural course in infants, and some of them were cross-sectional and retrospective. However, evaluation of the natural evolution of GER becomes difficult, since the emergence of widespread self-treatment and/or therapeutic interventions. It is important to determine which children have GER disease to offer optimal treatment and to avoid costly and potentially invasive diagnostic testing. Symptoms due to GER are troublesome when they have an adverse effect on the well-being of the pediatric patient. In regurgitating infants, decreasing the amount of regurgitation is often seen by the parents as the most welcomed intervention that physicians can provide. Many medications have been attempted to overcome GER in infants, each with their own advantages and limitations.

Key words: gastroesophageal reflux, infants, diagnosis, treatment.

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus with or without regurgitation and vomiting. GER is a normal physiologic process occurring several times per day in healthy infants. Most episodes of GER in healthy infants last <3 minutes, occur in the postprandial period, and cause few or no symptoms. Regurgitation is defined as the passage of refluxed gastric contents into the pharynx or mouth, sometimes with expulsion out of the mouth[1,2]. Regurgitation is generally assigned as effortless and non-projectile, although it may sometimes be forceful in infants[1].

Reflux episodes occur most often during transient relaxations of the lower esophageal sphincter (LES), unaccompanied by swallowing, which permit gastric contents to flow into the esophagus. A minor proportion of reflux episodes occur when the LES pressure fails to increase during a sudden increase in intraabdominal pressure or when LES resting pressure is chronically reduced[1].

Knowledge of the natural evolution of regurgitation is important to allow health care providers to manage infants and provide evidence-based advice to parents. Epidemiological data on the natural evolution of infant regurgitation will result in a reduction of parental anxiety, medical referral and overtreatment. Although most infants presenting with regurgitation have a normal physical examination, it is now recognized that infants may also present a wide variety of symptoms. It was demonstrated that normal infants also present reflux symptoms, but that the manifestations are significantly more prevalent in GER disease (GERD)[1,2].

Gastroesophageal reflux disease (GERD) is underdiagnosed in some developing countries because the clinical symptoms are not specific and because there is limited availability of diagnostic tools in the majority of the health care centers. This observation is in sharp contrast with data from the developed world, where GERD is likely to be overdiagnosed. The therapeutic approach to GERD in infants needs to be balanced, considering both the

therapeutic efficacy and side effects. There is no excuse for persisting with ineffective management of a disease that might result in stunting, chronic illness, persistent pain, esophageal scarring, or even death.

Natural Evolution

Evaluation of the natural progression of symptoms of GER becomes difficult, since self-treatment is widespread and/or therapeutic interventions by health care professionals are common. Regurgitation resolves spontaneously in most healthy infants by 12 to 14 months of age. In the Western world, evaluation of the natural progression of symptoms of GER at any age has become virtually impossible because of widespread self-treatment and lack of medical referral. In the Eastern part of the world, it is commonly thought that regurgitation is less frequent than in the United States and Europe.

Prevalence and severity of reflux may be expected to vary according to racial or ethnic background. Data from the United States, Australia, India, Thailand, Japan, and Indonesia reported a similar decreasing pattern of the prevalence of regurgitation from the age of 4 months onwards. However, data from the United States and Australia suggest an increase between birth and 2 months of age, while others report a decrease from birth onwards[3-10]. Data from Indonesia show that the prevalence of daily regurgitation during the first 2 months of life is greater than data in other reports. From the age of 6 months onwards, epidemiological data are comparable for different parts of the world.

Data from Indonesia obtained by prospectively interviewing mothers using a standard questionnaire about the prevalence of regurgitation during the previous two weeks showed that up to the age of 3 months, about half of the infants regurgitated between 1-4 times per day. Twenty-five percent of infants regurgitated >4 times a day during the first month of life[3]. Weight gain between birth and 4 months of age was statistically significantly less in infants regurgitating more than 4 times a day compared with infants who never regurgitated[4]. However, at the age of 1 year, there was no difference in weight according to the frequency and duration of regurgitation[4]. In all studies evaluating the natural evolution of infant regurgitation, there was a sharp decline around 6-7 months of age and a disappearance at the age of 12 months[3-10].

GER Symptoms

Alterations in several protective mechanisms allow physiologic reflux to become GERD: insufficient clearance and buffering of refluxate, delayed gastric emptying, abnormalities in epithelial restitution and repair, and decreased neural protective reflexes of the aerodigestive tract[1].

Gastroesophageal reflux disease (GERD) is present when reflux of gastric contents is the cause of troublesome symptoms and/or complications. Symptoms due to GER are troublesome when they have an adverse effect on the well-being of the pediatric patient. Symptoms of GERD vary by age[1,2]. Clinical presentations that should be considered as possibly related to GERD are regurgitation with weight loss, irritability, chronic crying, feeding refusal, or dysphagia. Chronic respiratory symptoms may also be consequences of GERD. Neurological diseases associated with hypertonia, spasticity, hypotonia, and myopathy or congenital anomalies are noted to cause more GER than in the general population.

Parental anxiety, need of treatment, and insufficient body weight gain, which was considered related to excessive regurgitation/vomiting, were reported as problems. However, the prevalence of these possible reflux-associated symptoms was very low. The prevalence of reflux esophagitis in infants is reported to be approximately 5%. According to epidemiological data from Europe and Australia, excessive regurgitation was a cause of concern and medical consult in about 20-25% of parents. Data from Indonesia gave similar results, with about 30% of mothers showing concern over regurgitation. During the first month of life, many infants regurgitated but few mothers expressed their concern. However, the mothers of older infants with persistent vomiting became concerned. The reasons for maternal concern in the Indonesian population were comparable with the data from the United States[8,9] and included excessive volume and frequency of regurgitation and symptoms suggesting a decreased quality of life, such as crying, irritability, back arching,

and food refusal. The volume of regurgitation was considered as a problem less often than the frequency of regurgitation (9% vs 66%). Crying and irritability were the second most frequent (57%) reasons for concern among the mothers. Food refusal and back arching were also reported as cause for concern in 26% and 20%, respectively[3,4]. There was a difference in the prevalence of regurgitation according to the method of feeding. The prevalence of regurgitation was less in the exclusively breastfed group than in partially breastfed babies[4]. However, this result could be due to the higher incidence of cow's milk allergy in formula-fed than in breastfed babies. Moreover, these data strengthen the advantage of breastfeeding.

Data from the United States reported that peak regurgitation as a 'problem' was most often seen at 6 months (23%) and decreased to 14% at 7 months of age, because many infants did regurgitate less[10].

Diagnostic Approach

It is important to determine which children have GERD to offer optimal treatment and to avoid costly and potentially invasive diagnostic testing. Esophageal pH monitoring is a technique that quantifies the incidence and duration of variations in esophageal pH, and has therefore become a standard technique to diagnose acid GERD.

The diagnostic approach of GERD in infants principally depends on its presenting features. Infants with typical symptoms of uncomplicated GER should be treated without investigation. Long-term esophageal pH monitoring is the investigation of choice in the diagnostic approach in the patient suspected of extra-esophageal presentations of GER. Endoscopy with biopsies is recommended if esophagitis is suspected.

The impact of pH monitoring itself on daily activity and feeding habits in infants and children hypothesized that changes in feeding and physical activity may influence the results of the pH monitoring. One study, according to the opinion of the parents, showed that pH-metry did not change feeding habits and physical activity in 72% and 69% of infants. Thus, although the type, frequency, volume of feeding, and physical activity can influence the number and duration of the reflux episodes and thus the pH monitoring results, the outcome of that study suggests that pH monitoring changes the feeding frequency, volume and physical activity equally as frequently in infants with both normal and abnormal results[11].

In order to better understand the relation between GER and extra-esophageal symptoms such chronic cough and other respiratory symptoms, a 24-hour (h) pH monitoring was performed in children with suspected GERD to measure the frequency and duration of reflux that reaches the proximal esophagus[12]. All parameters increased significantly in the proximal esophagus according to the increase in the same parameters in the distal esophagus. The data show that some, but not all, acid reflux episodes in normal individuals reach the proximal esophagus. The acid clearance time was shorter in the proximal than in the distal esophagus[12].

Esophageal pH monitoring was performed in the distal and proximal esophagus of infants and children presenting with excessive regurgitation or vomiting, inconsolable crying (more than 3 hours a day), chronic respiratory disorders such as wheezing and stridor, and Apparent Life-Threatening Event (ALTE) necessitating vigorous stimulation[13]. In the distal esophagus, there was no statistically significant difference between the reflux parameters. As could be expected, almost every parameter was statistically significantly smaller in the proximal than in the distal esophagus. These data do not support the hypothesis that reflux reaching the proximal esophagus is a frequent cause of ALTE[13]. However, multiple intraluminal impedance is of course a technique of much greater interest in this group, since it measures bolus reflux independent of pH and the height to which the reflux reaches.

Acid reflux and/or esophagitis may be responsible for irritability in infants[14]. However, data regarding the incidence of GER (disease) and/or esophagitis in these conditions are still contradictory. A 24-h esophageal pH monitoring and an upper gastrointestinal tract endoscopy with grasp biopsies were performed in irritable infants, aged 1 to 6 months[14]. The 24-h esophageal pH monitoring was considered abnormal in 66% of infants, and histological esophagitis was present in 43%.

Esophageal histology was normal in 55% of infants with an abnormal pH monitoring, and reflux index (RI) was <5% in 23% of infants with histological esophagitis. Histology of duodenal and gastric biopsies in this subgroup did not differ from that of the entire group, suggesting a limited role for cow's milk protein allergy with gastrointestinal manifestations[14].

The sensitivity and specificity to predict esophagitis with a RI of 5.0% or more were 69.2 and 35.3, respectively[14]. There was no RI that could be related to a clinically useful sensitivity and specificity to predict esophagitis. Painful and symptomatic reflux in irritable infants may be non-acid or pH-independent, since pH monitoring was normal in 55% of infants with esophagitis[14]. Only 45% of the infants with an abnormal pH monitoring had esophagitis. Specificity of symptoms and/or pH monitoring and/or impedance to predict esophagitis is very low[15,16].

Since acid GERD and/or histological esophagitis are diagnosed in 66% and 43% of irritable infants, respectively, it is difficult to formulate guidelines for management. Treatment without any investigation has the disadvantage that at least 34% (normal pH monitoring) or 57% (normal histology) of the infants would be treated without reason. Restricting treatment to those infants with esophagitis would neglect that a number of patients with acid GERD do not develop esophagitis. If only a pH monitoring is performed, then a number of patients with esophagitis but with normal pH-metry results would be left untreated[14].

Regurgitation is frequent in infants, but not frequently causing esophagitis. Since the pH of regurgitated milk is not acid, pH-metry can be normal. The correlation between the RI and reflux esophagitis is poor, probably because the RI does not consider the acidity of the reflux episodes. A simultaneous combined gastric and esophageal pH monitoring was performed in regurgitating infants (0.5–6 months old) [17]. The RI was calculated in three different ways: (i) the total duration of the investigation; (ii) excluding 90-minute (min) postprandial periods, starting from the beginning of a feeding; and (iii) excluding all periods with a gastric pH >4.0, which are the periods of gastric buffering with a theoretical impossibility of recording an esophageal pH <4.0. Surprisingly, the shortening of the duration available for detection of acid pH in the esophagus of 35–37% did not significantly increase the RI. This means that episodes of esophageal acidity were also detected during the 90 postprandial min or during the periods with a gastric pH >4.0, although occurring less frequently than when the infant was fasting or gastric pH was <4.0. Thus, acid GER can occur during periods of gastric buffering or during postprandial periods, indicating that gastric pH dispersion is not homogeneous, and simultaneous gastric and esophageal pH monitoring does not contribute to the detection of a larger number of infants with acid GERD[17].

Treatment

The physician should not forget the main reason for the patient to see the doctor is to be relieved from the symptoms that have a negative effect on his quality of life, and the main purpose for the physician is to give a safe and well-tolerated treatment with an optimal cost/benefit ratio. In the regurgitating infant, decreasing the amount of regurgitation is often seen by the parents as the most welcomed intervention that physicians can provide. Non-drug and dietary treatments are an effective and safe approach in infant regurgitation, but do not treat GERD.

Management of GERD in infants should therefore be well considered, and over-investigation and over-treatment of a self-limiting condition should be avoided. The underestimation of a potentially severe disease, accompanied by serious morbidity, should also be avoided.

The recommendation on management of GERD in children has always been a step-up approach, starting with parental reassurance, positional treatment and dietary recommendations. In the infant with uncomplicated recurrent regurgitation, a history and physical examination, with attention to warning signs, is generally sufficient to allow the clinician to establish the diagnosis of uncomplicated GER. Parental education, reassurance and anticipatory guidance are recommended.

Thickened Formula

In formula-fed infants, thickened formula

reduces the frequency of overt regurgitation and vomiting[1]. Although the actual number of esophageal reflux episodes may not decrease, the reduction in regurgitation may be a welcome improvement in quality of life for caregivers. The thickening of the formula with starch or bean gum decreases the frequency and volume of regurgitation. Some studies show that adding thickening agents such as rice cereal to formula does not decrease the time with pH <4 (RI) measured by esophageal pH studies, but it does decrease the frequency of overt regurgitation[1]. A placebo-controlled cross-over study using intraluminal impedance was done to see the effects of thickened feeding on GER in a small group of only 14 infants[18]. Regurgitation and severity score were significantly lower with the anti-reflux (AR)-formula compared to regular formula; however, the number of impedance reflux episodes was not different. Only the height of the reflux episodes was smaller in the AR group[18].

A systematic review and meta-analysis of randomized, controlled trials regarding use of thickened formulas compared with standard formula concluded that there was a significantly increased percentage of infants with no regurgitation, slightly reduced number of episodes of regurgitation and vomiting per day, and increased weight gain per day[19]. There was no effect on the RI, number of acid GER episodes per hour, or number of reflux episodes lasting >5 min, but there was a significantly reduced duration of the longest reflux episode with a pH <4[19]. No serious adverse effects were noted[19].

One study evaluated the natural evolution of infantile regurgitation versus the efficacy of formula thickened with rice cereal versus a commercially available thickened formula with bean gum[19]. Over a period of one month, regurgitation decreased significantly in all three groups. The decrease was largest in the group that received the bean gum–thickened formula. The untreated group in this study confirms once again that there is a natural evolution of regurgitation to decrease over age. There was no change in comfort (sleeping disturbance) and stool characteristics (consistency, frequency) in the infants fed with a formula thickened with bean gum versus those fed with a formula thickened with rice cereal or regular formula[20]. Formula with added rice cereal may require a nipple with an enlarged-bore opening to allow adequate flow. Rice cereal added to formula may provide more energy than needed. Standard formula with 5 gram rice cereal per 100 ml increases the energy to ± 20 kcal. Since its efficacy was shown, a commercial thickening formula was introduced in many countries, include in Asia. However, an expensive anti-regurgitation formula could not be recommended in communities with low socioeconomic level. Standard formula thickened with rice cereal, which is less expensive than commercially thickened formula, could be chosen as an alternative treatment for infants with regurgitation in low socioeconomic communities. In vitro studies have suggested a decrease in the absorption of minerals and micronutrients from formula commercially thickened with not digestible carbohydrates, but this was never confirmed in vivo[1].

Pharmacologic Treatment

There is no evidence to support an empiric trial of pharmacologic treatment in infants with symptoms suggestive of GER[1]. Many medications have been attempted to overcome GER in infants, each with their own advantages and limitations. Efficacy data on many medications are not available, are limited or are disappointing in infants. Prokinetic agents were recommended for the treatment of GERD. Prokinetics administered to infants who failed to improve with parental reassurance, milk thickening and positional therapy may induce an improvement in clinical symptoms and pH tracing.

Prokinetics act on regurgitation through their effects on LES pressure, esophageal peristalsis or clearance, and/or gastric emptying. It seems reasonable to add medications such as prokinetics to the treatment of cases that are refractory to dietary intervention. Cisapride increases salivary secretion[21]. This indicates that in combination with increased peristalsis and esophageal clearance, cisapride therapy may protect the esophagus by increased secretion of bicarbonate and non-bicarbonate buffers in the saliva, facilitating symptomatic relief and healing of the esophagitis. We could show that cisapride decreased pyrosis and heartburn in older children by improving long-term

manometric parameters[22]. Domperidone has antiemetic properties because of its dopamine-receptor blocking activity, whereas cisapride has a gastrokinetic action through indirect release of acetylcholine in the myenteric plexus. A Cochrane review on cisapride treatment in children analyzed data from seven trials, including 236 patients, comparing the effects of cisapride and placebo on symptom presence and improvement. It was concluded that there was a statistical difference for the parameter symptoms 'present/absent', but there was no statistically significant difference for 'symptom change' between placebo and cisapride. The Cochrane review also concluded that cisapride significantly reduced the number and duration of acid reflux episodes when compared to placebo, since there was a significant decrease in the RI[23]. An extensive review of the literature resulted in increasing safety consensus statements[1]. Due to safety concerns on its cardiac side effects, such as an increased QTc interval and cardiac arrhythmias, cisapride has now disappeared from the market or its use is limited.

Studies supporting the efficacy of domperidone in improving GERD in infants are limited[1]. The ability of oral domperidone to increase the LES pressure or to promote healing of reflux esophagitis has not been demonstrated in placebo-controlled trials[1]. A preliminary study that compared the efficacy of domperidone and cisapride showed that the frequency of regurgitation was smaller in the cisapride group compared to the domperidone group in week 1, but without a difference in week 2 and week 3, and the decrease tended to be faster in the cisapride group[19]. However, there was one prolonged QTc (475 msec) in a patient on cisapride and none with domperidone[24]. Studies on the effect of domperidone on the QT interval in neonates showed that oral domperidone-induced QTc prolongation correlated with advanced gestational age, birth weight, and elevated serum potassium[24].

In conclusion, doctors need a better understanding of the pathophysiology, symptoms, diagnosis, and treatment of GER and GERD. Since pH monitoring and endoscopy are not widely available, especially in developing countries, rational empiric therapy may be acceptable. The development of a simple questionnaire will be an essential diagnostic tool. Existing questionnaires can be used as a basis, but should be adapted to the local situation.

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