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Pregled
Review

GASTRO-OESOPHAGEAL REFLUX DISEASE

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GORD is one of the most frequent conditions a child to visit primary care paediatrician. But, only a small number of children presents with troublesome GORD (5-10%) (with complications like failure to thrive, oesophagitis, respiratory disease), and then special investigations are performed. Symptomatology differs with age, although the main pathophysiological mechanism (TLESR) is identical. Diagnostic and therapeutic approach to different clinical presentations is presented. Also, diagnostic methods are presented. A special attention is paid to MII, a new investigation that besides an acidic reflux detects non-acidic reflux. In future could be a real "gold standard" for diagnosis of GORD. A simple questionnaire may be among the best diagnostic aids in infants. Primary GORD is mainly a motility disorder, but there is no prokinetic drug available with efficacy and safety. Treatment of GORD is based on anti-acid drugs, particularly on PPI's. At last new therapeutic endoscopic methods are presented.

Descriptors: GASTRO-OESOPHAGEAL REFLUX, CHILD

INTRODUCTION

Gastro-oesophageal reflux (GOR) describes the *involuntary passage of gastric contents above the lower oesophageal sphincter*. GOR is a physiological phenomenon, occurring in every individual. Most episodes of reflux are limited to distal oesophagus, and are brief and asymptomatic. GER is common during infancy. Mainly causes regurgitation and/or vomiting episodes in a thriving infant. Parents poorly tolerate this clinical condition. It is responsible for parental anxiety and consequently for multiple visits to paediatrician. In recent years a large number of studies have been carried out to define the best clinical approach to infants and children affected with GOR (1-3).

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DEFINITIONS AND TERMINOLOGY

Gastro-oesophageal reflux disease (GORD) is a pathological condition characterized by regurgitation and/or vomiting associated with oesophagitis, failure to thrive or respiratory symptoms, signs and symptoms of distressed behavior and other complications. The difference between physiologic reflux and GOR disease is not defined by number, duration, and severity of reflux episodes, but more if the reflux episodes result in symptoms, severe enough to impair quality of life, or complications. Infants are often empirically treated with H-2 receptor antagonists and prokinetic agents and rare with operative treatment. The majority of infants outgrow GOR by 12 to 18 months of age. Regurgitation is defined as passage of refluxed contents into the oral cavity and the mouth, and is accompanied by gastric content drooling out of the mouth. Vomiting is defined as expulsion of the refluxed gastric contents from the mouth. Rumination is characterized by the voluntary, habitual regurgitation of recently ingested food, spitted or re-swallowed.

Primary GOR results from a primary disorder of function of the upper GI tract. In secondary GOR, reflux results from impaired motility occurring in systemic disorders (neurological impairment, systemic sclerosis) or infections (urinary tract infection, gastroenteritis), food allergy, metabolic disorders, intracranial hypertension, chemotherapy. Uncomplicated GOR in infants is considered as a self-limited process treated with thickened feeds, positional treatment and parental reassurance without performing any further investigation. GORD is less frequent in infancy, but it doesn't resolve spontaneously. An accurate diagnostic approach followed by appropriate therapeutic strategies is mandatory when facing an infant with complicated GOR. For this reason in recent years the attention of paediatric gastroenterologists has been focused on GORD. This review aims to highlight the main characteristics of GORD with regards to pathophysiology, clinical presentation, diagnostic strategies and therapeutic options.

EPIDEMIOLOGY

The epidemiological data and natural history of GORD is almost unknown especially after the first year of life. Studies have shown that uncomplicated GOR affects around 40-65% of infants in the

first year, and resolves in nearly all the patients within the first 12 months (4, 5). About 5-9% of infants have troublesome GORD (7, 12). It has also been shown that GORD affects 1:300 infants in the first year, but after this period very little are known about its prevalence and natural history. Heartburn is present in 1.8-3.5% children and adolescents, regurgitation in 2.3-1.4%. In western population GORD affected 4-30% of adults (8, 9). Reflux esophagitis is reported in 2-5% of general population (7). Children with GOR symptoms present esophagitis in up 15-60%, and Barrett's esophagus in 0.1-3%, and refractory GERD requiring surgery in 6-13%. Esophagitis in adults is present in 15-80%.

GENETIC AND ENVIRONMENT FACTORS

GORD is more frequent in men than in woman. Alcohol, smoking, drugs, dietary components have aggravating effects on the incidence of GOR. All forms of GORD affect Caucasians more often than African-Americans. The importance of the genetic backgrounds was hypothesized by demonstrating that oesophagitis and hiatus hernia were more common in population with the same genetic background with dyspeptic symptoms in England and Singapore (10). Carre et al described autosomal dominant inheritance of hiatal hernia (hiatal hernia in a large five-generation family), but without demonstrating the link to GORD (11). The concordance for GOR is higher in monozygotic than dizygotic twins (12). A locus on chromosome 13q has been linked to severe GORD in five multiply affected families, but not confirmed in another five families possibly owing to the genetic heterogeneity of GORD and the different clinical presentations of patients (13, 14).

PATHOPHYSIOLOGY

Research into the physiology and pathophysiology of paediatric GOR has advanced markedly over the last decade through the use of technologies such as micro-manometry, non-invasive breath testing and multichannel intraluminal impedance (MII). These techniques when used on their own or in combination have given more understanding of the mechanisms of *all reflux* (liquid, gas, acidic, weakly acidic and non acidic), oesophageal volume clearance and gastric emptying (15).

The wide variety of presenting symptoms of GORD reflects the complexity of pathogenic mechanisms operating in the disease. Pathophysiology is influenced by factors that are genetic, environmental (diet, smoking), anatomic, hormonal, neurogenic. Vandenplas et al recently reviewed the pathopysiology in GOR in infants and children. The most relevant factors are gastric (gastric acid, and non-acid content, gastric emptying), antireflux barrier (TLESR, hiatal hernia), the composition of refluxate (air-liquid, acid, non-acid, bile), and esophageal clearance. Three major defense factors minimize the risk of reflux-induced injury to the oesophagus: anti-reflux barrier (LES, angle of His, diaphragm), oesophageal clearance (gravity, oesophageal peristalsis, salivary and oesophageal secretions), and the third line is tissue or oesophageal mucose resistance (16). More than half of the acid and non-acid reflux episodes are associated with reflux of gas Acid reflux in patients with GORD is associated with inhibition of tone in the oesophageal body, (primary peristalsis), also in non-acid reflux (mainly postprandially) secondary peristalsis could be impaired (17).

Frequent and inappropriate transient lower oesophageal sphincter (LES) relaxations were found by the set investigations to be the predominant mechanism of all GOR in infants and children thus have clearly identified a therapeutic target for reflux inhibitor research, beyond current acid suppression based therapy (15). The following as delayed gastric emptying, anatomic abnormalities, oesophageal dismotility with slow esophageal clearing are also factors, and together with the integrity of the oesophageal mucosal barrier and the responsiveness of airways and central nervous system are responsible for GORD.

Delayed gastric emptying is hypothesised to play a role in reflux disease, particularly a cause of regurgitation in those children with failure to thrive and/or vomiting. Both normal and delayed GE has been reported in children with GOR disease. More recent studies in infants suggest GE was faster in those infants with more severe GOR disease (18). Studies that have examined the effect of posture on gastric emptying and/or GOR have consistently reported more rapid gastric emptying with right-side positioned compared to left-side positioning but, paradoxically, more reflux with right-side positioning compared to left-side positioning (19).

GOR has traditionally been considered a primary motility disorder. More recently, a secondary form due to food protein intolerance has been demonstrated. Both disorders overlap clinically and are often difficult to differentiate in young children (20, 21). As a consequence, the clinical presentation differs from one patient to another depending on age and on prevailing pathogenic mechanism. Delayed gastric emptying prevails during the first year of life, frequent and inappropriate transient LES relaxations are the main pathogenic mechanism in children and adolescent, oesophageal dismotility is present in a high percentage of patients with extra-oesophageal or atypical manifestations.

CLINICAL SIGNS/SYMPTOMS

GORD is a spectrum of diseases that can best be defined as the symptoms and signs of oesophageal or adjacent organ injury secondary to the reflux of gastric contents into the oesophagus or, beyond, into the oral cavity or airways.

Presentation may be with decreased food intake, and aversive behavior, abnormal sucking, and swallowing, poor weight gain. A wide spectrum of clinical presentation of GORD exists, with differences within ages. Regurgitation is the most common presentation of infantile GOR, with occasional projectile vomiting (22). In infants and young children, verbal expression is impossible and persistent crying, irritability, feeding and sleeping difficulties have been proposed as equivalents for heartburn in adults. Compared to adults, children report more regurgitation and emesis and less heartburn, dysphagia and chest pain.

Table 1
Spectrum of gastro-oesophageal reflux disease manifestation according to age (4)

Tablica 1.
Spektar bolesti gastroezofagealnog refluksa ovisno o dobi (4)

Symptom and sign	Infants	Children	Adults
Vomiting	++	++	+
Regurgitation	+++	++	++
Heartburn/pyrosis	?	++	+++
Epigastric pain	?	+	++
Chest pain	?	+	++
Dysphagia	?	+	++
Excessive crying/irritability	+++	+	-
Anemia/melena/hematemesis	+	+	+
Food refusal/feeding disturbances/anorexia	++	+	+
Failure to thrive/poor growth	++	+	-
Abnormal posturing/Sandifer's syndrome	++	+	-
Persisting hiccups	++	+	+
Dental erosions/halitosis/water brush	-	+	+
Hoarseness/globus pharyngeus	-	+	+
Persistent cough/aspiration pneumonia/wheezing	+	+	+
Laryngitis/ear problems	+	+	+
Laryngomalacia/stridor/croup	+	+	-
Laryngostenosis/resistant asthma/chronic sinusitis	-	+	+
Vocal nodule problems	-	-	+
ALTE/SIDS/apnea/desaturation	+	-	-
Bradycardia	+	?	?
Sleeping disturbances	+	+	+
Impaired quality of life	?	?	+++
Esophagitis	+	+	++
Stenosis	-	(+)	+
Barrett's esophagus/esophageal adenocarcinoma	-	(+)	+

ALTE - apparent life threatening events, SIDS - sudden infant death syndrome
+++ very common, ++ common, + possible, (+) rare, - absent, ? unknown

GORD in adolescents is more adult-like. Heartburn is predominant GOR symptom. Atypical symptoms such as epigastric pain, nausea, hiccups, chronic cough, asthma, chest pain, hoarseness and earache, account for 30-60% of the presentations of GORD. GORD is diagnosed in 50% of the adult patient with chest pain, and in 80% with chronic hoarseness and asthma. Recent evidence has shown that GERD affects the quality of life in adults, and probably also in children. According hygiene hypothesis Th2 - predominant immune response at birth in industrialized world is insufficiently skewed towards a well balanced Th1/Th2 response (23). The lack of chronic or repetitive inflammation during the first months of life account for dramatic increase in atopic disease during infancy and childhood. So, infant distress and colic are now recognized as manifestation of food hypersensitivity during early childhood. Histology of duodenal, gastric and oesophageal mucosa reveals eosinophilic infiltration characteristic of a Th2 type and thus allergic answer in many infants.

Symptoms such as regurgitation/vomiting, airway obstruction and feeding difficulties are more common in infants, whereas adult-like symptoms and airway irritation are more frequent in children older than 2 years. The reason for the differences in presentation of GORD according to age remains unclear. The persistence of symptoms and progression to complications are unpredictable. Alarm symptoms are similar in adults and children: weight loss, dysphagia, bleeding, anaemia, chest pain and choking. Additional alarm symptoms in children are failure to thrive, irritability/crying and feeding or sleeping difficulties. The approach taken managing patients with GORD depends on the presenting symptoms. In a clinical setting it is useful to divide patients in subsets according to age and symptoms, aiming at standardizing evaluation and management of each cluster (Table1).

COMPLICATIONS

Reflux oesophagitis

The severity of the complications is not clearly related to the duration or severity of symptoms. Difference in oesophageal mucosal resistance and genetic factors may partially explain the diversity of lesions. Complications are oesophagitis, stricture, Barrett's s oesophagus, and oesophageal adenocarcinoma (rare in children). More than 40 years ago, in the absence of reflux treatment, oesophageal strictures were reported in about 5% of children with reflux symptoms (24). Nowadays, except in Barrett's oesophagus, oesophageal stenosis and ulceration in children is rare (25). The differences in incidence are determinated by patient recruitment and availability of acid-blocking drugs (self-treatment). A 10-year follow-up of oesophagitis showed that over 70% had presenting symptoms and 2% had stricture (26). More for reflux oesophagitis you can read in the part for endoscopy.

Barrett's esophagus

It is uncommon premalignant disorder in children, but an important one not to miss. There is a risk of malignancy, and need for endoscopic surveillance. The pink mucosa at upper endoscopy is suspected (present in confluent erosive disease and hiatal hernia) for BE. The diagnosis is made definitely in adults and

children only by the presence of metaplastic columnar epitlelium with goblet cells that stains with Alcian blue at pH 2.5 (6, 27). In established BE, endoscopic surveillance is indicated; for dysplasia or cancer. Children with severe reflux, neurological impairment, chronic lung disease (cystic fibrosis especially) and oesophageal atresia are at higher risk of developing Barrett's oesophagus. The differences in incidence are determinated by patient recruitment and availability of acid-blocking drugs (self-treatment). A 10-year follow-up of oesophagitis showed that over 70% had presenting symptoms and 2% had stricture (28).

Gastro-esophageal reflux disease and respiratory disease

Reflux may cause respiratory symptoms through different pathways, such as (micro) aspiration, or vagally mediated mechanisms. A consequence of pulmonary aspiration of refluxed material may be the presence of an increased number of lipid-laden macrophages. The relation between respiratory disease and GOR may also be neurogenic, in this case designated as "gastric asthma". In other words it can be speculated that GOR increases the irritability of the vagal nerve endings in the esophagus, and as a result these nerve endings hyper-react together with the nerve endings in the airways because they have the same embryonic origin. The emerging presentations of GORD have received a lot of attention in recent years. It is now well documented their association with GOR, but a cause-effect relationship is still controversial. These presentations include:

- Infants with distressed behavior (feeding is associated with pain resulting in one or a combination of irritability, crying, food refusal, back arching or sleep disturbances) (29-31, 56). Heine out of 70 infants with distress, found 15% to have pathological GOR (29);
- Infants and children with otolaryngological problems;
- Children with asthma. In a prospective three-year study we investigated 227 children with respiratory disease (RD) for the presence of gastro-oesophageal reflux (GOR) with computed 24 hour pH monitoring (C24hpHM), and its data were analyzed. Children were aged 1-140 months. Incidence of GOR in children with RD was 55.95%, comparable with other reports in the literature (32);
- Infants with apnoea and apparent life threatening event (ALTE).

There is an opinion that these symptoms should be investigated for the possibility of GOR, since documenting abnormal GOR and starting an appropriate therapy may be helpful in preventing the occurrence of complications. For the same reasons in clinical practice in recent years efforts have been directed towards the detection and the evaluation of GORD in two classes of patients who are at risk of developing severe complications:

Neurologically impaired children

These children are known to have high incidence of swallowing difficulties, severe gastro-oesophageal reflux, recurrent respiratory infections and malnutrition. GOR in these patients may be responsible for both aspiration (that may aggravate respiratory symptoms) and regurgitation (that may decrease caloric intake with consequent worsening of malnutrition). In these subjects isolated swallowing dysfunction without GOR may be the prevalent cause of aspiration. A complete diagnostic work for GORD has to be performed in these patients.

Children with "silent GORD"

The term "silent GORD" applies to children who undergo instrumental examinations (C24HpHM and endoscopy) for reasons other than the detection of GOR (i.e. the diagnosis of celiac disease, or asthma) and who are discovered to be affected by severe oesophageal lesions. The performance of endoscopy have been intensified especially after the recent reports of high proportion of organic abnormalities found in patients with recurrent abdominal pain and after the increasing number of patients diagnosed with Helicobacter pylori (HP) infection. Subsequently, GORD was discovered in larger number of subjects.

HP has been shown to have causative role in GORD. Reflux oesophagitis may arise after eradication of HP, especially if hiatal hernia and corpus gastritis coexist.

From distribution of H. pylori within the stomach depends the risk for development of disease. Antral gastritis is associated with increased risk for peptic disease and GORD (in children). Eradication of H. pylori decreased acid gastric output, and can improve reflux. Or, atrophic corporal gastritis will develop (in adults), and decreased risk of GORD (33). In adults a decreased prevalence of gastric cancer and peptic ulcer are reported, but increase of esophageal adenoacarcinoma and GORD. This is attributed to higher fat intake, increased incidence of obesity and decreased incidence of Helicobacter pylori infection (51). Eradication of H. pylori led to an increase in acid production and increased risk for development of GORD, and adenocarcinome. There are discrepance between symptoms, *C24hpHM* findings and upper endoscopy and biopsy. Currently, the diagnosis of H. pylori - mediated disease can be made reliably only through the use of endoscopy with biopsy.

DIAGNOSIS

GORD is primary motility disorder or it can be secondary as the consequence of other abnormalities (such as neurological impairment, cystic fibrosis, pyloric stenosis, malrotation). It is always important to make a correct diagnosis of GORD even in silent cases, since undiagnosed chronic reflux carries a potential risk of severe complications such a potential risk of severe complications such as Barrett's esophagus, stricture formation and oesophageal neoplasms. The diagnostic approach depends on age of the patient and on clinical presentation (3).

While history and physical examination are the only steps required in infants with regurgitation and normal growth (uncomplicated GOR) the need for instrumental investigations is widely ac-

cepted in infants when regurgitation is associated with anaemia or poor weight gain (upper GI series, endoscopy with biopsy, hospitalization, tube feeding, rarely surgical therapy). In infants with vomiting and irritability invasive interventions are undertaken with caution. In children with recurrent vomiting after age of 2 years, upper GI series and endoscopy should be performed.

Heartburn in adolescents and children is treated with PPI for 2-4 weeks, if has no result is referred to paediatric gastroenterologist for upper endoscopy and biopsy. In infant and children with oesophagitis treatment with PPI and lifestyle changes is started. If histologic esophagitis is present, no control endoscopy is needed, in erosive one repeat endoscopy should be performed to assure healing.

In a child with dysphagia and odynophagia barium esophagogram is recommended. If initial history is suggestive for oesophagitis upper endoscopy may be performed as initial test. In the infant with apnoea or ALTE C24hpHM may be useful to determine if there is temporal association of acid reflux with ALTE. In patients where symptoms of asthma and oesophagitis co-exist, and in infants with chronic regurgitation and vomiting and recurrent episodes of cough and wheezing, a three-month trial of acid suppression therapy of GOR is recommended. If patients with persistent asthma do not have symptoms of GOR, esophageal pH monitoring is recommended in selected patients, who will benefit from GOR therapy (2).

No single instrumental examination can help in diagnosing GORD, each test is designed to answer a specific question. Even C24hpHM, which is still considered the "golden standard" test for quantifying acid reflux, is unhelpful if used to identify esophagitis.

The main limit of C24hpHM is its inability to detect non-acidic reflux. Buffering of gastric acidity by meals or by duodenal juice is responsible for the alkalization of refluxate (in infants in particular). It is impossible to detect all reflux using pH-based criteria. The C24hpHM fails to identify the reflux episodes and consequently, to establish a correlation with severe symptoms such as aspiration. Nevertheless, alkaline duodenal juice may damage the oesophageal mucosa just exactly as acid gastric refluxate. This can be one of the causes of poor correlation between C24hpHM and endoscopic findings, and association of GOR and respiratory disease. Second, it has been difficult to measure the upward extent of the reflux episode even if multiple pH sensors are used. Third, the degree of proximal reflux is similar in patients with and without respiratory symptoms. The fourth, proximal sensor is unable to differentiate between swallowed and refluxed contents. The fifth, even we found positive proximal pH probe, the clinical response to acid suppression medication is variable, suggesting that acid reflux did not entirely explain the severity of respiratory disease (34).

This problem may be overcome in future years with wider use of multichannel intraluminal impedance (MII), which has been recently described as a "pH-independent" method for the detection of oesophageal bolus movement (35-37). In this context measurement has clearly demonstrated the limitations of C24hpHM for the global assessment of reflux. Despite these limitations, C24hpHM is still performed in most centres due to the fact it is readily available, cost-effective and the result of the test can be interpreted in relations to established normative values for oesophageal acid expose time. In support of the continued use of C24hpHM, even though this technique fails to record all reflux episodes, existing evidence shows that acid reflux is a significant pathophysiological factor in GOR. This appears to be the case in all human age groups, even premature infants as it has been shown that (TLESR triggered) acid GOR occurs more commonly inpatients with GOR disease compared to asymptomatic controls (18).

The absence of normative data is a significant limitation of MII as a routine clinical diagnostic test (unethical to evaluate healthy infants and children). But, the major advantage of MII measurement of reflux over C24hpHM is that it enables, virtue of measuring ALL reflux (acid, non-acid; composition of refluxate), content (gas, liquid or mixed), and the reflux height. The latter advantage, is critical in differentiating the cause for respiratory disease (microaspiration-full column reflux, or vagally mediated spasm-distal reflux), and the precise temporal association of reflux events with putative "reflux-related symptoms", like apnea, cough, irritability, crying. (34). Mousa found that patient with ALTE have GOR in 4 out of 25 patients (no difference for acid and non-acid reflux) (38). Wenzl found out of 22 infants with apnoea, one third of apnoeic were associated with reflux (77.6% was non-acid) (37).

In any case the complete evaluation of the C24hpHM tracing is necessary. The reflux index is a good complexive measure of the test, but the morphology of the tracing is important in differential diagnosis (i.e. cow's milk allergy) (39, 40). Upper GI series shows poor sensitivity and specificity in the diagnosis of GOR, but is useful for the evaluation of anatomic abnormalities (pyloric stenosis, malrotation, annular pancreas in a vomiting infant a hiatal hernia and esophageal stricture in the older child). A good correlation of this test with esophagitis has been previously described.

In experience of Cavataio ultrasonography is particularly useful to evaluate gastric emptying in infants less than 6 months (39). Its usefulness has also been reported in evaluating gastro-oesophageal junction morphology. Endoscopy and biopsy are essential to determine the presence and severity of oesophagitis, stricture, Barrett's oesophagus, and oesophageal adenocarcinoma. Histological findings are extremely important in determining the nature of oesophagitis (i.e. allergic vs. peptic oesophagitis).

Some endoscopic findings in the esophagus are non-specific, such as erythema, increase or loss of vascularity, and pallor. At present it seems that erosions, i.e. mucosal breaks are the main endoscopic findings that are considered definitely abnormal (41). GORD is far the commonest cause of erosions in children and adults. They could be as

Table 2
Differential diagnostic tools

Tablica 2.
Postupci u diferencijalnoj dijagnostici

DISEASE/MAIN DIAGNOSTIC TOOLS
Food allergy
SPTs, RASTs, elimination diet food challenge, Endoscopy
Pyloric stenosis
Ultrasonography, upper GI series
Malrotation
Ultrasonography, upper GI series, contrast enema
Peptic ulcer disease
Endoscopy
Infections (intestinal and extraintestinal)
Serology, urinanalysis, stool and urine culture
Primary pulmonary disease
Sweat test, chest x-ray, SPTs, RASTs
Otolaryngological problems
Specialistic consultation, laringoscopy, paranasal sinuses x-ray
Metabolic disorders
Anamnestic and family history, organomegaly, specific serologic tests
Neurologic disorders
Head computed tomography, MRI, EEG, fundus oculi
Drugs/toxins
Serum and urine drug screen

discrete erosions on the tops of folds in the distal oesophagus, and confluent erosions in most severe oesophagtis.

Reflux oesophagitis is a patchy lesion (42, 43). While several abnormalities have been described in reflux esophagitis, histological criteria vary among even expert pathologists. The presence and number of intraepithelial eosinophils is disease (42). The density of eosinophils on biopsy does not correlate with the severity of reflux (44, 45). For these reasons, some experts use scoring systems that does not include eosinophils as a diagnostic criterion for reflux (46, 47). Against histology for GORD is that there is poor correlation between esophageal histology and symptoms, endoscopic findings, or C24pHM (49, 50).

According new reports for GORD the sensitivity and specificity of histology are relatively poor, even in expert hands, and the diagnosis often can be imputed from other approaches. Pope argued that for adults biopsy in the "usual case" of erosive esophagitis is a waste of time and money (51). His "usual case" is an adult presenting with typical symptoms of reflux i.e. heartburn, regurgitation etc. In this case one could justify not doing an endoscopy at all, just giving the patient a trial of PPI, and performing endoscopy and biopsy only in case of a chronic need for drug. This approach is supported by recent guidelines for adults (52, 53). The reason to perform endoscopy in the chronic relapsing case is to verify the diagnosis of GORD and to rule out Barrett's esophagus. Then the patient can be committed to long-term PPI or antireflux surgery. Therefore, for reflux esophagitis without Barrett's there is little evidence that esophageal histology makes a difference to initial clinical care decisions, beyond ruling out other conditions. Severity is determined by symptoms and endoscopic changes (54).

Most important is patient's response to an adequate dose of antireflux medication. These practices make sense for paediatrics as well, and reflect what many practitioners are doing. The difference in paediatrics is that heartburn is much less common than in adults and reflux often presents with upper abdominal pain or atypical manifestations, i.e. there are fewer "usual" cases. Nevertheless, in cases of suspected GORD upper endoscopy with biopsy can be used in the same way, to make diagnosis in case of poor response to PPI, and to have diagnosis in those cases requiring chronic therapy. The most common scenario would be to determine whether the diagnosis is GORD, or eosinophilic oesophagitis, or a combination (55).

The upper GI endoscopic technique has been greatly improved. Gastroscopes have become more flexible and even thinner. Oesophageal biopsy is considered a rapid, safe and effective diagnostic test for GORD. It is recommended endoscopy to be performed even on infants and children that present with unusual, but severe symptoms of GORD.

The role of nuclear scintigraphy (milk scan) in the diagnosis and management of GORD in infants and children is unclear .It evaluate postprandial reflux, and provide some information on gastric emptying. Normal ranges are not well established. Regarding gastric emptying 13-C breath test are more standardized. Scintigraphy may show pulmonary aspiration (low sensitivity).

Videofluoroscopic swallowing studies (VFSS) investigate swallowing coordination and esophageal motility. It is considered VFSS and C24hpHM as part of an evaluation for recurrent stridor and/or wheezing in children with otolaryngological problems and in neurologically impaired children. Surgical treatment in neurologically impaired children sometimes failed to resolve symptoms. The use of VFSS has led to observe that an isolated swallowing dysfunction may be responsible for the persistence of symptoms after surgery (especially those due to aspiration). Nasogastric tube feeding was necessary to restore acceptable clinical conditions in these subjects.

Because reflux in infants is common, because there is no "gold standard" investigation, and because are

invasive and expensive, interest has focused on the development of an "infant GOR-questionnaire" (22). Recently, an improved questionnaire was developed (57). It offers the advantage of an objective, validated and repeatable quantification of symptoms suggesting GORD. However, although the correlation between the questionnaire and symptoms seems fair, the correlation between the questionnaire and results of investigations for reflux is poor (also C24hpHM and endoscopy).

Differential diagnosis

Before diagnosing GORD, other gastrointestinal or systemic disorders have to be excluded (Table 2).

In the first year of life *cow's milk protein allergy* (CMPA) should be strongly considered especially with increased evidence of its association with GORD (58, 59). CMPA may overlap with many symptoms of GER, and may coexist or complicate GORD in up to 40% of infants. A 3-year prospective study was conducted, following a large group of infants with symptoms compatible with GORD (60). Infants were either formula or breast-fed. They performed a complete diagnostic work-up in these infants including C24hpHM and upper GI endoscopy. In this way 204 infants were diagnosed with GORD. On hospital admission these infants were assessed for CMPA by careful clinical history and laboratory investigation.

All patients with clinical signs suggesting CMPA or at least one positive test result began an exclusion diet with a hydrolysed protein formula. After a minimum of 3 months the infants had a double-blind challenge with cow milk protein (CMP) to confirm the diagnosis of CMPA. In addition, infants had an intestinal biopsy at the ligament of Treitz, 24 hours before and after the CMP challenge. In accordance with the criteria established by ESPGHAN, only infants with clear clinical reaction to CMP, with or without concomitant changes in immunological test results, were considered as having CMPA. On this basis they diagnosed 85/204 (41.7%) infants as having CMPA. This study on CMPA and GORD appeared to imply that in almost half of GORD cases in infants less than 12 months there is an association with CMPA. Nielsen et al also reported for an association between GORD and cow milk hypersensitivity (in 10 out of 18 with GORD) both in infants and children with severe GERD, but simultaneous cow milk challenge and C24hpHM had limited value as a method to identify this subgroup (60). In those with CMPA elimination diet (protein hydrolisates and amino acid based formula) is treatment of choice (61, 62).

The next to be excluded is *eosinophilic oesophagitis* (EE). EE in children account for 1% of oesophagitis in adults is very rare (62). It is a specific disorder characterized by the presence of high eosinophil counts (>15-20/hpf) in the esophageal epithelim, typically through the length of the oesophageal body. There is no basal cell hyperplasia or elongation of papillae. The clinical presentation is sometimes suggestive of EE, but there is much overlap with GORD. Some endoscopic feature are strongly suggestive of the presence of EE, such as small-caliber oesophagus, ringed oesophagus, proximal stricture, white specks or papules in patches or through the length of the oesophagus (latter resemble candida infection). The oesophagus may also be normal at endoscopy. Intraepithelial eosinofils have poor sensitivity as indicators of reflux, and more often represent food allergy or a form of eosinophilic esophagitis and the treatment is different. EE is a biopsy diagnosed, and this governs treatment. Atopy features are reported in more than 90% and peripheral eosinophilia in 50% of patients. Corticosteroids (inhaled or systemic) are the main treatment for EE, together with hypoallergenic feeding, and montelukast (63).

TREATMENT OPTIONS

The goal of GORD therapy is to remove the cause of GOR or, otherwise, to resolve symptom and to prevent the eventual harmful complications. Anyway, it aims at improving the quality of life of young patients. To date there are many therapeutic options available, depending on the age of the patient and on the severity of the disease.

In infants with *uncomplicated GOR* thickened feeds or short trial of a hypoallergenic formula, positional treatment and parental reassurance are sufficient to keep the patient comfortable and thriving, and to minimize possible oesophageal damage until the condition is outgrown. Milk-thickened agents do not improve reflux index scores, but do decrease the number of episodes of vomiting. There is evidence to support a one to two week trial of a hypoallergenic formula in formula fed infants with vomiting. C24hpHM has demonstrated that infants have significantly less GOR when placed in the prone position than in the supine position. But prone is associated with a higher rate of SIDS, therefore non-prone position during sleep is generally recommended in infants to 12 months of age, in older there is benefit to left side positioning and elevation of the head of the bed. It is recommended that children and adolescent with GORD avoid caffeine, chocolate, and spicy foods. Obesity, tobacco smoke and alcohol are also associated with GER (2).

In infants and children with *mild to moderate GORD* (who do not spontaneously outgrow their disease) a pharmacological therapy is required. The two major classes of drugs used in the treatment of GORD are acid suppressant and prokinetic drugs. Acid suppressant include antacids (magnesium hydrohide and aluminium hydroxidem, alginate), H-2 receptor antagonists (H2RA) (ranitidine, cimetidine, famotidine) and proton pump inhibitors (PPI) (omeprazole, lansoprazole, pantoprazole) (4).

Antacids have a buffering effect on gastric acidity, but are rapidly removed by gastric emptying. Experience by some authors showed that magnesium hydroxide and aluminium hydroxide is more effective (when given in association with domperidone) than alginate. Since more convenient and safe alternative are available (H2RA and PPIs) chronic antacid therapy is generally not recommended. H2RA decrease acid secretion by inhibiting histamine-2 receptor on the gastric parietal cell. They are effective and safe in relieving symptoms and healing esophagitis.

PPI are considered the most effective acid suppressant drugs inhibiting H+K+ - ATPase pump, exerting a 24 hours control on gastric acid secretion (64). They are superior to H2RA in relieving symptoms and healing esophagitis. The paediatric doses required to heal erosive esophagitis (recently established for omeprazole), on a per-kilogram basis are much greater than those required for adults and are 0.2-3.5mg/kg per day, from 14 days to 36 months (46, 48). Other PPIs used are: esomeprazole, pantoprazole, lanzoprazole, rabeprazole. PPIs have side effects: headache, neurological and psychiatric side effect, cutaneus reactions, haemolytic anaemia, leukopenia, gynecomastia, gastrointestinal side effects. Hypergastrinemia occurs in nearly all patients treated with omeprazole, by hyperplasia and pseudohypertrophy of the parietal cells (4).

In clinical practice is confirmed that omeprazole is well tolerated, highly effective and safe to treat erosive oesophagitis and to relieve symptoms of GOR in those children in whom other medical therapy or antireflux surgery has failed. Prokinetic drugs include metoclopramide and domperidone (dopamine antagonists) and cisapride (mixed serotonergic agent). The latter appears to be more effective when compared to metoclopramide and domperidone, unfortunately cisapride has recently been withdrawn after the reports of its potential harmful effects.

A Cochrane review on cisapride in children analyzed data from seven trials, including 236 patients, they compared the effect of cisapride to that of placebo on symptom presence and improvement (65). There was a statistical difference in the parameter symptoms "present/absent", and reduced number and duration of acid reflux episodes, since there was a significant decrease in reflux index between placebo and cisapride. The effect of cisapride on relevant cardiac events such as QT prolongation and arrhythmia is related to dose and risk.

Cisapride reduces the frequency of regurgitation and vomiting. However, because of concerns about the potential for serious cardiac arrhythmia in patients receiving cisapride, appropriate patient selection and monitoring as well as proper use, including correct dosage (0.2mg/kg/dose qid) and avoidance of co-administration of contraindicated medications, are important. Cisapride is available in the USA only through a limited-access program. Other prokinetic agents have not bee shown to be effective in the treatment of GORD in children. The therapeutic choice for GORD was found to be a dynamic process depending upon the severity of signs and symptoms and upon the degree of oesophagitis.

Good results are achieved in less severe cases of GORD treated with a combination of domperidone and magnesium hydroxide plus aluminium hydroxide. In mild to moderate oesophagitis a combination of ranitidine and cisapride was used. Since the withdrawal of cisapride, ranitidine and domperidone are used in combination. As regards the use of PPIs, omeprazole and other PPIs are restricted to *severe esophagitis or to refractory GORD*. Patients only undergo surgical therapy if harmful symptoms occur or if they are neurologically impaired.

New perspectives for the future probably will come from availability of other drugs, such as new prokinetics. A potential prokinetic effect of erythromycin a sub-antimicrobial doses has been suggested given orally or intravenously, but further studies are necessary to confirm this observation. Baclofen, a GABA-B receptor agonisthas been shown to decrease GOR in healthy adults, also administration in paediatric patients was reported to be safe (4).

During recent years, new endoscopic techniques to improve the antireflux barrier are introduced. The results of endoscopic gastroplasty (Endocinch system), radiofrequency delivery at the cardia (Stretta system) and injection therapy (Enteryx procedure) in adults have been reported. The first series in adolescents have been performed. Experience is limited to recommend broad use (4).

Case series indicate that surgical therapy generally results in favorable outcomes. The potential risks, benefits and costs of successful prolonged medical therapy versus fundoplication have not been well studied in infants or children with varying symptom presentation. Ninety percent of patient remained free from significant reflux symptoms after a laparoscopic Nissen operation, with 22% side effects (4).

CONCLUSIONS

In clinical practice is suggested:

- to adopt conservative measures in infants with uncomplicated GOR without performing any prior investigation (except the evaluation for cow's milk protein allergy);
- to start pharmacological therapy in infants and children with mild to moderate GORD;
- to "treat and test" or to "test and treat" depending on the severity of the clinical picture and on the duration of the disease;
- to choose surgery only in rare and selected cases.

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Sažetak

GASTROEZOFAGEALNI REFLUKS

A. Kostovski

Gastroezofagealni refluks (GER) je jedna od najčešćih bolesti zbog koje djeca posjećuju pedijatra primarne zdravstvene zaštite. Međutim, samo mali broj djece ima tegobe posljedično GER-u (s komplikacijama poput nenapredovanja tjelesne težine, ezofagitisa, bolesti dišnog sustava), kad je potrebno uraditi posebne pretrage. Simptomatologija se mijenja ovisno o dobi, iako je osnovni patofiziološki mehanizam isti. Prikazan je dijagnostički i terapijski pristup različitim kliničkim pojavnostima. Posebna pozornost je posvećena višekanalnoj intraluminalnoj impedanciji, novoj pretrazi, koja osim kiselog refluksa, bilježi i nekiseli refluks. To bi u budućnosti mogao biti zlatni standard za dijagnozu GER-a. U dojenčadi je jednostavni upitnik od najveće dijagnostičke pomoći. Primarni GER je većinom bolest motiliteta, ali učinkovitog i sigurnog prokinetičkog lijeka nema. Liječenje GER-a temelji se na protukiselinskim lijekovima, posebice na inhibitorima protonske pumpe. Na kraju, prikazan je novi terapijski endoskopski postupak.

Deskriptori: GASTROEZOFAGEALNI REFLUKS, DIJETE