Diagnosis and treatment of gastroesophageal reflux disease in infants and children

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Y Vandenplas. Diagnosis and treatment of gastroesophageal reflux disease in infants and children. Can J Gastroenterol 2000;14(Suppl D):26D-34D. Gastroesophageal reflux is a frequent, nonspecific phenomenon in infants and children. The recommended approach for infants with uncomplicated regurgitation is the reassurance of the parents about the physiological nature of excessive regurgitation, and if necessary, completed with dietary recommendations for formula-fed infants. If, despite these efforts, the symptoms persist, the administration of prokinetics such as cisapride is recommended before investigations such as esophageal pH monitoring are begun. Cisapride is the drug of choice because it has the best efficacy and safety profile. In infants and children presenting with symptoms that suggest esophagitis, endoscopy of the upper gastrointestinal tract is recommended. If there is severe esophagitis, acid suppression with H_2 receptor antagonists or proton pomp inhibitors is recommended, eventually in combination with prokinetics. In life-threatening situations, or in patients who are resistant to or dependent on acid suppressive medication, a surgical procedure such as laparoscopic Nissen should be considered.

Esophageal pH monitoring is recommended to document gastroesophageal reflux disease in children presenting with unusual presentations such as chronic respiratory disease. Treatment consists of prokinetics and/or acid suppressive drugs, and surgery should be considered in many of these patients.

Key Words: *Acid suppression; Endoscopy; Esophagitis; Gastroesophageal reflux; H_2 receptor antagonist; Regurgitation; pH monitoring; Prokinetic therapy; Proton pomp inhibitor*

Diagnostic et traitement du reflux gastro-œsophagien chez le nourrisson et l'enfant

RÉSUMÉ : Le reflux gastro-œsophagien (RGO) est un phénomène fréquent et non spécifique chez le nourrisson et l'enfant. En présence d'une régurgitation non compliquée chez le nourrisson, on recommande de simplement rassurer les parents et, au besoin, si le nourrisson reçoit du lait maternisé, de leur faire quelques recommandations alimentaires. Si les symptômes persistent malgré ces efforts, on recommande d'administrer un agent procinétique comme le cisapride avant de procéder à des examens comme la surveillance du pH de l'œsophage. Le cisapride est le médicament à utiliser en première intention, car c'est lui qui offre le meilleur profil d'efficacité et d'innocuité. Chez le nourrisson et l'enfant qui présentent des symptômes évocateurs d'une œsophagite, on recommande l'endoscopie des voies digestives supérieures. En présence d'une œsophagite sévère, on recommande le recours à un antagoniste des récepteurs H_2 ou à un inhibiteur de la pompe à protons, possiblement en association avec un agent procinétique, pour supprimer la sécrétion acide. Dans les situations où le pronostic vital est menacé ou en cas de résistance ou de dépendance aux inhibiteurs de la sécrétion acide, il faut envisager une intervention chirurgicale comme la laparoscopie selon la méthode de Nissen. La surveillance du pH œsophagien est recommandée pour objectiver le RGO chez les enfants qui présentent un tableau clinique inhabituel, p. ex., une maladie respiratoire chronique. Le traitement consiste alors en l'administration d'un agent procinétique ou d'inhibiteurs de la sécrétion acide; la chirurgie doit être envisagée chez un grand nombre de ces patients.

This mini-review was prepared from a presentation made at the World Congress of Gastroenterology, Vienna, Austria, September 6 to 11, 1998

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Received for publication June 18, 1999. Accepted June 23, 1999

Gastroesophageal reflux (GER) is a physiological phenomenon that occurs occasionally in every human being, especially during the postprandial period. Regurgitation occurs daily in almost 70% of four-month-old infants, and about 25% of parents consider regurgitation 'a problem' (1,2). It seems illogical that the normal function of the stomach would be to reflux ingested material back into the esophagus. Whether all infants presenting with regurgitation need drug treatment is a different question.

DEFINITIONS

GER is best defined as the involuntary passage of gastric contents into the esophagus. The origin of the gastric contents can vary and includes saliva, ingested foods and drinks, and gastric, pancreatic or biliary secretions. Vomiting is used as a synonym for emesis, and means that the refluxed material comes out of the mouth 'with a certain degree of strength' or 'more or less vigorously', usually involuntary and with sensation of nausea. The term 'regurgitation' is used if the reflux dribbles effortlessly into or out of the mouth, and mostly is restricted to that occurring in infancy (from birth to 12 months) (2,3). Vomiting can be regarded as the tip of the iceberg in its relation to the incidence of GER episodes.

CLINICAL PRESENTATION

Symptoms of reflux may be observed incidentally in normal individuals; however, they occur more often and are more severe in pathological situations. The usual manifestations and unusual presentations of gastroesophageal reflux disease (GERD) are listed in Table 1 (3).

Emesis and regurgitation are the most common symptoms of primary GERD but are also manifestations of many other diseases (2,3). Secondary GERD can be caused by infections such as urinary tract infection, gastroenteritis, metabolic disorders and especially food allergy (2,4). Secondary reflux may be difficult to separate clinically from primary reflux. Secondary reflux is the result of a stimulation of the vomiting centre in the dorsolateral reticular formation by many efferent and afferent impulses such as visual stimuli, the olfactory epithelium, labyrinths, pharynx, gastrointestinal and urinary tracts, and testes. Secondary GER is not discussed further in this paper. Treatment of primary GERD should focus on motility and/or acid suppression, and therapeutic management of secondary GER should focus on the etiological phenomenon.

PATIENT GROUPS

The following approach is a generalization that, like all generalizations, may need to be modified for each individual patient (3). First, interest is focused on uncomplicated GER, mostly restricted to regurgitating infants. Optimal management in patients with complicated GERD (symptoms suggestive for esophagitis) is proposed. There is a continuum between normal infants with regurgitation and GER, and those with severe GER that leads to disability, discomfort or impairment of function. An approach for the management of patients with atypical presentations of GER is proposed.

TABLE 1
Symptoms of gastroesophageal reflux disease

Usual manifestations
Specific manifestations
Regurgitation
Nausea
Vomiting
Symptoms possibly related to complications of GER*
Symptoms related to anemia (iron deficiency anemia)
Hematemesis and melena
Dysphagia (as a symptom of esophagitis or due to stricture formation)
Weight loss and/or failure to thrive
Epigastric or retrosternal pain
'Noncardiac, angina-like' chest pain
Pyrosis or heartburn, pharyngeal burning
Belching, postprandial fullness
Irritable esophagus
General irritability (infants)
Unusual manifestations
GER related to chronic respiratory diseases (bronchitis, asthma, laryngitis, pharyngitis, etc)
Sandifer Sutcliffe syndrome
Rumination
Apnea, apparent life-threatening event and sudden infant death syndrome
Manifestations associated with congenital and/or central nervous system abnormalities
Intracranial tumours, cerebral palsy, psychomotory retardation

**A number of these symptoms may also be caused by other mechanisms. GER Gastroesphageal reflux*

GROUP 1: UNCOMPLICATED REFLUX – REGURGITATION

Regurgitation may occur in children who are normal and do not have complaints of GERD such as nutritional deficits, esophagitis, blood loss, structures, apnea or airway manifestations. There is no difference in the incidence of regurgitation between breastfed and formula-fed infants (5). However, infants with uncomplicated regurgitation frequently are perceived by their parents as having a problem, and their parents often seek medical attention. The treatment approach of the infant presenting with excessive regurgitation and for his or her parents must be well balanced, and cannot be subject to overconcern or disregard. This group of patients is restricted mostly to infants younger than six months, or at the most 12 months (1,3,5). A careful evaluation of history, observation of feeding and physical examination of the infant are mandatory; however, the possibility has not been validated thoroughly because randomization is not possible (only anxious parents seek medical help). It is rather unlikely that regurgitation will result in severe GERD. Many parents who have a regurgitating infant are anxious about the pathophysiological mechanism and prognosis. Parents especially fear long term complications if the regurgitation is not stopped. Therefore, it is important to have a long discussion with the parents to learn the frequency and volume of

TABLE 2
Effects of special formulas and milk-thickening products on GOR, gastric emptying (GE) and clinical parameters in infants with GOR disease

Author (reference)	n	Mean age (range)	Study design	Feed thickener/special formula	GOR and GE parameters	Clinical assessments	Comments
Special formula							
Sutphen et al (26)	19	3.7 months (0.7–13.2 months)	O, XO	Dextrose in water 5–10% Standard enteral glucose polymer solution	2 h pH monitoring (postprandially): 10% dextrose < 5% dextrose = standard solution	nd	Infants placed in horizontal prone position
Tolia et al (27)	28	<1 year	O, XO	CPF SF WHF	Scintigraphy (1 h postprandially): GOR: CPF = SF = WHF GE: CPF = SF, CPF>WHF	nd	
Vandenplas et al (28)	11	Preterm infants	DB, XO	HF/LC LF/HC	24 h pH monitoring: LF/HC<HF/LC (postprandially)	nd (asymptomatic GOR)	
Feed thickeners							
Bailey et al (29)	52	3.6 months (4 days – 14 months)	O, XO	Rice cereal (added to apple juice)	2 h pH monitoring (postprandially): FT=noFT in prone, supine and unrestricted position FT<noFT in 30° prone position	nd	Several positions investigated
Orenstein et al (30)	20	(4–34 weeks)	O, XO	Rice cereal (added to usual formula)	Scintigraphy (postprandially): GOR (1.5 h): FT=noFT GE (30 min): FT>noFT	Regurgitation: FT>noFT Time spent crying: FT>noFT Time spent awake: FT>noFT	Position not mentioned
Orenstein et al (31)	25	7.5 weeks (2–26 weeks)	SB, XO	Rice cereal (added to usual formula)	nd	Coughing (after feeding): FT<noFT	Position not mentioned
Ramenofsky et al (32)	34	(1 week – 12 months)	O, XO	Rice cereal (added to infant formula)	2 h pH monitoring (before FT): FT>noFT (n=21) (after FT): FT<FT (n=10)	nd	Position not clearly mentioned (possibly changed in a controlled fashion)
Vandenplas et al (33,34)	30	(6–8 weeks) (4–12 weeks)	O, XO	Carob bean gum 1 g/115 mL	24 h pH monitoring: FT=noFT or FT<noFT normalization: n=6 (20%)	Regurgitation: FT>B (n=25; 83%)	Infants kept in 30° prone position
Vandenplas et al (35)	40	(1–48 weeks)	O, PA	Commercial formula +bean gum versus –bean gum	24h pH monitoring: FT=noFT (FT>B for reflux index)	Regurgitation: FT>noFT (NS)	Parental reassurance, infants kept in 30° prone position in both groups
Borelli et al (9)	24	(5–11 months)	O, randomized	Commercial formula + rice Nutrilon AR (bean gum)	24h pH monitoring RI bean gum > rice	Bean gum >> rice Rice > baseline Regurgitation symptomatic score	Different composition formula

CPF Casein formula; FT Thickened meal; GOR Reflux parameters on pH monitoring; HF/LC High fat/low carbohydrate; LF/HC Low fat/high carbohydrate; n Number of subjects; nd No data; noFT Unthickened meal; NS Not significant; O Open; PA Parallel; RI Reflux index; SB Single blind; SF Soy formula; WHF Whey hydrolysate formula; XO Crossover

feedings, how the baby is handled during and after feedings, etc. It is also very important to explain the normal, physiological origin of regurgitation. It has been observed in several studies, that just by reassuring the parents and giving them some very practical advice on how to feed the infant is helpful (6,7). The effects of parental reassurance have been suggested by many placebo controlled studies to show similar efficacies between the placebo and the tested intervention (6,7). If simple reassurance fails, dietary intervention is recommended, including restriction of the volume in overfed babies, and change to a thickened 'antiregurgitation' formula (5-7). Larger food volumes and high osmolality increase the number of transient lower esophageal sphincter (LES) relaxations and decrease LES pressure to almost undetectable levels (8). Both are well known pathophysiological mechanisms that provoke GER in infants, which may also explain why feed thickeners sometimes aggravate the symptoms. Thickening the formula with starch (eg, from rice or potato) or non-nutritive thickeners (bean gum) decreases the frequency and volume of regurgitation (5-7,9)(Table 2). Some of these 'antiregurgitation' formulas are casein-predominant (casein/whey; 80%/20%) to optimize the curd formation, while others contain 100% whey hydrolysate to enhance gastric emptying. However, the effect of these formulas on GER parameters, when measured with pH monitoring or scintigraphy, is not convincing; most studies showed that reflux parameters improved, remained unchanged or worsened in approximately one of three infants for each possibility (6,7,10). In other words, 'antiregurgitation' formulas did what they claimed to do – they reduced regurgitation (5-7) but they did not influence acidic GER. Thickened formula also increased the duration of sleep (5,6). Therefore, antiregurgitation formula should be considered as the first step in medical treatment and should only be available by prescription (3,5-7). Antiregurgitation formula and/or dietary intervention in general should be nutritionally safe (11). However, regurgitation may be part of the spectrum of symptoms of GERD, necessitating an effective intervention to decrease the number and intensity of the GER episodes. In this situation, an intervention that is limited to alleviating the presenting manifestation (regurgitation) will not suffice. Clinical differentiation between regurgitation and (pathological) vomiting can be difficult because there is a continuum between both conditions (5). It is not always obvious in this patient group whether the parental complaints relate to physiological regurgitation or whether they suggest GERD. In practice, feed thickeners or special formula cannot be given to breastfed infants. Therefore, if the infant is breastfed and/or has GERD, drug treatment with prokinetics should be considered before diagnostic procedures.

It seems reasonable to add medication such as prokinetics to the treatment of cases that are refractory to dietary intervention. They reduce regurgitation via their effects on the LES pressure and motility, esophageal peristalsis and gastric emptying (12). For this reason, they interact with the pathophysiological mechanisms of regurgitation in infants, which are related to immaturity of the gastroesophageal motor function (13). A link between cisapride and increased salivary secretion has been demonstrated (14). This indicates that, in combination with increased peristalsis and hence esophageal clearance, cisapride therapy may protect the esophagus via salivary components, such as bicarbonate and nonbicarbonate buffers, thus facilitating symptomatic relief and healing of the esophagus. Metoclopramide and domperidone have antiemetic properties due to their dopamine receptor blocking activity, whereas cisapride is a prokinetic agent acting through indirect release of acetylcholine in the myenteric plexus (12). Although all three agents have been shown to reduce regurgitation in infants (6,7), data for cisapride are more convincing (Tables 3,4). Compared with metoclopramide, cisapride may be more effective in reducing pH-metric parameters (15), has a faster onset of action (16) and is better tolerated (16). Cisapride has also been shown to heal esophagitis (17). Domperidone has been reported to be as effective as metoclopramide (18) (and thus less effective than cisapride). Extrapyramidal reactions and increased prolactine levels are effects related to the dopamine receptor-blocking activity of these drugs. In the case of cisapride, which is devoid of dopamine-blocking properties at therapeutic doses, the most common adverse effects are transient diarrhea and colic (in about 2%) (12,19). Isolated incidents of more serious adverse reactions such as side effects on the central nervous system, extrapyramidal reactions and seizures (in epileptic patients), cholestasis (in extreme premature infants) and cardiac interactions have been reported. Cisapride is metabolized by cytochrome P450 3A4 and has the potential to prolong the QT interval (19). However, an extensive review of the literature resulted in reassuring safety consensus statements (19). Serious cardiac adverse reactions have not been reported in patients treated with a dosage within the recommended regimen (0.8 mg/kg/day; 40 mg/day maximum) and in the absence of any of the additional risk factors (Table 4). Cisapride should not be taken with systemic or oral azole antifungals, or with macrolides. Both azole antifungals and macrolides interact with cytochrome P450 3A4, resulting in elevated cisapride plasma levels. In view of its mode of action, efficacy and safety, as well as its lower or equal cost compared with that of other therapeutic agents for GER, cisapride is recommended when dietary treatment fails or in regurgitating breastfed infants, if therapy is indicated. It merits consideration that prokinetics stimulate a physiological activity (peristalsis), while acid-suppressive medication inhibits a physiological secretion.

In the nonbreastfed infant, a change to a thickened hydrolysate or amino acid formula should be considered if regurgitation is resistant to a thickened formula with normal proteins or to prokinetics, because protein allergy may present as therapy-resistant GERD.

Non-drug treatment (positional therapy, dietary advice) can help to convince parents of the physiological nature of regurgitations (3). The influence of position on the incidence and duration of GER episodes has been demonstrated in adults, children and infants, both in asymptomatic

TABLE 3
Effects of cisapride (CIS) on GOR disease in infants

Study	n	Mean age (range)	Study design	Treatment	Dietary measures	GOR and GE parameters	Clinical assessments	Comments
Brueton et al (36)	7	nd	O	CIS 0.2 mg/kg tid (3 weeks)	nd	24h pH monitoring: CIS=B except for number of episodes: CIS>B	nd	Neurologically impaired children (6 cerebral palsy, 1 Down syndrome)
	15	nd	O	CIS 0.2 mg/kg tid (3 weeks)	nd	24 h pH monitoring: CIS>B	nd	
Carrasco et al (37)	34	(4 months to two years)	O	CIS 0.2 mg/kg tid (3 months)	nd	24 h pH monitoring: CIS>B	Symptoms: CIS>B Endsocopy/histology: CIS>B	
Carroccio et al (38)	20	8 months (3–13 months)	O	CIS 0.33mg/kg tid (8 weeks)		24 h pH monitoring: CIS>B Ultrasound (GE): CIS>B	nd	Compared with CO group without GOR: B<<CO; CIS=CO
Castro et al (39)	30	(3 months to 5 years)	DB, PA	CIS 0.2 mg/kg bm PLA (2-4 weeks)	nd	24 h pH monitoring: CIS>PLA	Symptoms: CIS>PLA Respiratory symptoms: CIS>PLA	
Cucchiara et al (40)	17	24.5 months (2.5–47 months)	DB, PA	CIS 0.33mg/kg tid PLA (12 weeks)	nd	Manometry (LOSP): CIS=PLA=B; (peristalsis): CIS>B 5 h pH monitoring (postprandially after apple juice): CIS>B; PLA=B	Symptoms: CIS>PLA Histology: CIS>B; PLA=B Endoscopy: CIS>PLA	Infants with peptic esophagitis (normal basal LES pressure)
Cucchiara et al (41)	14	15.7 (2–38 months)	DB, PA	CIS 0.15 mg/kg PLA (intravenous, single)	FT	Manometry (LOSP, peristalsis): CIS>PLA	nd	Single, intravenous administration
	24		O, PA	CIS 0.2 mg/kg tid CO (4–6 weeks)	FT	24 h pH monitoring: CIS>CO normalization: CIS>CO	Symptoms: CIS>CO	Both groups receiving postural and dietary treatment
Daoud et al (42)	9	83 days (6–150 days)	O	CIS 0.2 mg/kg qid (3 months)	nd	24 h pH monitoring: CIS>B (both upright and seated)	nd	Infants with GOR and apnea
Daoud et al (43)	42	2.6 years (12 days – 12 years)	O	CIS 0.2 mg/kg tid (3 months)	nd	24 h pH monitoring: CIS>B (both upright and seated)	Respiratory symptoms: CIS>B	Infants with GOR-related chronic respiratory symptoms
Evans et al (44)	22	7 months (2–44 months)	DB, PA	CIS 0.2 mg/kg qid+GAV CIM 5mg/kg qid+GAV (6 weeks)	nd	24 h pH monitoring: CIS=CIM		Wide variation in GOR variables; 62% improved with CIS versus 50% with CIM
Greally et al (45)	50	(2–18 months)	O, PA	CIS 0.2 mg/kg qid (–FT) GAV (half sachet/ 90 mL feed) + bean gum (=FT) (4 weeks)	±FT	24 h pH monitoring: CIS–FT=GAV+FT	Symptoms: CIS–FT=GAV+FT	Design misleading: CIS without FT, GAV with FT
Iacono et al (46)	25	16.2 months (1 month – 7 years)	O	CIS 0.33mg/kg tid (8 weeks)	nd	24 h pH monitoring: CIS>B	Symptoms: CIS>B	
Malfroot et al (47)	38	26 months (2 weeks – 7 years)	O	CIS 0.3 mg/kg bm (6 months)	nd	Scintigraphy: CIS>B 24 h pH monitoring: CIS>B	Respiratory symptoms: CIS>B	Infants with GOR-related respiratory disease
Mundo et al (48)	35	(1–36 months)	DB, PA	CIS 0.2 mg/kg bm MCL 0.2 mg/kg bm (10 weeks)	nd	nd	Symptoms: CIS>MCL Overall response: CIS>MCL (NS)	Adverse events: n=4 with CIS and n=9 with MCL (diarrhea, irritability)
Rode et al (49)	40	6.5 months	O	CIS 1 mg/kg/day (in 3 doses) (1 day)	SD	28 h pH monitoring: CIS>B (erect, supine and prone)	nd	Acute study

Continued on page 31D

TABLE 3 (continued from page 30D)
Effects of cisapride (CIS) on GOR disease in infants

Study	n	Mean age (range)	Study design	Treatment	Dietary measures	GOR and GE parameters	Clinical assessments	Comments
Rode et al (14)	18	6.5 months	O, XO	CIS 0.33 mg/kg tid MCL 0.2 mg/kg tid (1 day)	SD	28 h pH monitoring: CIS>MCL long lasting GOR, clearance: CIS>MCL % time, number of episodes: CIS=MCLB	nd	Acute study CIS>MCL in all positions (erect, supine and prone)
Rode et al (50)	30	10 months	O	CIS 1 mg/kg/day (in 3 doses) (3 weeks)	nd	28 h pH monitoring: CIS>B (erect, supine, prone)	Symptoms: CIS>B	
Saye et al (51)	14	29 months (4 months – 11 years)	DB, PA	CIS 0.3 + 0.15 mg/kg/4 h PLA (1 day)	nd	16 h pH monitoring: CIS>PLA (except number of episodes: CIS=PLA)	nd	Older children with GOR-related chronic respiratory symptoms
Saye et al (52)	19	7 years (3 months – 10 years)	O	CIS 0.3 mg/kg tid (4 weeks)	nd	24 h pH monitoring: CIS>B (except number of episodes: CIS=BA)	nd	Older children with GOR-related chronic respiratory symptoms
Vandenplas et al (53)	22	(4–22 weeks)	O	CIS 0.2 mg/kg qid (13–16 days)	nd	24 h pH monitoring: CIS>B (asleep, awake, postcibal, fasted)	Belching, cough, nocturnal wheezing, irritability: CIS>B Sleep dysfunction: CIS>B	Infants with irregular sleep pattern Simultaneous positional treatment (30° prone)
Vandenplas et al (54)	29	(2–4 months)	DB, PA	CIS 0.2 mg/kg qid PLA (13–16 days)	FT	24 h pH monitoring: CIS>B Long-lasting episodes: CIS>PLA=BA	Symptoms: CIS>PLA (NS)	Both groups placed on positional and dietary treatment
Van Eygen et al (55)	69	(5–12 months)	O	CIS 0.15–0.3 mg tid (4 weeks)	CF*	nd	Global response: CIS>B	
	23		DB, PA	CIS 0.15 mg tid PLA (2–4 weeks)	CF*	nd	Global response: CIS>PLA Symptoms: CIS>PLA	
	45		DB, PA	CIS 0.2–0.3 mg tid PLA (2–4 weeks)	CF*	nd	Global response: CIS>PLA Symptoms: at 1 week: CIS (0.2mg)>PLA at 2 weeks: CIS (0.1mg)>PLA	
Scott et al (56)	45	(6 weeks – 2 years)	DB, PA	CIS 0.2 mg tid PLA (6 weeks)	nd	24 h pH monitoring CIS PLA duration reflux upright,supine CIS=PLA RI, n° epi, PLES,	CIS=PLA regurgitation frequency; global evaluation score	No side effects
Cohen et al (57)	95	>36 months	DB, PA	CIS 0.2 mg tid PLA (2 weeks)	nd	24h pH monitoring CIS PLA RI, n°>5 min,duration longest episode	CIS=PLA crying, vomiting, gagging; parental global evaluation	No stepwise treatment

**Prior therapeutic measures continued (positional and/or dietary). Symptoms: if not specified, clinical assessment including regurgitation and/or vomiting. AA Antacid; afm After meals; B Baseline; bm Before meals/each feeding; CF Customary formula; CIM Cimetidine; CO Controls; DB Double- blind; dex Dextrose; DM Dietary measures; DO Domperidone; epi Epinephrine; FT Feed thickener; GAV Gaviscon; GE Gastric emptying; glu Glucose; GOR Reflux parameters on pH monitoring; LES Lower esophageal sphincter; LOSP Lower esophageal sphincter pressure; MCL Metoclopramide; n Number of subjects; n° Number; nd No data; NS Not significant; O Open; PA Parallel; PLA Placebo; PLES Pressure lower esophageal sphincter; PN Parenteral nutrition; RI Reflux index; SD Standard diet; SF Solid food started if not yet done so; XO Crossover with washout period*

healthy controls and symptomatic individuals. The 30° prone reversed Trendelenburg position generally is recommended and accepted as an essential element of treatment (3,6,7). However, positional treatment in practice is very difficult to apply correctly in infants and rather upsetting for the babies, because they must be tied up in their beds or cot to prevent them from sliding down under the blankets in order to achieve and maintain an angle of 30°. There is ample evidence that the prone sleeping position is a risk factor in sudden infant death, independent of overheating, smoking or way of feeding (6). Positional treatment remains, in view of its efficacy, a valid adjuvant treatment in patients not responding to other therapeutic approaches or beyond the age of sudden infant death syndrome (6).

TABLE 4
Contraindications and risk factors for the use of cisapride

Contraindications to cisapride administration in pediatric patients
Use of medication also known to prolong the QT interval or potent CYP3A4 inhibitors, such as astemizole, fluconazole, itraconazole, ketoconazole, miconazole, eythromycin, clarithromycin, troleandomycin, nefazodone, indinavir, ritonavir, josamycin, diphemanil, terfaridine
Use of the above medications by a breastfeeding mother because secretion in mother's milk of most of these drugs is unknown
Known hypersensitivity to cisapride
Known congenital long QT syndrome or known idiopathic QT prolongation
Precautions* for cisapride administration in pediatric patients
Prematurity (a starting dose of 0.1 mg/kg, 4 times daily may be used, although 0.2 mg/kg is also the normal dose for premature infants)
Hepatic or renal failure (particularly when on chronic dialysis). In these cases, it is recommended to start with 50% of the recommended dose
Uncorrected electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), as may occur in premature infants, in patients with severe diarrhea, in treatment with potassium-wasting diuretics such as furosemide or acetazolamide
History of significant cardiac disease including serious ventricular arrhythmia, second- or third-degree antrioventricular block, congestive heart failure or ischaemic heart disease, QT prolongation associated with diabetes mellitus
History of sudden infant death in a sibling, and/or history of a 'serious' apparent life-threatening event in the infant or a sibling
Intracranial abnormalities, such as encephalitis or hemorrhage
Grape fruit juice

**An electrocardiogram should be performed once before cisapride administration and two to three times after administration*

GROUP 2: OVERT GERD

Patients with overt GERD either did not respond to previous approaches such as parental reassurance, dietary treatment and prokinetics, or presented with symptoms suggesting esophagitis (hematemesis, retrosternal and epigastric pain, etc) (Table 1). Therefore, an underlying anatomical malformation should be excluded, and endoscopy is the investigation of choice (3,20). Upper gastrointestinal endoscopy in infants and children should only be performed by experienced and qualified physicians, and should always be done as a duodenogastroesophagoscopy (20). If the question being asked is restricted to underlying anatomical malformations, upper gastrointestinal series may be considered (20). If symptoms and/or the esophagitis do not improve despite adequate medical treatment and controlled compliance, upper gastrointestinal series should be performed to exclude anatomical problems such as gastric volvulus, intestinal malrotation or annular pancreas.

Antacids have been reported to be effective in the treatment of GER (6), although experience with their use in infants is limited. Their capacity to buffer gastric acid is strongly influenced by the time of administration (21) and requires multiple doses. Gaviscon (SmithKline Beecham, USA), a combination of antacid and sodium salt of alginic acid, is as effective as antacids and appears to be relatively safe because only a limited number of side effects have been reported. Occasional formation of large bezoar-like masses of agglutinated intragastric material has been reported with the use of Gaviscon, and it can increase the sodium content of the feeds to an undesirable degree, especially in preterm infants (1 g Gaviscon powder contains 46 mg sodium, and the suspension contains twice this amount of sodium) (6).

H_2 receptor antagonists, of which ranitidine is the most used, are effective in healing reflux esophagitis in infants and children (6). Many new drugs, such as misoprostil, sucralfate and omeprazole, have been developed. Of these, the proton pump inhibitors (PPIs) have been studied most effectively, although experience in infants and children is limited (22,23). PPIs are effective in suppressing the acidity in patients with gastric stress ulcers and also in neurologically impaired children. Even in patients with circular esophageal ulcerations, recent experience suggests a trial of PPIs before surgery (22). Omeprazole has been shown to be effective in cases of patients with severe esophagitis refractory to H_2 blockers (22). Sucralfate was shown to be as effective as cimetidine for esophagitis in children (24).

Immediate or early surgery is rarely indicated in life-threatening conditions where medical management is of no benefit. Surgery can be life-saving in severely affected patients (notably neurologically impaired children with recurrent and life-threatening aspiration). Before surgery, a full diagnostic workup including upper gastrointestinal series, endoscopy, pH monitoring, and manometry and gastric emptying studies is recommended.

GROUP 3: PATIENTS WITH UNUSUAL PRESENTATIONS OF GER

The most obvious difference between this patient group and groups 1 and 2 is that group 3 does not present with emesis and regurgitation (Table 1). Because these patients do not vomit, GERD is 'occult'. Before considering GER as a cause of the symptoms, classic causes of the manifestations such as allergy in a wheezing patient and tuberculosis in a patient with chronic cough must be excluded.

If GERD is suspected, pH monitoring of long duration (18 to 24 h) is the investigation of choice. In this group of patients, pH monitoring may need to be performed simultaneously with other investigations in order to relate pH changes to events (for example, polysomnography in infants presenting with an apparent life-threatening event). In patients suspected of pulmonary aspiration, a scintigraphy might prove the association (although a negative scintigraphy does not exclude reflux-related aspiration, and the therapeutic approach is identical).

If pH monitoring parameters are abnormal or if events are clearly related to pH changes, prokinetics, eventually in combination with H_2 receptor antagonists or PPIs, are indi-

cated (20,22). In this group, repeated pH monitoring under treatment conditions in combination with a clinical follow-up is mandatory. Depending on the unusual presentation, treatment can be stopped after six to 12 months because a possible mechanism for GER in association with unusual manifestations may be self-perpetuating GER (25). Once reflux occurs, acid gastric contents, containing pepsin and sometimes bile, come into contact with the esophageal mucosa, which increases the esophageal permeability to acid and makes the esophageal mucosa much more susceptible to inflammatory changes. Esophageal inflammation, even restricted to the lower esophagus, impairs LES pressure and function, and favours GER (25).

SEVERELY NEUROLOGICALLY IMPAIRED CHILDREN

The vast majority of neurologically impaired children suffer from severe GERD. Most of these children are under specialized follow-up, and only brief recommendations are given here. The pathophysiological mechanism of GERD in these children is particularly multifarious: the neurological disease itself may cause delayed esophageal clearance and gastric emptying; most of these children are bedridden (gravity improves esophageal clearance); and many children are constipated (which increases abdominal pressure and favours GER).

CONCLUSIONS

The diagnostic approach of GERD in infants and children principally depends on its presenting features. Infants with typical symptoms of uncomplicated GER (the majority of regurgitating babies) should be treated without prior investigations. Endoscopy, in specialized centres, is recommended if esophagitis is suspected. Long term esophageal pH montoring is the investigation of choice and occupies a central position in the diagnostic approach for the patient suspected of unusual or atypical presentations of GERD, such as 'occult' GERD. Nondrug treatment (the importance of parental reassurance cannot be stressed enough) and dietary treatment are effective and safe approaches in infant regurgitation therapy but do not treat GERD. If the symptoms are refractory to this approach, or in reflux disease, cisapride is the drug of choice. PPIs or H_2 receptor antagonists, in combination with prokinetics, are recommended in ulcerative esophagitis. There is no excuse to persist with an ineffective management of a disease that might result in stunting, chronic illness, persistent pain, esophageal scarring or even death. Management of GERD in infants and children, therefore, should be thoroughly considered, avoiding overinvestigations and overtreatment of a self-limiting condition, but also avoiding underestimation of potential severe disease, accompanied by serious morbidity.

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