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REVIEW

Diagnosis and treatment of gastro-oesophageal reflux disease in infants and children

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Abstract Gastro-oesophageal reflux is a frequent, aspecific phenomenon in infants and children. The recommended approach in infants with uncomplicated regurgitation consists of reassurance of the parents and, if this fails, dietary recommendations in formula-fed infants. If, despite these efforts, symptoms persist, administration of prokinetics, such as cisapride, is recommended prior to investigations such as oesophageal pH monitoring. Oesophageal pH monitoring is also recommended to document gastro-oesophageal reflux disease in children with unusual presentations such as chronic respiratory disease. Today, cisapride is the drug of choice because it has the best efficacy and safety profile. In infants and children presenting with symptoms suggesting oesophagitis, endoscopy of the upper gastrointestinal tract is recommended. If there is severe oesophagitis, acid suppression with histamine H_2-receptor antagonists or proton pump inhibitors in combination with prokinetics, are recommended. In life-threatening situations, or in patients that are resistant to or dependent on acid-suppressive medication, a surgical procedure such as laparascopic Nissen procedure should be considered.

Key words: acid suppression, antiregurgitation formula, cisapride, endoscopy, gastro-oesophageal reflux, histamine H_2-receptor antagonist, oesophagitis, pH monitoring, prokinetic, proton pump inhibitor, regurgitation, thickened formula.

INTRODUCTION

Gastro-oesophageal reflux (GOR) is a physiological phenomenon occurring occasionally in all humans, especially during the postprandial period. Regurgitation occurs daily in almost 70% of 4-month-old infants and approximately 25% of these parents consider regurgitation as a problem.[1,2] Indeed, it seems against all logic that the normal function of the stomach would be to reflux ingested material back into the oesophagus. Whether all infants presenting with regurgitation need drug treatment is a different question.

DEFINITION

Gastro-oesophageal reflux is best defined as the involuntary passage of gastric contents into the oesophagus. The origin of the gastric contents can vary from saliva, ingested foods and drinks to 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 involuntarily and with the sensation of nausea. The term regurgitation is used if the reflux dribbles effortlessly into or out of the mouth, and is mostly restricted to 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 GOR episodes.

CLINICAL PRESENTATION

Symptoms of reflux may be observed in normal individuals, but in those cases they are only observed incidentally and they occur more often and are more severe in pathological situations. The usual manifestations and unusual presentations of GOR disease (GORD) are

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listed in Table 1.[3] Infants with a Roviralta Astoul syndrome have pyloric stenosis associated with hiatal hernia.

Emesis and regurgitation are the most common symptoms of primary GORD but they are also a manifestation of many other diseases.[2,3] Secondary GORD can be caused by infections (e.g. urinary tract infection, gastroenteritis), metabolic disorders, and especially, food allergies.[2,4,5] Clinically, secondary reflux may be difficult to separate from primary reflux. Secondary reflux is the result of a stimulation of the vomiting centre in the dorsolateral reticular formation by all kinds of efferent and afferent impulses (visual stimuli, the olfactory epithelium, labyrinths, pharynx, gastrointestinal, urinary tracts and testes). Secondary GOR is not discussed further in this paper. It is obvious that treatment of primary GORD should focus on motility and/or acid suppression, and that therapeutic management of secondary GOR should focus on the aetiological phenomena.

Table 1 Symptoms of gastro-oesophageal reflux (GOR) disease

Usual manifestations
Specific manifestations
Regurgitation
Nausea
Vomiting
Symptoms possibly related to complications of GOR*
Symptoms related to iron deficiency anaemia
Haematemesis and melaena
Dysphagia (as a symptom of oesophagitis or from stricture formation)
Weight loss and/or failure to thrive
Epigastric or retrosternal pain
Non-cardiac angina-like chest pain
Pyrosis or heartburn, pharyngeal burning
Belching, postprandial fullness
Irritable oesophagus
General irritability (infants)
Unusual presentations
GOR related to chronic respiratory disease (bronchitis, asthma, laryngitis, pharyngitis, etc.)
Sandifer–Sutcliffe syndrome
Rumination
Apnoea, apparent life-threatening event and sudden infant death syndrome
Associated with congenital and/or central nervous system abnormalities
Intracranial tumours, cerebral palsy, psychomotor retardation

*A number of these symptoms may also be caused by other mechanisms. This table is modified from Vandenplas *et al*.[3]

PATIENT GROUPS

The following approach is a generalization that, like all generalizations, may need to be modified for an individual patient.[3] First, interest is focused on uncomplicated GOR, mostly restricted to regurgitating infants. A proposal is made for optimal management of patients with complicated GORD (symptoms suggestive of oesophagitis). There is a continuum between normal infants with regurgitation and GOR and those with severe GOR leading to disability, discomfort or impairment of function. An approach is proposed for the management of patients with atypical presentations of GOR (Fig. 1).

Early treatment of regurgitation will reassure the parents, and therefore improve the quality of life of the baby and its environment, decreasing medical consultations and avoiding investigations. As GOR causes GORD,[3] early treatment will probably also limit the severity of GORD. Therefore, early treatment will substantially contribute to a reduction of medical costs.

UNCOMPLICATED REFLUX: REGURGITATION

Regurgitation may occur in children who are normal and do not have complaints of GORD, such as nutritional deficits, oesophagitis, blood loss, structures, apnoea or airway manifestations. There is no difference in the incidence of regurgitation between breast-fed and formula-fed infants,[5] but infants with uncomplicated regurgitation are frequently perceived by their parents as having a problem, and these parents often seek medical attention. The approach to the infant presenting with 'excessive' regurgitation and its parents has to be well balanced, and cannot be subject to over-concern or disregard. This group of patients is mostly restricted to infants younger than 6 months, or at the most 12 months.[1,3,6] A careful history, observation of feeding, and physical examination of the infant are mandatory. Although the following statement has not been thoroughly validated because randomization is not possible (only anxious parents seek medical help), it is rather unlikely that regurgitation will result in severe GORD. The effect of parental reassurance is suggested by many placebo-controlled studies showing a similar efficacy of placebo and the tested intervention.[7–9] If simple reassurance fails, dietary intervention is recommended, including restriction of the volume in clearly overfed babies, and change to a thickened antiregurgitation formula.[6–8] Larger food volumes and high osmolality increase the number of transient lower oesophageal sphincter (LES) relaxations and drifts to almost undetectable levels of LES pressure.[10] Both are well known pathophysiological mechanisms provoking GOR in infants, which might also explain why feed thickeners added to regular formula at home sometimes aggravate the symptoms. The thickening of the formula with starch (e.g. from rice or potato) or non-nutritive thickeners (bean gum), decreases the frequency and volume of regurgitation[6–9,11] (Table 2). Some of these antiregur-

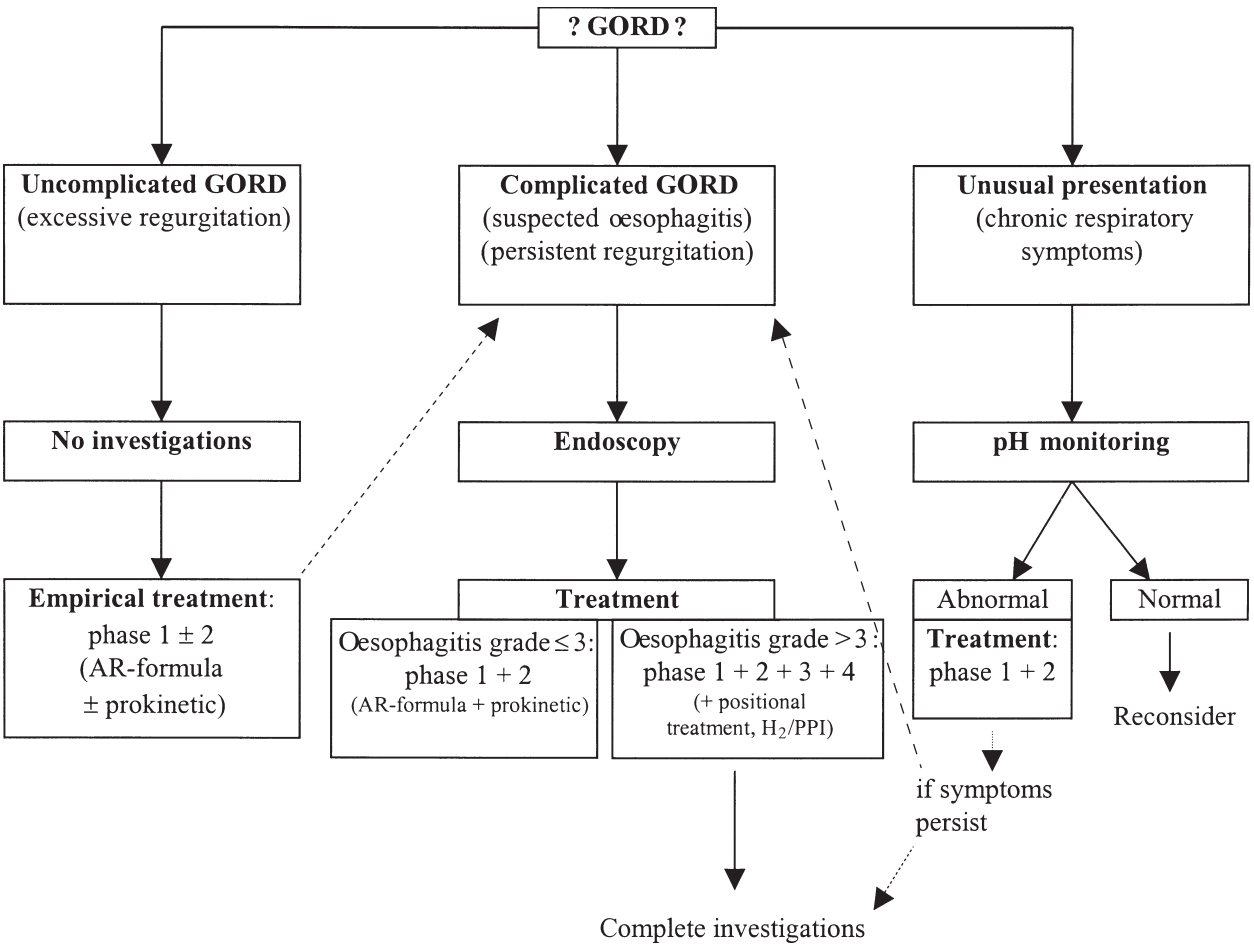

Figure 1 Schematic diagram of the diagnostic and therapeutic approach in children with suspected gastro-oesophageal reflux disease (GORD). H_2, histamine H_2; PPI, proton pump inhibitor; AR formula, antiregurgitation formula.

gitation formulae are casein-predominant (casein : whey 80:20%) to optimize curd formation, while others contain 100% whey (hydrolysate), enhancing gastric emptying. Breast milk is whey-predominant. However, the effect of both types of formulae on GOR parameters, measured by using pH monitoring or scintigraphy, are not convincing: reflux parameters can improve, remain unchanged or worsen in approximately one-third of infants given each formula.[7,8,12] In other words, antiregurgitation formulae do what they claim to do: they reduce regurgitation[6–9] but they do not influence acidic GOR. Thickened formulae also increase the duration of sleep.[6,7] Therefore, antiregurgitation formula should be considered as the first step in medical treatment.[3,6–8] In general, antiregurgitation (AR) formulae and/or dietary intervention should provide optimal nutrition.[13] Casein increases[14] and bean gum decreases[15] plasma cholesterol levels. The unchanged blood cholesterol level observed in infants fed an AR formula with bean gum may be the result of these opposing effects.[16] However, regurgitation may be part of the spectrum of symptoms of GORD, necessitating an effective intervention to decrease the number and intensity of the GOR episodes. In this situation, an intervention that is limited to alleviating the presenting manifestation (regurgitation) will not suffice. Differentiation between regurgitation and pathological vomiting can be difficult as there is a continuum between both conditions.[6] It is not always obvious in this patient group whether the parental complaints relate to physiological regurgitation or whether they suggest GORD. In practice, food thickeners or special formulae can not be given to breast-fed infants. Therefore, if the infant is breast-fed and/or in case of GORD, drug treatment with prokinetics should be considered, even prior to diagnostic procedures.

It seems reasonable to add medication such as prokinetics to the treatment of cases that are refractory to dietary intervention. Prokinetics reduce regurgitation by their effects on LES pressure and motility, oesophageal peristalsis and gastric emptying.[17] For this reason, they interact with the pathophysiological mechanisms of regurgitation in infants, which are related to immaturity of gastro-oesophageal motor function.[18] A link between cisapride and increased salivary secretion has been demonstrated.[19] This indicates that, in combination with increased peristalsis and oesophageal clearance, cisapride therapy may protect the oesophagus by

Table 2 Effect of special formula and milk-thickening products on gastro-oesophageal reflux (GOR), gastric emptying (GE) and clinical parameters in infants with GOR disease

Study	*n*	Age (months)*	Design	Feed thickener/ special formula†	GOR and (GE) parameters	Clinical assessments	Comments
Special formula							
Sutphen and Dillard[31]	19	3.7 (0.7–13.2)	O, XO	5–10% dextrose in water, 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.*[32]	28	< 12	O, XO	CPF, SF, WHF	Scintigraphy (1 h postprandial): GOR: CPF = SF = WHF GE: CPF = SF, CPF > WHF	ND	
Vandenplas *et al.*[33]	11	Preterm infants	DB, XO	HF/LC LF/HC	24 h pH monitoring: LF/HC < HF/LC (postprandial)	ND (asymptomatic GOR)	
Feed thickeners							
Bailey *et al.*[34]	52	3.6 (4 days–14 months)	O, XO	Rice cereal (added to apple juice)	2 h pH monitioring (postprandially): FT = noFT in prone, supine and unrestricted position FT < noFT in 30° prone position	ND	Several positions investigated
Orenstein *et al.*[35]	20	(4–34 weeks)	O, XO	Rice cereal (added to usual formula)	Scintigraphy (1.5 h postprandially): GOR: 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.*[36]	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 and Leape[37]	34	(1 week–12 months)	O, XO	Rice cereal (added to infant formula)	2 h pH monitoring (before and after FT): FT > noFT ($n = 21$) and FT < noFT ($n = 10$)	ND	Position not clearly mentioned (possibly changed in a controlled fashion)
Vandenplas and Sacre[38,39]	30	(6–8 weeks)[5] (4–12 weeks)[6]	O, XO	Carob bean gum 1g/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.*[9]	40	(1–48 weeks)	SB, PA	Commercial formula + bean gum *vs* – bean gum	24 h pH monitoring: FT = noFT (FT > B for reflux index)	Regurgitation: FT > noFT	Parental reassurance, infants kept in 30° prone position in both groups
Borelli *et al.*[11]	24	(5–11)	O, randomized	Commercial formula + Rice Nutriltion AR (bean gum)	24 h pH monitoring RI bean gum > rice	Bean gum ≫ rice > baseline Regurgitation symptomatic score	Different composition formula

=, unchanged; <, worse; >, better. WHF, whey-hydrolysate; SF, soy formula; CPF, casein-formula; HF/LC, high fat/low carbohydrate formula; LF/HC, low fat/high carbohydrate formula; O, open; SB, single blind; XO, crossover; PA, parallel; ND, no data; NS, not significant. *Figures in parentheses are the mean age of the group. †Thickened meal (FT) versus unthickened meal (noFT) or versus baseline (B) or comparison of special formula.

increased secretion of bicarbonate and non-bicarbonate buffers in the saliva, thus facilitating symptomatic relief and healing of the oesophagus. Metoclopramide and domperidone have antiemetic properties from their dopamine-receptor blocking activity, whereas cisapride has a gastrokinetic action through indirect release of acetyl choline in the myenteric plexus.[17] Although all three agents have been shown to reduce regurgitation in infants,[7,8] data for cisapride are more convincing (Tables 3,4). When compared with metoclopramide, cisapride appears to be more effective in reducing pH-metric reflux,[20] has a faster onset of action,[21] and is better tolerated. Cisapride has also been shown to heal oesophagitis.[22] Domperidone has been reported to be as effective as metoclopramide[23] (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 commonest adverse effects are transient diarrhoea and colic (in approximately 2%).[17,24] There are isolated reports of more serious adverse reactions: side-effects on the central nervous system, including extrapyramidal reactions and seizures in epileptic patients; cholestasis in extremely premature infants; and cardiac interactions. Indeed, cisapride, which is metabolized by the cytochrome P450 3A4, has the potential to prolong the QT interval.[24] However, an extensive review of the literature resulted in reassuring safety consensus statements.[24] To date, serious cardiac adverse reactions have not been reported in patients treated with a dosage within in the recommended regimen (0.8 mg/kg per day, max. 40 mg/day) and in the absence of any of the additional risk factors (Table 4). The association of cisapride with systemic or oral azole antifungals and with macrolides is contraindicated. Both azole antifungals and macrolides interact with the 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 when compared to other therapeutic agents for GOR, cisapride is recommended when dietary treatment fails or in regurgitating breast-fed 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 non-breast-fed infant, a change to a thickened hydrolysate or amino-acid formula should be considered if regurgitation is resistant to a formula thickened with normal proteins or to prokinetics, as a protein allergy may present as therapy-resistant GORD.[4,5]

Non-drug treatments, such as positional therapy and dietary advice, can help convince parents of the physiological nature of regurgitation.[3] The influence of position on the incidence and duration of GOR episodes has been demonstrated in adults, children and infants both in asymptomatic healthy controls and in symptomatic individuals. The 30° prone, reversed, Trendelenburg position is nowadays generally recommended and accepted as an essential element of treatment.[3,7,8] However, positional treatment is, in practice, very difficult to apply correctly in infants and rather unfriendly to the babies, as they have to be tied up in their bed or cot to prevent them from sliding down under the blankets, as an angle of 30° has to be achieved and maintained. There is ample evidence that the prone sleeping position is a risk factor for sudden infant death, independent of overheating, being exposed to tobacco smoke or method of feeding.[7] Positional treatment remains, in view of its efficacy, a valid adjunctive treatment in patients not responding to other therapeutic approaches or beyond the age of sudden infant death.[7]

OVERT GASTRO-OESOPHAGEAL REFLUX DISEASE

Patients in this group either do not respond to parental reassurance, dietary treatment and prokinetics or present with symptoms suggesting oesophagitis (haematemesis, retrosternal and epigastric pain; Table 1). Therefore, an underlying anatomical malformation should be excluded, and endoscopy is the investigation of choice.[3,25] Upper gastrointestinal endoscopy in infants and children should only be performed by experienced and qualified physicians, and should always be a duodenogastro-oesophagoscopy.[25] If the question being asked is restricted to underlying anatomical malformations, an upper gastrointestinal series can be considered.[25] If symptoms and/or the oesophagitis do not improve despite adequate medical treatment and controlled compliance, an upper gastrointestinal series should be performed to exclude anatomical problems such as gastric volvulus, intestinal malrotation and annular pancreas.

Antacids are reported to be effective in the treatment of GOR,[7] although experience is limited in infants. Their capacity to buffer gastric acid is strongly influenced by the time of administration[26] and requires multiple doses. Gaviscon^{R} (an antacid plus sodium salt of alginic acid) is as effective as an antacid and appears to be relatively safe, as only a limited number of side-effects have been reported. Occasional formation of large bezoar-like masses of agglutinated intragastric material have been reported with the use of Gaviscon^{R}, which can increase the sodium content of the feeds to an undesirable degree, especially in preterm infants (1 g Gaviscon^{R} powder contains 46 mg sodium, while the Gaviscon^{R} suspension contains twice this amount).[7]

Histamine H_2 receptor antagonists, of which ranitidine is by far the most used, are effective in healing reflux oesophagitis in infants and children.[7] Many new drugs have been developed (misoprostol, sucralfate, omeprazole, etc.). Of these, the proton pump inhibitors (PPI) have been the best studied, although experience in infants and children is limited.[27,28] The PPI are effective in suppressing acidity in patients with gastric stress ulcers and also in neurologically impaired children. Even in patients with circular oesophageal ulcerations, recent experience suggests that PPI should be tried prior to surgery.[27] Omeprazole is known to be effective in cases of patients with severe oesophagitis refractory to H_2-blockers.[21] Sucralfate was

Table 3 Effects of cisapride (CIS) on gastro-oesophaeal reflux disease in infants

Study	*n*	Age (months)	Design	Treatment	DM	GOR and GE parameters	Clinical assessments	Comments
Brueton *et al.*[40]	7†	ND	O	CIS 0.2 mg/kg, t.i.d. (3 weeks)	ND	24 h pH monitoring: CIS = B Except for no. of episodes: CIS > B	ND	Neurologically impaired children (6 cerebral palsy, 1 Down syndrome)
	15	ND	O	CIS 0.2 mg/kg, t.i.d. (3 weeks)	ND	24 h pH monitoring: CIS > B	ND	
Carrasco *et al.*[41]	34	(4–24)	O	CIS 0.2 mg/kg, t.i.d. (3 months)	ND	24 h pH monitoring: CIS > B	Symptoms: CIS > B Endoscopy/histology: CIS > B	
Carroccio *et al.*[42]	20	8 (3–13)	O	CIS 0.33 mg/kg, t.i.d. (8 weeks)		24 h pH monitoring: CIS > B Ultrasound (GE): CIS > B	ND	Compared to CO-group without GOR: B < CO; CIS = CO
Castro *et al.*[43]	30	(3–60)	DB, PA	CIS 0.2 mg/kg, b.m. PLA (2–4 weeks)	ND	24 h pH monitoring: CIS > PLA	Symptoms: CIS > PLA Respiratory symptoms: CIS > PLA	
Cucchiara *et al.*[44]	17	24.5 (2.5–47)	DB, PA	CIS 0.33 mg/kg, t.i.d. 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 oesophagitis (normal basal LES pressure)
Cucchiara *et al.*[45]	14	15.7 (2–38)	DB, PA	CIS 0.15 mg/kg PLA (i.v., single)	FT	Manometry (LOSP, peristalsis): CIS > PLA	ND	Single, i.v. administration
	24		O, PA	CIS 0.2 mg/kg, t.i.d. 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.*[46]	9	83 days (6–150 days)	O	CIS 0.2 mg/kg, q.i.d. (3 months)	ND	24 h pH monitoring: CIS > B (both upright and seated):	ND	Infants with GOR and apnoea
Daoud *et al.*[47]	42	2.6 years (12 days–12 years)	O	CIS 0.2 mg/kg, t.i.d. (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.*[48]	22	7 (2–44)	DB, PA	CIS 0.2 mg/kg, q.i.d. + GAV CIM 5 mg/kg, q.i.d. + 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.*[49]	50	(2–18)	O, PA	CIS 0.2 mg/kg, q.i.d. (– FT) GAV ($\frac{1}{2}$ sachet/90 mL feed) + Carobel (= 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.*[50]	25	16.2 (1–72)	O	CIS 0.33 mg/kg, t.i.d. (8 weeks)	ND	24 h pH monitoring: CIS > B	Symptoms: CIS > B	
Malfroot *et al.*[51]	38	26 (2 weeks–7 years)	O	CIS 0.3 mg/kg, b.m. (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.*[21]	35	(1–36)	DB, PA	CIS 0.2 mg/kg, b.m. MCL 0.2 mg/kg, b.m. (10 weeks)	ND	ND	Symptoms: CIS > MCL Overall response: CIS > MCL (NS)	Adverse events: $n = 4$ with CIS and $n = 9$ with MCL (diarrhoea, irritability)
Rode *et al.*[52]	40	6.5	O	CIS 1 mg/kg per day (in 3 doses) (1 day)	SD	28-h pH monitoring: CIS > B (erect, supine and prone)	ND	Acute study
Rode *et al.*[20]	18	6.5	O, XO	CIS 0.33 mg/kg, t.i.d. MCL 0.2 mg/kg, t.i.d. (1 day)	SD	28-h pH monitoring: CIS > MCL long-lasting GOR, clearance: CIS > MCL % time, No. episodes: CIS = MCL > B	ND	Acute study CIS > MCL in all positions (erect, supine and prone)
Rode *et al.*[53]	30	10	O	CIS 1 mg/kg per day (in 3 doses) (3 weeks)	ND	28-h pH monitoring: CIS > B (erect, supine, prone)	Symptoms: CIS > B	
Saye and Forget[54]	14	29 (4 months–11 years)	DB, PA	CIS 0.3 + 0.15 mg/kg per 4 h PLA (1 day)	ND	16-h pH monitoring) CIS > PLA (except no. episodes: CIS = PLA)	ND	Older children with GOR-related chronic respiratory symptoms
Saye *et al.*[55]	19	7 years (3 months–10 years)	O	CIS 0.3 mg/kg, t.i.d. (4 weeks)	ND	24 h pH monitoring: CIS > B (except no. episodes: CIS = BA)	ND	Older children with GOR-related chronic respiratory symptoms
Vandenplas *et al.*[56]	22	(4–22 weeks)	O	CIS 0.2 mg/kg, q.i.d. (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.*[57]	29	(2–4)	DB, PA	CIS 0.2 mg/kg, q.i.d. 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 and Van Ravenstein[58]	69	(5–12)	O	CIS 0.15–0.3 mg, t.i.d. (4 weeks)	CF†	ND	Global response: CIS > B	
	23		DB, PA	CIS 0.15 mg, t.i.d PLA (2–4 weeks)	CF†	ND	Global response: CIS > PLA Symptoms: CIS > PLA	
	45		DB, PA	CIS 0.2–0.3 mg, t.i.d. PLA (2–4 weeks)	CF†	ND	Global response: CIS > PLA Symptoms: at 1 week: CIS (0.2 mg) > PLA at 2 week: CIS (0.1 mg) > PLA	
Scott *et al.*[59]	45	(6 weeks–2 years)	DB, PA	CIS 0.2 mg, t.i.d. 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.*[60]	95	< 36	DB, PA	CIS 0.2 mg, t.i.d. PLA (2 weeks)	ND	24 h pH monitoring CIS > PLA RI, n° > 5min, duration longest episode	CIS = PLA crying,vomiting,gagging parental global evaluation	No stepwise treatment

*Figures in parentheses are mean age. O, open; DB, double blind; PA, parrallel; XO, cross-over with wash-out period; CIS, cisapride; PLA, placebo; MCL, metoclopramide; DO, domperidone; CIM, cimetidine; GAV, Gaviscon; AA, antacid; FT, feed thickener; B, baseline; CO, controls; b.m., before meals/each feeding; afm, after meals. DM, dietary measures; SD, standard diet; dex, dextrose; glu, glucose; CF, customary formula; SF, solid food started if not yet done so; PN, parenteral nutrition; PLES, pressure lower oesophageal sphincter; ND, no data. †Prior therapeutic measures continued (positional and/or dietary). GOR, gastrointestinal reflux; reflux parameters on pH monitoring; GE, gastric emptying; >, better than; <, worse than; =, unchanged, for the main/all parameters evaluated in paper; exceptions for single parameters which are mentioned separately. Symptoms: if not specified, clinical assessment includes regurgitation and/or vomiting.

Table 4 Contraindications and risk factors for the use of cisapride in paediatric patients

Contraindications
Combination with medication also known to prolong the QT interval or potent CYP3A4 inhibitors, such as astemizole, fluconazole, itraconazole, ketoconazole, miconazole, erythromycin, clarithromycin, troleandomycin, nefazodone, indinavir, ritonavir, josamycin, diphemanil, terfenadine.
Use of the above medications by a breast-feeding mother, as 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 administration
Prematurity (a starting dose of 0.1 mg/kg, four 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 (hypokalaemia, hypomagnesaemia, hypocalcaemia), which may occur in premature infants, in severe diarrhoea or in treatment with potassium-wasting diuretics, such as furosemide or acetazolamide.
History of significant cardiac disease including serious ventricular arrhythmia, second or third degree atrioventricular 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 an apparent life-threatening event in the infant or a sibling.
Intracranial abnormalities, such as encephalitis or haemorrhage
Grape fruit juice

shown to be as effective as cimetidine for oesophagitis in children.[29]

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

PATIENTS WITH UNUSUAL PRESENTATIONS OF GASTRO-OESOPHAGEAL REFLUX

The most obvious difference between this patient group and those with uncomplicated reflux or overt GORD, is that this patient group does not present with emesis and regurgitation (Table 1). As these patients do not vomit, GORD is occult. Before considering GOR as a cause of the symptoms, classic causes of the manifestations need to be excluded, such as allergy in a wheezing patient or tuberculosis in a patient with chronic cough.

If GORD is suspected, 18–24 h pH monitoring 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 (e.g. polysomnography in an infant presenting with an apparent life-threatening event). In patients suspected of pulmonary aspiration, scintigraphy might prove the association, although a negative scintigraphy does not exclude reflux-related aspiration, and the therapeutic approach will be identical to the treatment in patients with a negative scintigraphy.

If pH monitoring is abnormal or if events are clearly related to pH changes, prokinetics in combination with H_2-receptor antagonists or PPI, are indicated.[25,27] In this group, repeat pH monitoring under treatment conditions in combination with a clinical follow up is mandatory. Depending on the unusual presentation, treatment can be stopped after 6–12 months, as a possible mechanism for GOR in association with unusual manifestations may be self-perpetuating GOR.[30] Once reflux occurs, acid gastric contents containing pepsin, and sometimes bile, come into contact with the oesophageal mucosa, which increases the oesophageal permeability to acid and makes the oesophageal mucosa much more susceptible to inflammatory changes. Oesophageal inflammation, even restricted to the lower oesophagus, impairs LES pressure and function, and favours GOR.[30]

SEVERELY NEUROLOGICALLY IMPAIRED CHILDREN

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

CONCLUSIONS

The diagnostic approach of GORD in infants and children principally depends on its presenting features. Infants with typical symptoms of uncomplicated GOR (the majority of regurgitating babies) should be treated without investigation. Endoscopy, in specialized centres, is recommended if oesophagitis is suspected. Long-term oesophageal pH monitoring is the investigation of choice and occupies a central position in the diagnostic approach to the patient suspected of unusual or atypical presentations of GORD (occult GORD). Non-drug and dietary treatments are an effective and safe approach in infant regurgitation, but do not treat GORD. If the symptoms are refractory to this approach or reflux disease is found, cisapride is the drug of choice. Proton pump inhibitors or H_2-receptor antagonists, in combination with prokinetics, are recommended in ulcerative oesophagitis. There is no excuse for persisting with ineffective management of a disease that might result in stunting, chronic illness, persistent pain, oesophageal scarring or even death. Management of GORD in infants and children 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.

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