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REVIEW

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A critical appraisal of current management practices for infant regurgitation – recommendations of a working party

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Abstract Regurgitation is a common manifestation in infants below the age of 1 year and a frequent reason of counselling of general practitioners and paediatricians. Current management starts with postural and dietary measures, followed by antacids and prokinetics. Recent issues such as an increased risk of sudden infant death in the prone sleeping position and persistent occult gastro-oesophageal reflux in a subset of infants receiving milk thickeners or thickened “anti-regurgitation formula” challenge the established approach. Therefore, the clinical practices for management of infant regurgitation have been critically evaluated with respect to their efficacy, safety and practical implications.

The updated recommendations reached by the working party on the management of infant regurgitation contain

five phases: (1A) parental reassurance; (1B) milk-thickening agents; (2) prokinetics; (3) positional therapy as an adjuvant therapy; (4A) H₂-blockers; (4B) proton pump inhibitors; (5) surgery.

Key words Regurgitation · Vomiting · Gastro-oesophageal reflux · Infant · Treatment

Abbreviations GOR(D) gastro-oesophageal reflux (disease) · LOS lower oesophageal sphincter · TLOS transient lower oesophageal sphincter relaxation · SID Sudden infant death · CNS central nervous system

Introduction

Regurgitation is the sudden effortless return of small volumes of gastric contents into the pharynx and mouth. It is a manifestation of gastro-oesophageal reflux (GOR) which per definition occurs whenever gastric content refluxes into the oesophagus. Regurgitation does not necessarily present with GOR disease (GORD), but it is a frequent cause of discomfort to the infant, a matter of concern to the parents and a common reason for consulting primary care physicians and paediatricians. Counselling of the parents about its frequently inoffensive nature is recommended and may solve the problem, although parents often request more effective control of the symptoms and greater improvement of the discomfort.

In 1993, the European Society of Paediatric Gastroenterology and Nutrition published guidelines for the treatment of GORD in infants [132]. These recommendations were published prior to, or simultaneously with ‘anti-prone-sleeping position’ campaigns conducted and supported by governments and medical societies. Moreover, some of the recommendations of 1993 can be challenged upon critical analysis of the efficacy data, such as the effect of milk thickeners on pH-metric or scintigraphic parameters [4, 92, 99, 127, 128, 133].

This paper reviews the recommended therapeutic approaches to regurgitation in infants, with special at-

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tention to practical implications, benefits and risk. Complicated GORD is only indirectly covered, being implicated in persistent regurgitation, refractory to initial treatment. Guidelines for management of regurgitation in infants below 1 year of age are updated according to the recent consensus of the working party.

Symptoms, epidemiology and diagnosis

Symptoms

Regurgitation is the almost spontaneous return of gastric contents into the pharynx and the mouth [125]. It can be best differentiated from emesis by the absence of preceding nausea, retching, or autonomic symptoms, and lack of abdominal and thoracic muscle contraction. Vomiting is synonymous with emesis; the refluxed material is emitted from the mouth with force. However, it sometimes may be difficult to distinguish regurgitation from vomiting and both symptoms may occur in the same patient.

More subtle symptoms associated with GORD in infants include excessive crying and irritability (possibly related to oesophageal pain), which are sometimes erroneously attributed to 'colic' or 'gas'. A close correlation between this behaviour and GOR has been confirmed by pH monitoring and split-screen video [48]. In addition to regurgitation, drooling and burping, also episodes of discomfort with crying or frowning, yawning, stridor, stretching and mouthing, are found closely and temporarily associated with reflux events. Respiratory symptoms, such as recurrent cough, wheezing, stridor and apnoea may occur with and without regurgitation or vomiting, and are more frequently present in the preterm or older child.

Some children present with symptoms of more severe GORD, such as oesophagitis, failure to thrive or weight loss – the latter symptoms being consequences of insufficient food intake due to oesophageal pain and/or excessive loss of calories due to the vomited volume [125].

Fitting the above symptoms into the broad spectrum of GORD, three types can be distinguished (Fig. 1) [132]: (1) infants with regurgitation; (2) infants with GORD: with persistent regurgitation, vomiting, failure to thrive and/or oesophagitis (eventually haematemesis); sometimes with persistent crying (pain), sleeping problems or concomitant extra-intestinal symptoms; (3) children with chronic respiratory symptoms, apnoeic spells or apparent life-threatening events, but without regurgitation and vomiting.

Epidemiology and prognosis

The prevalence of regurgitation varies between 18% (general infant population) [10] and 40% (of children consulting a physician's practice) [24]. The latter prevalence corresponds to the finding that, although with regional differences, 40%–50% of the milk formulae sold in Belgium are thickened "anti-regurgitation" formulae (Institute National Statistics, Belgium). However, the prevalence of excessive GOR according to pH-metric criteria, is lower (8%) [106].

Little has been published about the natural history of regurgitation and GORD in infants and its impact on morbidity or mortality if untreated. Generally, regurgitation is considered a 'benign' condition, spontaneously resolving 12–18 months after birth. However, limited studies have shown better prognosis if treatment starts early with positional measures, thickening of feeds and/or prokinetics [16–18, 24, 66, 111]. The data indicate that early recognition and attention to the problem are mandatory.

Diagnosis

The approach to diagnosis of uncomplicated GORD in regurgitating infants has been well described elsewhere [132]. Stepwise empirical treatment is recom-

Fig. 1 The approach to diagnosis of GORD in infants according to the ESPGAN recommendations of 1993 [1].

mended and a therapeutic trial of a prokinetic is recommended prior to invasive investigation (Fig. 1). Symptoms which should prompt the primary care physician to refer immediately include overt emesis (possibly secondary to another problem), suspected oesophagitis, haematemesis, failure to thrive, or persistent extra-intestinal symptoms (crying, coughing, wheezing, sleeping problems). pH monitoring is the investigation of choice to diagnose GOR in non-regurgitating or non-vomiting children, while endoscopy is recommended for oesophagitis.

Pathophysiology

Little is known about the mechanisms of regurgitation. Current knowledge mainly relates to the pathophysiology of GORD [51, 58]. Factors relevant to GORD in infants include: the length of the lower oesophageal sphincter (LOS), an immature LOS, transient LOS relaxations, (TLOSRS) decreased gravitational and peristaltic clearance of the refluxed material from the distal oesophagus and delayed gastric emptying.

Although it can be argued that standard values on LOS length and function are lacking in infants below 1 year, there are indications that children with GOR may have a shorter LOS than those without GOR [86] (the intra-abdominal segment of the oesophagus almost being absent during early life) and that LOS pressure and oesophageal clearing peristalsis may be reduced or disordered [9, 29, 57]. Gastric emptying may or may not be delayed [19, 44]. Inappropriate TLOSRS, independent of swallowing, have been identified as a major pathological mechanism in infants with increased GOR or oesophagitis [31, 138]. Increased abdominal or intragastric pressure [31] associated with delayed gastric emptying [26] or gastric distension [59] or attenuated swallows failing to induce peristalsis [84] may be involved in causing the inappropriate relaxations. But also during appropriate relaxations, reflux can be observed [31].

Clearance of the refluxed material from the oesophagus by gravitational and peristaltic forces is an important mechanism limiting GOR in infants. For instance, the effect of the prone 30° anti-Trendelenburg position reducing GOR [83, 90, 91, 126], is probably partly related to the effect of gravity. Reduced swallowing rates during sleep [114] and dysfunction of oesophageal peristalsis [9, 29, 57] have been found in infants with GORD. Increased intragastric pressure may play a role because infant GOR is worse in seated than in prone position [91, 99].

Gradual functional maturation of the LOS [8, 9] may explain the benign course of infant GOR. It is also interesting that the oesophageal motor defects seen in infants with oesophagitis (not secondary to other disease) resolve following healing of the oesophagitis [29]. However, relapse is almost the rule in children with GORD after repaired oesophageal atresia or GORD-associated with connective tissue disorders and neuro-

logical disease [37]. In these children, oesophageal motor abnormalities persist after healing of the oesophagitis [36] and resemble that in adults [46, 60, 112, 113, 115, 120].

Treatment by parental reassurance

Parental reassurance is essential. Careful questioning (and observation) of how the mother prepares the formula, feeds and handles the baby after feeding, may help in solving the complaints. Reassuring the parents that nothing is wrong with their baby may preclude the need for any further measures.

The impact of the infant's reflux symptoms on the parents' anxiety is difficult to qualify or quantify. Identical manifestations of GOR elicit different reactions, the degree of anxiety being influenced by former experiences. Therefore, it is important for the physician to listen to the parents and to explain the physiological nature of regurgitation and its spontaneous resolution in the majority of infants.

From the above results the following recommendation: whatever the subsequent management, parental reassurance remains important: a good therapeutic setting may act as a 'positive placebo' (Treatment Phase 1A).

Dietary advice

Small, frequent feedings. This dietary measure is based on the observation that pH-metric GOR decreases when the feeding volume (of a single 5% dextrose feeding) is decreased [129]. However, to maintain sufficient caloric intake, feeding smaller volumes demands more frequent feeding, with more postprandial periods. In practice, the measure is difficult to apply, as frequent feedings may compromise work and daily activities of the parents; the reduced feeding volumes may also cause distress to the baby, when hungry and not wanting to stop drinking.

Low-fat, high-carbohydrate formula. These formulae are based on the idea that long-chain fatty acids delay gastric emptying and their reduction may result in less reflux due to improved gastric emptying. Controlled studies [117, 122, 129] do not support their efficacy in improving pH-metric GOR variables (Table 1). Such formulae should in any case fulfil the nutritional needs of the infant.

Milk-thickening agents, include bean gum preparations prepared from St John's bread, a galactomannan (Nutrilon, Carobel, Nestargel, Gumilk; Nestargel also contains 3.5% calcium lactate); sodium carboxymethylcellulose (Gelilact) and a combination of pectin and cellulose (Gelopectose); cereal and rice products.

Milk thickeners have been reported to reduce regurgitation in infants [4, 92, 99, 127, 128, 133] and to improve sleep (possibly due to an improved satiety related to the higher caloric intake in the case of rice-thickened

Table 1 Effect of special formula and milk-thickening products on GOR, gastric emptying (GE) and clinical parameters in infants with GOR disease ('=': unchanged, '<': worse, '>': better) (*O* open, *SB* single blind, *XO* crossover, *ND* no data, *NS* not significant)

Reference	No	Age ^a	Design ^b	Feed thickener/special formula ^b	GOR and GE parameters	Clinical assessments ^c	Comments
Special formula							
[117]	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
[122]	28	< 1 year	O,XO	Casein-formula (CPF) Soy (SF) Whey-hydrolysate (WHF)	Scintigraphy (1 h postprandially): • GOR: CPF = SF = WHF • GE: CPF = SF, CPF > WHF 24 h pH monitoring: • LF/HC < HF/LC (postprandial)	ND	
[129]	11	Preterm infants	DB,XO	High fat/low carbohydrate formula (= HF/LC) Low fat/high carbohydrate formula = (LF/HC)		ND (asymptomatic GOR)	
Feed thickeners							
[4]	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
[92]	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 • Coughing (after feeding): FT < noFT ND	Position not mentioned
[93]	25	7.5 weeks (2–26 weeks)	SB,XO	Rice cereal (added to usual formula)	ND		Position not mentioned
[99]	34	(1 weeks–12 months)	O,XO	Rice cereal (added to infant formula)	2 h pH monitoring (before and after FT): • FT > noFT (<i>n</i> = 21) and FT < noFT (<i>n</i> = 10) 24 h pH monitoring: • FT = noFT or FT < noFT • normalization: <i>n</i> = 6 (20%) 24 h pH monitoring: • FT = noFT • (FT > B for reflux index)	• Regurgitation: FT > B (<i>n</i> = 25; 83%) ND	Position not clearly mentioned (possibly changed in a controlled fashion) Infants kept in 30° prone position
[127, 128]	30	(6–8 weeks) (4–12 weeks)	O,XO	Carob bean gum 1 g/115 ml			
[133]	40	(1–48 weeks)	O,PA	Commercial formula + bean gum vs – bean gum		Regurgitation: FT > noFT (N.S.)	Parental reassurance, infants kept in 30° prone position in both groups

^aMeans of age in groups (range between brackets), ^bThickened meal (FT) versus unthickened meal (noFT) or versus baseline (B) or comparison of special formula

formula) [92]. However, their effects on the oesophageal acid exposure are inconsistent, as shown by pH monitoring [4, 99, 127, 128, 133] and scintigraphy [92] (Table 1). The number of reflux episodes may increase or decrease [99], the oesophageal acid exposure increase depending on the baby's position [4]. The duration of the long-lasting reflux episodes has been reported to significantly increase [127, 128] or remain unchanged [133]. These findings are in line with the recent observations in infants that increased food volume and osmolality increase the rate of TLORs and drifts in LOS pressure to almost undetectable levels [35]. Increased coughing has also been demonstrated in infants receiving milk thickeners [93].

Milk thickeners are usually well tolerated, although abdominal pain, colic and diarrhoea may ensue from fermentation of bean gum derivatives in the colon. Serious complications are rare and limited to anecdotal cases of acute intestinal obstruction in newborns [85]. The use of Gelopectose is not advised in infants with cystic fibrosis and Hirschsprung disease.

Although often wrongly considered 'inexpensive', they are not. In practice, milk thickeners or "anti-regurgitation formula" cannot be given to breast-fed infants. Nevertheless, in view of their safety and efficacy in decreasing regurgitation, milk thickeners remain a valuable first-line measure in relieving regurgitation in many infants. In contrast, their efficacy as single therapy is questionable in complicated GORD, since their impact on GOR parameters is unpredictable.

From the above follows another recommendation: small, frequent feedings with low-fat high carbohydrate formulae are not recommended because of their benefit has not been proven and they are difficult to realise. It is recommended to thicken the formula since it decreases the amount and severity of regurgitation, although it does not have a beneficial effect on GOR (Treatment Phase 1B).

Prokinetic agents

Prokinetic agents, i.e. metoclopramide, domperidone, and cisapride, act on regurgitation via their effects on LOS pressure, oesophageal peristalsis or clearance and/or gastric emptying [135]. Metoclopramide and domperidone also have anti-emetic properties due to their dopamine receptor blocking action, while cisapride is a prokinetic, mainly acting via indirect release of acetylcholine from the myenteric plexus [135].

Metoclopramide

Data supporting the efficacy of this prokinetic (Primperan, Reglan) in relieving infant regurgitation are contradictory and positive results are limited to some observations with i.v. doses (Table 2) [2, 14, 42, 49, 61, 62, 76, 79, 97, 121]. Application in infants is limited

because of severe adverse events, including Central nervous system (CNS) effects and interactions with the endocrine system. The adverse effects regarding the CNS are mainly related to its dopamine receptor blocking properties in the substantia nigra, and include extrapyramidal effects (dystonic reactions, irritability) and drowsiness. Isolated cases of metoclopramide-induced methaemoglobinaemia have been reported [71, 140].

Domperidone

The studies supporting efficacy of domperidone (Motilium, Nauzelin) in improving regurgitation and GOR in infants are limited (Table 3) [5, 20, 25, 42, 45, 53, 63, 127]. Most studies have been performed in older children, or investigate the effects of domperidone co-administered with other anti-reflux agents [20, 63, 127]. Although pH-metric results [5, 20, 45, 53] appear somewhat better than those with oral metoclopramide [49, 76], domperidone controls GOR more consistently when used in combination with antacids or Gaviscon. Domperidone is better tolerated than metoclopramide [22] since dystonic reactions (tremors) and anxiety are infrequent. Plasma prolactin levels may increase [43] due to pituitary gland stimulation.

Cisapride

Cisapride (Prepulsid, Propulsin, Alimix, Acenalin) (Table 4), a benzamide derivative, is a non-dopamine-receptor blocking, non-cholinergic prokinetic drug with 5HT₄-antagonistic properties [102]. It promotes gastrointestinal motility by facilitating the release of acetylcholine from the myenteric (Auerbach) plexus, without interfering with dopamine receptors [135]. This agent has been shown to improve regurgitation [15, 21, 30, 33, 64, 131, 134], gastric emptying [19] and pH-metric GOR variables [12, 15, 21, 30, 33, 38, 39, 47, 64, 80, 103–105, 107, 108, 130, 131] in infants. Studies using a control group or placebo are limited [19, 21, 30, 33, 108, 131, 134] (Table 4). Improvement of pH-metric GOR parameters has been demonstrated during different periods of the day (total period, night, awake, asleep, postcibal, fasted) [33, 38, 39, 107, 108, 130, 131, 134] and in different positions (sitting up/erect, prone, supine) [38, 39, 103–105]. Cisapride increases the LOS pressure [33], although this effect was not seen in infants with oesophagitis having a normal LOS pressure [30]. It also increases amplitude and duration of oesophageal contractions [30, 33] and improves gastric emptying [19]. When compared to conservative measures alone (30° prone and milk thickening), its addition normalises the pH-metric parameters in more infants [33] and reduces the long-lasting reflux episodes [33, 103–105, 131]. However, cisapride might be less effective in neurologically impaired children [12].

Table 2 Effects of metoclopramide (MCL) on GORD in infants.

ReferenceNo	Age (range)	Design	Treatment	DM	GOR and GE parameters	Clinical assessments ^b	Comments
[2]	20 N D	DB, PA	MCL 0.1 mg/kg, bm PLA (bm) (6 weeks)	ND	ND	• Vomiting: MCL = PLA	
[14]	13 6–8 months (1–24 months)	O	MCL 0.1 mg/kg, bm (iv, 1 day)	N D	Manometry (LOSpressure), 24 h pH monitoring: MCL > B	ND	IV administration
[42]	47 6–9 months 3 weeks–8years)	DB, PA	DO 0.3 mg/kg tid MCL 0.3 mg/kg tid PLA tid (2 weeks)	FT	ND	• Nausea: DO > MCL = PLA • Vomiting: DO > MCL > PLA (week 2) • Global response: DO = MCL > PLA	Older children
[49]	10 65–71months (4months–17years)	O	MCL 0.5 mg/kg/day (3 doses) GAV 10–20 ml qid PL tid (1 day)	SD	24 h pH monitoring: MCL = GAV = PL = B	ND	IV administration
[61]	42 3.2 months (0.5–13months)	O	MCL 0.1–0.2–0.3 mg/kg tid iv, 1 day	5% dex CF	24 h pH monitoring: • fed 5% dex: MCL(0.3) > MCL(0.1–0.2) = B • fed CF: MCL = B	ND	Supine in infant seat (30°) Acute dystonic reaction (n = 1)
[62]	9 6 months (4–12 months)	O	MCL 1 mg/kg iv, 1day	5% glu	Dilution technique (GE): MCL > B	ND	IV administration Infants failing to improve with postural (30° prone) or dietary changes. Solid food started with treatment; 30° prone recommended Side effects (n = 5; drowsiness, irritability, oculogyric crisis)
[75]	32 5 months (0.6months–3years)	O	MCL 5 mg/kg/day (4 doses) CO (n = 9) (4 weeks)	SF	ND	Regurgitation: MCL > CO	IV administration (GOR, GE) Infants kept 45° prone during sleep Exacerbation of symptoms and marked irritability with MCL (n = 3) Single, iv administration Supine position
[76]	28 9 months (8)	O (DB, PA)	MCL 0.125 mg/kg qid (iv, manometry and pH monitoring) (po, 6 months in DB trial)	FT	• Manometry (LOSP): MCL > B • 24 h pH monitoring: MCL = B	Regurgitation (n = 8): MCL = PLA	Feed thickening and postural treatment kept constant GOR variables remained abnormal in infants
[97]	24 (1–18months)	DB, PA	MCL 0.1–0.2–0.4 mg/kg bm PLA bm (iv, single dose)	CF	5 h pH monitoring (1 hr after feeding): MCL = PLA • Scintigraphy (supine, 1-h after meal): MCL = PLA • 18–24 h pH monitoring: MCL > or = PLA	ND	
[121]	30 < 1year (1–9 months)	DB, PA	MCL 0.1 mg/kg qid PLA qid (1 week)	CF ^a		Regurgitation: MCL = PLA Weight gain: MCL = PLA	

^a Prior therapeutic measures continued (positional and / or dietary)^b Outcome: ' > ' = better than, ' = worse than, ' = ' = unchanged, referring to the main/all parameters evaluated in paper; exceptions for single parameters are mentioned separately. Symptoms: if not specified, clinical assessment including regurgitation and/or vomiting.

(O) open, DB double blind, PA parallel, XO cross-over will wash out period CIS cisapride, PLA placebo, MCL metoclopramide, DO domperidone, GAV Gaviscon, AA antacid, FT feed thickener, B baseline CO controls; bm before meals/each feeding; qid after meals. DM dietary measures, SD standard diet, dex dextrose, CF customary formula, SF solid food started if not yet done so, PN parenteral nutrition)

Table 3 Effects of domperidone (DO) on GORD in infants (for abbreviations: see Table 2).

Reference	No	Age	Design	Treatment	DM	GOR and GE parameters	Clinical assessments	Comments
[5]	17	2–3.6 years (5 months–11.5 years)	DB, PA	DO 0.6 mg/kg qid PLA qid (4 weeks)	CF	<ul style="list-style-type: none"> 8–12 h pH monitoring: DO > or = PL Scintigraphy (GE): DO = PL 	Symptoms: DO = PL	Older children non-responsive to non-pharmacological therapy
[25]	32	4–6 years (2 months–10 years)	DB, PA	DO 0.3–0.6 mg/kg tid PLA tid (2–4 weeks)	FT	ND	Vomiting: DO > PLA (week 4) Regurgitation: DO > PL Global response: DO > PL	Older children
[20]	80	4.6 months (1–18 months)	O, PA	DO 0.3 mg/kg bm + PLA afm DO bm + AA 1 + 2 h afm DO bm + GAV afm PLA bm + afm (8 weeks)	FT	24 h pH monitoring: <ul style="list-style-type: none"> DO + AA > DO + GAV = DO = PLA except longest episode: DO + AA = DO + GAV = DO > PLA 	Histological oesophagitis: DO + AA > DO + GAV = DO = PLA No erosive oesophagitis	
[42]	47	6–9 months (3 weeks–8 years)	DB, PA	DO 0.3 mg/kg tid MCL 0.3 mg/kg tid PLA tid (2 weeks)	FT	ND	Nausea: DO > MCL = PL Vomiting: DO > MCL > PLA Global response: DO = MCL > PL	
[45]	18	4.9 years (1 months–12 years)	O	DO 2 mg/kg/day (3 months)	n.d.	24 h pH monitoring: DO = B <ul style="list-style-type: none"> except % time at night: DO > B 	Respiratory symptoms: DO > B	Mostly older children with GOR-associated respiratory disease
[53]	15	7.9 months (3–13 months)	O	DO 0.3–0.6 mg/kg tid (im, single, manometry) (po, 6 weeks)	FT	<ul style="list-style-type: none"> Manometry (LOSP, amplitude contractions): DO = B 3 h pH monitoring: DO = or > B Scintigraphy (GE): DO = B 	Spitting, vomiting, coughing: DO > B Weight gain: DO = B	'Vomiting' or GOR-associated problems
[63]	28	15 months (1 months–10 years)	O	DO 0.3 mg/kg tid + AA afm DO 0.3 mg/kg tid + GAV afm	FT	24 h pH monitoring: <ul style="list-style-type: none"> DO + AA > B DO + GAV²B 	Regurgitation: DO + AA = DO + GAV Overall: DO + AA > DO + GA	
[127]	24	(4–12 weeks)	O	DO 0.8–1 mg/kg/day bm + GAV 3–5 ml afm (10–14 days)	FT	24 h pH monitoring: <ul style="list-style-type: none"> DO + GAV > B normalization: $n = 17$ 	Regurgitation: DO + GAV > B	

Table 4 Effects of cisapride (CIS) on GORD in infants (for legend and abbreviations: see Table 2)

Reference	No	Age	Design	Treatment	DM	GOR and GE parameters	Clinical assessments	Comments
[12]	7 [†]	ND	O	CIS 0.2 mg/kg tid (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]
	15	ND	O	CIS 0.2 mg/kg tid (3 weeks)	ND	24 h pH monitoring: CIS > B	ND	
	34	(4months–2years)	O	CIS 0.2 mg/kg tid (3 months)	ND	24 h pH monitoring: CIS > B	Symptoms: CIS > B Endoscopy/histology: CIS > B	
[19]	20	8months (3–13months)	O	CIS 0.33 mg/kg tid (8 weeks)		• 24 h pH monitoring: CIS > B • Ultrasound (GE): CIS > B	ND	Compared to CO-group without GOR: B < CO; CIS = CO
[21]	30	(3months–5years)	DB, PA	CIS 0.2 mg/kg bid PLA (2–4 weeks)	ND	24 h pH monitoring: CIS > PLA	Symptoms: CIS > PLA Respiratory symptoms: CIS > PLA	
[30]	17	24.5 months (2.5–47months)	DB, PA	CIS 0.33 mg/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 • Manometry (LOSP, peristalsis): CIS > PLA	Symptoms: CIS > PLA Histology: CIS > B; PLA = B Endoscopy: CIS > PLA	Infants with peptic oesophagitis (normal basal LES pressure)
[33]	14	15.7 (2–38months)	DB, PA	CIS 0.15 mg/kg PLA (iv, single)	FT	• Manometry (LOSP, peristalsis): CIS > PLA	ND	Single, iv administration
	24		O, PA	CIS 0.2 mg/kg tid CO (4–6 weeks)	FT	24hr H monitoring: CIS > CO • normalization: CIS > CO	Symptoms: CIS > CO	Both groups receiving postural and dietary treatment
[38]	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
[39]	42	2.6 years (12 days–12years)	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
[47]	22	7 months (2–44 months)	DB, PA	CIS 0.2 mg/kg qid + GAV CIM 5 mg/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
[52]	50	(2–18months)	O, PA	CIS 0.2 mg/kg qid (–FT) GAV (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
[84]	25	16.2 months (1months–7years)	O	CIS 0.33 mg/kg tid (8 weeks)	ND	24 h pH monitoring: CIS > B	Symptoms: CIS > B	

[80]	38	26 months (2weeks-7years)	O	CIS 0.3 mg/kg/bm (6 months)	ND	Scintigraphy: CIS > B • 24 h pH monitoring: CIS > B ND	Respiratory symptoms: CIS > B Symptoms: CIS > MCL Overall response: CIS > MCL (NS)	Infants with GOR-related respiratory disease Adverse events: n = 4 with CIS and n = 9 with MCL (diarrhoea, irritability) Acute study
[87]	35	1-36 months	DB, PA	CIS 0.2 mg/kg/bm MCL 0.2 mg/kg/bm (10 weeks)	ND			
[103]	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
[104]	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, No. episodes: CIS = MCL > B	ND	CIS > MCL in all positions (erect, supine and prone)
[105]	30	10 months	O	CIS 1 mg/kg/day (in 3 doses)	ND	28-h pH monitoring: CIS > B (erect, supine, prone)	Symptoms: CIS > B	
[107]	14	29 months (4months-11years)	DB, PA	CIS 0.3+ 0.15 mg/kg/4 hrs PLA (1 day)	ND	16-h pH monitoring: CIS > PLA (except No. episodes: CIS = PLA)	ND	Older children with GOR-related chronic respiratory symptoms
[108]	19	7 years (3months-10years)	O	CIS 0.3 mg/kg tid (4 weeks)	ND	24 h pH monitoring: CIS > B (except No. of episodes: CIS = BA)	ND	Older children with GOR-related chronic respiratory symptoms
[130]	22	(4-22weeks)	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 Symptoms: CIS > PLA (NS)	Infants with irregular sleep pattern Simultaneous positional treatment (30° prone) Both groups placed on positional and dietary treatment
[131]	29	(2-4months)	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	Global response: CIS > B	
[134]	69	(5-12months)	O	CIS 0.15-0.3 mg tid (4 weeks)	CF ^a	ND	Global response: CIS > B	
	23		DB, PA	CIS 0.15 mg tid PLA (2-4 weeks)	CF ^a	ND	Global response: CIS > PLA Symptoms: CIS > PLA	
	45		DB, PA	CIS 0.2-0.3 mg tid PLA (2-4 weeks)	CF ^a	ND	Global response: CIS > PLA Symptoms: • at 1 week: CIS (0.2 mg) > PLA • at 2 weeks: CIS (0.1 mg) > PLA	

^aPrior therapeutic measures continued (positional and for dietary)

Cisapride also improves GOR-related manifestations, such as a disturbed and irregular sleep pattern [38, 130], coughing, wheezing, restlessness at night and belching in infants with GOR-related respiratory dysfunction [130] or chronic bronchopulmonary disease [39, 80, 107, 108]. As indicated by a few observations in infants [15, 30] and several studies in adults [6, 101], the drug can heal oesophagitis. When given in monotherapy, it is as effective as the combination of Gaviscon (an alginate-antacid) and a milk thickener (Carobel) [52]. It is at least as effective as cimetidine in reducing oesophageal acid exposure time (both given in combination with Gaviscon) [47].

In general, cisapride is well tolerated. The most common adverse events at therapeutic doses (0.2 mg/kg, 3–4 times daily, maximum 0.8 mg/kg/day) are transient diarrhoea and colic (in about 2%). Serious adverse events in infants have not been reported in clinical trials. Package labelling indicates isolated reports of more serious adverse events: notably extrapyramidal reactions, seizures in epileptic patients, cholestasis in very preterm infants [50] (not confirmed by others [65]), and cardiac interactions with 'azole antifungals' (ketokonazole, fluconazole, itraconazole, miconazole), erythromycin, claritromycin and troleandomycin [142]. All these medications are metabolized by the cytochrome P-450 3A4 isozyme. The cardiac effects appear to be associated with high plasma cisapride levels as recently illustrated by an adult case [11] and by two cases of cisapride poisoning [141]. A study of therapeutic doses in newborns showed no adverse effects on cardiac function [23], although a long QT interval induced by cisapride in a 2-month-old infant has been reported [77]. Cisapride is not more expensive than alginate-antacid preparations or milk-thickening agents.

From this follows the next recommendation: cisapride is recommended when other measures are insufficient or in regurgitating breast-fed infants, when therapy is indicated (Treatment Phase 2).

Postural treatment

Despite gravity, the upright seated position leads to significantly more and larger reflux episodes than the simple prone [99, 126] and 30° elevated prone position [83, 90, 91], both when the infant is awake or asleep [83]. This is likely due to increased abdominal or intragastric pressure. The seated position is also associated with less sleeping time and more crying than the prone position [89]. This position is not to be recommended in infants.

The supine (lying on back) and lateral positions (lying on left or right side) usually result in intermediate pH-metric GOR values and do not appear to influence GOR [7, 83, 126].

The prone elevated position, with the baby fixed prone (face down) in a cot at an angle of 30° (head elevated), has been proven to be more effective in reducing the incidence of GOR than in comparison with

the upright, supine or lateral position [83, 90, 91, 126]. This position reduces abdominal wall tension, elevates the gastro-oesophageal junction [90] and increases the effect of gravity. One study has shown that GOR variables normalize in 25% of infants [127].

However, there is now ample evidence that the prone sleeping position is a risk factor in sudden infant death (SID), independent of overheating, smoking or way of feeding [98, 139]. Although a direct causal relationship between the prone elevated position and SID has not been demonstrated [73], and only a small number of children at risk for SID may suffer from GOR (and vice versa), it has become difficult to recommend positional treatment as a 'first-line' measure in the regurgitating infant for ethical, legal and psychological reasons. Parents may not accept the idea that exactly the position told inappropriate for their (healthy) baby, will be appropriate for their sick baby.

Conflicting opinions and data are published regarding the role of GOR in apparent life-threatening events and, obstructive and central apnoea, with or without bradycardia [3, 40, 67, 68, 75, 78, 94–96, 100, 124, 136]. Most data, although there is no consensus, suggest that GOR episodes need to be acid to be related to obstructive apnoea. Central apnoea does not occur when the reflux contains a saline solution or tracheal fluid. Reflex bradycardia is reported during feeding and reflux. However, these associations are reported in a limited number of infants and are not considered as relevant if large groups of patients are studied. The absence of scientific data regarding the association between apnoea and GOR in preterm and term infants makes it hazardous to recommend a given approach in this particular population. It is obvious that further studies in this field are needed.

From this results the following recommendation: positional treatment remains, in view of its efficacy, as a valid 'adjuvant' treatment in patients not responding to other therapeutic approaches or beyond the age of SID risk (Treatment Phase 3).

Antacids, H₂-receptor antagonists and proton pump inhibitors

Antacids, alginate-antacid preparations, H₂-receptor antagonists and proton pump inhibitors attempt to neutralise or reduce the gastric acidity, rather than acting on the primary causes of regurgitation in infants [1].

Experience with antacids (Gelusil, Maalox, Mylanta, Muthesa, etc) is limited in infants [132]. Their effects on regurgitation are not well documented. Intensive antacid treatment with large quantities has been shown as effective as cimetidine in reducing pH-metric parameters and in healing oesophagitis [28]. However, their efficacy in buffering gastric acidity in infants is strongly influenced by the time of administration [118] and requires multiple administrations. Side-effects include diarrhoea

with magnesium-rich preparations [28], and excessive absorption of aluminium in infants [123].

Alginate-antacids (Gaviscon and Algicon) form a viscous fluid with surface-active properties, floating as a raft on the surface of the gastric contents, and hence form an artificial protective barrier against reflux. Their efficacy as a monotherapy for regurgitation is not convincing [13, 137]. The reported effects of Gaviscon on pH-metric GOR variables are contradictory [13, 49], even in combination with prokinetics [20, 127]. They are less effective in healing oesophagitis than H₂-receptor antagonists [88]. Gaviscon contains a considerable amount of sodium carbonate, so that its administration may increase the sodium content of the feeds to an undesirable degree, especially in preterm infants (1 g of Gaviscon contains 46 mg of sodium and the suspension contains twice this amount) [72]. Algicon, having a better taste than Gaviscon, has a lower sodium load, but a higher aluminium content. Occasional formation of large bezoar-like masses of agglutinated intragastric material has been reported in association with Gaviscon [56].

Dimethicone (Polysilon, Dimethicon, Polysilon gel) is used in some regions for regurgitation. Although often classified as an antacid, it acts more as a feed thickener, as it contains more than 50% of bean gum and has hardly any acid neutralising properties. There are no reliable studies demonstrating its efficacy in the treatment of GOR in infants [132].

H₂-receptor antagonists, such as cimetidine (Tagamet), ranitidine (Zantac) and famotidine (Pepcid), are effective in healing reflux oesophagitis in infants [28, 32, 88]. High-dose ranitidine appears to be comparable to omeprazole in this respect [34]. The experience with proton pump inhibitors (omeprazole, lansoprazole) is limited. Excellent results have been reported in refractory GORD in older children at doses of 0.7 to 2.0 mg/

kg per day [1, 34, 54, 55, 69, 74], while pH-metric improvement was not seen at the normal therapeutic dose in young infants [54, 55, 81]. The most frequent side-effects of H₂-receptor antagonists and proton pump inhibitors, are fatigue, dizziness, headache, dyspepsia, nausea, abdominal pain, flatulence, constipation and diarrhoea. Their incidence is 1%–6%. Serious adverse effects of omeprazole, such as impaired liver function, haemolytic anaemia, peripheral neuropathia, gynaecomastia, skin rash, subacute myopathy, and excessive urinary sodium loss have been reported in isolated cases [27, 41, 81, 82] or are mentioned in the package insert. The safety of its long-term administration in children is still a matter of debate. Hypergastrinaemia occurs in nearly all patients treated with omeprazole [55], causing hyperplasia and pseudohypertrophy of the parietal cells as recently shown in 93% of adult patients on long-term omeprazole [70].

From this results the next recommendation: anti-acid agents such as antacids, alginate-antacids, H₂-receptor blockers and proton pump inhibitors should be reserved for cases of complicated reflux which persist after conservative measures plus a prokinetic, or in case of (severe) oesophagitis, such as in neurologically impaired children, children with repaired oesophageal atresia and those with severe chronic lung disease such as cystic fibrosis (Treatment Phase 4).

Conclusions and recommendations

The number of placebo-controlled studies is rather limited, which probably reflects the reluctance of parents to participate. Few followup studies are available documenting the long-term outcome of treatment of regurgitation and GORD. A practical dilemma presents

Table 5 Schematic therapeutic approach for regurgitation in infants

Recommended by ESPGAN 1993	Recommended by Working Party 1995
Phase 1 1.A. Parental reassurance 1.B. Position: prone reversed (head elevated) Trendelenburg position (30°) 1.C. Milk-thickening agents 1.D. Dietary recommendations (increased frequency/small volume) ^a 1.E. Alginic acid (± antacid) ^a	Phase 1 1.A. Parental reassurance 1.B. Milk-thickening agents
Phase 2 Prokinetics: cisapride (If symptoms resistant to cisapride: domperidone, metoclopramide)	Phase 2 Prokinetics: cisapride (If symptoms resistant to cisapride: domperidone, metoclopramide)
Phase 3 3.A. H ₂ -blockers: cimetidine, ranitidine etc. 3.B. Proton pump inhibitors: omeprazole	Phase 3: Adjuvant therapy in patients resistant to phase 1 and 2 Position: prone reversed (head elevated) Trendelenburg position (30°)
Phase 4 Surgery	Phase 4 3.A. H ₂ -blockers: cimetidine, ranitidine etc. 3.B. Proton pump inhibitors: omeprazole
	Phase 5 Surgery

^aThe use of these measures for regurgitation in infants is not supported by clinical studies in the published literature and, therefore, no longer recommended.

in the initiation of treatment of regurgitation. Scarce reports suggest that early effective treatment of infant regurgitation [10] or GORD [16, 18, 66] improves the prognosis.

The guidelines for the treatment of regurgitation and GORD are listed in Table 5. Management should always start with adequate parental counselling and reassurance, explaining the physiological nature of regurgitation and spontaneous resolution in the vast majority of infants. Milk thickeners can be used only if infants are bottle-fed. They frequently result in a decrease of the number and severity of regurgitations. However, objective evidence for an unequivocal effect on GOR or GORD is missing: (occult) GOR may persist in a subset of infants, likely due a negative effect of high food volumes and osmolality of milk thickeners on gastro-oesophageal motility, gastric emptying and transient relaxations. If pharmacological treatment is needed, prokinetics are indicated. Cisapride has the most consistent effect on GOR parameters and the best safety profile. Positional treatment in the prone-elevated (30°) position is recommended as an adjuvant therapeutic intervention. H₂-receptor antagonists and proton pump inhibitors are reserved for cases with oesophagitis or persisting GORD. Surgery [1] is to be considered in cases of persistent, complicated GORD.

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