SPECIAL ARTICLE

CURRENT CONCEPTS IN THE MANAGEMENT OF GASTRO-OESOPHAGEAL REFLUX IN INFANTS

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Pathological gastro-oesophageal reflux (GOR) is primarily a disorder of gastro-intestinal (foregut) motility characterised by episodes of inappropriate relaxation of the lower oesophageal sphincter.[1-3] However, the disorder may involve a complex mix of foregut dysfunction including impaired oesophageal clearance, gastro-oesophageal reflux, antropyloric inco-ordination and delay in gastric emptying. Individually or together, depending on the pattern and severity, these may have a wide spectrum of adverse effects.

Normal infants often regurgitate recently ingested gastric contents during the first hour after feeding.[4] It remains difficult to delineate the boundary between physiological reflux, causing uncomplicated positing, and pathological reflux (gastro-oesophageal reflux disease — GORD), requiring active therapy to prevent morbidity and mortality. Physicians are often called upon to decide on the need for appropriate investigations and management in these children. Because of the great propensity for physiological reflux to resolve spontaneously within the first 10 - 12 months of life, physicians have customarily been cautious in evaluating and treating such infants in the absence of complications.

Signs and symptoms of pathological GOR include persistent vomiting with failure to thrive; objective evidence of reflux oesophagitis; reflux leading to nasopharyngeal irritation and recurrent otitis media; or reflux-associated respiratory disease. The latter may vary in presentation from an asthma-like syndrome to recurrent migratory pneumonia, chronic obstructive airways disease and 'death attacks' resulting from reflux-associated laryngeal spasm and vagal stimulation.[5] In addition acid reflux may stimulate reactive airways via neurological pathways, thus exacerbating the asthma diathesis.[6]

Ontogenetically the gastro-intestinal tract appears at approximately the 4th week of gestation as a hollow tubular structure, and at 13 weeks the oesophageal muscular layer, myenteric plexus and regulatory peptides are present. Swallowing has been documented to commence in the fetus between 11 and 17 weeks' gestation, and the lower oesophageal sphincter (LOS)'s high-pressure zone has been identified from 33 weeks.[7] Despite the oesophagus being structurally and functionally intact from this early age, synchronous peristaltic activity is present in less than 60% of newborns, and approximately 40% of the peristaltic waves are incomplete or retrograde.[8]

Pathological reflux is predominantly linked to inappropriate transient relaxation of the LOS, or relaxation that occurs in the absence of a peristaltic sequence in the body of the oesophagus. These findings have contributed to a better understanding of the pathophysiology and complexity of gastro-oesophageal disease.[1-3]

The European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) published guidelines in 1993 for the treatment of GOR in infants (Table I).[9] We believe these guidelines require scrutiny, as in our experience some are impractical and may be inappropriate. Particularly controversial are the roles of positional therapy, feed thickeners, antacids, and the medical treatment of persistent occult gastro-oesophageal reflux in older children. The 30° prone reversed Trendelenburg position may not be indicated in children under 6 months of age. Feed thickeners such as cereals or rice are rapidly hydrolysed in the stomach and sodium alginate antacids may cause sodium overload in premature babies (approximately 8 mmol sodium/day at a dose of $^1/_4$ sachet Infant Gaviscon per feed). Experience with H_2-blockers is very limited in infants, and these drugs may cause rebound nocturnal acid secretion.[10-12] Persistence with ineffective long-term medical therapy may unnecessarily place the infant at risk.

Clinically paediatric GOR can be divided into two broad categories, cases with predisposing disease and those without.

Table I. Schematic therapeutic approach to GOR

Phase 1
- 1A. Position: prone reversed (head elevated) Trendelenburg position (30°)
- 1B. Milk-thickening agents
- 1C. Dietary recommendations: increased frequency, small volume
- 1D. Alginic acid (± antacid)

Phase 2
- Prokinetics: cisapride (if symptoms are resistant to cisapride: domperidone, metoclopramide, alizapride, bethanechol)

Phase 3
- 3A. H_2-blockers: cimetidine, ranitidine, famotidine
- 3B. 'Experimental' treatment: sucralphate, omeprazole, misoprostol

Phase 4
- Surgery (Nissan fundoplication, Thal fundoplication, anterior gastropexy of Boerema, etc.)

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The latter category comprises two types. The 'infantile' refluxer becomes symptomatic in the first few months of life, with spontaneous resolution occurring in most cases.[13] If therapy is started early, 90% will have resolved by 10 - 12 months of age.[8] The second type is the so-called 'childhood' refluxer, in whom either infantile reflux persists, or the condition reappears when the child is older. The intensity of symptoms fluctuates in the latter group, but in at least 50% of cases the condition does not resolve and will require intermittent ongoing or definitive therapy.[8]

The first category comprises GOR with predisposing or associated disease, neurological impairment being the most important. Other conditions occurring with equal frequency are genetic and chromosomal disorders; intrathoracic gastric herniation; reflux after oesophageal atresia repair, usually with gastrostomy; reflux following caustic stricture of the oesophagus; and established lung disease.

The most difficult of these patients, both to assess and to treat, are those with respiratory disease. In some the respiratory disease comes first, reflux exacerbating and perpetuating the lung disease; in others it is the reflux, with recurrent aspiration or stimulation via neural pathways, that precipitates and maintains the respiratory disease. It is difficult to prove a diagnosis of reflux-induced asthma, although pH studies often show a close correlation between GOR with coughing and acute episodes of wheezing in asthmatic children.[14] Treatment of GOR in asthmatic children with prokinetic agents has been shown to improve the incidence and severity of the disease.[15]

The prevalence of pathological reflux among low-birth-weight infants is 3 - 10%, with symptoms of irritability, apnoea, bradycardia, vomiting and deterioration of bronchopulmonary disease.[8] The overall prevalence among infants under 1 year of age is difficult to establish. In the USA approximately 7% of infants are brought to a medical practitioner for GOR; of these 80% will resolve on minimal therapy and without investigations, 12% will be investigated and treated successfully with conservative measures, and 8% will undergo antireflux surgery.[8,13] The prevalence of pathological reflux in children over 1 year of age is unknown. Each year some 80 children are referred to the surgical department at Red Cross War Memorial Children's Hospital for consideration for surgical management.

Diagnostic studies

In the work-up of suspected GOR, it is important to avoid inappropriate investigations. The diagnostic evaluation must include a complete history and physical examination. Orenstein *et al.*[16] have developed a questionnaire for parents with a positive predictive value of 100%, thereby improving the efficiency and reliability of history taking.

A *barium meal* is a prerequisite in the symptomatic child for the anatomical assessment of the foregut and identification of possible associated structural abnormalities and disorders of peristaltic function which may cause vomiting. *Twenty-four hour pH monitoring* is only indicated in patients with nonspecific or intermittent symptoms to confirm the presence of GOR and to quantitate its severity. Monitoring of pH may also be helpful in the evaluation of the effect of posture and specific treatment on reflux.[5] The correlation between oesophageal pH monitoring and respiratory disease may be improved by the use of a dual pH recording probe in the upper and lower oesophagus as well as by monitoring reflux episodes during sleep periods.[17,18] *Oesophageal manometry* is difficult to perform in infants and reference values have not been standardised.[7] However, a lower oesophageal sphincter pressure of less than 10 mmHg usually correlates with significant reflux. Manometry can be combined with motility studies using a continuously perfused lumen catheter attached to a multichannel recorder. About one-third of all patients with GOR have some oesophageal dysmotility.[19]

Technetium scintigraphy provides a good functional assessment of physiological oesophageal motor function and transit time, as well as gastric emptying.[20] Quantification of reflux episodes and documentation of pulmonary aspiration are of less value as scanning is of short duration, being immediately postprandial and performed in an infant restrained in the supine position.[20] *Ultrasonography* is a new and non-invasive method to determine the presence of reflux and associated hiatus hernia under physiological circumstances. It has been validated against existing methods, and may play a major role in assessing pathological reflux immediately after meals, and elucidating symptoms such as irritability, unusual posturing, chronic cough, wheezing and chronic respiratory tract infection.[21]

Endoscopy with biopsy is most valuable for the diagnosis of organic oesophageal disease. Visual evidence of oesophagitis is present in the minority (about 30%) of children with GOR, but its absence does not exclude pathological reflux, which may only be detected histologically.[5,22] Barrett's oesophagus can only be diagnosed on specific histological findings, and although rare it may be important in the assessment of children with prolonged reflux disease, especially those with neurological impairment and chronic lung disease, and following atresia repair.[23]

Medical treatment

Treatment of GOR is directed at the various identified pathophysiological components. The majority of infants can be successfully treated conservatively while awaiting improvement as spontaneous maturation of the physiological antireflux mechanisms occurs. As immaturity of foregut function predisposes premature infants to pathological reflux disease, treatment is more effective in this group of patients.[8] The vast majority will outgrow the condition, especially if aggressive medical therapy is initiated early, good compliance is assured and adequate nutrition is maintained.

Neurologically impaired children have a considerably higher incidence of GOR due to a predominant supine position, scoliosis, diaphragmatic flaccidity, abdominal spasticity, swallowing difficulties, general body weakness, and muscular inco-ordination.[24] Among these children therapy and compliance remain difficult, and should be adapted to individual requirements. Antireflux surgery may be combined with a feeding gastrostomy.

Reassurance of parents forms an integral component of management. Babies who are thriving and whose parents' main complaint is soiling of clothes from regurgitant vomits ('spitting') require no investigation other than a full medical history and examination. Modification of the feed preparations and the volume per feed, as well as of the handling of the baby postprandially, may improve many of the symptoms. Parents should also be asked to avoid tight clothing, feeding just before bedtime, and high-osmolality feeds.[25] Symptoms which should prompt more extensive investigation include inconsolable crying and irritability, feeding or sleeping difficulties, and persistent vomiting.[13] However, there must be a clear understanding that conservative measures should not be continued over a protracted period without first excluding anatomical abnormalities by radiological investigation with a contrast swallow and meal.

Posture

The prone elevated position (anti-Trendelenburg) at 30° inclination has been shown to reduce critical components of GOR. The frequency and duration of reflux episodes and associated pulmonary aspiration are decreased, energy expenditure is diminished and gastric emptying is improved.[26] Positional therapy aimed at maintaining an erect posture is difficult to maintain, especially in infants who tend to assume a slumped or supine posture. The flat-prone position does not improve oesophageal clearance as assessed on pH-metry and has been associated with an increased risk of sudden infant death syndrome (SIDS).[27] The therapeutic effect of varying degrees of the anti-Trendelenburg position — 5°, 10° or 20° — or the right lateral prone position has not been evaluated. Despite these observations the prone 30° head-up position is recommended for a child with severe reflux in the absence of any previous life-threatening respiratory episodes (apnoea, bradycardia, aspiration), or in older infants (> 6 months, where the SIDS risk is decreased[27]) who are not responding to other therapeutic procedures. The left lateral position is an alternative to the prone position in young infants.[28] Appropriate positional therapy can be further directed by analysis of the pH study, where wide differences in incidence and severity of reflux may be documented in different positions in a single patient.[29]

Dietary measures

Feed thickeners have been shown to improve sleep and may provide a 'feeling of well-being' in a significant number of infants, as well as reducing the number and volume of reflux episodes, although the results are unpredictable.[5,30] However, they fail to improve oesophageal acid clearance.[30] Feeds of a larger volume or a higher osmolality may increase the rate of LOS phasic relaxation, which is important in the pathogenesis of GOR.[24]

A commonly used feed thickener is one tablespoon (15 ml) of dry rice cereal added to each 25 ml of formula. This adds additional calories, decreases vomiting and crying time and increases sleep time during the postprandial period.[8] However, it delays gastric emptying and is difficult to use in breast-fed babies.[8] Constipation, a common side-effect, is best treated with magnesium-containing antacids. Carob seed flower with calcium lactate (Nestargel, 1 g/100 ml feed) and sodium alginate (Gaviscon, 1 - 2 g/120 - 240 ml feed) may also be utilised as feed thickeners, although their efficacy appears to be inconsistent.[31,32] These agents are expensive and may be a significant financial burden on the parents. Cornflour (Maizena 5 - 10 g/200 ml feed) as an alternative feed thickener has been shown to be effective in a pilot study at our hospital, is cheap and is in our opinion the first choice.[33]

A feeding regimen of small frequent feeds may not provide adequate nutrition, especially to the hungry and agitated child, and may interfere with sleeping patterns and other social activities. During sleep, the LOS pressure usually increases and transient lower oesophageal sphincter relaxation decreases.[8] However, oesophageal acid clearance is reduced by a factor of 5 - 6 and salivary flow decreases from approximately 150 ml/h to 1 ml/h resulting in the sleeping child losing the ability to neutralise and clear refluxed acid.[8] In our experience compliance with a frequent-feeding regimen is poor and the benefits are questionable, especially during the first year of rapid growth. It is imperative to maintain the nutritional requirements of the infant.

Prokinetic agents

Pharmacological agents are used in conjunction with other conservative measures once reflux disease has been documented by special investigations. These agents collectively improve oesophageal peristalsis, increase the LOS pressure and promote gastric emptying. Four prokinetic agents have been used for infant GOR (bethanecol, domperidone, metoclopramide and cisapride) and work either by blocking dopamine receptors or by potentiating the effect of acetylcholine.[29]

The cholinergic action of bethanecol increases LOS pressure and oesophageal motor function, but systemic parasympathetic activity limits its implication as a first-line drug. Domperidone

(Motilium), a dopamine receptor antagonist, reduces the frequency of reflux but has no beneficial effect on acid clearance and is not commonly used.[29] Metoclopramide (Maxolon), an antidopaminergic and cholinomimetic drug, is effective in reflux disease but psychotrophic, extrapyramidal and dystonic side-effects, which are idiosyncratic, limit its long-term use in children.[34] The narrow therapeutic margin may result in a considerable number of infants being irritable and somnolent on a dosage as low as 0.4 mg/kg/d, and it is therefore not recommended for infants younger than 1 year of age.[29]

Cisapride (Prepulsid) has specific pharmacological activities directed at those factors implicated in the pathogenesis of GOR. It is the only prokinetic agent with documented improvement, in pH meter studies, in children with GOR.[29,35] It has been safe and effective in our experience and we believe should be the first-line prokinetic agent for GOR. Optimal effects are seen when cisapride is combined with dietary and postural methods. It has minimal side-effects, viz. colic and transient diarrhoea, but may take up to 1 week to exert its full effect.[29] New pharmacokinetic data in premature infants have revealed that plasma concentrations of cisapride, even when the drug is given at the prescribed dosage, are extremely variable and unpredictable. Cisapride may reach levels that put these premature infants at risk of QT prolongation, which may be associated with serious cardiac arrhythmias. In this patient population electrolyte disturbances such as hypokalaemia should be corrected before the administration of cisapride. The concomitant use of other drugs metabolised via the P450 enzyme system (ketoconazole, itraconazole, miconazole, troleandomycin, fluconazole, erythromycin, clarithromycin, nefazodone and ritonavir) may result in elevated plasma levels of cisapride.[36] The recommended oral dose is 0.2 mg/kg given 6 - 8 hourly, 20 minutes before a feed.[35,36]

Antacids

Antacids, H_2-receptor antagonists and proton pump inhibitors can be used both to reduce gastric acidity and for the treatment of oesophagitis. They do not influence the primary cause of reflux disease in infants, but may improve oesophagitis, reduce incompetence of the LOS and pyloric spasm, and improve the oesophageal dysmotility associated with acid reflux. Magnesium- or aluminium-containing antacids at a dose of 1 ml/kg/d in 4 divided doses may be useful in neutralising gastric acid. Side-effects from overdose may rarely occur, especially in low-birth-weight infants. Similarly, the benefit of alginate antacid preparations in improving GOR is debatable,[37] and these drugs can increase the sodium content of the feed to an undesirable degree, especially in premature infants. Beneficial results were observed in our own observations with Gaviscon and Nestargel.

Acid secretion-inhibiting agents such as the H_2-receptor antagonists and proton pump inhibitors are currently the antacid therapies of choice.[38,39] They are effective in healing mucosal lesions. Dosing schedules for infants have not been determined and these drugs are therefore used empirically. Omeprazole at a dose of 40 mg/1.73 m^2 body surface area per day or 0.7 mg/kg/d as a divided twice-daily dose improved symptoms, healed oesophagitis, and reduced intragastric acidity.[38-40] For effective suppression of gastric acidity high-dose ranitidine (20 mg/kg/d) could be used as an alternative.[38] However, omeprazole has been shown to be more effective than ranitidine, with improved symptomatic relief and rapid healing of ulcerative oesophagitis.[38] The tendency for recurrence of symptoms in up to 60% of children after withdrawal of these drugs indicates the need for long-term maintenance therapy.[39] The implications of the long-term use of these drugs on growing children are unknown and concern about the negative side-effects of hypo-acidity and hypergastrinaemia (30%) have been raised.[39] Their use in infants should therefore be restricted to severe or refractory oesophagitis, and for a defined time period. Titration of the omeprazole dosage against repeated 24-hour intragastric pH metry could limit excessive administration.

Nasojejunal tube feeding

Duodenal or jejunal feeding with a fine-bore nasal tube has been proposed as an alternative to surgery. It has been used in premature and full-term infants, where age-related resolution is anticipated. It is also useful for improving nutritional and respiratory status prior to surgery in children with uncontrollable symptoms, severe pulmonary complications from aspiration, persistent vomiting and failure to thrive. If this course of therapy is employed, it is important that antireflux therapy be continued together with the addition of mycostatin to prevent fungal infection.

Financial implications

The financial implications of an extended course of medical therapy should not be underestimated. The cost of therapy for a 10 kg child on cisapride, omeprazole and antacid is approximately R650 per month at 1997 prices.

Surgery

The role of surgery for GOR in infancy is more clearly defined than in adults. Surgery offers a highly effective cure for a problem which, if left untreated, may cause long-term morbidity and even mortality. There is no justification for persisting with ineffective medical therapy if the condition may result in chronic illness, multiple hospitalisations, ongoing pulmonary disease and stunted growth.

In cases of proven GORD indications for surgical intervention are failure of adequate medical therapy or poor compliance; persistent failure to thrive; recurrent aspiration syndrome; apnoeic spells or near-death attacks; ulcerative oesophagitis/Barrett's oesophagus; oesophageal stricture; anatomical abnormality, e.g. rolling hiatus hernia and neurological impairment with poor feeding, vomiting or rumination.[40]

In children with chronic respiratory tract infections and concomitant GOR it remains very difficult to prove a cause-and-effect relationship. Likewise, it is imperative to exclude laryngopharyngeal inco-ordination leading to laryngeal incompetence and aspiration. Common causes are post-herpetic dysfunction, cerebral palsy and anatomical abnormalities, e.g. laryngeal cleft. Clearly, surgery in these situations is inappropriate.

Surgical correction should include four main elements — mobilisation and maintenance of 2 - 3 cm of intra-abdominal oesophagus; posterior crural repair; re-establishment of the oesophagogastric angle of His; and an effective antireflux barrier. Some have strongly advocated a fifth component, namely a pyloroplasty or gastropyloroplasty, in cases with proven delayed gastric emptying. Claimed advantages are a lower incidence of recurrence and wrap disruption, particularly in children with a seizure disorder.[18] However, we have shown improved gastric emptying in most cases after fundoplication without disruption of the pyloric sphincter.[41] Theoretical disadvantages of pyloroplasty/pyloromyotomy may be a lifelong predisposition to bile reflux, although one study demonstrated minimal bile acid reflux and no change in intragastric pH at 1- and 1½-year follow-up evaluation.[42]

A short floppy (i.e. loose) Nissen fundoplication is the operation performed most frequently, although several other effective operations have been described. A variation of the Nissen is the Toupét, a partial posterior fundoplication over ± 270° of the oesophageal circumference.[43] The fundus of the stomach is secured posteriorly to the hiatal crura and anteriorly to the anterolateral oesophagus on each side.[44] Claimed advantages over the Nissen are a lower incidence of complications, particularly dysphagia, gas bloat and para-oesophageal hernia.[45] The procedure may be of particular benefit in infants with poor oesophageal peristalsis; however, there are no prospective studies confirming this advantage.

Another operation is an oblique 180° partial anterior fundoplication (Boix Ochoa), which has been shown to be effective in preventing GOR with a low incidence of postoperative side-effects such as a gasbloat, dumping and diarrhoea.[46] This operation is similar to the Watson procedure in adults and is effective in up to 95% of cases.[47] Early failure of the antireflux procedure has been seen in neurologically impaired and very malnourished children, with para-oesophageal herniation of the fundus occurring in approximately 10% of cases, usually as a late phenomenon. When this does occur, it causes dysphagia, is often associated with recurrence of GOR and requires revision surgery. Discharge from hospital after these operations should be possible within 72 - 96 hours. Although these operations are highly effective in preventing GOR, the underlying respiratory problem in patients with asthma-like syndrome might persist because of primary pulmonary disease, prior damage from aspiration or ongoing aspiration due to cricopharyngeal inco-ordination. Reoperation may be required in up to 10% of cases, mainly because of wrap breakdown and/or hiatal hernia formation.

Laparoscopic fundoplication

Over the past 5 years there has been an explosion of activity in laparoscopic and minimally invasive surgery.[48] Laparoscopic fundoplication has appeal in children over 12 months of age, as visibility is excellent and in experienced hands the same technical steps are followed as in open surgery. Although there is undoubtedly a 'learning curve', equivalent results with less postoperative morbidity have been achieved.[49]

Conclusions

In infants with suspected GOR, clinical evaluation and selective investigations will identify those with pathological reflux requiring intensive medical treatment. Infants with typical uncomplicated symptoms of reflux should be treated without prior investigations. However, persistent symptoms in any child require a contrast swallow and meal to exclude anatomical abnormalities in the upper gastro-intestinal tract. The natural history of spontaneous improvement in infants and young children and the success of medical therapy should militate against early surgery. However, with life-threatening reflux disease, or with well-defined indications, a surgical antireflux procedure offers a safe treatment option with satisfactory long-term outcome.

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