Personal Practice

Anti-Reflux Therapy

Bhupinder K. Sandhu

Gastroesophageal reflux (GER) is a common symptom in infants and children. It may be a physiological event, not requiring any treatment. It becomes pathological when its frequency and intensity is increased and there are associated symptoms and/or complications, such as esophagitis or respiratory infections. Pathological GER may cause significant morbidity and mortality(l). The symptoms can be subdivided into three main categories: esophageal, respiratory or neurobehavioral *(Table 1).* When discussing GER and its management in this paper, the author is referring to primary GER, but it is important to exclude secondary GER due to underlying disease processes, such as gastroenteritis, intestinal obstruction, food allergy, metabolic disease, urinary tract infection, and renal failure where, of course, the primary disease needs treatment. New methodologies, particularly prolonged esophageal pH monitoring have become available to assess the presence and severity of GER and this has led to an improvement in our understanding of the pathophysiology of this condition. Clinical evaluation is still the most important aspect of the management of a child presenting with symptoms suggestive of GER.

Reprint requests: Dr. Bhupinder K. Sandhu, Consultant Pediatric Gastroenterologist, Institute of Child Health, Royal Hospital for Sick Children, St Michael's Hill Bristol, BS2 8BJ, U.K.

Clinical Evaluation

Vomiting is the most obvious and common symptom of 'primary' GER but vomiting may also be due to 'secondary' GER. In our experience, although vomiting as a symptom shows the best correlation with GER and no patient with severe vomiting had normal esophageal pH profile, the presence or the severity of vomiting does not always correlate well with the severity of GER *(Fig. 1).* Other symptoms give a varied picture of correlation to esophageal pH monitoring. Cyanosis and apnea alone showed no correlation with GER *(Fig. 2).* However, 66% of patients with severe wheeze demonstrated some degree of GER, whilst 80% of patients with recurrent chest infections demonstrated some GER. Three out of seven patients presenting with near miss sudden infant death syndrome showed severe GER. The presence of gastro-intestinal symptoms of hematemesis, dysphagia and abdominal/ substernal pain correlated well with the severity of GER *(Fig, 3).* In most cases, the diagnosis of GER is based upon clinical history and examination and no special tests are needed. If the GER does not respond to simple medical measures or if history and examination suggest complications, such as esophagitis, then investigations including upper gastrointestinal endoscopy and 24 hr esophageal pH monitoring are desirable. With the advent of esophageal pH monitoring, it has become apparent that GER may be silent(2). Another group of children that need special consideration are those with neurological abnormalities. The association with GER and cerebral palsy was first reported in 1970(3) when reflux was documented in *75%* of such cases. Symptoms of

TABLE *l-Symptoms of GER.*

A. *Esophageal Symptoms*

1. *Specific symptoms*
   - * Regurgitation
   - * Vomiting
   - * Nausea
   - * Failure to thrive

2. *Symptoms due to esophagitis*
   - * Hematemesis and melena
   - * Dysphagia
   - * Epigastric or retrosternal pain
   - * Heartburn
   - * Symptoms related to anemia
   - * General irritability
   - * Feeding problems
   - * Esophageal obstruction due to stricture

B. *Neurobehavioral Symptoms*
   - * Sandifer-Sutcliffe syndrome
   - * Seizure-like events in infants

C. *Respiratory Symptoms*
   - * Aspiration pneumonia, especially recurrent
   - * Apnea, especially in the preterm infant
   - * Apparent life-threatening events (ALTEs) and sudden infant death syndrome (SIDS)
   - * Cyanotic episodes
   - * Cough
   - * Stridor
   - * Bronchospasm or wheezing, especially intractable asthma
   - * Worsening of existing respiratory disease, *e.g.*, cystic fibrosis

recurrent chest infections and failure to thrive, irritability and vomiting are often accepted as being part of neurological disability. If fully investigated, a significant portion of these children are found to have GER(4) which may be silent. Natural resolution of GER is less common in these children and esophagitis is common. In some children GER may mimick neurological disease, resulting in gross dystonic posturing (Sandifer's syndrome) or seizure like events which are cured by effective anti-reflux therapy(5).

Investigations

If vomiting is absent but serious symptoms (near miss cot death or chest pain) suggest the possibility of silent GER, esophageal pH monitoring may be very useful. For this a pH sensitive probe is placed 3 vertebral bodies above the diaphragm and records esophageal pH over 24 hours. Twenty-four hour esophageal pH monitoring has increasingly become the 'gold standard' for documenting acid GER(6-9). Reflux is a dynamic phenomenon and therefore the ability to monitor over a prolonged time makes the test more physiological and reliable. Several different scoring systems have been used for pH studies. The most commonly used system is shown in *Table II* with normal values based on studies by Vandenplas and Sacre-Smits(7). A reflux episode is commonly defined as occurring when lower esophageal pH falls below 4. The percentage time pH is less than 4 in the lower esopahgus (often referred to as the reflux index) provides a convenient single summary for clinical purposes. Children with reflux index of 5-10% (mild) or 10-20% (moderate) will often be controlled by medical therapy. Those with over 20% reflux (severe) may require surgical intervention. The Working Group on GER of the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) has published a protocol for lower esophageal pH monitoring and this is worthwhile consulting by those carrying out this procedure(9). It is important that the tip of the pH probe is sited correctly and the position checked radiographically. If facilities for carrying out esophageal pH monitoring

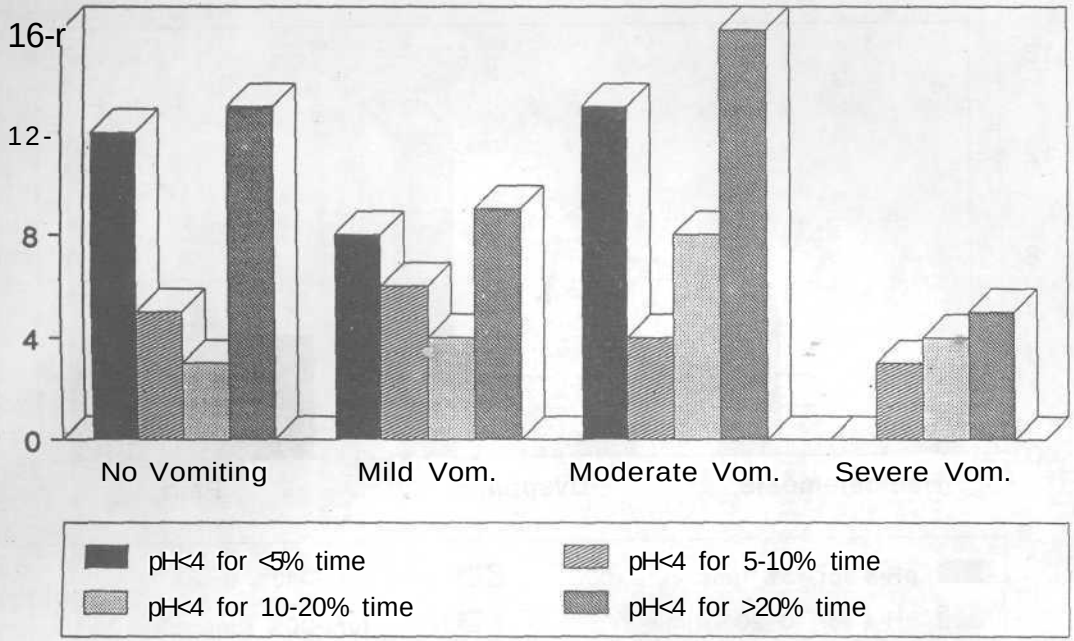

Fig. 1. Correlation between severity of GER and severity of vomiting.

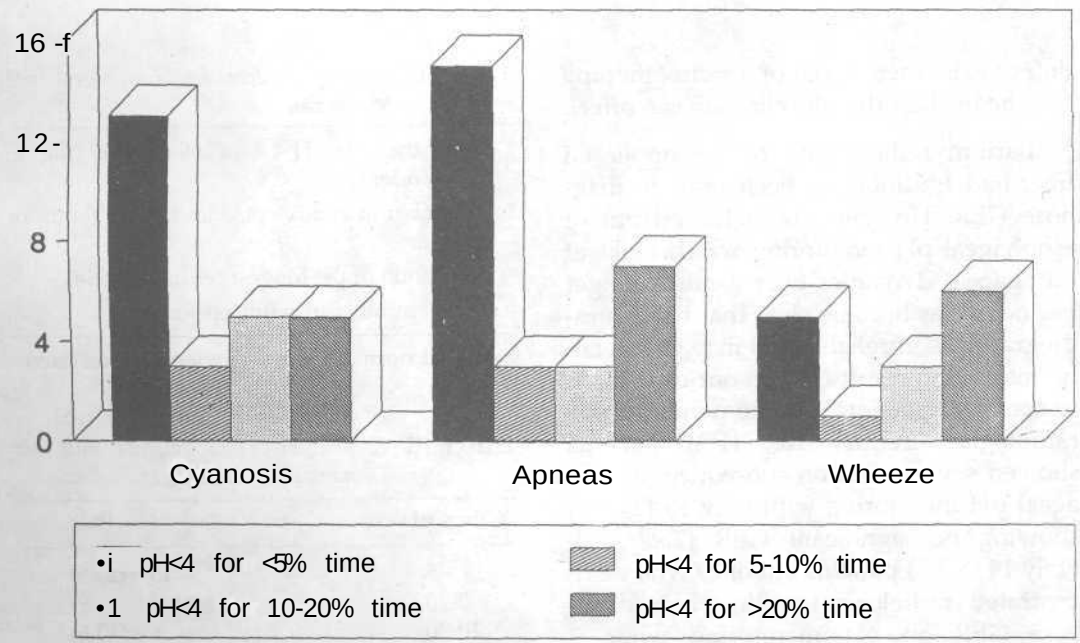

Fig. 2. Correlation between severity of GER and respiratory symptoms.

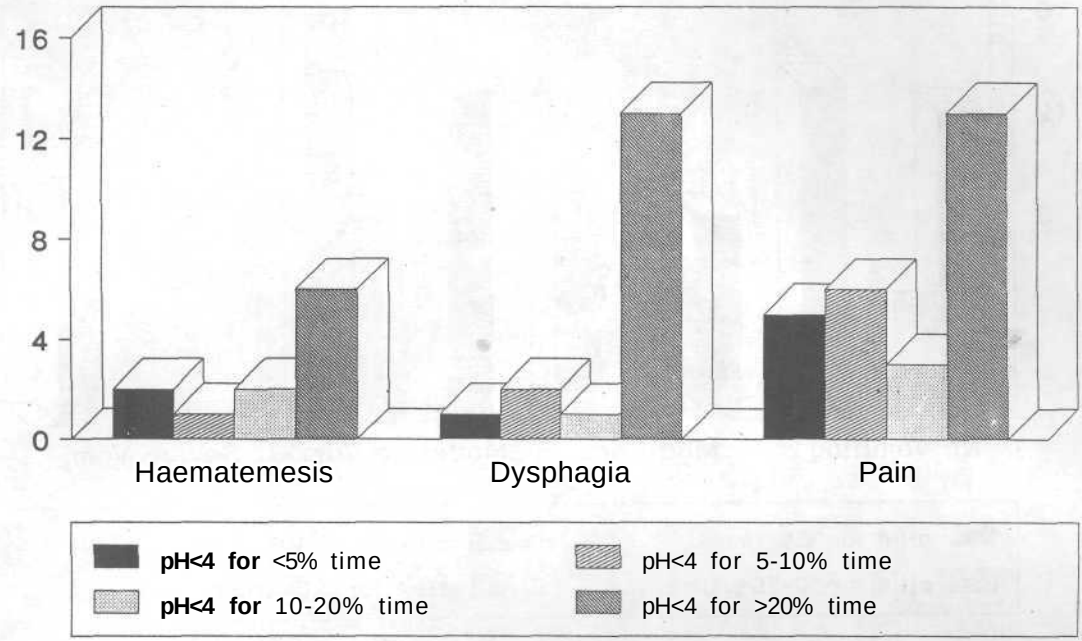

Fig. 3. Correlation between severity of GER and hematemesis, dysphagia and chest or epigastric pain.

do not exist then a trial of a reflux therapy may be the best that the clinician can offer.

Barium radiography of the upper GI tract had traditionally been used to diagnose GER. However, with the advent of esophageal pH monitoring which looks at esophageal dynamics over a much longer period, it has become clear that barium radiography is unreliable and may give totally misleading results(lO). In our own experience of 44 patients with no demonstrable radiological reflux, 18 (41%) patients showed severe GER on subsequent esophageal pH monitoring with only 13 (29.5%) showing no significant GER *(Table III).* Only 14 (8.3%) patients out of 29 who demonstrated radiological reflux showed severe GER on pH monitoring while 7 (24.1%) showed no significant reflux *(Table IV).* Although barium radiography is use-

TABLEII—*Scoring System for Esophageal pH Monitoring.*

* % of the time pH < 4 for total period (the reflux index)
* Number of reflux episodes lasting 5 min or longer
* Duration of the longest reflux episode
* Total number of reflux episodes

Expected normal values-Vandenplas and Sacre-Smits(7).

TABLE III-*Esophageal pH in Patients with 'No Demonstrable Radiological Reflux'.*

% time pH <4	No. (%)
<5	13 (29.5)
5-10	7 (15.9)
10-20	6 (13.6)
>20	18 (41.0)
Total	44 (100.0)

TABLE *W-Esophageal pH in Patients with 'Demonstrable Radiological Reflux'.*

% time pH <4	No. (%)
<5	7 (24.1)
5-10	3 (10.4)
10-20	5 (17.2)
>20	14 (48.3)
Total	29 (100.0)

ful for detecting anatomical abnormalities, such as esophageal stricture, malrotation and hiatus hernia, it should not be used for the purpose of diagnosing the presence or severity of GER.

In cases of suspected esophageal or anatomical abnormality, such as esophageal stricture, upper GI endoscopy is the choice investigation. Other investigations that may be useful in evaluating GER include radionuclide scintography. This may be beneficial in assessing esophageal transit time, efficacy of esophageal clearance, gastric emptying and severity of GER-(11,12). Ultrasound has been used to measure rate of gastric emptying(13,14).

Therapy for GER

The ESPGAN Working Group on gastro-esophageal reflux disease, of which the author is a member, have published a proposition for the diagnosis and treatment of GER in children(15) and the following recommendations are to a large extent based upon these guidelines.

Treatment of Uncomplicated GER

Vast majority of children with symptoms such as vomiting suggestive of GER who do not have an underlying cause for their symptoms can be diagnosed clinically. These are mostly infants under one year of age with regurgitation and symptoms may overlap with physiological GER. Parental reassurance following careful questioning, observation and explanation may preclude the need for any further medical intervention. Special attention should be paid to the possibility of secondary GER due to underlying disease. If symptoms are troublesome then *Phase I treatment* can be started *(Table V).* If this is not effective over 2-4 weeks then a prokinetic agent can be added.

Phase I Treatment

Positioning

The influence of position on the severity of GER is well documented. In 1982, it was documented that infants had four times more reflux in the traditional chalasia chair than when lying prone(16). The 30° prone position was found to be the best position. We recommend that the baby should sleep on its back or side with the head raised to 30° from the horizontal and not the prone

TABLE *V-Recommended Treatment of GER.*

Phase 1	
1A	Positioning-prone, head elevated to 30°
IB	Milk thickening agents
1C	Dietary advice-frequent feeds of small volume
ID	Antacids-Infant Gaviscon
Phase 2	
	Prokinetic agents-cisapride 0.8 mg/kg/day in 3-4 doses given before feeds*
	If symptoms persist, try domperidone, 1 mg/kg/day, or metoclopramide 0.5 mg/kg/day.
Phase 3	
3 A	H2-receptor antagonists
	- cimetidine 30 mg/kg/day
	— ranitidine 10-15 mg/kg/day
3 B	Omeprazole[5]
	Sucralfate 0.35-1.0 g qds
Phase 4	
	Surgery-Nissen fundoplication, or Thai procedure

* Doses of 0.4 mg - 1.2 mg/kg/day may be used
$ Dose schedule currently under evaluation

position as the prone sleeping position has been found to be an independent risk factor for sudden infant death syndrome(17). The positional treatment is effective in over 25% of infants. There may be practical difficulties in maintaining the position and the clinician needs to discuss how it may be produced for a particular home circumstance, *e.g.,* placing bricks under the head of the cot or bed and a rolled up blanket or towel under the feet to stop the child slipping down.

Dietary Advice

Severe failure to thrive may arise through loss of calories in vomit. It is crucial to ensure adequate calorie intake. It is important to provide enough calories for the child's expected weight rather than the actual weight. In infants the historical approach of small frequent feeds has advantages but does increase post-prandial periods. In older children dietary advice includes normal lowish fat diet, avoidance of spicy food, carbonated drinks, tea, coffee and chilled drinks.

Milk Thickening Agents

These produce favorable clinical results in infants with simple regurgitation, although the effect on various parameters of GER during 24 hour pH monitoring of the esophagus have been inconsistent(18-20). Feed thickeners may delay the clearance of reflux material from the esophagus and hence their use is not recommended in children with esophagitis(21). Milk thickeners are difficult to administer in breastfed babies. Breastfed babies are in any case less likely to have GER than formula fed babies (personal data).

Antacids

Addition of powdered antacids, such as Gaviscon (sodium salt of Alginic Acid) to infants milk (1-2 g/100 ml) have been shown to have some effect in GER(22,23) although other studies have given less convincing results(24-24) but increased sodium load may be inappropriate in premature babies. Older children can be given antacids in liquid or tablet form to be taken before meals and at bed time or in relation to symptoms.

Phase 2 Treatment

Prokinetics

These are recommended when Phase I treatment is insufficient. Prokinetics, including Cisapride, Metoclopramide, Domperidone and Erythromycin have been studied in pediatric patients. Cisapride is considered as the prokinetic of choice in pediatric patients as in double blind placebo controlled trials, only Cisapride has given consistent positive effects on clinical and reflux parameters(26-28).

(ż) *Cisapride:* The non dopamine receptor blocking prokinetic drug, Cisapride, acts by enhancing acetylcholine release in the gut and hence enhancing contractile amplitude and improving antroduodenal co-ordination^). It has also been shown to increase lower esophageal sphincter pressure and esophageal contractility and gastric emptying(15,30,31). The usual dose is 0.2 mg/kg, 4 times per day (0.1-0.3 mg/kg). Reported side effects are transient colic, borborygmia, diarrhea, headache and drowsiness. It may have little effect on vomiting and may not be effective in neurologically abnormal children(32).

(żż) *Domperidone:* This is a benzomidazol derivative with dopamine receptor antagonist properties(33). It has been shownt o increase basal lower esophageal sphincter pressure, inhibit relaxation of the gastric fundus, enhance contractility of the antrum and improve antroduodenal co-ordination^). However, results on its clinical effect, as well as objective measurements, have been disappointing(26,27). The rec-

ommended dose is 0.6 mg/kg, 4 times a day. Side effects include diarrhea and effects on the central nervous system, especially in young infants.

(Hi) Metoclopramide: This is a derivative of procanamide without cardiac or anesthetic actions(35). It binds to dopamine D2 receptors in the brain and gastrointestinal tract and it inhibits the actions of dopamine. It enhances intestinal smooth muscle tone, resulting in faster gastric emptying and improved entroduodenal co-ordination (36-37). Different studies have shown no consistent effect on reflux parameters(38). Side effects are common, especially in the first 6 mo of life and include restlessness, insomnia, dystonia and extrapyramidal movements, including oculogyric crisis (39,40). The recommended dose is 0.1 mg/kg with a maximum of 0.5 mg/kg/day(40).

Phase 3 Treatment

H_2-Receptor Antagonists

H_2- receptor antagonists are indicated in GER complicated by esophagitis. They have been shown to be effective in the treatment of mucosal lesions in esophagitis(41). In adequate dosage, both Cimetidine and Ranitidine reduce gastric acid output; Ranitidine is regarded to be more potent with a longer duration of action(42,43). Sufficient information on long term use of Famotidine is not yet available. Side effects have been reported with Ranitidine, including headache, dizziness, brachycardia, drowsiness and hyporeflexia(42). A wider additional spectrum of adverse effects have been reported with Cimetidine, including mental confusion, hallucinations, hepato-toxicity and hypertension. The recommended dose for Ranitidine is 6-15 mg/kg/day and Cimetidine 20-40 mg/kg/day.

Proton Pump Inhibitor

Omeprazole, a NA^+/K^+ - ATPase, or proton pump blocker has been shown to be effective in treating GER-esophagitis, resistant to H_2 antagonist therapy(44-46) even in high risk patients, including those with esophageal atresia repair and neurological impairment(47,48). Adverse effects are comparable with H_2 receptor antagonists^) but in rodents receiving long term Omeprazole therapy entero chromaffin-like cell hyperplasia has been reported, an . effect not seen in humans with short term treatment(50). In adults, long term treatment with Omeprazole has been shown to be effective and safe. Recommended dose is 0.5-1 mg/kg per day in infants and 20-40 mg/1.73m^2 in older children.

Phase 4 **Treatment**

Surgery

In most patients surgery should only be considered after a full trial of medical treatment as spontaneous improvement is part of the natural history of GER in infants and young children. In children with apparent life threatening event (ALTE) or pre-existing neurological abnormalities surgery should be considered earlier(51). Nissen fundoplication is the preferred procedure in most centers but other techniques may be used(52).

Therapy for Patients with Suspected Esophagitis

If symptoms suggest esophagitis then this should ideally be documented with upper GI endoscopy. This should be performed by an experienced pediatric gastroenterologist and should preferably always be a duodeno-gastroesophagoscopy(53). Barium studies may be appropriate if an anatomical malformation such as malrotation or gastric outlet obstruction is suspected. Minimal esophagitis (Grade 1-3; mucosal redness) may heal with Phase I and 2 therapy alone. Phase 3a, H_2 antagonist, treatment is indicated for more severe

esophagitis (>Grade 3; mucosal ulceration). If this is not effective, Phase 3b (Omeprazole) should be tried. Between 4-12 weeks after starting treatment, a repeat endoscopy and biopsy needs to be performed to check healing. If the esophagitis has healed, only Phase 1 and 2 treatment needs to be continued but for a prolonged period of 6 months or so, depending on the clinical response and then gradually withdrawn. If despite adequate Phase-3 treatment there is no improvement, underlying causes including anatomical abnormalities, allergy, infection, *etc.* need to be excluded. If there is no specific underlying cause, Phase 3 therapy can be continued for a further 4-12 weeks. If the symptoms, such as marked failure to thrive, apnea or hematemesis persist, despite full medical treatment, surgery becomes inevitable. It may be life saving in children with recurrent and life threatening aspiration and improve the quality of life in neurologically abnormal children(51). Children with Barrett's peptic stricture or esophagitis require surgery as primary therapy. Surgical treatment may have complications, such as dumping, retching, intestinal obstruction, bloating, wrap hernia and recurrence of GER(3,4,51) and should ideally only be undertaken after full evaluation including endoscopy, gastric emptying evaluation, barium studies, as well as esophageal pH monitoring.

Conclusion

Children with a clinically based diagnosis of GER who have no complications can be treated with parental reassurance, positional and feeding advice and, if necessary, feed thickeners and antacids. This is all that is needed, together with adequate calorie intake for vast majority of children with GER. If symptoms persist, prokientic agents, such as Cisapride can be added. However, investigations are indicated if there are complications, such as esophagitis or silent GER causing serious symptoms is suspected. At this stage, referral to a specialist center able to carry out investigations, such as endoscopy, may be appropriate. Esophageal PH monitoring is an important new tool for investigating complicated GER and may have a place in specialist centers in countries, like India.

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