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Gastrointestinal Conditions

Postfundoplication retching: Strategies for management

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ABSTRACT

Background: Retching is a common symptom in children following antireflux surgery, particularly in those with neurodisability. There is now a strong body of evidence that implicates retching as a major cause of wrap breakdown. Retching is not a symptom of gastroesophageal reflux disease; it is a component of the emetic reflex. In addition to causing wrap breakdown, it is indicative of the presence of nausea. It is a highly aversive experience and warrants treatment in its own right.
Methods: A framework was constructed for the management of postoperative retching, with strategies targeting different components of the emetic reflex. The impact of differing antireflux procedures upon retching was also considered.
Conclusions: Once treatable underlying causes have been excluded, the approach includes modifications to feeds and feeding regimens, antiemetics and motility agents. Neuromodulation and other, novel, therapies may prove beneficial in future.
Children at risk of postoperative retching may be identified before any antireflux surgery is performed. Fundoplication is inappropriate in these children because it does not treat their symptoms, which are not because of gastroesophageal reflux, and may make them worse. They are also at risk of wrap disruption. Alternative strategies for symptom management should be employed, and fundoplication should be avoided.
Level of evidence: II–V

Contents

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1. Introduction: the pathophysiology of postoperative retching

Chronic retching (or 'dry heaves') and repeated attempts at vomiting following fundoplication are common symptoms in children. It is widely believed that retching is a symptom of gastroesophageal reflux disease (GORD) and that retching is caused by wrap failure. However, there is now a substantial body of evidence to show that the repeated contraction of the anterior abdominal wall muscles and diaphragm during retching (with or without vomiting) is a clinically important *cause* of anatomical wrap failure, implicated both in wrap herniation and in wrap disruption [1,2]. Moreover, retching is *not* a symptom of GORD, but is part of the emetic (or vomiting) reflex [2].

The purpose of the emetic reflex is defense: to remove contaminated food from the upper gastrointestinal tract [3,4]. When the emetic reflex is activated, gastric emptying ceases, and intestinal retroperistalsis returns contaminated food from the proximal small intestine to the stomach, ready to be expelled by retching and vomiting [3,4]. The accompanying nausea is associated with appetite suppression, stops further ingestion, and facilitates learned taste aversion to that food when presented on future occasions. Nausea is a ***very aversive stimulus*** — much more so than pain [5]. This is a normal, protective reflex; it acts as a warning that the gut is being challenged and is a signal to 'Stop!'

It is well known that retching and vomiting are sufficiently powerful to cause direct physical injury and even esophageal rupture — Boerhaave's syndrome [6]. These same forces are also sufficient to disrupt a fundoplication postoperatively [2]. In children, chronic retching and attempted vomiting are common morbidities following fundoplication [7,8]; their role in causing wrap failure has important implications for management. In the past, one approach has been to modify the wrap — to 'strengthen' it to resist the disrupting forces [9–12]. However, a more logical approach would be to prevent or eliminate the postoperative retching and avoid these excessive forces upon the wrap. Moreover, if children are retching, this implies that the emetic reflex is being activated. In addition to the distress caused by retching itself, these children are also suffering prolonged episodes of the emetic prodrome, including nausea. By physically blocking and preventing the final act of vomiting, fundoplication prevents relief; instead, children experience prolonged nausea and retching. Failure to control retching in these children is failure to relieve intensely aversive symptoms [1,2].

2. Methodology

In addition to the author's personal library of published, peer-reviewed papers, the English-language literature was surveyed for the following studies and reviews:

1. The normal physiology of activation of the emetic (vomiting) reflex
2. The mechanism and effectiveness of antiemetics
3. The mechanism and effectiveness of gastrointestinal motility agents
4. The mechanism and effectiveness of treatments for visceral afferent hypersensitivity affecting the gastrointestinal tract
5. Reports on the management of symptoms following fundoplication
6. Reports on the incidence of symptoms following fundoplication and other forms of antireflux surgery.

Search terms were combinations of the following: fundoplication, pyloroplasty, vagotomy, esophagogastric dissociation, laparoscopy, jejunostomy, retch, vomit, emetic reflex, antiemetic, feed intolerance, hypersensitivity, hyperalgesia, visceral pain, treatment, management.

Adult and animal studies were included; pediatric studies are particularly deficient in the areas of normal physiology and drug development owing to practical and ethical issues. The aim of the literature survey was to understand the causes of retching, comprehensively to seek reports of successful management of postfundoplication retching (whether or not the main focus of the paper) and to search widely for other potential solutions to the problem.

The published data were used to create a physiological model of the impact of fundoplication upon gastric motor and sensory function, and retching arising as a result of activation of the emetic reflex. This model was then used to construct a framework for management of patients with postoperative retching. The different components of the emetic reflex pathway were each considered as targets for treatment, and the potential for interventions at each stage determined. The impact of different forms of antireflux surgery upon retching and the emetic reflex – and hence the potential to reduce the incidence postoperatively – was also examined.

3. Analysis and discussion: overview of the management of postoperative retching

The impact of fundoplication upon gastric function and the emetic reflex. The immediate, short term effects of general anesthesia and surgery to stimulate the emetic reflex (postoperative nausea and vomiting; PONV) are well recognized. This may result in retching and attempted vomiting in the immediate postoperative period. However, fundoplication may also have a more specific and longer-lasting effect upon gastric function and the emetic reflex. As will be discussed, fundoplication may have an adverse impact upon gastric neurophysiology, in addition to acting as a physical impediment to the final act of vomiting when the emetic reflex is activated.

Fundoplication changes the morphology of the stomach, with the region of the cardia and fundus wrapped around the distal esophagus. The cardia and adjacent fundus become adherent to the esophagus owing to the development of intervening scar tissue; histological study of this region also shows a variable amount of scarring within the gastric and esophageal muscular walls, and there may also be damage to nerve branches [13]. This change in configuration of the stomach and the presence of intramural fibrosis have the potential to cause a variety of changes in gastrointestinal function. There is evidence of altered afferent input and development of visceral afferent hypersensitivity, gastrointestinal dysmotility, and changes in reflex pathways, including the gastric accommodation reflex and the emetic reflex [14]. Neuromas developing at the site of injury may also have the potential to generate afferent signals that lead to activation of the emetic reflex [15]. The impact of any motility disorder will be compounded by afferent hypersensitivity.

While studies in humans still appear to show a reasonable overall gastric volume (and physiological 'gastric capacity') following fundoplication, more subtle disturbances of tone and of accommodation have been implicated in those subjects (both adults and children) who develop postoperative dyspeptic symptoms, including early satiety and nausea [2,16,17]. The sensitivity of mechanoreceptors depends upon the prevailing tension in the gut wall, increasing when the resting tension is higher. This means that changes in motility can cause secondary hypersensitivity, in addition to changes that may arise as a result of direct afferent nerve injury.

Adults who develop dyspeptic symptoms following Nissen fundoplication have reduced tolerance of intragastric volume (as determined by capacity to drink water), which may reflect impaired accommodation, visceral hypersensitivity, or both, whereas asymptomatic patients have the same tolerance as controls [18]. Pauwells et al. attributed post-Nissen dyspepsia mainly to impaired gastric accommodation, which correlated with symptoms of upper abdominal bloating, early satiety and postprandial fullness [19]. Scheffer et al. demonstrated that the distribution of a liquid meal within the stomach changes after fundoplication, with greater filling of the distal portion. This was particularly marked in those patients who developed dyspepsia and postprandial fullness, and they suggested that impaired accommodation of the gastric fundus to a meal leads to increased filling of the more sensitive, less compliant antrum, resulting in symptoms

[20]. The mechanoreceptors of the antrum are particularly sensitive to overdistension, resulting in vomiting [3]. This redistribution of gastric contents, impaired accommodation and increased tone within the fundus during administration of a feed may also lead to faster gastric emptying (and result in dumping syndrome). Conversely, damage to motor efferents may cause dysmotility that slows gastric emptying and thereby intensifies and prolongs afferent stimulation from the full stomach.

Zangen et al. identified a variety of motor and sensory disturbances of the upper gastrointestinal tract of children with feed intolerance after fundoplication [21], although it is possible they were present preoperatively. In the animal model of ferret fundoplication there is some evidence that emetic sensitivity to a centrally acting agent is increased postfundoplication compared with controls, in addition to development of disturbances of gastric tone and gastric dysmotility [14]. It is interesting to note that, in the ferret, the incidence of retching and vomiting during urethane anesthesia is greatly increased three weeks following vagotomy (i.e. nerve injury without fundoplication), attributed to neuronal plasticity and unmasking of other emetic pathways [22]. Vagotomy was also been reported to result in a trend for the ratio of retch:vomit to increase (i.e. more retches occur before a successful vomit), which may reflect hypersensitivity owing to nerve damage, or may be because of altered/deficient afferent feedback during retching, at the time of activation of the reflex [15].

The retrograde expulsion of gastric contents through the gastroesophageal junction that normally occurs during reflux, belching, and vomiting owing to activation of the emetic reflex, is impaired by the presence of the fundoplication wrap. The result is that gastric contents, whether gas, liquid or solid, are retained in the stomach, which is now challenged to cope with increased volumes (regardless of whether or not accommodation is impaired, or afferents sensitized). Fundoplication is often combined with formation of a feeding gastrostomy; a feeding tube imposes enteral feed upon the child, who is unable to refuse (unlike oral feeding) and is reliant upon their carers to recognize signs of discomfort or distress. The nature of the feed may also have changed— exchanging 'normal' food given orally for a commercial formula, which may also lead to adverse afferent stimulation. Even if the child has been previously on nasogastric tube feeding, the wider bore, more secure gastrostomy tube will tend to permit faster feeding and possibly a greater feed volume. In addition, expectations change— a common view is that patients with a fundoplication, because they can no longer vomit, 'should' be fed with intermittent bolus feeds, even though they may have been on continuous feeds before surgery. The presence of the fundoplication raises expectations; it causes us to demand more and to push the patient harder, with larger feeds given more quickly, which is often unrealistic.

Moreover, as will be discussed later (section 3.6.3), dysmotility may already be present, or the emetic reflex may already be active or sensitized, before fundoplication. This is likely to persist or even worsen postoperatively, and the parents may describe the postoperative retching as being more troublesome than before [23].

Children retch following fundoplication because their emetic reflex is activated; it is not because of recurrent gastroesophageal reflux. The presence of the fundoplication markedly impairs expulsion of vomit, so the reflex is not completed and activation is not 'turned off'. Instead, the emetic stimulus persists and the retching continues. The emetic reflex is a defensive reflex, protecting us from ingesting substances that are poisonous, excessive in volume or otherwise inappropriate. ***The presence of retching after fundoplication is a warning that there is excessive stimulation of the visceral afferents and that the stomach is unable to tolerate the administered volume and/or composition of feed.***

Retching need not be apparent immediately after antireflux surgery, but may emerge over a period of weeks postoperatively, which might reflect the development of scarring, or neuronal plasticity. In some children, retching will improve with time— this may reflect progressive physiological adaptation or it may reflect successful treatment and 'lifestyle' alterations to feeding regimens that are better suited to the postfundoplication stomach, made by the carers consciously or unconsciously. In some cases, retching will improve because an underlying cause resolves (Appendix A e.g. cow milk protein intolerance). This chronic or persistent postoperative retching contrasts with that in the child who is usually well, who develops sudden onset of retching owing to an acute, intercurrent illness or mechanical obstruction.

A management strategy for postfundoplication retching. There is no single solution to the problem of postoperative retching; however, an appreciation that retching is because of activation of the emetic reflex broadens the range of potential therapeutic strategies and allows a framework to be created for a systematic and structured approach that aims to remove or suppress the emetogenic stimulus. Individualized management, and a willingness to use multiple and novel interventions, would appear to be key, and can achieve a significant reduction in symptoms [21,24]. Despite increasing recognition that postfundoplication retching is a problem, there are few published papers that specifically address its management. For this reason, the ensuing discussion draws upon the author's clinical experience in addition to the published literature. Where evidence is available, complementary therapies are included; some families will choose to use these alongside, or instead of, other modalities.

The overall approach is to work within the physiological limitations of each child's gastrointestinal system, rather than imposing preconceived and unrealistic expectations upon it [24,25]; to avoid overchallenging the gut, and to reduce/modulate potentially adverse stimuli. It is also important to remember that there are very many stimuli that activate the emetic reflex, and these may originate external to the gastrointestinal tract. The main strategies to have met with some success, when used by this, or other, authors, can be summarized as follows:

1. Seek and treat specific conditions that lead to recurring activation of the emetic reflex
2. Reduce or modify the stimulation of afferents that input into the vomiting center
3. Reduce or modify the impact of gastrointestinal dysmotility
4. Use of antiemetics to block the emetic reflex
5. Neuromodulation, novel and alternative therapies
6. Avoid treatments that worsen or cause retching.

There is a degree of overlap between these different strategies, and many interventions will have more than one mode of action; they are presented in separate categories to provide a framework for a multimodal approach. The order and combination in which they are utilized will depend upon the clinical context, family preferences, and local expertise. In addition, Zangen etal. [21] emphasize the importance of explanations to the family and carers, and management of expectations for these children, who often have multiple complex clinical problems.

3.1. Seek and treat specific conditions that lead to activation of the emetic reflex

In some children, recurrent retching (and vomiting) is the result of a specific, treatable chronic condition (Appendix A). These should be sought and addressed first.

Such conditions should have been identified as part of preoperative evaluation, and managed accordingly, but it is clear from the literature that children are not uniformly and systematically investigated prior to fundoplication [26,27], so children who retch postoperatively should be reevaluated. Acute triggers that may cause activation of the emetic

reflex with retching and vomiting should also be sought and treated as appropriate e.g. infection or intestinal obstruction.

3.1.1. Treat constipation

Retching and vomiting are often worsened in the presence of undertreated constipation, which has an adverse impact upon more proximal gastrointestinal motility [24,28]; adequate bowel clearance is an important step in the management of retching. Constipation should be treated in the same way as for non-neurodisabled children (ESPGHAN recommendation 17a [29]). In addition, the fluid and fiber content of the feed can be increased (ESPGHAN recommendation 17b [29]). Blenderized diet (section 3.2.2) is also reported by families to improve constipation and make the bowel habit more 'normal.'

3.1.2. Evaluate for side effects from drugs

Children with neurodisability are often on multiple drugs that target the central nervous system, (e.g. for management of epilepsy or dystonia) which may also interact with the enteric nervous system and adversely affect gastrointestinal function e.g. anticholinergic side effects will impair gastrointestinal motility. Nausea and vomiting, abdominal pain and other gastrointestinal symptoms represent some of the commonest drug-induced side effects, and this is particularly the case for the anticonvulsants and antidystonia agents. In addition, liquid drugs are often of high osmolarity, which may also contribute to gastrointestinal symptoms [24] (see section 3.2.2).

All medications should be reviewed periodically for potential adverse effects versus efficacy and overall benefit to the child.

Level of evidence: V

3.2. Reduce or modify the stimulation of gastrointestinal afferents that input into the vomiting center

Although often considered a motor nerve, the human vagus is 80%–90% afferent fibers. The most densely innervated part of the gut is the stomach, making it ideally placed quickly to detect the presence of contaminated food, and react accordingly. The highly sensitive gastric mucosa allows rapid activation of the emetic reflex [4]. However, many children with neurodisability appear hypersensitive, and subphysiological quantities of feed induce retching and vomiting, together with distressed or aversive behavior attributable to nausea [30]. The effect of fundoplication is to exaggerate this hypersensitivity. A logical strategy is to try to reduce the intensity of this excessive and dysfunctional vagal afferent stimulation that arises whenever the child is fed. This will include modification of the feeding formula and feeding regimen. (Further interventions are discussed in section 3.5.)

3.2.1. Modify the feeding regimen

Avoid overfeeding and giving excessive calories. Children with severe neurological impairment often have reduced activity, reduced muscle mass and lower nutritional requirements compared with other children [24,28]. The availability of a feeding tube may lead to overfeeding, which will place an unnecessary load, and excessive stimulation, upon the gastrointestinal tract. Cook and Blinman found that in 20% of their series of children with postfundoplication retching, overfeeding was contributing to their symptoms [24]. In some cases, permissive feeding (i.e. giving only what is tolerated, rather than a calculated target) may be the most appropriate management.

Small frequent boluses or continuous gastric feeds. Smaller, more frequent boluses are often better tolerated [24,25]. The combination of impaired gastric accommodation, increased tone, and afferent sensitivity causes the stomach to function as though the capacity is reduced, and unable to tolerate standard volume feeds. High bolus volume was a contributory factor in 28% of Cook and Blinman's series [24]; they found that tolerance was much improved when boluses were limited to 15 ml/kg/h and continuous overnight feeds to 8 ml/kg/h. Smaller gastric boluses will reduce both mechanical distension of the stomach which stimulates the stretch receptors, and the degree of mucosal chemoreceptor stimulation, which may then avoid triggering the emetic reflex. Continuous gastric feeds will minimize the level of afferent stimulation of the gut. Romano etal. recommend continuous nocturnal feeds with daytime bolus feeds for patients unable to tolerate bolus-only feeding (ESPGHAN Recommendation 22 [29]).

Gastric venting. Fundoplication is associated with reduction in the frequency of transient relaxations of the lower esophageal sphincter and the common cavity phenomenon [31], and leads to difficulty in belching. This may result in gastric distension with air, which will be in addition to the volume of feed. The effect of this excessive air will be compounded if there is impaired accommodation of the fundus, which may also be more sensitive postoperatively, leading to symptoms of 'gas-bloat', and culminating in retching/gagging. Venting a gastrostomy between feeds will remove this accumulation of air, reduce overall gastric volume and help to prevent the resultant bloating [24].

Level of evidence: IV–V

3.2.2. Modify the feed composition

Modifications to the type of feed also have the potential to alter mucosal receptor activity and vagal afferent stimulation. This will include chemoreceptors and osmoreceptors (the latter being of particular importance in the proximal duodenum for regulation of gastric emptying).

Modified protein content. Whey-based feeds may be better tolerated than casein-based. This has been attributed to faster gastric emptying of the liquid whey, which will reduce gastric filling and therefore, gastric sensory stimulation. Casein, on the other hand, tends to form solid curds in the acidic pH of the stomach, which empty more slowly; moreover, it has been suggested that breakdown products of casein include opioid peptides that decrease gut motility [24]. ESPGHAN recommends a trial of whey-based formula for children with gastroesophageal reflux and for children with symptoms of gagging and retching (ESPGHAN Recommendation 21e [29]).

A predigested or amino-acid-based formula may be better tolerated than a whole-protein formula, even when evidence of food allergy is lacking. Romano etal. [29] comment that 'some children may require a semi-elemental or elemental formula.' No published evidence is quoted, but this would seem to be a common experience among pediatric gastroenterologists. However, the increased osmolarity of hydrolyzed feeds may be counterproductive in some cases.

Avoidance of hyperosmolar feeds. Hyperosmolar feeds may induce symptoms of discomfort or retching and are poorly tolerated by some children [24,28]; Cook and Blinman found this to be the commonest cause of symptoms postfundoplication (34%) and recommended avoidance [24]. Causes of increased osmolarity include concentrating or fortifying feeds, hydrolyzed protein feeds, and drugs (which may have extremely high osmolarity). Osmoreceptors are particularly dense in the proximal duodenum, and modulate proximal gastrointestinal motility by inhibitory feedback— a rise in the osmolarity of proximal duodenal contents slows gastric emptying and therefore prolongs gastric filling. It is also recognized that hyperosmolar solutions are an emetic stimulus [32]. Experiments using direct infusion into the duodenum of healthy adult volunteers have shown that increasing osmolarity causes symptoms of nausea [33], and significant inhibition of jejunal contractile and propagative activity, with symptoms of bloating [34].

Blenderized-by-gastrostomy-tube feeds. There is growing interest in the use of blenderized feeds in children who are tube-fed. Families state that they are better tolerated than the commercial formulae, and they are reported to have a substantial impact in some children, relieving symptoms of retching and vomiting, and reducing gastric aspirates, including those children who are symptomatic postfundoplication [24,25,35-7]. Formal clinical trials are lacking, and there are theoretical concerns about nutritional adequacy and hygiene, but there is a wealth of anecdotal reports of superior tolerance and families are introducing the change themselves. In response to patient interest and demand, gastrostomy manufacturers are now developing blenderized-friendly feeding devices and companies are beginning to offer bulk-produced versions of blenderized liquid feeds.

Blenderized feeds are likely to differ from the standard commercial formulae in their direct effects upon the vagal afferents. In order to achieve a blend that is sufficiently nonviscous, they often have a lower osmolarity and are less calorie-dense than the standard commercial formulae (so greater volumes may be required), which may improve tolerance. The nature and greater variety of feed composition compared with ordinary formula will impact upon the gut microbiome, and thereby gut immunity and the enteric nervous system. Blenderized-by-tube feeding has the potential for significant influence upon gut function.

Level of evidence: IV–V

3.3. Reduce or modify the impact of gastrointestinal dysmotility

Gastrointestinal dysmotility will secondarily result in abnormal or excessive stimulation of visceral afferents, thereby causing activation of the emetic reflex. Improved motility should lessen the degree of afferent nociceptive stimulation.

3.3.1. Management of dumping syndrome

Dumping syndrome describes a constellation of symptoms attributed to over-rapid gastric emptying. Early dumping (within 30–60 min) reflects the effects of an osmotic load to the small intestine (with intestinal distension and hypovolemia); late dumping (after 90min or more) reflects initial transitory hyperglycemia followed by rebound hypoglycemia. Both forms cause nonspecific symptoms of retching and vomiting and sympathetic activation; e.g. Bufler etal. [38] reported six children with symptoms including retching and diagnosed with dumping syndrome following Nissen fundoplication +/− pyloroplasty, although not all had abnormal glucose tolerance tests or abnormal gastric emptying studies. Five out of six were improved with feed manipulation (continuous feeds, avoiding mono- and disaccharides in feeds, and addition of complex carbohydrates).

Other options may be considered for unresponsive cases:

Acarbose is a potent competitive inhibitor of alpha-glycoside hydrolase. It delays carbohydrate digestion and blunts the postprandial rise of glucose and insulin. Since it is a competitive inhibitor, carbohydrate digestion is delayed rather than blocked completely. It has a recognized role in the reduction of the postprandial rise in glucose in adults with diabetes, but has been reported to be a useful adjunct in the management of late dumping symptoms unresponsive to dietary measures alone in both adults [39] and children [40].

Octreotide and synthetic analogues have been found to be effective in adults with early or late dumping post gastric surgery that is refractory to standard therapy [39,41]. They are thought to act by a number of mechanisms, including slowing of accelerated gastric emptying, inhibition of hormone secretion (including insulin), inhibition of postprandial vasomotor changes and increase in intestinal absorption of water and sodium [39]. Disadvantages include the need for injection and side effects are common e.g. headache, diarrhea.

Level of evidence: IV–V

3.3.2. Prokinetics

Agents that stimulate motility and improve delayed gastric emptying have the potential to reduce nausea, retching and vomiting.

Dopamine receptor-2 antagonists. The dopamine receptor-2 antagonists (DA_2RA) have been widely used in children with upper gastrointestinal symptoms, including those with 'gas-bloat syndrome' and retching/gagging after fundoplication [17]. The peripherally acting domperidone acts on DA_2 receptors in the stomach and duodenum, to improve delayed gastric emptying, and in the *area postrema* (where the blood–brain barrier is lacking) to have a direct antiemetic action. The best-established clinical role for domperidone is for treatment of symptoms of upper gastrointestinal dysmotility and as an antiemetic. It has often been used in the treatment of children given a diagnosis of reflux, despite a lack of evidence for antireflux effectiveness in controlled trials [42]. Individual treatment successes may well reflect that in these cases, the problem being treated is gastric dysmotility, or vomiting owing to an active emetic reflex, rather than GORD. However, it may be useful in the symptomatic management of retching in some children. Carachi etal. [43] used the centrally acting DA_2RA metoclopramide (which also has $5HT_4$ agonist effects [4]) or celiac axis block in children with symptoms postfundoplication, although it is not stated which symptoms were responsive to the metoclopramide. However, the use of DA_2RAs is now limited by concerns regarding potential extrapyramidal or cardiac arrhythmia-inducing side effects, and they are not always effective.

Motilin and ghrelin agonists. Motilin is a peptide hormone secreted by gut endocrine cells (mainly duodenum and jejunum) to regulate gastrointestinal motility. High concentrations can act directly on smooth muscle receptors to elicit contractions; however, low concentrations can also induce gastric antral contractions indirectly by facilitating acetylcholine release from nerve-endings.

Erythromycin, a macrolide antibiotic, is a motilin agonist that in low doses evokes gastric contractions (whereas high doses cause cramps and nausea). It has been used to treat symptoms of gastroparesis butalso reduces symptoms of nausea and vomiting in humans and animal models [44,45]. Azithromycin has also been shown to be active [44,46]. There are no published reports of the use of erythromycin or azithromycin specifically for the management of retching; however, this prokinetic action might account for improved tolerance of feeds that the author has observed in neurodisabled children given azithromycin for respiratory prophylaxis. Currently the use of these agents is limited by concerns about inducing antibiotic resistance and lack of guidelines regarding optimal dosage. Research is ongoing to develop nonantibiotic agonists.

Ghrelin is a peptide hormone secreted by gut endocrine cells (mainly proximal stomach) to regulate appetite, but also has effects on motility. It increases gastric emptying, possibly via the vagus nerve or *area postrema*. Ghrelin receptor agonists have been shown to reduce vomiting in animal models and humans [44]. Trials are ongoing, but such agents might prove useful in future.

Level of evidence: V

3.3.3. Jejunal feeding

The jejunal route may succeed when a child is unable to tolerate gastric feeding. It may be advocated as an alternative to fundoplication for the management of tube-fed children diagnosed with GORD, and has been utilized as a rescue therapy for retching and other symptoms after fundoplication [47–52]. Feeding directly into the jejunum will reduce gastric distension and triggering of transient lower esophageal sphincter relaxations. It will also abolish the gastric reservoir of feed available to reflux in those children with GORD owing to deficient

lower esophageal sphincter tone. It has been used in infants as a 'reversible' method of managing troublesome reflux symptoms while awaiting natural resolution as the child matures.

Jejunal feeding may also be useful in the management of children with recurrent activation of the emetic reflex and chronic retching [1,21,29]. In addition to circumventing any problems owing to gastric dysmotility and poor gastric emptying, jejunal feeding will avoid gastric distension and bypass the sensitive gastric and duodenal mucosa, and is therefore less likely to trigger emesis and symptoms of retching.

Additional gastric drainage. In some children, gastric emptying may be so delayed that the pooling of gastric secretions alone causes symptoms, especially if high volumes are produced in response to jejunal feeding. In this situation, additional gastric drainage may be beneficial. In others, the visceral afferent stimulation induced by even very small volumes of water or medicines administered into the stomach, or by feeding into the jejunum, may activate the vomiting reflex and cause retching; they too may require regular aspiration or periods of gastric drainage to keep them symptom-free. In these children, the drainage is often green or yellow, owing to the retrograde intestinal peristalsis that is part of the emetic reflex, sweeping proximal intestinal contents back into the stomach.

Jejunal feeding and fundoplication are often referred to as interchangeable forms of management, but this is not the case. Fundoplication is not a treatment for symptoms owing to activation of the emetic reflex or to dysmotility. Fundoplication creates a mechanical valve at the gastroesophageal junction [53] and is a treatment for 'pure' GORD, whereas many children with neurodisability also have some degree of generalized gut dysmotility, impaired accommodation, or heightened emetic reflex. Jejunal feeding, on the other hand, is applicable to either situation, or in the presence of a mixture of symptoms, so has a much broader application. The jejunal route is commonly viewed as a last resort, to be used after fundoplication or other modalities fail. It is not seen as a valid approach in its own right; it is often considered as 'palliative' (and that antireflux surgery is 'curative') and consequently many clinicians regard jejunal feeding as a 'failure.' However, an understanding of the pathophysiology of these children's symptoms shows that this is not an appropriate view. Jejunal feeding should not be regarded as a regressive step, but as a logical mode of treating visceral hyperalgesia or dysmotility [21].

Insofar as we cannot 'fix' the gastrointestinal dysfunction in these children, all our treatment is aimed at relieving symptoms and therefore palliative. Moreover, palliation is a valid aim of treatment.

Different routes for accessing the jejunum are available and may be broadly categorized as transpyloric (nasojejunal or gastrojejunal) or direct (which may be surgically, radiologically or endoscopically fashioned). The advantages and complications of each are beyond the scope of this review, although a therapeutic trial of transpyloric feeding is readily instituted and readily reversed.

Level of evidence: IV

3.4. Use of antiemetics to block the emetic reflex

If a specific cause for retching cannot be identified, it is logical to use antiemetics, although no single agent is universally effective. A wide variety of agents that target different components of the emetic pathway is available. A few reports focus on one specific drug for treatment of retching following fundoplication e.g. alimemazine [54], metoclopramide [43], cyproheptadine [55]. Other useful agents include the 5-HT_3 receptor antagonists [1,28]. New classes of antiemetic such as cannabinoids or neurokinin receptor-1 antagonists are also of potential value [1].

It should be remembered that the newer antiemetic agents, in particular, were developed for the management of acute chemotherapy induced nausea and vomiting (CINV) and PONV and may not yet be recognized for other indications or for long term use. However, clinicians may consider their use in carefully selected individual patients to be justifiable if it relieves distressing symptoms.

3.4.1. Domperidone and metoclopramide

Dopamine receptor-2 antagonists (DA_2RA) have direct antiemetic actions in addition to improving delayed gastric emptying; they are considered with the prokinetics (section 3.3.2).

Level of evidence: IV

3.4.2. Alimemazine

Alimemazine is a sedating phenothiazine histamine receptor-1 antagonist (H_1RA) with significant antimuscarinic activity, recognized for treatment of urticaria/pruritis and as a premedication. H_1RAs also have antiemetic properties via H_1RA action in the nucleus of the *tractus solitarius* and anticholinergic action in the vestibular apparatus. As a phenothiazine, alimemazine will also have centrally acting DA_2RA effects. Antao etal. [54] report a prospective, double-blind, randomized, crossover, placebo-controlled study of neurologically impaired children with symptoms of retching following Nissen fundoplication. Each child was randomly allocated to receive one week each of alimemazine and placebo with crossover. 12/15 completed the study; the mean number of retching episodes per week was lower, 10.42 ± 9.48 with alimemazine compared with 47.67 ± 2.79 on placebo ($p<0.0001$). A limiting factor is the sedating side effects of alimemazine.

Level of evidence: II (single small RCT)

3.4.3. Cyproheptadine

Cyproheptadine is a potent serotonin (5-hydroxytryptamine, 5-HT) receptor antagonist, used to stimulate appetite. It acts as an antagonist at multiple sites, including serotonin (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}), histamine (H_1) and muscarinic receptors. It has been found to be effective in treating retching and vomiting in children [56], including that following fundoplication [21,55]. Rodriguez etal. [55] reported a retrospective open label study of cyproheptadine in 80 children with refractory dyspeptic symptoms (nausea, early satiety, vomiting early or late after meals, retching after fundoplication and abdominal pain). The 14 children with retching following Nissen fundoplication showed the highest response rate (86%), with eight significantly improved and four with symptom resolution. The authors suggested that the mechanism of action was improved gastric accommodation; given its broad spectrum of affinity, there may well be multiple sites and mechanisms of action. Cyproheptadine may also help alleviate gut-related pain symptoms; e.g. Madani etal. have found cyproheptadine beneficial in the management of functional abdominal pain in children [57].

Level of evidence: IV

3.4.4. Ondansetron

The newer 5-hydroxytryptaminereceptor-3 antagonists (5-HT_3RA), such as ondansetron, suppress triggering of the emetic reflex by blocking receptors on both peripheral and central terminals of abdominal vagal afferents, including those from the gastric mucosa, where enterochromaffin cells release 5-HT [4]. Approved uses in children include CINV and PONV. They may also effect relief from chronic retching following fundoplication in some children with neurodisability [21,28].

Level of evidence: IV

In some children, their symptoms of distress, retching and vomiting with enteral feeds persist despite the more established antiemetics. Such children are potential candidates for newer or

lesser-used agents. Although there are no published reports specific for postfundoplication retching, these centrally acting agents have the potential for superior emetic control when others fail to control symptoms.

3.4.5. Aprepitant

Neurokinin receptor-1 antagonists (NK_1RA) were first developed to target delayed CINV, which is mediated by substance P within the brainstem [58]. They have a very broad spectrum of activity, uniquely effective against stimuli acting via abdominal vagal afferents, the *area postrema* and the vestibular system [4]. This suggests that they act centrally to modulate the integration of the emetic reflex.

Aprepitant (and its intravenous prodrug fosaprepitant) was the first NK_1RA licensed for clinical use; it is approved together with a 5-HT_3RA in the prevention of CINV in adults. It has also been used in adults for the management PONV. There are reports of its successful use in adults with gastroparesis and symptoms of nausea and vomiting [59,60]. There are little data for the pediatric population, but reports are now emerging of safe, superior symptom control for children and young people undergoing emetogenic chemotherapy for brain tumors [58,61] and in resistant cyclical vomiting [62]. The broad spectrum of efficacy of aprepitant (and other, newer, NK_1RA such as rolapitant and netupitant) offers potential for use in children with chronic retching if other strategies fail [1,28].

Level of evidence: V

3.4.6. Levomepromazine

Levomepromazine is a first-generation neuroleptic. A phenothiazine derivative, it acts predominantly as a DA_2RA within the brain (including the *area postrema*) [28]. It has pronounced sedative effects (which limit its use) and moderate antimuscarinic and extrapyramidal side effects. It is indicated in palliative care for management of intractable nausea and vomiting (and, in larger doses, for restlessness and confusion) [4].

Level of evidence: V

3.4.7. Cannabinoids

Nabilone is a synthetic cannabinoid with good antiemetic properties. It is an agonist at cannabinoid-1 (CB_1) and cannabinoid-2 (CB_2) receptors. CB_1 receptors are numerous and widespread throughout the central nervous system, including the dorsal vagal complex and other regions involved in the emetic reflex. Nabilone modulates the emetic reflex via presynaptic CB_1 receptors; it may also have effects via $5HT_3$ and DA_2 receptors [63]. It has been used (unlicensed) for CINV unresponsive to conventional antiemetics.

Level of evidence: V

3.5. Neuromodulation, other novel and alternative, potential therapeutic antiemetic strategies

3.5.1. Management of chronic pain and discomfort related to enteral feeds

The following interventions would be regarded as management strategies for feeding-induced abdominal pain and discomfort. They are included briefly because such symptoms often coexist with retching and vomiting and it may be difficult or impossible to distinguish between postprandial pain and nausea in the nonverbal child. Parents identify that their child is distressed, but the nature of the unpleasant sensation may be more difficult to determine. Pain and discomfort may reflect the presence of an underlying visceral afferent sensitivity, impaired gastric accommodation, or dysmotility that acts as trigger for the vomiting reflex and retching [21]. Reducing the level of visceral afferent stimulation by reducing pain and discomfort, may in turn reduce emetic sensitivity. The tricyclic antidepressants and the gabapentinoids are now recognized to have antiemetic properties [4], and both have been used for symptom relief in children with postoperative retching [21,64]. Furthermore, the presence of other symptoms may determine which is the drug of choice in the management of retching in a specific child.

Tricyclic antidepressants. Amytriptyline and other tricyclics are used in the management of neuropathic pain and visceral hyperalgesia. They act by presynaptic reuptake inhibition of serotonin and norepinephrine in the central nervous system, thus modulating descending pain inhibition (in addition to $5HT_2$, H_1 and ACh antagonism) [65]. They were used with success by Zangen etal. in the treatment of children with chronic retching, vomiting and food refusal following fundoplication [21].

Level of evidence: IV

Gabapentinoids. Gabapentin and pregabalin are used for neuropathic pain and visceral hyperalgesia. They act within the central nervous system as a gamma-aminobutyric acid analogue to inhibit excitation of voltage-gated calcium channels and reduce release of excitatory neurotransmitters such as glutamate and substance P [65]. Gabapentin has been used in the management of visceral hyperalgesia in children with severe neurodisability and was found to improve symptoms of retching and vomiting and feed intolerance [21,64]. O'Mara etal. [66] found gabapentin improved symptoms of retching and feed intolerance attributed to visceral hyperalgesia in infants with gastroschisis or congenital diaphragmatic hernia after Nissen fundoplication; Edwards etal. [67] found gabapentin improved symptoms of restlessness during feeds and of vomiting in neurodisabled preterm infants.

Level of evidence: IV

Cannabinoids. Cannabinoids have a potential role in the management of pain, and of spasticity; e.g. Dronabiol (a synthetic form of tetrahydrocannabinol with agonist activity at CB_1 and CB_2 receptors) is used in the USA for central neuropathic pain and spasticity in adults with multiple sclerosis and also as an appetite stimulant [65]. It also has antiemetic properties [63]. Conversely, the antiemetic nabilone (see section 3.4.7) has been used for the management of neuropathic pain in adults [65]. There are no reports so far of their use postfundoplication.

Level of evidence: V

'Herbal remedies'. Ginger and ginseng are effective in the relief of nausea and vomiting in a variety of situations, acting in part by $5HT_3R$ inhibition [68,69]. There are no reports of their use in children with recurrent retching after fundoplication, but they would be a logical choice for families who wish to use 'natural' therapies or traditional medicines.

Rikkunshinto (a combination of eight different herbs) is widely used in Japan (by both adults and children) for a variety of 'gastric complaints,' including dyspepsia, and may also improve symptoms of vomiting in children with neurodisability [70]. (There is also clinical trial evidence for efficacy in the treatment of GORD [71].) There are no reports of their use postfundoplication at present.

Level of evidence: V

Sympathetic nerve blockade. Sympathetic afferents transmit nociceptive information from the gut and its adnexae, and splanchnic nerve blockade is recognized to be of value in some patients with chronic visceral pain, particularly pancreatic disease [72,73]; sympathetic afferents may also have a role in activation of the emetic reflex. Splanchnic nerve blockade by temporary celiac plexus block or permanent splanchniectomy [43] is reported to relieve gut-related symptoms postfundoplication in children with severe neurodisability. It is unclear which symptoms were improved (whether pain or retching or both), but the postulated mechanisms were both increasing (and therefore improving) gastrointestinal motility by removing excessive sympathetic inhibition, and removing a source of nociceptive signaling.

Level of evidence: IV

3.5.2. Acupuncture

The Chinese tradition of acupuncture involves the insertion of fine needles into the skin and muscle at specified locations – 'acupoints' – followed by mechanical or electrical stimulation. The effect is specific to the different acupoints. Acupuncture has been used to treat a variety of gastrointestinal disorders including gastroparesis, functional dyspepsia, irritable bowel syndrome, constipation, diarrhea and visceral hypersensitivity. Although clinical evidence specifically addressing effectiveness in children is of poor quality [74], and there are no reports relating to postfundoplication retching, there is good evidence that acupuncture is an effective antiemetic. Acupuncture stimulates the somatic afferent nerves of skin and muscles at the acupoint. There is physiological and anatomical evidence that this results in neuromodulation at the level of the nucleus of the *tractus solitarius* and alters gastrointestinal motility via vagal and sympathetic pathways. Stimulation of acupoint PC-6 (wrist) has been used to treat nausea and vomiting. There is evidence that this is via the opioid antiemetic pathway in the vomiting center deep in the brainstem. There is clear evidence that it is effective in PONV and CINV in adult patients and it also reduces gastric tachydysrhythmia induced by motion sickness. There is also evidence that acupoint ST-36 (adjacent to the knee) attenuates visceral pain, again via a central opioid pathway (for review see Takahashi 2011 [75]).

Level of evidence: V

3.5.3. Vagus nerve stimulation

It is now clear that the vagus nerve has roles far beyond that of a conduit for autonomic reflex pathways for the thoracic and abdominal viscera, and that these roles are crucial to the proper functioning of the immune system and the gastrointestinal tract. This offers new insights into the effects upon the gastrointestinal tract of vagal dysfunction, and new therapeutic strategies that may prove effective in future.

The vagal anti-inflammatory pathway. The vagus nerve has an important role in the modulation and limitation of inflammation, both systemically and within the gastrointestinal tract, via the cholinergic anti-inflammatory pathway [76]. In experimental studies, vagal efferent stimulation has anti-inflammatory effects, whereas vagotomy is proinflammatory [77]. Inhibition of this pathway is implicated in the pathogenesis of disorders such as inflammatory bowel disease, and methods of vagal efferent stimulation to increase 'vagal tone' to activate this pathway are of potential therapeutic value, without the significant side effects of current biological tumor necrosis factor-α (TNFα) inhibition [78]. This has implications for the pathogenesis and management of gastrointestinal dysmotility in children with neurodisability, in whom vagal dysfunction may have far-reaching consequences, previously unappreciated. Postoperative ileus is a result of macrophage-induced inflammation within the myenteric plexus; failure of inhibition by the normal (vagal) cholinergic anti-inflammatory pathway might account for the severe and prolonged exacerbations of dysmotility that may be seen in these children after abdominal surgery (including fundoplication).

Abnormalities of 'vagal tone' to the gut might result in local gut inflammation, dysmotility and feed intolerance. This could provide an immunological explanation for the superior tolerance of hydrolyzed formula in some children on enteral tube feeds. Alternatively, blenderized feeds, by altering the microbiome favorably and thereby impacting upon immunoregulation, might compensate for a deficient vagal anti-inflammatory input, leading to better tolerance.

The vagal nociceptive pathway. Historically, the main visceral pain pathways were considered to follow the sympathetic innervation, but it is now becoming clear that the vagus has an important role in modulating the perception of visceral pain, offering vagal afferent stimulation as another therapeutic target [79,80].

Electrical vagus nerve stimulation may target afferent or efferent fibers (dependent upon the stimulator parameters), using transcutaneous or implanted electrodes. Various sites are available—preauricular, cervical, subdiaphragmatic (potentially with different effects). The reader may be familiar with the result of physiological stimulation e.g. forced deep breathing, which has an antiemetic effect (likely via thoracic vagal afferents to the 'antiemetic center' deep to the *area postrema*) and slows the heart rate. Vagal nerve stimulation has the potential to modulate the cholinergic anti-inflammatory pathway, and hence by modulating gastrointestinal inflammation, impact upon gastrointestinal motility and nociception. Additional direct modulation of pain pathways offers further potential for the management of pain perception from the gastrointestinal tract [79,80].

Level of evidence: V

Gastric electrical stimulation. Gastric electrical pacing or gastric electrical stimulation (using implanted serosal or mucosal electrodes) has been used to treat a number of conditions, including gastroparesis. Short-pulse electrical stimulation has been shown to have antiemetic actions in dog emetic models, via vagal pathways. Case series in humans with gastroparesis from a variety of causes have shown improvement in symptoms of nausea and vomiting (especially in diabetic autonomic neuropathy) but little effect on other symptoms such as bloating and pain. Symptom relief does not correlate with improvement (or lack thereof) in gastric motility or emptying rates. It is highly likely that rather than a direct effect upon gastric musculature, the mechanism of action is via modulation of *vagal afferent* activity (reviewed by Hasler [81]).

Level of evidence: V

3.6. Avoid treatments that worsen or cause retching:

3.6.1. Would a different type of fundoplication result in less retching?

Ideally, we would avoid the development of retching following antireflux surgery, rather than treating it postoperatively. The commonest-performed fundoplication is the Nissen, but would a different type of fundoplication be followed by less retching? The main differences might be between:

1. Partial versus full wraps

2. Laparoscopic versus open surgery
3. Limited versus extensive dissection of the diaphragmatic hiatus.

Is retching less frequent after a partial wrap compared with a full wrap?. It is plausible that a partial wrap could allow vomiting more readily, and therefore terminate retching more quickly, leading to a lower reported incidence or severity of postoperative retching. Ramachandran etal. [82] reported a retrospective cohort of 141 children with severe neurological impairment undergoing Thal fundoplication. Of the patients with an intact Thal who could be assessed, 40 could, and 20 could not, vomit if required; they suggest this ability to vomit put less stress upon the wrap compared with Nissen fundoplication. However, data comparing the incidence of retching in complete versus partial wraps are scanty. In a systematic review and meta-analysis of partial versus complete fundoplication, Glen etal. [83] identified only two retrospective papers out of two randomized controlled trials and 12 retrospective cohort studies [84,85] that compared the incidence of postoperative retching; neither found a significant difference between groups. The reviewers found that overall, study quality was poor. i.e. the available data are very limited and subject to bias.

Level of evidence: IV

Moreover, the difference between complete and partial wraps may not be as great as supposed— in a *post mortem* study, Butterfield [53] compared four different wraps (Nissen, Hill, Belsey, Thal) and found that if the wrap was competent at low pressure (i.e. on filling of the stomach via the pylorus there was no leak from the gastroesophageal junction), then it was also competent to the application of high pressure (250 mmHg/340 cmH_2O) to the stomach, as might be experienced during retching. On dissection of the preparations and viewing from the luminal aspect, all four wraps, whether full or partial, looked very similar. There will also be significant variation between surgeons performing a fundoplication of the same name e.g. some Nissen fundoplications are much 'floppier' than others, and a comparison of different surgeons performing different wraps is likely to introduce many variables. Furthermore, a partial wrap that allows easier vomiting, with less retching, may be confused with a wrap that does not control reflux, leading to a designation of a failed wrap.

Is retching less frequent after laparoscopic surgery compared with open surgery?. There are very little data available comparing the incidence of retching in children following laparoscopic versus open fundoplication. Laparoscopic surgery might result in less nerve damage and less scarring, and might reduce postoperative retching. One early retrospective cohort study of children undergoing a variety of antireflux procedures or formation of a gastrostomy found no difference in the overall incidence of retching postoperatively [86] (Table1).

Of the published meta-analyses of laparoscopic versus open fundoplication, many do not report on retching. Wei etal. [87] and Zhang etal. [88] both identified two randomized controlled trials (RCTs), one from the UK [89,90] and one from Norway [91] (Table1).

The trial reported by McHoney etal. [89] and updated by Pacilli etal. [90] does report a lower incidence of postoperative retching in the laparoscopic group, but the preoperative incidence in each group is unknown and patient numbers are very small. Factors such as use of antiretching treatments are not recorded. The same institution previously reported a much higher incidence of retching (19/79 infants i.e. 24%) following laparoscopic fundoplication [92].

Of these two RCTs, only the larger study by Fyhn [91] prospectively recorded and presented data on preoperative retching. They state that there was no significant difference in postoperative retching between the groups. This 2015 report of one, two and four-year outcomes enumerates the presence/absence of postoperative retching *only in those without recurrent GORD* (confirmed to be owing to wrap failure in those who underwent reoperation), but there was a large and significant difference in the incidence of wrap breakdown which was much commoner in the laparoscopic group. This might be attributable to a higher incidence of postoperative retching in the laparoscopic group exerting disruptive forces, or (more likely) to a laparoscopic wrap being less 'robust,' but this means that the postoperative retching status of many of the laparoscopic patients was not stated in this paper. However, a new report from this group that focuses on early outcomes (one month postoperatively) [93] gives a much clearer indication of the incidence of retching before wrap breakdown has occurred. These data show that the incidence of retching is increased postoperatively in both laparoscopic and open groups (Table1).

Level of evidence: II (two small contradictory RCT with incomplete reporting)

Does minimal dissection of the hiatus reduce retching?. Minimal dissection around the esophageal diaphragmatic hiatus should result in less disruption of the normal tissues and may cause less nerve damage (especially to the vagal trunks and major branches), less scarring, and less disturbance of motility. This might reduce postoperative retching. In addition, preservation of the anatomy and elasticity of the hiatus will allow the normal (subdiaphragmatic) position of the gastroesophageal junction to be restored more readily after any retching stops.

Desai etal. found that minimal dissection of the esophageal hiatus results in a significant reduction in the rate of, and later occurrence of, wrap herniation/disruption [94]. The proportion with wrap herniation versus disruption alone also decreased significantly. At long term follow up, the incidence of retching – and the number of children on antiretching medication – was the same in both groups [94], suggesting that the mechanism is not the reduction of retching.

Level of evidence: II (one small RCT)

3.6.2. Would a different antireflux procedure result in less retching?

Some surgeons advocate an additional or alternative (often historical) antireflux procedure to overcome the high rate of wrap failure. Do such procedures cause fewer problems with retching? These might be:

1. An additional gastric emptying procedure
2. Fundoplication with additional vagotomy and pyloroplasty
3. Esophagojejunostomy with Roux-en-Y loop.

Additional gastric emptying procedure. There are no prospective studies of the effect of a gastric emptying procedure, in addition to fundoplication, upon the incidence of postoperative retching. Reports assessing the impact of an additional gastric emptying procedure have often been retrospective, and the outcome has been 'recurrent reflux' or redo fundoplication. The current consensus is that fundoplication results either in no change, or an increase, in gastric emptying rates [95,96], and that abnormally slow preoperative emptying may be normalized after fundoplication [97].

In a prospective randomized controlled trial of laparoscopic versus open Nissen fundoplication, Knatten etal. [98] were able to assess the gastric emptying rate preoperatively in 35/74 subjects. They found no significant difference in the incidence of postoperative retching in patients with preoperatively delayed gastric emptying (liquids), compared with the rest of the group. However, numbers are small,

Table1
Comparison of the incidence of retching following open versus laparoscopic wraps.

Author	Patient Group	Outcome
Collins etal. 1996 [86]	Retrospective cohort study of 60 open procedures followed by 60 laparoscopic procedures in comparable groups, single surgeon Open surgery 42/60 severe neurodisability Laparoscopic surgery 40/60 severe neurodisability (follow up for 2 years from the date of the first patient in each cohort) Open surgery: 47 antireflux procedure (various) (plus 39 gastrostomy, 5 gastric emptying procedure) and 13 gastrostomy only Laparoscopic surgery: 55 antireflux procedure (various) (plus 36 gastrostomy, 20 gastric emptying procedure) and 5 gastrostomy only Postoperative interventions for retching not reported	Preoperative: 24/60 (40%) pre-open surgery had retching 14/60 (23%) pre-laparoscopic surgery had retching Postoperative (0–2 years): 3/13 (23%) open gastrostomy had retching 0/5 (0%) laparoscopic gastrostomy had retching 10/47 (21%) open fundoplication had retching 8/55 (15%) laparoscopic fundoplication had retching (not significant)
Pacilli etal. 2014 [90] (update of McHoney etal. 2011 [89])	31/39 neurologically impaired; results for 34 children at 22 months and 31 children at 4 years presented Randomized controlled trial open versus laparoscopic Nissen 22 month and 4 year follow-up data Randomized trial but not stratified for retching Incidence of preoperative retching not reported Postoperative interventions for retching not reported	At 22 months: 10/18 (55%) retching post-open fundoplication 1/16 (6.3%) retching post-laparoscopic fundoplication P = 0.02 At 4 years: 8/16 (50%) retching post-open fundoplication 1/15 (7%) retching post-laparoscopic fundoplication P = 0.01 At 4 years: 2/16 (13%) vomiting post-open fundoplication 3/16 (19%) vomiting post-laparoscopic fundoplication
Fyhn etal. 2015 [91]	87 children, 46/87 with neurodisability (23 in each group) Randomized controlled trial of open versus laparoscopic Nissen Incidence of preoperative retching ascertained but not stratified between groups. Retching underreported a) Only retching occurring 4–7 days per week included in analysis b) Only reported postoperatively in those without wrap failure (thus omitting a group at high risk of retching, and potential for relative underreporting in the laparoscopic group) c) Postoperative interventions for retching not reported	Preoperative: 10/43 (23%) retching pre-open fundoplication 14/44 (32%) retching pre-laparoscopic fundoplication At 1 year: 5/38 (13%) retching post-open intact fundoplication 4/25 (16%) retching post-laparoscopic intact fundoplication At 2 years: 4/38 (13%) retching post-open intact fundoplication 2/24 (8%) retching post-laparoscopic intact fundoplication At 4 years: 4/36 (11%) retching post-open intact fundoplication 0/25 (0%) retching post-laparoscopic intact fundoplication At 4 years: 3/43 (7%) recurrence of GORD post-open fundoplication 16/44 (37%) recurrence of GORD post-laparoscopic fundoplication P = 0.001
Fyhn etal. in press [93]	(Subgroup of Fyhn etal. 2015) 55 children, 29/55 with neurodisability Randomised controlled trial of open versus laparoscopic Nissen Incidence of preoperative retching ascertained but not stratified between groups. Postoperative interventions for retching not reported	Preoperative: 15/55 (27%) retching 5/28 (18%) retching pre-open fundoplication 10/27 (37%) retching pre-laparoscopic fundoplication (not significant open versus laparoscopic) Postoperative At 1 month: 26/55 (47%) retching 11/28 (39%) retching post-open fundoplication 15/27 (56%) retching post-laparoscopic fundoplication (not significant open versus laparoscopic)

and as already discussed, there may be relative underreporting in the laparoscopic group [91].

A prospective study by Johnson etal. [99] is of interest. They investigated 27 children (11 with neurodisability); gastric emptying rates of both solids and liquids were assessed before and after fundoplication. 17 completed the full protocol. There was no significant change in solid emptying after fundoplication, but the liquid rate significantly increased within the group overall. However, the individual effects were very variable, with increase, no change or decrease (Figure2 [99]). Although those with delayed gastric emptying of liquids *after* fundoplication were much more likely to be symptomatic (one or more of fullness, decreased appetite, retching) (Table1 [99]), it was not possible to predict this from the preoperative study. Moreover, three children with persistent postoperative symptoms, who subsequently underwent pyloroplasty, failed to improve their gastric emptying and failed to be relieved of their symptoms (Figures4–6 [99]). They concluded that a fundamental gastric motility disorder is the likely cause of delayed gastric emptying in these children, and caution against a procedure that has not been demonstrated to be beneficial, and that may cause complications such as duodenogastric reflux.

The data suggest that it is impossible to predict preoperatively which patients might have delayed gastric emptying after fundoplication. Moreover, given that retching is because of activation of the emetic reflex, an association between retching and delayed gastric emptying may arise either because activation of the emetic reflex leads to both, or because emptying that is too slow causes gastric distension with retching +/− vomiting. Conversely, gastric emptying that is too fast may lead to activation of retching +/− vomiting owing to dumping syndrome. Indeed, Jolley etal. [100] found that postoperative retching was related to extremes of gastric emptying rate. Current evidence does not support the use of an additional gastric emptying procedure at the time of fundoplication to prevent postoperative retching.

There remains the possibility that a subsequent gastric emptying procedure might benefit a selected group of children with proven delayed gastric emptying postfundoplication where more conservative measures have failed, although this was not the experience of Johnson etal. [99]. Due consideration should be given to the possibility that the delayed emptying is part of the emetic process, rather than the cause, and the potential surgical complications.

Level of evidence: IV

Fundoplication with additional vagotomy and pyloroplasty. Fundoplication plus vagotomy and pyloroplasty [101–103] was used previously in adult practice before antisecretory agents were available, for patients with both reflux disease and peptic ulcer disease. It is no longer performed in adults because there is no advantage in reflux control, whereas the side effects of vagotomy cause symptoms as a result of motility disturbances.

There is only one paper reporting on the use of fundoplication with additional vagotomy and pyloroplasty in children [104]. It is a retrospective cohort study; diagnostic criteria and indications for surgery are not clearly defined. More children in the fundoplication-only group underwent redo surgery, but retching and vomiting symptoms at most recent follow-up appear to be more common in the vagotomy and pyloroplasty group (Table2 [104]), and two of the vagotomy and pyloroplasty patients had symptoms attributed to dumping (although neither had postprandial hypoglycemia), although this may have been a worse group preoperatively.

The reduction of pathological vagal afferent input from the gastrointestinal tract is an attractive prospect, and experimental studies have shown that acute vagotomy can block retching and vomiting that are induced by activation of gastric vagal afferents [32]. However, as already discussed, chronic vagotomy may induce or uncover a novel emetic mechanism [15,22]. Moreover, vagotomy will also interrupt the motor and anti-inflammatory pathways. The resulting impact upon dysmotility and inflammation is unpredictable and potentially detrimental, and vagotomy is irreversible. Reversible methods of modulation of vagal traffic (sections 3.2–3.5) might be a preferred alternative.

Level of evidence: IV

Esophagojejunostomy withRoux-en-Yloop*(also referred to in the pediatric literature as 'esophagogastric disconnection' or 'esophagogastric dissociation')*

This was described in detail by Allison [105] and subsequently reported in children by Bianchi [106] and by Danielson and Emmens [107]. It is argued that there is no longer any (direct) connection between stomach and esophagus and, unlike fundoplication, there is no wrap to disrupt; therefore the procedure is 'permanent' and will not require a 'redo.' However, reflux of gastric contents into the esophagus *can* occur, albeit indirectly [108]; jejunoesophageal reflux may also be an issue [109]. Division of the esophagus puts the vagus at risk (even if not knowingly or intentionally divided) and although patients do not require further surgery for a redo wrap, there is an incidence of reoperation for internal or transhiatal herniation, or anastomotic leak [108], and the procedure carries higher mortality compared with fundoplication. To date, pediatric series have been retrospective studies with little information on diagnosis or patient selection. Physiological evaluation before or after surgery is lacking. The best-documented outcomes relate to surgical complications. Symptom outcomes are less well reported, although it is clear that postoperative retching is extremely common— 96% in the series of Coletta etal. [108], and 20% also with postprandial bloating. Little attention has been paid to other postoperative issues such as reflux of bile into the esophagus or stomach [109] or weight loss and nutritional deficiencies [110].

The esophagojejunal Roux loop is still used in adult practice, but it is reserved for difficult reiterative surgery and not as a first-line procedure owing to significant morbidity [111].

Level of evidence: IV

3.6.3. Patient selection: is any form of antireflux surgery indicated?

There is scope for improved selection of patients for fundoplication, thereby avoiding the development or worsening of retching, rather than treating it postoperatively.

The key to prevention of postoperative retching is the distinction between volume regurgitation owing to reflux, and vomiting with retching owing to activation of the vomiting reflex. There is considerable confusion in the pediatric literature between GOR/GORD and activation of the emetic reflex [1]. This began with the early reports stating that GORD is common in children with neurodisability and advocating fundoplication to stop the vomiting [112–114]. The diagnosis was frequently made on a contrast x-ray. However, radiology will not distinguish episodes of physiologic GOR, as occurs in all humans, from GORD. Nor will it distinguish GOR/GORD from vomiting owing to activation of the emetic reflex. The 'hiatus hernia and reflux' reported by the radiologist may not be GOR at all, but rather the normal accompaniment of activation of the emetic reflex. Retching causes temporary migration of the normal gastroesophageal junction into the thorax and return of gastric contents into the esophagus (which is not 'GORD') [2]. It is now recognized that radiology must not be used to diagnose reflux disease [42]. This is not just because of the occurrence of physiological reflux but also because of the confusion with the emetic reflex, a fact that is, for the most part, unappreciated.

Even with the development of more sophisticated diagnostic techniques (endoscopy and biopsy, 24-h intraesophageal pH monitoring and most recently impedance monitoring) these have not

been used consistently or rigorously [26,27]. There persists in pediatric practice the widespread but mistaken view that chronic vomiting and GOR/GORD are one and the same. As a result, chronic vomiting symptoms are frequently misattributed to GORD. The possibility that the vomiting is because of activation of the emetic reflex is often overlooked. Moreover, the possibility that the patient's various symptoms may have more than one cause is not considered. This has led to the attribution of a wide variety of symptoms to GORD and considerable disappointment with the results of antireflux surgery. When medical management for GORD fails, this should prompt a review of the diagnosis and a search for other causes of those symptoms (see Appendix A) [17]. Instead, children are referred, and accepted, for antireflux surgery.

Recent reviews and meta-analyses of pediatric fundoplication have drawn attention to the lack of systematic rigorous preoperative evaluation and diagnosis prior to antireflux surgery. Many patients are not demonstrated to fulfill the definition of GORD i.e. bothersome symptoms or complications attributable to GOR, and are not demonstrated to have undergone an adequate trial of nonsurgical management [42,95,115,116]. Current guidelines on the management of GORD emphasize the need to demonstrate that GOR is the cause of the symptoms in question [42].

The presence of neurodisability has become an indication for surgery in its own right, despite multiple reports that this group does not do well postoperatively. The reality for many of these children is that their symptoms do not respond because they are not caused by GOR or GORD; rather they are a result of generalized dysfunction of the central, autonomic and enteric nervous systems. These children either do not have reflux disease, or reflux is only part of the problem, and many of their symptoms are because of dysmotility (including impaired gastric accommodation), visceral afferent hypersensitivity, and impaired central processing; separately or in combination, these lead to activation of the emetic reflex. Fundoplication is treatment for GORD that is resistant to optimized medical therapy or requiring long term treatment. It is not treatment for activation of the vomiting reflex; by preventing expulsion of vomit, it *prolongs* activation of the reflex. Not only does fundoplication fail to relieve the symptoms, it may exacerbate the situation and the persistently recurring retching forces destroy the wrap [2]. An antireflux procedure is not appropriate treatment for these children, and we need to improve the selection of patients for fundoplication.

Careful prospective questioning reveals that many children have symptoms of retching *before* antireflux surgery [8]; preoperative retching is predictive of postoperative retching [7] and postoperative wrap failure [117,118]. Preoperatively, children can be divided into two groups: a 'high risk' group comprising those with symptoms reflecting the prodromal phase of the emetic reflex (e.g. nausea, sweating, pallor) and/or retching in association with their vomiting, and a 'low risk' group of those who lack such symptoms and present with effortless 'vomiting,' regurgitation and posseting/spitting up, or who do not 'vomit' but have other symptoms [7]. This suggests that many children already have some sensitization of the emetic reflex contributing to their symptoms, and that this is revealed and even enhanced by antireflux surgery. Vomiting will attract more attention than retching, especially if retching is quickly followed by vomiting, so unless specifically sought as a symptom, retching may only be reported for the first time postoperatively. Other children may have more subtle evidence of activation of the emetic reflex. The biological 'purpose' of nausea is in learning to avoid repeated ingestion of food that causes illness and vomiting. In some children, food refusal is an indication of nausea [30]. By refusing food, the child is limiting the emetic stimulus and controlling their own symptoms. Giving the child a feeding gastrostomy means that avoidance is no longer possible, and the child will start to vomit. Performing a fundoplication means that the child retches persistently, unable to expel the noxious stimulus. A fundoplication that allows vomiting more readily (with cessation of the retching) is still not addressing the underlying problem of activation of the emetic reflex and the associated nausea.

Although hyperemesis is often present in neurologically impaired children preoperatively, in some cases it does appear to be worse postfundoplication. The parents may describe retching as being more troublesome [23], and there are changes in the gastric electrical control activity after surgery that are related to postoperative retching [8]. As previously discussed (section 3 Overview) there is also some evidence that fundoplication may predispose to activation of the emetic reflex even in neurologically normal subjects. In the ferret model, there is damage to the vagus nerve and branches, and to the gastric muscle, in the region of the wrap [13]; emetic sensitivity is increased postfundoplication compared with controls, in addition to evidence of gastric dysmotility [14]. Fyhn etal. [93] reported an increase in the incidence of retching postoperatively in both neurologically normal and neurologically impaired children. Emetic symptoms (e.g. nausea with or without vomiting) developing postoperatively in adults following fundoplication have also been described [16].

Di Lorenzo etal. report a group of 28 children whose symptoms were considered worsened or unchanged by fundoplication [119]. All had normal or delayed gastric emptying (ruling out dumping) on radionuclide scanning. 13 had vomiting or repeated retching. 25/28 had abnormalities on antroduodenal manometry, including absence of the migrating motor complex, and postprandial hypomotility. The abnormalities resembled those found in children with chronic intestinal pseudo-obstruction and children with unexplained chronic vomiting. They comment that, in the presence of a disorder involving the gastrointestinal tract distal to the esophagus, fundoplication, by elimination of the ability to vomit, may make symptoms worse, and advise against fundoplication in children with a generalized motility disorder. Van Winckel and Robberech writing about the poor results of antireflux surgery in profoundly disabled children comment that these children have 'complete bowel dysmotility,' including 'recurrent bilious vomiting and constipation' [120]. Miki etal. [121] describe a group of 11 neurologically impaired children and young people with gastrointestinal symptoms, all of whom had abnormalities on antroduodenal manometry. Zangen etal. [21] investigated a group of 14 young children who had persistent retching, vomiting and food refusal following fundoplication. All had gastrointestinal dysmotility and/or sensory abnormalities. In a subsequent study of neurologically handicapped children, Werlin [122] reports that foregut dysmotility may explain many of their upper gastrointestinal symptoms and may mimic reflux. He warns that the decision to perform a fundoplication should be made very cautiously, particularly in children with gagging, retching and forceful vomiting. Similarly, Bratu and Kupper [26] warn that the relatively high failure and complication rates seen after fundoplication are partly because the surgery has been applied to inappropriate patients. They comment that as a result of this appreciation, the rate of fundoplication at their institution had decreased markedly over the previous decade. Thus, fundoplication is *inappropriate* in children who retch and is predictive of postoperative symptoms and wrap failure; alternative treatment strategies should be sought.

By improving selection of patients for fundoplication, it should be possible to reduce the incidence of postoperative symptoms, including retching, and improve the management of these children overall. Fundoplication, whether a full or partial wrap, whether laparoscopic or open, is treatment for GORD. It is not treatment for dysmotility or activation of the emetic reflex, and when used in this situation may make symptoms worse. Additional or alternative antireflux procedures do not address the underlying problem either; they also risk worsening dysmotility and patients still retch postoperatively. *Antireflux surgery should be reserved for patients whose symptoms are clearly demonstrated to be owing to GORD and who do not have evidence of other gut disorders. Children with symptoms of gut dysmotility or features of activation of the emetic reflex, such as retching, should not undergo antireflux surgery.* They should be investigated for treatable causes and managed as

already described for children with postoperative retching. Children who have undergone fundoplication and who are retching postoperatively should have their retching treated promptly to prevent wrap breakdown [2], in addition to relieving the associated nausea.

Level of evidence IV

3.6.4. Redo fundoplication. Is it appropriate?

In children with postoperative retching and wrap disruption/herniation, a redo fundoplication will not relieve their symptoms—which are not because of GORD. These children continue to retch after reoperation and risk repeated disruption because the underlying retching has not been addressed. Their symptoms often appear worse following redo surgery, which may reflect a greater degree of tissue damage and fibrosis in disrupted wraps [13], in addition to further surgically induced scarring. The 'paraesophageal hernia' that is reported by the radiologist is not a true rolling paraesophageal hernia; it is a sliding hernia of the remains of the wrap around the gastroesophageal junction, induced by retching. Repair is unlikely to confer any benefit, but carries the risks of repeat surgery in the presence of adhesions with increased complications including blood loss and mortality [123], further scarring, and vagal injury [23]. In the ferret model, wrap disruption is associated with increased fibrosis and greater nerve damage compared with an intact fundoplication [13], together with abnormalities of gastric motility and a tendency to increased emetic sensitivity under urethane anesthesia [14]. In these ferrets the abnormalities are a result of the surgery and the consequent scarring. Patients with preexisting dysmotility/emetic sensitization are predisposed to wrap disruption and are at risk of being caught in a downward spiral of worsening dysmotility and emetic symptoms. Children undergoing a redo fundoplication have a higher rate of symptom recurrence/wrap failure than those undergoing their first procedure, a higher rate of surgical complications, and may subsequently convert to jejunal feeding in order to manage feeding-related symptoms [118,124,125]. Baerg etal. found that redo fundoplication failed to control symptoms; satisfaction in their redo population was only 17%, with parents indicating that they would not proceed with fundoplication again [126].

Redo fundoplication in a child who retches is inappropriate and risks worsening symptoms and repeated failure. The retching/vomiting should be managed using alternative strategies as above. Redo fundoplication should be reserved for children whose symptoms are objectively demonstrated to be because of recurrent GORD or technical complications, such as dysphagia arising as a result of an overtight or misplaced wrap.

Level of evidence IV

4. Conclusion

Many children undergoing fundoplication for recurrent vomiting experience retching or other features of the emetic reflex as part of their symptomatology. Retching is not because of GOR/GORD; it is a component of activation of the emetic reflex. It is associated with a significant transdiaphragmatic pressure gradient and is sufficiently powerful to cause migration and disruption of a fundoplication. Although there are many potential targets for reduction of retching, and many potential interventions, systematic data are lacking. An appreciation that retching is part of the emetic reflex enables a structured approach to the relief of symptoms. This review presents, for the first time, a comprehensive framework for management of retching, and considers the roles of nutritional, medical, surgical and complementary therapies.

There is no single solution and trial and error, with a willingness to use a multidisciplinary and multimodal approach, would appear to be key. The overall approach is to treat the postfundoplication stomach with respect, and to avoid overchallenging the child's gastrointestinal tract. Individual strategies include seeking and treating specific causes of activation of the emetic reflex, modification of feeds and of feeding regimens (including jejunal feeding), the use of antiemetics and motility agents, and neuronal modulation. The evidence is of low level, comprising almost entirely of case series and expert opinion (with a very few small clinical trials), but does appear to represent a consensus reached by various independent groups across the world.

There are insufficient data to determine whether different types of fundoplication or different antireflux procedures – or whether a laparoscopic versus open approach – are more or less likely to be associated with postoperative retching. However, these procedures are to treat GORD, not dysmotility or activation of the emetic reflex, and none eliminates retching. There is some limited evidence to suggest that fundoplication and other antireflux procedures may cause or worsen retching symptoms in some cases.

Although there is still much progress to be made in the management of retching, examples of successful treatment are emerging. This means that when reporting upon outcomes of antireflux surgery, it is no longer sufficient to report only the presence or absence of retching, but also the use of antiretching therapy.

The presence of gastrointestinal dysmotility, or vomiting associated with retching, is a contraindication to fundoplication and other forms of antireflux surgery, and an alternative approach to management of the child's symptoms is required. Postoperative retching should be treated promptly to avoid wrap disruption and to relieve what is a very aversive experience.

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Conflict of interest

None.

Appendix A. Preoperative assessment: screening for preexisting conditions that cause recurrent retching and vomiting before consideration of fundoplication, including (but not limited to)

A.1 Mechanical causes

Prior to antireflux surgery, children should have had mechanical causes of vomiting excluded, e.g. duodenal stenosis (web or malrotation) or superior mesenteric artery syndrome, which may cause persistent incomplete obstruction leading to recurrent retching and vomiting. Otherwise, the obstruction coupled with an inability to expel vomit risks acute gastric dilatation and necrosis.

A.2 Mucosal disease

The symptoms of cow milk protein intolerance (CMPI) or eosinophilic esophagitis are often mistaken for GORD, but do not respond to antireflux treatment. Kelly etal. [127] reported a series of 10 children with intense eosinophilic inflammation of the esophagus and persistent symptoms despite medical treatment for GORD; six had also undergone fundoplication. Both symptoms and inflammatory changes resolved with the use of an amino acid-based feed; subsequent

food challenge resulted in recurrence of retching and mucus-containing vomiting.

Iacono etal. [128] found that 42% of 204 infants thought to have GOR were shown to have CMPI as the underlying cause for their symptoms. Ravelli etal. [129] demonstrated that in infants with vomiting owing to CMPI, a cow milk challenge caused gastric antral dysrhythmia and delayed gastric emptying, reflecting activation of the vomiting reflex. These changes were not observed in infants with GOR.

A.3 Intracranial pathology

Hydrocephalus/shunt dysfunction [130] and other intracranial pathology [130,131] may be a specific cause of chronic retching and vomiting, resolving with appropriate intracranial decompression.

A.4 Metabolic disturbances

Children with renal failure, for example, commonly experience food refusal, anorexia and retching/vomiting; this gastrointestinal dysfunction can be attributed to their metabolic disturbance [132]. This may be reduced by optimizing their fluid and electrolyte status (and modifications to their feeding regimen), although transplantation may be needed for complete resolution.

A.5 Chronic respiratory disease

Chronic respiratory disease, and recurrent cough with mucus secretions may aggravate or precipitate vomiting and treatment should be optimized [24]. Azithromycin prophylaxis (three times a week on alternate weeks) in addition to reducing overt respiratory symptoms, may be accompanied by a reduction in retching/vomiting, although an alternative explanation might be its motilin-agonist-like properties [44,46] (see section 3.3.2.).

A.6 Dystonia

In children prone to generalized dystonic episodes, these are often accompanied by worsening gastrointestinal dysmotility; management of the dystonia, and any precipitating cause, (for example, pain) may be accompanied by improved gastrointestinal function.

A.7 Recurrent vomiting syndromes

There are also specific syndromes with recurrent, intense, episodes of activation of the emetic reflex, with prominent retching and vomiting as symptoms, that should be recognized as such e.g. cyclical vomiting syndrome, or the autonomic crises of children with Riley–Day syndrome (in whom fundoplication may prevent vomiting, but not severe nausea and retching [133]).

A.8 Gastrointestinal dysfunction of neurological origin

However, for many children, particularly those with severe neurodisability, a specific cause cannot be identified and the assumption must be that recurrent retching is a consequence of a generalized neurological disorder, with visceral afferent hypersensitivity, visceral dysmotility, and dysfunctional central nervous system processing. This may result in abnormal gut reflex pathways that directly or indirectly (e.g. via impaired gastric accommodation) lead to recurrent activation of the emetic process. The management approach for these children is that of symptomatic relief.

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