Gastroesophageal Reflux and the Neonatal Airway

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Introduction

Confusion surrounds the clinical implications of the phenomena in which gastric contents travel backward into the esophagus, mouth, or parts of the airway. In no small part, this confusion seems to arise first in the imprecise manner in which terms are used in discussions and published literature. In particular, failure to distinguish explicitly between "GER" and "GERD" confuses both clinicians and parents, and apparently leads to overuse of medications in children who do not actually have "disease" associated with their reflux [1]. Similarly, the terms "reflux" and "emesis" are used interchangeably, even though these are quite different processes. Meanwhile, it is not clear that many of the apparent manifestations traditionally ascribed to "GERD"—arching, emesis, coughing, irritability, or apneic episodes—are caused by reflux. Because *reflux* is nearly universal in infants while *reflux disease* is rare, some clinicians caring for infants have even gone so far as to label declare as "myth" the proposition that gastroesophageal reflux may be pathologic in infants [2]. Finally, care of children can be confused by biases left over from experience with adults, e.g., that when we talk about "reflux" we mostly mean "acid reflux," or that "reflux disease" is primarily a disease of the stomach. This is not what we mean in children.

This chapter attempts to clear up this murky topic of reflux disease in sick neonates with particular emphasis on the effects of reflux on the airway. It describes what we think are the essential contributors to neonatal gastroesophageal reflux disease (GERD); what is believed about the detrimental effects on the airway; aspects of nonsurgical and surgical amelioration; and how to manage postoperative feeds and common complications in order to obtain the best surgical result.

To begin with, let us state the first premise: gastroesophageal reflux (GER) disease is not a problem of the stomach or even the esophagus, but a problem of the *foregut*, or what some call the aerodigestive tract.

To be more explicit, consider these terms:

Foregut: the cephalic portion of the embryonic alimentary canal. Foregut consists of endoderm, and gives rise to the pharynx, esophagus, stomach, liver, pancreas, most of the small intestine, and respiratory ducts [3]. While some have questioned whether the lungs and airways are actually embryologically foregut, the innervation of both proximal gut and airways by the vagus nerve displays these structures' functional unity: the lungs and gut are "wired" together.

GER: the passive flow of gastric contents retrogrades through the lower esophageal sphincter complex (LES) into the esophagus or higher, typically during transient LES relaxations (TLESRs). When GER reaches beyond the esophagus, it is common in the otolaryngology literature to see it referred to as "laryngopharyngeal reflux" (LPR) [4].

Refluxate: the material that moves in a retrograde fashion from stomach to esophagus during reflux symptoms.

GERD: GER, plus some detrimental effect attributed to GER e.g., growth failure, abnormal oxygen requirement, esophageal or tracheal stricture, aspiration pneumonia, pneumonitis, pulmonary hypertension, chronic otitis, etc. As with GER and LPR, a subset of GERD produced by refluxate reaching above the esophagus is sometimes called "larygopharyngeal reflux disease" (LPRD) [4]. It is these "extra-esophageal" manifestations of GER that we are interested in treating, and what most general pediatric surgeons and neonatologists mean when they talk about "GERD." As with GER and LPR, in this chapter, "GERD" and "LPRD" are lumped together as "GERD."

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Emesis: an active motor program originating in the vagal nuclei and mediated by the vagal nerve, producing retrograde gastric peristalis and forceful expelling of gastric contents through the LES. Observe that while "reflux" and "emesis" both involve retrograde movement of gastric contents into the esophagus, reflux is essentially a *passive* process stemming from decreased motor activity, whereas emesis is essentially an *active* process stemming from increased motor activity. These terms are often confused, in no small part because of the "reflux-->retch-->regurgitate" phenomenon, when refluxate stimulates the vagus nerve triggering the emesis motor program.

Fundoplasty v. fundoplication: Both terms refer to operations to attenuate reflux. The more commonly used *fundoplication* comes from Latin *plicare,* "to fold." Others prefer *fundoplasty*, from the Greek *plasso* "I fold" or *plastikos* "able to be shaped or molded." Either is correct, but it is interesting to note that neither means "to wrap". As will be seen the actual mechanisms by which anti-reflux operations work involves a reshaping of the lower esophageal sphincter region, with the "wrap" performing only one part of the work. Interestingly, the root of both words, *fundus*, comes from the Latin for "bottom" or "base" a curious choice of naming for a portion of the stomach that is at the uppermost part. So while both terms are a bit upside down, *fundoplication* is more etymologically pure (all Latin roots), while *fundoplasty* more correctly describes the operation. In modern English usage, these terms are interchangeable.

Pathophysiology

Reflux is a function of fluid, pressure, viscosity, and the mechanisms of the so-called LES. More than simply a circular muscle that maintains tonic constriction while opening when required physiologically, the LES is really part of a greater "LES complex" that includes the diaphragmatic crura and the Angle of His. The function of the LES is imperfectly understood, even with sophisticated mathematical models [5]. But it is probably not oversimplifying the case too much to say that the LES is a control point between chest and abdominal cavities, a valve with *asymmetric resistance*: Resistance is relatively low for swallowing (antegrade flow), and relatively high for reflux and emesis (retrograde flow). The anatomical mechanisms that allow this asymmetric resistance are complex.

The lower 2/3 of the esophagus is not under voluntary control. It automatically propagates a peristaltic wave initiated by a swallow, and the last few centimeters of the esophagus normally hold intrinsic tone that relaxes in response to these swallows. But the lower esophageal tone is also lost in events known as *transient lower esophageal sphincter relaxations* (TLESR's). Transient LES relaxation appears to be the chief physiologic antecedent of GER in children [6].

But other mechanical effects contribute. In particular, there must be a *pressure gradient* from abdomen to chest (or, more particularly, between stomach and lower esophagus), a gradient that is magnified during, for example, pregnancy. Importantly for infants, a full stomach also translates to greater intragastric pressure. Meanwhile, the *viscosity* of the gastric contents also plays a part. The *radius* and *length* of the LES are also important. The general relationship of these mechanical factors is seen in the "reflux equation," which is really just a version of Hagen–Poiseuille equation [7]:

$$Flow \propto \frac{\left(P_g - P_e\right) \cdot R^4}{c \cdot L \cdot \eta}$$

where

$P_g - P_e$ = the pressure gradient between stomach and lower esophagus

R = the radius of the esophagus

L = the length of the LES (essentially, the distance from crura to GE junction)

η = the fluid viscosity

As a model of flow through the LES, this equation is wrong, but useful. The flow through the LES is not laminar, the tube is not rigid, and none of the parameters is constant. Still, the relationship given in the equation does reveal what constrains the mechanics of the LES as a valve. Several elements of the LES work together to create its asymmetric resistance [8]. All of these physiological elements (and all successful treatments for GERD) work through at least one element of this equation. The functional elements of the LES include:

1. Crus muscle: When contracted, the diaphragmatic crura shorten and pinch the esophagus. This decreases the radius R, blocking reflux. It also contributes to the pressure gradient ΔP blocking GER by increasing P_e.
2. Intrinsic tone (or elastance) of the distal esophagus: most reflux occurs during "transient lower esophageal relaxations" (TLESRs), or brief episodes when the LES relaxes [6]. In contrast, the elastance of the LES inhibits reflux by reducing R and by creating higher pressure P_e in the LES than in the stomach.
3. Intra-abdominal esophageal length: the length of the esophagus inferior to the diaphragmatic crus (L). A "negative" length here would be a hiatal hernia, where the gastroesophageal junction (GEJ) sits superior to the crura. In the newborn, the intra-abdominal esophagus may be less than 1 cm, but is reported to be 3 cm at 3 months of age [8]. Perhaps this anatomical development (as well as other effects) explains in part how infants tend to "grow out of" reflux problems.

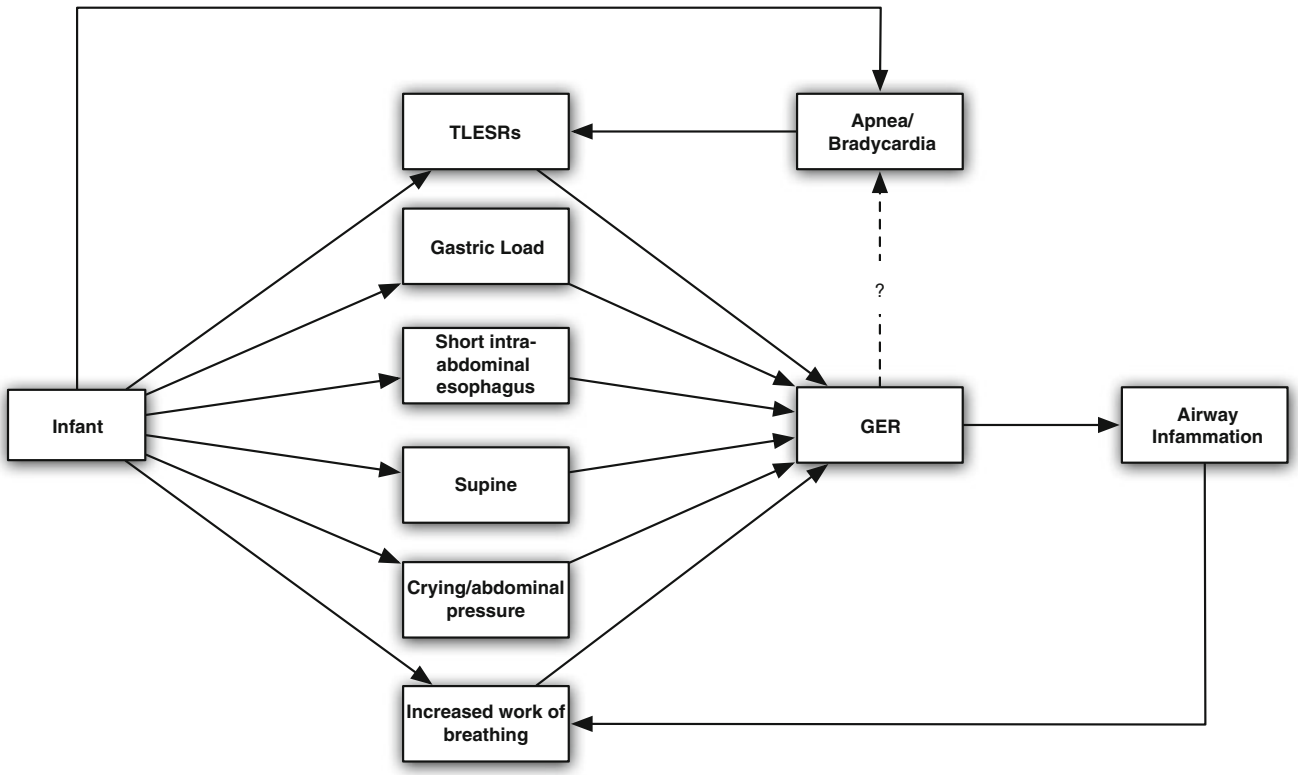

Fig. 1 Multiple mechanisms are likely to contribute to GER in infants, but GER only becomes GERD when the airway and lungs become damaged. The connection between GER and apnea is less clear. At least two positive feedback loops may exist here, where the effects of reflux potentiate factors that contribute to reflux

4. The cardiac angle: Also known as the "Angle of His." It is believed that an acute angle protects against reflux because a filling fundus will tend to close the LES if the angle is acute, but tends to open the LES if the angle is obtuse. When functioning properly, this mechanism should both reduce *R* and produce a restrictive pressure gradient between stomach and LES.

All of these are weaker in small children, increasing the propensity to have GER events. But even if the LES was functioning well, it bears repeating that it is not a perfect one-way valve. As most pregnant women can attest, a strong enough pressure gradient from abdominal to throracic cavities can overcome the resistance in the LES. Infants have extra mechanisms that similarly increase the tendency to overcome the LES:

Scaling: Mismatch between gastric scaling and energy scaling means that the stomach of an infant carries a larger burden than an adult's. While the capacity of the stomach scales with body mass *linearly* (a reasonable heuristic is around 22 mL/kg), energy scales *nonlinearly*, roughly according to an inverse power law [9, 10]. For example, a 3 kg infant will require around 128 kcal/kg/day but his 80 kg father uses just 34 kcal/kg/day. However, both have similar gastric capacity relative to body mass. It is this mismatch that explains why infants need to eat every 3 h, and why they are so "spitty": To ingest 128 kcal/kg/day of breast milk (~20 kcal/30 mL) requires drinking 576 mL/day, or 72 mL every 3 h, or 24 mL/kg/feed—right at the limit of gastric capacity. A constantly "loaded" stomach increases opportunities for reflux events.

Relatively slower gastric emptying: It appears that infants (especially premature infants) have relatively slow emptying of gastric volumes compared to adults, a problem easily made worse by various medications administered to neonates [11, 12]. This longer dwell time probably contributes to GER by increasing the probability of refluxate with a given TLESR.

Work of breathing: Breathing requires energy, and is associated with cyclical pressure gradients between abdominal cavity and chest cavity. Here again we see a mismatch between linear and nonlinear physiological scaling [13]. The disproportionally greater energy requirements (V_{O_2}) and carbon dioxide production (V_{CO_2}) plus the linear tidal volume (~7–8 mL/kg/breath) translate necessarily into a higher respiratory rate. For a given airway impedance, work is a function of this rate. Of course, several diseases greatly increase impedance per breath, compounding increases of WOB in sick infants.

These mechanisms explain why babies universally have some GER (Fig. 1). Moreover, "some GER" may be quite a lot, with around 70 GER events/day recorded in normal newborns [14, 15]. But nothing here explains why some infants cross a threshold into GERD. It is reasonable to assert that GERD appears whenever the amount of airway soiling exceeds some capacity of the airways to recover. It follows that GERD will become manifest whenever the *amount of refluxate* in GER is very high (e.g., hiatal hernia, increased frequency of TLESRs, etc), the *ability to protect* the airway from refluxate is inhibited (e.g., neurological degradation, tracheomalacia, etc.), *pulmonary repair* mechanisms are degraded (e.g., bronchopulmonary dysplasia (BPD), pulmonary hypertension, cystic fibrosis, etc.), or the *character of the refluxate* is particularly toxic (e.g., acid, bile acids, pepsins, bacteria).

Several surgical diseases in the neonate also come accompanied by GERD. Patients with diaphragmatic hernia, tracheoesophageal fistula, and gastroschisis commonly exhibit difficulties with enteric feeds, and resort to surgical control of reflux is common here. In all of these, a specific failure of the LES can be posited. For instance, in CDH, the diaphragmatic crus is typically dysfunctional and GERD is common [16–18]. In TEF, the distal esophagus has decreased tone and motility [19]. In gastroschisis, hiatal hernia is common [20], and intra-abdominal pressure can be elevated for weeks while downstream small bowel motility [21] (and therefore gastric emptying) can be slowed for months (or longer).

Regardless of etiology, lungs are damaged by large amounts of debris (milk proteins and fats); acid, bile acids, bacteria, and digestive enzymes. Of these, it seems that acid, while plainly damaging to the respiratory epithelium, is the least problematic in infants. Certainly acid in the esophagus produces a noxious feeling that can lead to arching, pain, and reduced oral intake ("food fear"). But babies tend to have weakly acidic refluxate [15]. As a result, in neonates there may not be enough acid reaching the airway to provoke the intense inflammatory reaction seen in GERD both clinically and experimentally.

The same cannot be said about the effects of digestive enzymes, particularly the pepsins. This family of proteases (particularly Pepsin 3) is manufactured only in the stomach. While pH-dependent, the enzyme remains active at relatively high pH (i.e., pH 5) and does not denature until pH > 7.2. Once aspirated into the airways, these enzymes spark intense inflammation [22]. These inflammatory changes degrade the ability of pulmonary epithelium to clear debris and aspirated organisms. Probably, the lungs become more vulnerable as their "clearance capacity" is overwhelmed by large amounts of aspirate, and later even relatively small amounts of aspirated refluxate may provoke inflammation, wheeze, cough and elevated work of breathing. These inflammatory changes are posited to exacerbate BPD, pulmonary hypertension, and prolonged oxygen requirements in infants. However, despite a great deal of opinion and investigation, this causal chain has not been established. Still, in documented refluxers, damage to the airway may sometimes be demonstrated on inspection (see Fig. 2).

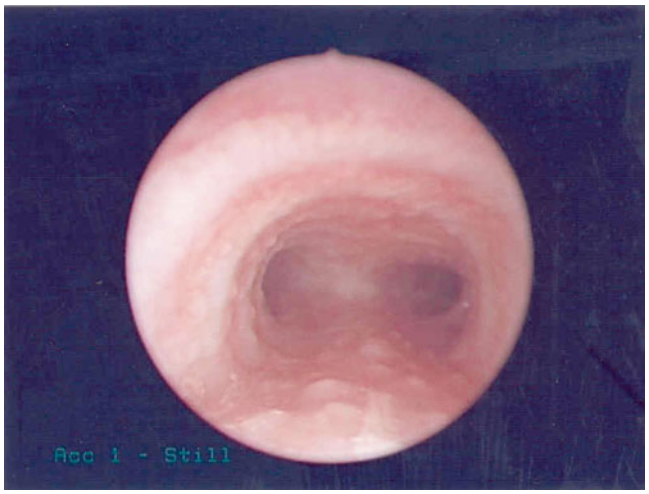

Fig. 2 A bronchoscopic view of the trachea and carina in an infant with GERD. Observe the "cobblestone" eruptions along the epithelium attributed to constant microaspiration of gastric contents

At this point, one may notice that the elements of this list could comprise a harmful positive feedback loop between lung damage and reflux. As reflux damages the lung parenchyma, work of breathing and inspiratory pressure may rise. As these rise, energy needs for growth increase, further increasing the filling pressure on the stomach while the inspiratory pressure steepens the pressure gradient between abdominal and thoracic cavities. Meanwhile, apneic spells may not always be caused by GER as commonly believed, but may not be effective but *cause*, contributing to TLESRs [23]. All of these effects must increase refluxate, leading to further lung damage. Treatment, then, should be aimed at interrupting this positive feedback loop.

Diagnosis

Diagnostic interventions seek to determine whether GER may be the cause of pulmonary manifestations or failure to thrive. There is no single best test for "GERD" in infants. Instead, the clinician must combine specific testing with clinical context of a given patient. Several diagnostic tests are available.

pH-probe/impedance probe: probes introduce an esophageal tube with multiple side ports each able to detect pH or electrical impedance or both. For pH probes, a falling pH at a certain detector site in the esophagus is a proxy for gastric contents, presumably with low pH. Similarly, a decline in impedance suggests fluid at the detector. With multiple channels, these devices reliably detect GER (and its character—acidic, weakly acidic, or alkaline), and give an indication of its severity: how far up the esophagus refluxate travels, how often refluxate appears, and how fast it is cleared [24]. pH/impedance is often referred to as the "gold standard" for diagnosis of GER.

It cannot however provide sole evidence that GER is actually GERD, nor can it reveal problems with gastric emptying or altered anatomy (like malrotation or hiatal hernia).

Fluoroscopy: To reveal anatomical problems that may present as GER, esophagosocopy and upper gastrointestinal (UGI) series are helpful. While insensitive to GER (reported sensitivity is under 50 %) [25], the images are far more specific in revealing hiatal hernia, H-type tracheoesophageal fistula, microgastria, esophageal stricture, and malrotation. Some surgeons insist on UGI before fundoplasty in order to plan the operation, for example to allow for the need to perform a Ladd's procedure concomittantly [26] or even *instead of* fundoplication [27]. Data suggests that at least 4 % of patients being considered for fundoplasty will be found to have a surgically important abnormality [28]. But this value alone does not give the value of information from the UGI. For example it is reasonable to place premium value on decreased uncertainty about malrotation; that is, to assert that avoiding one missed malrotation is worth more than the cost of 24 negative studies. Value judgments of this kind resist standard calculus.

Manometry: this method uses a series of pressure sensors in the esophagus to describe esophageal pressure waves. Critical for diagnosis of motility disorders like achalasia in older children and adults, manometry contributes little to the workup of GERD in infants.

Esophagoscopy: Regarded as a mandatory diagnostic step by some, esophagoscopy is critical for diagnosis of esophageal metaplasia, ulcers, eosiniphilic esophagitis, conditions rarely encountered in newborns. Like manometry, esophagoscopy is not routinely used in newborns for workup of GERD.

Bronchoscopy: Bronchoscopy may provide compelling evidence of reflux with aspiration (see Fig. 2) but is not a front line tool in initial workup. On the other hand, patients who appear to have severe "reflux" may require interrogation of the airway to identify other structural problems that can mimic GERD, e.g., laryngeal cleft, H-type tracheoesophageal fistula, or tracheomalacia.

Nuclear scintigraphy: Radionuclide scintigraphy is attractive because it is noninvasive, carries no X-ray exposure, and can purportedly detect GER and microaspiration while quantifying gastric emptying. When compared to pH monitoring, the sensitivity of radionuclide scintigraphy is reported to be between 75 and 100 %, and specificity between 81.2 and 100 % [29]. But the usefulness of these "milk scans" in practice is less clear. Milk scans confirm that reflux is common in preterm infants, but it turns out that "positive scintigraphy has no correlation with symptoms" [30]. In that study, the authors found no discrimination at all in detection of GER between symptomatic babies and asymptomatic babies. Others report that the scans do not offer any information that guides whether pyloroplasty is indicated along with fundoplasty (Pyloroplasty is very rarely indicated in any case, and its routine use with fundoplication is condemned) [31]. Most likely, these scans are of little value in infants in the NICU: virtually always "positive" (even in children who have intact and working fundoplasty), their specificity appears considerably lower than reported for other populations. At the same time, the sensitivity to detect aspiration also appears in daily practice to be far below reported levels. In other words, in infants, they merely confirm reflux that is nearly universal, while failing to detect the "disease" in GERD.

Biomarkers: In patients undergoing bronchoscopy, who are intubated, or have a tracheostomy, bronchoalveolar lavage allows examination of the fluid in the airways. While traditional diagnosis relied on the presence of "lipid-laden macrophages" as a proxy for lung soilage, this finding appears to lack specificity [32]. Others have used the presence of pepsin [22, 33], measured according to various assays, to indicate GERD. This method seems to have promise, but lack of guidelines regarding interpretation of results, lack of standard methods for measurement, limited availability of the tests and restriction to patients with some tube in the airway all prevent widespread use for now.

N-of-one trials: While this method has the least published evidence, it is arguably the method to which experienced neonatal clinicians resort the most. N-of-1 trials are single-patient trials with "multiple-period crossover experiments comparing two or more treatments within individual patients" [34]. In detecting GERD, the clinician will observe the patient while being fed normally (orally or by tube) into the stomach. Frequency of apneas, oxygen requirement, discomfort, and other signs of symptomatic reflux are noted. Then feeds are withheld, with nutrition supported either by nasojejunal enteral feedings or parenteral nutrition. If GER is really GERD, improvement in respiratory and other symptoms will manifest within 2 or 3 days (sometimes less). Return to gastric feeds will reproduce the symptoms, and a second period of non-gastric nutrition relieves them. Each "block" of these trials is about 1 week long. While this method does not rule out laryngeal cleft or other anomalies in orally fed children, these confounders can be controlled by restricting enteral nutrition to tube feeding. While evidence is scant regarding this method, and criticisms are plain (jejunal feeds are imperfect protection against reflux; trials take a long time; etc.), this pragmatic method may yield the highest individual validity.

Medical Treatment

Traditionally, the mainstay of control of GERD has been drugs which fall into two categories: motility agents and acid blockers.

From the discussion above on pathophysiology, the usefulness of acid blockade on the control of GERD manifestations should seem suspect. Nothing in the function of the LES depends on pH; acid is weak in infants already; and decreased pH creates an important "deflector screen" against enteric organisms migrating from the stomach back into the airway. It is plausible that reliable acid control could act to deactivate pepsin and other digestive enzymes, but this has not been shown. At the same time, while improvements in pediatric asthma have been shown in the past, more recent trials show no benefit, and even harm in asthmatic children [35]. Meanwhile, there is increasing skepticism about acid blockade in infants. Proton-pump inhibitors (PPIs) carry serious risks and little effect on GERD symptoms [36], and even H2 blockers were recently associated with serious, even fatal, problems in infants [37]. While these medications have their place in gastritis with bleeding, or GERD manifesting largely as oral resistance and discomfort, it is plain that they are over-prescribed [1] and undereffective.

Motility agents fare little better. Metoclopramide (Reglan), bethanechol, cisapride, and erythromycin have all been tried as frontline treatments for GERD. In theory, increasing "motility" (i.e., decreasing gastric emptying time, decreasing intestinal transit time) should decrease GER events associated with TLESRs by reducing the dwell time of feeds in the stomach.

These posited effects have not been demonstrated practice. Reglan has no measurable effect on GERD in infants but carries a high risk of dystonic reactions [38]. Cisapride was shown to be effective, but was removed from the US market after several patients developed cardiac dysrythmias attributed to it [39]. Bethanechol, a parasympathomimetic, was posited to aid GERD by increasing intestinal motility, but trials have failed to demonstrated effectiveness (for example [40]). Erythromycin, a motilin agonist, certainly increases gastric emptying, but has not been shown to be an effective treatment for GERD, perhaps because of its strong tendency toward tachyphylaxis [39, 41]. At one time, it was common to place almost every baby in the NICU on "R&R" (reglan and ranitidine), a practice now, unsurprisingly, out of favor.

The reflux equation described above illustrates why other therapies that seem reasonable have unclear power to attenuate GER. Chief among these is the practice of "thickening" feeds. In this practice, a thickening agent (rice cereal, guar gum, cornstarch) is added to milk or infant formula. This "thickening" is actually a change in viscosity, η. From the equation, it is apparent that in order to halve GER, one would need to double the viscosity. The viscosity of human breast milk is around 3 cP (pumped, untreated), but addition of a commercial thickener (Nestle ThickenUp®, a preparation of cornstarch) demonstrated a large increase in measured viscosity: "In relation to untreated pumped human milk without thickener, we observed that the addition of 7 % of the thickener increased the viscosity up to ninefold" [42]. So far so good. But this improvement comes at a cost—delayed gastric emptying. There are other costs: infants have diminished alpha-amylase and thus diminished ability to digest cornstarch which can produce diarrhea [43] Increasing viscosity delays gastric emptying [44]. With contrary effects and varied effects of different thickeners plus the confounder of varied viscosity of human infant milk formulas, mixed results with use of thickeners is unsurprising. Pectin, another thickening agent, appears to delay gastric emptying [45] but a trial in neurologically injured children showed improvement in GERD [46]. In sum, no reliable evidence exists to support or decry use of thickeners as GER treatment in infants. A Cochrane review in 2002 concluded "There is no evidence from randomised controlled trials to support or refute the efficacy of feed thickeners in newborn infants with [GER]" [47]. In a more recent study, the results are, again, mixed: "A formula thickened with amylopectin did not reduce the number of apnea of prematurity or GER-related apneas. It reduced acid GER features but had no effect on non-acid GER indexes" [48].

Others have turned to "elemental" formulas in order to treat GERD. There is nothing in these formulas that can be expected to improve the function of the LES or to increase gastric emptying. Rather the opposite is true—all of these formulas share one counterproductive characteristic, relatively high osmolarity. While breast milk has an osmolarity similar to serum (~290 mOsm/L), elemental formulas are much higher (e.g., Alimentum™, 370 mOsm/L when prepared at 20 kcal/30 mL). The stomach responds to elevated osmolarity by holding the fluid longer and diluting, since the small bowel does not tolerate high osmolarity fluid well (producing cramping, flushing, and diarrhea recognized as dumping syndrome). Changing a baby to an elemental formula may certainly be the right intervention for many diseases (protein hypersensitivity, malabsorption, etc.). But pathophysiologically, if a change to an elemental formula does ameliorate some observed manifestation of "feeding intolerance," it is unlikely that the cause was GERD.

Surgical Treatment

Surgical control of GER aims to restore normal functioning of the LES. "Normal" function does not include the inability to vomit, the inability to burp, or total elimination of reflux. Instead, surgery aims to re-establish or reinforce the mechanical functions that the LES normally employs [8]. To review:

1. The "pinch cock" effect of the crus muscle.
2. Adequate intra-abdominal esophageal length.
3. An acute angle at the cardia (Angle of His).
4. Decreased compliance (increased elastance) at the lowest portion of the esophagus, i.e., "tone".

Table 1 Common types of fundoplasty for reflux control

Complete wrap (360°)	–	Nissen
		Nissen–Rossetti
		Collis–Nissen
		Floppy Nissen
Partial wrap	Anterior	Dor (180°)
		Thal (240°)
		Boix Ochoa (240°)
		Belsey Mark IV (240°)
	Posterior	Toupet (270°)
No wrap	–	Hill gastropexy

An additional surgical objective is *removal of barriers to gastric emptying* (e.g., malrotation, overdistended stomach, etc.). The underlying objective is to attain these results without creating unwanted problems like dysphagia.

All surgical fundoplasties achieve these mechanical objectives. It may surprise readers familiar only with the "Nissen" fundoplication, but surgical control of GERD does not begin and end with the Nissen. Instead, there are several approaches (Table 1).

While all these procedures have an eponym, rarely does the modern application of various procedures conform to the original description. This chapter confines discussion to the three most common fundoplasty types performed in North America:

Nissen: the modern Nissen is sometimes called a "floppy Nissen" to distinguish it from its original namesake, or even its modified form the "Nissen–Rossetti." The modern Nissen creates as 360° wrap looser and shorter (e.g., 2 cm) than originally described, and involves division of the short-gastric vessels between spleen and the greater curvature. Unlike the variant called a "Collis-Nissen," the modern Nissen places the wrap entirely above the GEJ (Fig. 3).

Toupet: Observe the spelling, distinguishing this wrap named after French surgeon Andre Toupet from the hairpiece (a toupee') which some have imagined that this wrap might somehow resemble. It does not. Instead, the modern version is a posterior 270° wrap that cushions the esophagus. Essentially an open and longer form of the Nissen, the Toupet resembles a hot dog (esophagus) in a bun (the sides of the wrap) (Fig. 4).

Thal: More popular in the 1980s, the Thal has become rare in the laparoscopic era. This is an anterior 240° wrap that also differs from other fundoplasties in the direction of the wrap. While both the Nissen and Toupet (and Dor) pull the fundus across the esophagus laterally, the Thal creates a kind of "hood" by pulling the anterior portion of the stomach from inferior to superior (Fig. 5).

All of these procedures may be done in infants via an open or laparoscopic approach. Experienced pediatric surgeons increasingly favor a laparoscopic approach because of the demonstrated superiority in surgical comorbidities (pain, time to feeds, adhesions, abdominal wall scarring, etc.) as well as opportunities for improved visualization and surgical precision [49]. For patients who are candidates, laparoscopic fundoplasty yields results at least as good as open approaches.

Moreover, it has been repeatedly shown that no particular fundoplasty type is superior to any other. All are expected to provide clinical improvement in manifestations of GERD in at least 85 % of patients [50], and to provide similar protection [51–54]. This equivalence may seem counterintuitive, but is only surprising if one believes that a fundoplasty must be "tight" to be effective. This is untrue. Instead, an effective fundoplasty must reinforce the normal physiological mechanisms of the LES without creating dysphagia. That is, an ideal fundoplasty must increase retrograde resistance without increasing antegrade resistance. The Nissen, Toupet, and Thal all restore the crus, increase intra-abdominal esophageal length, restore an acute angle of His, increase the elastance of the LES (i.e., reduce TLESRs) and probably increase gastric emptying. When these mechanisms are understood, it is clear that a "tight" fundoplasty is beside the point.

Moreover, surgical amelioration of reflux, regardless of particular type of fundoplasty, appears to provide powerful protection to the lungs. Rothenberg et al. demonstrated that pulmonary function was improved by Nissen fundoplication in children with asthma in a large cohort [55]. Oxygen requirement appears to be lower and ventilator weaning appears to be aided [56]. In pediatric patients with severe reactive airway disease, fundoplication reduces symptoms and medications (including steroids) [57]. However, there is no convincing evidence in the literature to demonstrate that fundoplication effectively treats apneic spells in premature or full-term neonates. This is unsurprising given the unclear causal relationship between apnea and GER [23].

Where these variations on fundoplasty differ is in mechanical complications. While the rate of "slipped" or failed fundoplasty appears to be independent of type, excessive dissection of the hiatus certainly shortens the expected lifetime of a working fundoplasty [58]. Fundoplication is expected to continue to provide reflux protection to 90 % of patients who had initial improvement at 5 years [59]. However, both the Thal and Toupet have markedly better results in terms of dysphagia, bloat, and inability to burp or vomit (e.g., [53]). In order to overcome these problems, surgeons work to make Nissens very "floppy," and a good "floppy Nissen" yields results very much like the partial fundoplasties.

Nevertheless, there is no consensus regarding the choice of one procedure over another. Most surgeons in North America are most familiar with the Nissen, and this procedure is

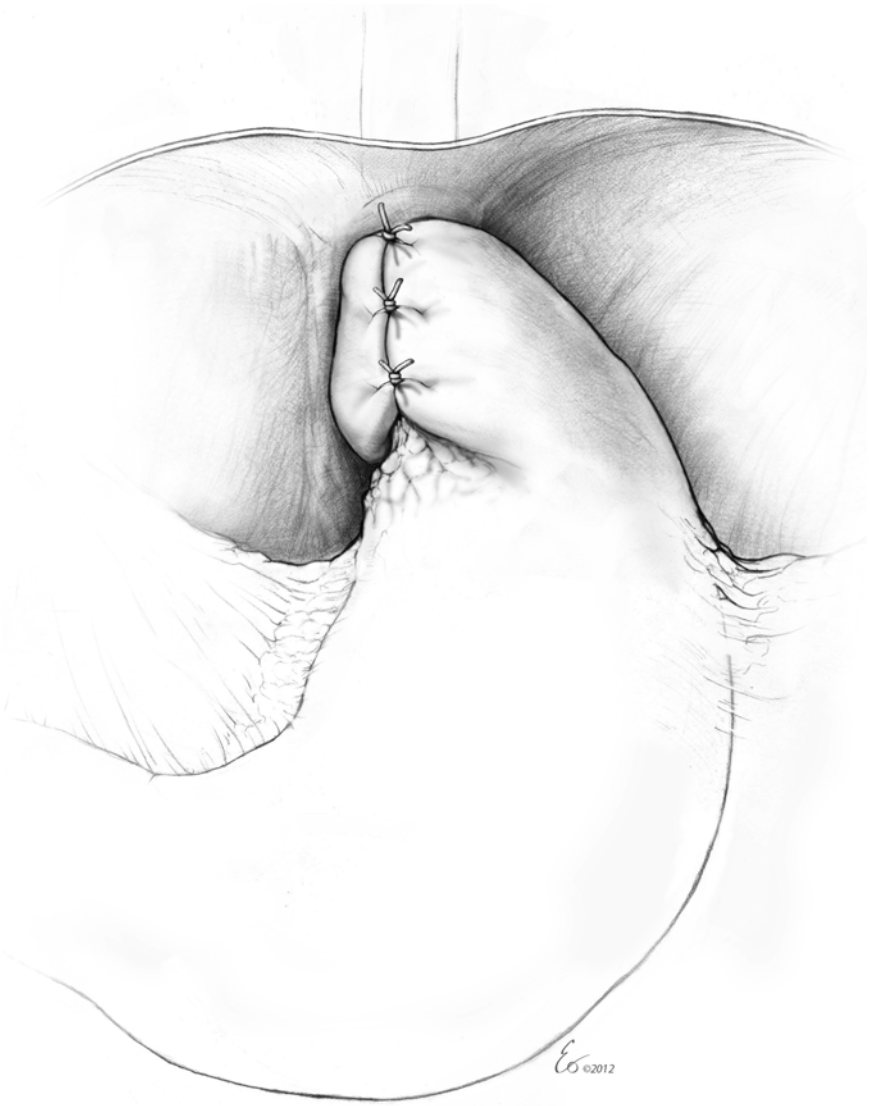

Fig. 3 The modern Nissen fundoplication is a 360°, loose wrap located between the diaphragm and gastroesophageal junction (GEJ)

arguably easier to complete laparoscopically than the others (for example, the Nissen may be completed with as few as four sutures, but the Toupet requires at least seven). Still, in special circumstances, a Nissen may be the wrong choice. For example, in babies with poor esophageal motility (e.g., esophageal atresia), a Toupet may be a better choice. Similarly, some babies can be better served by a Thal which can be performed in the setting of a small gastric fundus whereas a Nissen would be forced. Surgical pragmatism works where evidence is scant.

Respiratory Support as Adjunct Treatment

From the discussion above, it follows that any intervention that decreases work of breathing may aid reflux. In particular, use of positive airway pressure (or other means, e.g., plication of a paralyzed hemidiaphragm) to improve functional residual capacity and chest mechanics may decrease the tendency to defeat the LES. These interventions, including even surgical tracheostomy in some patients, may improve lung mechanics and reduce the effects of GERD by interrupting the cycle on the ventilatory part.

But this effect may not only depend on chest mechanics. Any brake on oxygen delivery will be borne heavily by the gut. Mild hypoxia combined with heavy work load to the gut is likely to produce some gut dysfunction, especially, dysmotility. This failure of downstream flow in the gut can easily manifest as signs that look like reflux (or other kinds of intolerance). In more severe circumstances, mismatch between oxygen delivery and demand in the gut may lead to "cleaving" of the villi at the tips where the countercurrent vascular system leaves the tip most vulnerable [60]. The result is a marked reduction in gut surface area, and setup of another potential destructive positive feedback loop as the same absorptive work must be done with less absorptive

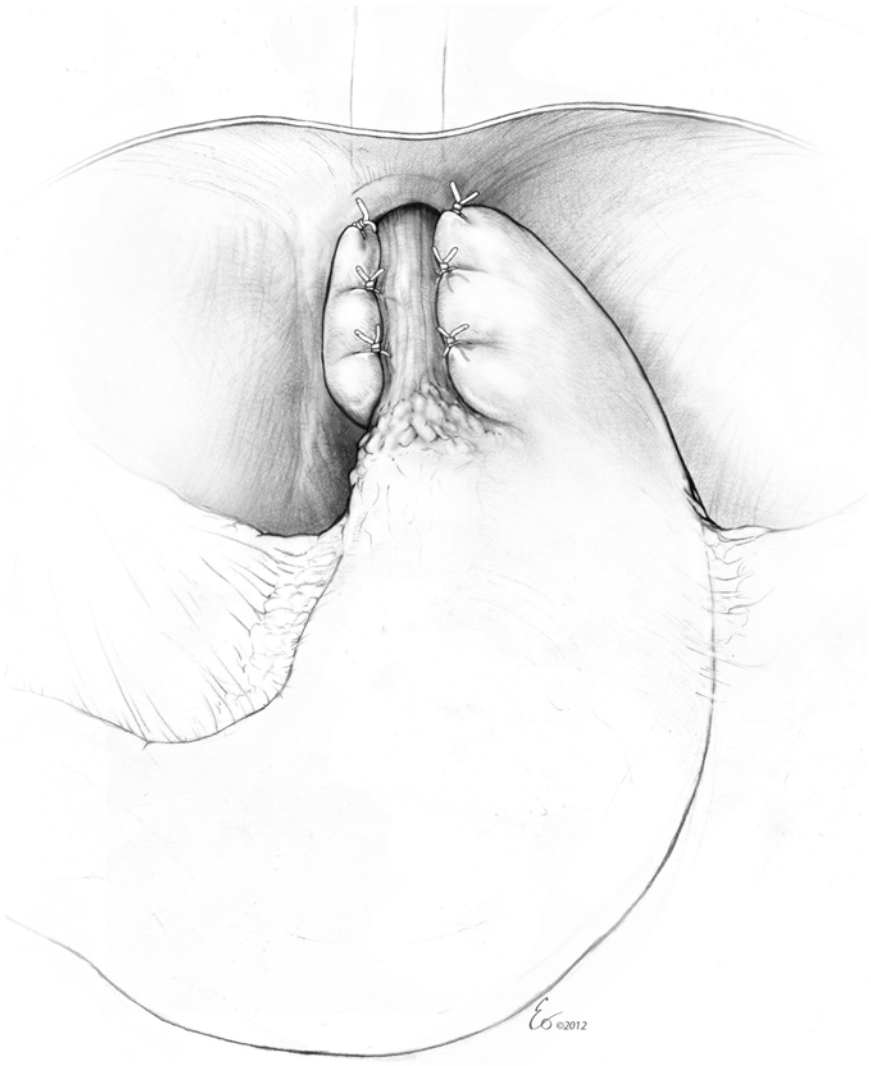

Fig. 4 The modern Toupet fundoplasty is a posterior, 240–270° wrap. Slightly longer than the Nissen, this wrap also is located above the GEJ

surface area. What the clinician may see is a child who is "stooling out," with loose watery stools. Alternatively, the clinician may see gut slowing, delayed gastric emptying, high gastric residuals, and retching.

When surgeons say that the purpose of the lungs is to perfuse the gut, they seem to know what they are talking about. More seriously, however, these interrelationships between intestinal and airway function belie the notion that functional divisions neatly separate these organ systems.

Care of the Post-fundoplasty Patient: The Missing Manual

In general, fundoplasty is extremely successful at alleviating symptoms of GERD, with a relatively low rate of complications. Nevertheless, significant problems are seen after fundoplasty, and these can be exacerbated by a clinician unaware of the risk or of the altered state of the stomach after fundoplasty. Fundoplasty may be hugely successful in improving the nutrition and lungs of the child with bad GERD, but the surgeon who cedes all postoperative management to others does his patients a disservice. As with other surgical diseases like imperforate anus, many patients require ongoing gentle attention from a clinician who understands the mechanical constraints imposed by the operation.

Feeding

While actual volumetric measurements of the human stomach are elusive, a heuristic estimate is that the normal human stomach holds around 20–25 cm^3/kg of body weight. After fundoplasty, tube-fed babies usually can handle bolus feeds of only about 15 (±2) cm^3/kg. This is certainly adequate for growth, but ignoring this limit is one of the prime causes of retching (see below) postoperatively. In general, feeds can be started within 12 h of fundoplasty (the delay allows anesthetics

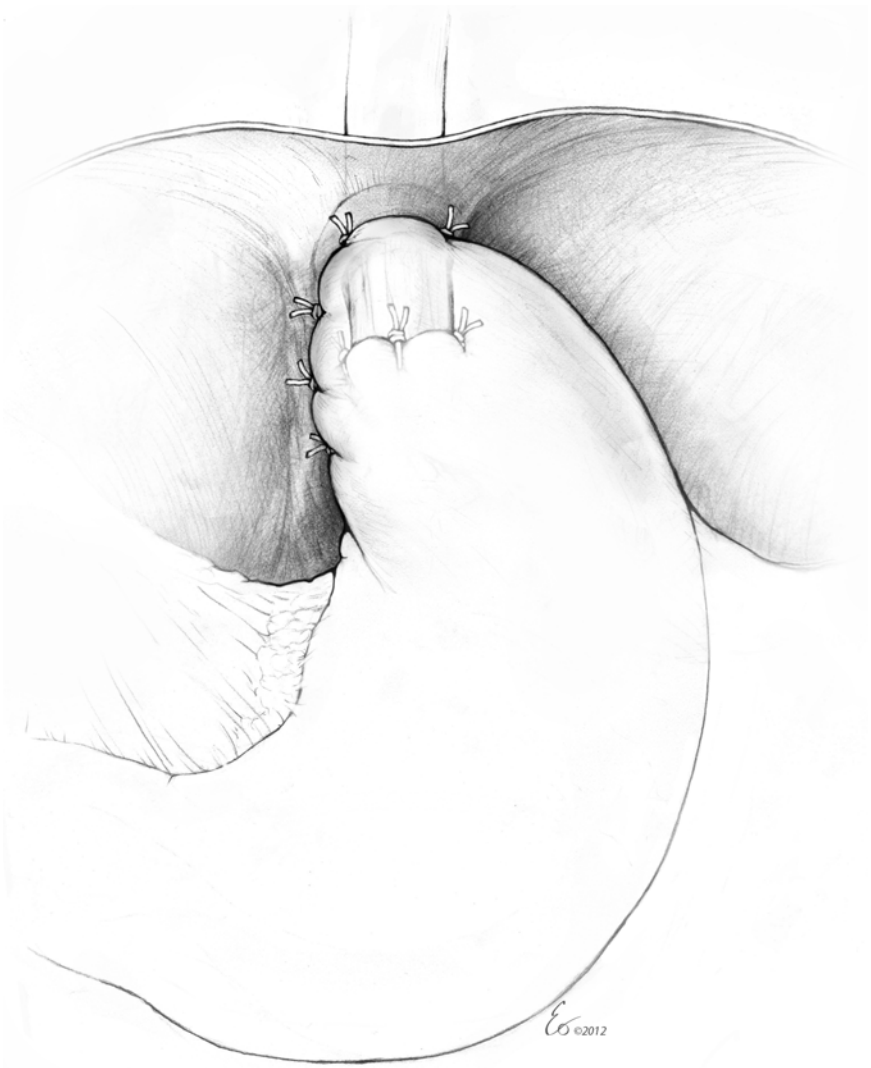

Fig. 5 The Thal fundoplasty is another partial wrap. Unlike the Toupet, the Thal brings stomach anterior to the esophagus to complete a 240° wrap. The inner layer of gastroesophageal sutures are revealed in the ghosted image

and anesthetic-associated nausea to resolve). Typically in infants, a gastrostomy is placed at the time of fundoplasty, and can be used for feeds as soon as indicated. Babies that are *orally* fed can be rapidly advanced to ad-lib feeds, and because of the vagally-mediated accommodation reflex originating in the pharynx, tend to be less volume-limited than gastrostomy fed babies. There is no evidence to support the practice of using all continuous feeds for the immediate postoperative fundoplasty patient, but different surgeons have strong opinions here.

Medications

Once the fundoplasty is completed, anti-reflux medications can be stopped. Ranitidine has no rebound associated with it, and continuing metoclopramide after (and indeed before [38]) fundoplasty is pointless since the mechanical repair of fundoplasty dwarfs any small effect this drug could provide while still risking side effects (diarrhea, dystonic reactions). PPIs should generally be weaned off. If the patient has been on PPIs for months, there will be elevated serum gastrin levels. This hypergastrinemia can persist for up to 6 weeks, raising the risk of hypersecretion of acid in the stomach with subsequent erosive gastritis [61–63]. Empirically, this problem can be ameliorated if PPIs are weaned off over 2–4 weeks. In cases where acid blockade is indicated for some other reason (e.g., to protect the esophageal atresia or laryngoplasty repair, or to guard against steroid-induced gastritis), PPIs should be continued after fundoplication. In other words, PPIs should be continued in any patient for whom they are indicated for mucosal protection or healing. Without an indication, these PPIs offer only complications (fungal overgrowth, hypocalcemia, etc.).

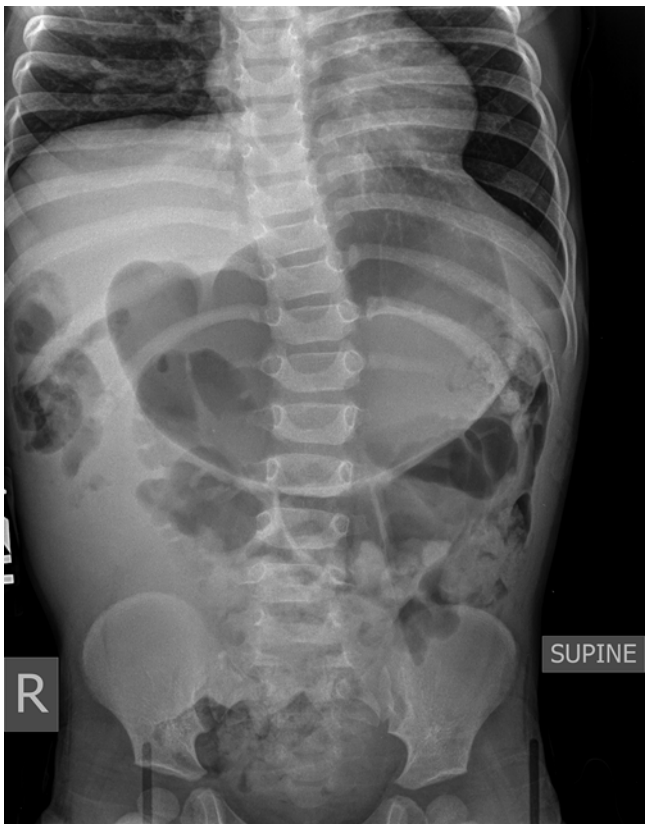

Fig. 6 Gas bloat syndrome. The X-ray shows a massively distended stomach in a baby unable to burp after Nissen fundoplication

Gas Bloat

Gas bloat syndrome is a somewhat-poorly defined "syndrome" in which air introduced into the GI tract either from the tube or via swallowing (aerophagia) is trapped in the stomach by the wrap. Instead of burping, the child can only handle the air two ways: by venting via the gastrostomy, or by passing the air through the anus. The resulting distension, cramping, and pain are the manifestations labeled as "colic" and the irritated child may cry inconsolably or retch. The best way to treat gas bloat is good venting. Some favor the use of a Farrell valve (™), but this long thin tube tends to have uneven performance in small babies in whom the Farrell valve is not the path of least resistance for ingested air. Often, better results are obtained by use of "chimney" venting. Other adjuncts include the use of simethicone, "tummy time," and avoidance of fiber or other feedings that promote gas formation in the colon (Fig. 6).

Dumping

When clinicians talk about "dumping" they really refer to two distinct phenomena after gastric surgery. The first is "early dumping" syndrome, in which relatively high osmotic foods enter the small bowel and induce a period of intestinal hypermotility. The exact pathogenesis is not known, but links to GLP-1, renin-angiotensin, VIP, cholesystokinin, and other mediators have been demonstrated or proposed. The manifestations include pain, cramps, flushing, tachycardia, and watery diarrhea in response to a bolus feed. Of the two syndromes labeled as dumping, this is more rarely seen in practice. Treatment consists of changing to lower osmotic feeds, slowing the rate of delivery, and in intractable cases, very cautious administration of octreotide. Meanwhile, because of the risk of this syndrome, rarely (if ever) should a pyloroplasty be done at the same time as a fundoplasty. The second type of dumping, "late dumping," is better understood as postprandial hypoglycemia (PPHG).

Postprandial Hypoglycemia

PPHG can occur after any gastric procedure, but as a practical matter it is encountered virtually exclusively after fundoplasty in children. Because the reactive hypoglycemia can be severe, this complication is arguably the most dangerous complication of fundoplasty. Because it may be asymptomatic, the method and criteria of diagnosis is in doubt, and awareness is poor, estimates of its prevalence range widely, from 2 to 30 %. PPHG appears to be essentially an overshoot feedback-and-control failure, with a spike in blood glucose leading to an "overshoot" of insulin secretion mediated by the incretin GLP-1. This insulin overshoot then produces hypoglycemia [64].

In practice, we screen every patient after fundoplication for PPHG by checking a series (30, 60, 90, and 120 min) of postprandial glucose levels (d-sticks) once the children are at full feeds, or anytime they exhibit unexplained lethargy, somnolence, irritability or retching. A very high (>180 mg/dL) followed by a very low (<50 mg/dL) sugar is diagnostic. Some premies will exhibit low sugars after feeds without a spike; this is not true PPHG, and more likely represents relatively poor hepatic sugar mobilization.

Treatment of PPHG is aimed at decreasing the rate and magnitude of the rise in glucose after a feed. Obviously, continuous feeding will avoid cyclic blood glucose levels, but also ties the child to a pump, and can exacerbate bloating and retching. Other options include use of any combination of acarbose (which blocks intestinal alpha glucosidase to slow absorption of intraluminal polysaccharides), uncooked cornstarch, microlipid, or even a simple change from formulas containing "corn-syrup solids" (pure glucose) to those containing maltodextrin (variable length short polymers of glucose) or other more complex sugars. Whatever strategy is employed, ongoing home monitoring of post-feed sugars is essential to safe management (and eventual weaning of the interventions used).

Retching

Of all of the complications after fundoplasty, retching is one of the most distressing to parents. Clinicians often mistake retching for evidence of new reflux after fundoplasty, and restart anti-reflux medications to treat this mistaken diagnosis. But wrap failure is actually a very unlikely cause of retching. Retching is not reflux; it is frustrated emesis. Any noxious stimulus that provokes emesis in a baby can cause retching when an intact wrap prevents this active retrograde flow. While mechanical problems such as a herniated wrap or esophageal obstruction certainly can cause retching, more commonly retching is actually evidence that the wrap is intact!

The approach to treating retching is to remove the noxious stimuli. For example, one of the most common causes of retching is over-large feeding boluses. Dropping feeding boluses below 15 cm^3/kg/bolus usually removes this stimulus. Meanwhile, high osmolarity either of feeds (such as elemental formulas) or drugs (especially KCl) decrease emptying while also appearing to directly stimulate vagal afferents in the stomach and duodenum. It is also important to look beyond the stomach. For example, some children retch because they cannot handle their postnasal drip, or because they have an acute exacerbation of pulmonary hypertension, or because they have an occult infection, or because they have unstable blood sugar. In general, a "whole-patient" approach to retching may be required to solve post-fundoplasty feeding intolerance. To solve retching, the doctor must find and eliminate the triggers of nausea, intestinal irritability, and vomiting that are the real sources of retching [65].

Dysphagia

Dysphagia (and odynophagia) occurs more often after Nissen than the partial fundoplications, but in patients of all ages is reported after any type of wrap in around 1 in 20 patients [53, 66]. However, these reports probably fail to capture the mild dysphagia often seen in the immediate postoperative period. While a surgeon can make a proper loose wrap over a large guide, he cannot control inflammation, edema, and related esophageal dysmotility after surgical manipulation. As a result, patients may have a transient (usually no more than 2 weeks, but some as long as 6 months) period of dysphagia. For this reason, for older patients most surgeons recommend a soft diet free of hard-to-swallow meats or breads initially, advice that is moot in the neonate. In some cases of persistent dysphagia, surgeons have tried a short burst of solumedrol or other corticosteroids to relieve the swelling but this has not been studied. Others patients may require gentle dilatation. Dysphagia that persists requires further workup (endoscopy, manometry) to determine if the wrap needs to be revised, or if actually there was another diagnosis (achalasia, eosinophilic esophagitis, etc.) that was mimicking GERD.

Essential Points

- GER is not the same as GERD. While virtually all infants exhibit GER, pulmonary manifestations are the hallmark of GERD.
- Pathological reflux is a mechanical disease that benefits from a mechanical (that is, a surgical) solution. Acid blockade appears to be ineffective or even dangerous for routine use in infants.
- There is no single best test for GERD.
- Surgical fundoplasty is highly effective in properly selected patients, and the effectiveness of the operation is enhanced by proper postoperative feeding strategies.

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