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Reza Shaker
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Gastrointestinal Motility Disorders

A Point of Care Clinical Guide

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Preface

Motility disorders include a number of chronic conditions which can involve various parts of the gastrointestinal tract. In addition, a number of aerodigestive and airway disorders can be caused by reflux of gastric content into the pharynx, larynx, and the airway requiring a multidisciplinary knowledge and approach for proper management. As such, gastrointestinal motor disorders can present not uncommonly with a complex set of overlapping signs and symptoms that frequently negatively affects health and quality of life. The diagnosis of these disorders is often viewed as being somewhat algorithmic. However, clinical experience shows that it is rarely straightforward and can be confusing. Similarly, the approach to managing motility disorders has been at times viewed as being algorithmic, but again this is rarely the case especially for patients referred to tertiary care centers. Frequently lack of effective medication for some motility disorders, compliance, or medication side effects arise as roadblocks to optimally managing patients with dysmotility.

Patients with newly diagnosed motility disorders frequently have many questions for their providers. This is perhaps more so for those patients failing therapy or who have experienced severe side effects or complications. Every provider has been faced with the questions: “Why did this happen to me?,” “So do I have delayed gastric emptying?, Are my symptoms caused by it?, or Do I have esophageal spasm and it’s causing me chest pain and not heart disease?,” “Where did I get this from?,” “What happens to me in the long term?,” “Do I really have to do the manometry?,” “What if I get pregnant?,” “I heard reflux medications can harm the baby, is that true?, “or “What about alternative therapies that I can try because I heard reflux medicine can weaken my bones?” These questions, while seemingly straightforward, require the provider to boil down a complex, overlapping, and sometime contradictory volume of literature into a simple answer the patient can comprehend.

This book will focus on answers to the patient questions that are frequently posed to providers who care for patients with GI motility disorders. Pre- and postsurgical patient management will be addressed in a way it can best be conveyed to patients. Additionally, it will guide clinicians through the complicated diagnostic and therapeutic/management approaches to motility disorders including common and specialized tests.

The purpose of this book is to be a point-of-care reference for busy clinicians who need the best evidence-based answers to patient questions at their fingertips.

Each chapter is predicated on a real patient question that has been encountered in the motility center at the Medical College of Wisconsin. Every clinician in his/her early training has frequently struggled to answer patients in a simple and coherent manner. This requires spending a great deal of time researching and evaluating the literature to provide patients with the most understandable and comprehensive answers. In speaking with other gastroenterologists who focus on motility disorders, it was found that many have shared this same experience and deliver many of the same answers to the same patient questions. This shared experience was the origin of the concept for this handbook: put the expert's answers to common patient questions in the hands of busy providers right at the point-of-care.

The beginning of each chapter starts with a patient question, which leads to a much bigger topic. Following the suggested response is a brief review of the literature as it pertains to the patient question and the chapter topic. These reviews are designed to be read in a few minutes and provide high yield information. This information will further enable the provider to adapt their response to any follow-up questions patients may have.

It is hoped that clinicians in different clinical settings will benefit from this review of the literature: students, midlevel providers, GI fellows, and busy general gastroenterologists alike.

We hope you will find "Motility Disorders: A Point-of Care Guide" to be a valuable clinical tool when it comes to managing your patient.

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Part I

Esophageal and Supraesophageal Motor Disorders

Achalasia and Esophageal Outlet Obstruction

1

Daphne Ang and Mark Fox

Commonly Posed Patient Questions

1. What is achalasia and how did I acquire this condition?

Achalasia is an uncommon esophageal motility disorder characterized by failure of relaxation of the lower esophageal sphincter (LES), the valve that controls passage of food from the oesophagus (gullet) into the stomach. The cause is unknown, although there is evidence that the condition is triggered by an autoimmune response in a patient who is genetically susceptible. This injury results in degeneration of inhibitory "nitroxinergic" (NO) neurones in the myenteric plexus leading to failure of LES relaxation and impaired contractility of the esophageal body. Three subtypes of achalasia are recognized based on the results of high-resolution manometry (see below). All have impaired LES function. Type I "classic" achalasia, often with oesophageal dilatation has no contractions in the esophagus. Type II displays "pan-esophageal pressurization" on swallowing. Type III "vigorous" achalasia is accompanied by esophageal spasm. Symptoms of achalasia include dysphagia, slow eating, regurgitation of undigested food, chest pain, and weight loss. The presence of reflux symptoms is not uncommon and can delay diagnosis. It should be emphasized that up to 40% of achalasia patients do not report difficulty swallowing because of habituation to chronic impaired bolus transport. Unexplained, treatment-resistant esophageal symptoms or difficulty eating requires investigation!

2. What are the investigations that I need to undergo?

Once a structural lesion has been excluded by upper gastrointestinal endoscopy and appropriate imaging (e.g., "barium swallow"), the gold standard for diagnosis of achalasia is esophageal High-Resolution Manometry (HRM). This involves swallowing a catheter with multiple pressure sensors arranged along its length that provides a representation of esophageal function from the throat to the stomach. The information is categorized by the "Chicago Classification" that defines three distinct subtypes of achalasia based on the pattern of esophageal contractility (see above). Identifying the subtype of achalasia directs treatment choices and provides information about prognosis (i.e., likelihood of successful treatment outcome). Overall, achalasia subtype II responds best to all forms of treatment and has the best prognosis. Esophageal HRM also defines the condition of esophagogastric junction (EGJ) outflow obstruction

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where there is evidence of impaired LES or EGJ function similar to achalasia, except that peristalsis is preserved. In some cases this represents an early stage or "variant" of achalasia. In others it can be caused by structural pathology that has not been identified by initial investigation such as peptic stenosis (i.e., related to acid reflux), inflammation (e.g., eosinophilic esophagitis), previous surgery (e.g., after fundoplication, gastric banding), or a neoplastic lesion (e.g., esophageal cancer). Further investigation including endoscopic ultrasound and/or abdominal computed tomography (CT scan) may be required. Structural causes of EGJOO are treated according to the underlying disease. In the absence of a structural cause, the treatment of functional EGJOO is similar to achalasia.

3. What are the treatment options? Is there a cure for this condition? Are there any novel treatment options available?

Achalasia is a chronic condition without a definitive cure. Current treatment options disrupt the LES muscle to improve passage of food and fluid. Although pharmacological agents can reduce LES pressure, the clinical response is rarely adequate and side effects of these medications are common. Injection of botulinum toxin into the LES has been described, even when effective, to have a relatively short-term effect and is generally used only in elderly patients with comorbidities who are poor candidates for definitive treatment. Botulinum toxin may have more of a role in the treatment of spasm in patients with achalasia type III.

The established treatment options are endoscopic pneumatic dilation (PD) and laparoscopic Heller myotomy (LHM) combined with an antireflux procedure. Randomized controlled trials have shown that, overall, the long-term outcomes of these two procedures are comparable; however, initial surgery is recommended for young patients (especially young men), individuals with high LES pressure and difficult-to-treat disease (e.g., type I achalasia with esophageal dilatation). Per-oral endoscopic myotomy (POEM) is an endoscopic treatment for achalasia and this procedure has shown promising short-term results. However, as this procedure is not combined with an antireflux procedure, there are concerns about complications and long-term outcome data is awaited.

Routine follow-up of achalasia patients that have had definitive treatment is not advocated by the American Society of Gastrointestinal Endoscopy (ASGE), although this practice may differ in other countries and amongst gastroenterologists. There is a slightly elevated risk of squamous cell carcinoma of the esophagus in the long term. This may be higher in patients with poor clearance and severe esophageal dilatation. A reasonable approach is to survey 10–15 years after the initial diagnosis of achalasia; however, this is not evidence based.

Background and Pathogenesis

Lendrum first proposed that achalasia was a condition characterized by incomplete relaxation of the lower esophageal sphincter (LES) and introduced the name "achalasia" derived from the Greek word "chalasis" for relaxation [1]. Achalasia is a primary esophageal motor disorder that is characterized by the absence of deglutitive LES relaxation and, in most cases, loss of esophageal peristalsis. This disorder results in impaired esophageal clearance and, typically, leads to dysphagia, chest pain, regurgitation, and weight loss.

The etiology of achalasia is unknown [2]; however, a key mechanism of disease is the selective loss of inhibitory nitroxinergic (NO) and vasoactive intestinal peptide (VIP) postganglionic neurons in the distal esophagus and LES [3]. A leading hypothesis is that a viral infection [4, 5] in a genetically susceptible host triggers autoimmune, T-call-mediated neuronal degeneration of specific postganglionic neurons in the myenteric plexus of the smooth muscle esophagus [6]. A similar condition seen in South America is "Chagas" disease and is caused by destruction of the myenteric plexus as a late consequence of infection with the parasite *Trypanosoma cruzi* [7]. The resulting imbalance between the

excitatory control (acetylcholine (ACh) mediated) and inhibitory control (NO, VIP mediated) impairs LES relaxation and, in many cases, increases LES tone. The loss of the so-called deglutitive inhibition (also NO mediated) in the esophagus can also lead to a loss of "latency gradient" along the esophagus that coordinates sequential peristaltic contractions resulting in esophageal spasm [8]. As the disease progresses, the cholinergic neurons may also be involved, leading to aperistalsis and esophageal dilatation. Alternatively, aperistalsis may be secondary to esophageal dilatation due to chronic LES obstruction [9]. In a recent review, Kahrilas and Boeckxstaens propose that the etiology of achalasia may be heterogeneous with type I and type II achalasia being caused by the loss of inhibitory control described above, but type III achalasia being related to excessive excitatory control [10]. Depending on the immune response, patients may develop an immune response which causes loss of myenteric neurons, eventually leading to aganglionosis and fibrosis. This progressive plexopathy results in a clinical presentation that evolves from achalasia with preserved peristalsis, to Type II achalasia and eventually to Type I achalasia. Alternatively, patients may develop a "less aggressive" noncytotoxic immune response which affects neuronal function but not causing apoptosis. The resultant cytokine-induced alterations in neuronal gene expression lead to downregulation of nitric oxide (NO) synthase expression and increased cholinergic sensitivity. This imbalance between inhibitory and excitatory postganglionic neuronal function results in Type III achalasia [10] (Fig. 1.1).

Esophagogastric junction outflow obstruction (EGJOO) is a condition characterized by HRM findings of impaired EGJ function but, at least in part, preserved peristalsis. The diagnosis of EGJOO in case series appears to be increasingly common, likely due to increased availability of HRM in routine clinical practice. EGJOO has been referred to as variant achalasia; however, it can be caused not only by functional but also by structural pathology (Table 1.1). Functional causes include early-stage achalasia in which the nonrelaxing LES is not yet accompanied by severe motor disorders of the esophageal body (i.e., early achalasia). Structural causes include peptic stenosis (i.e., related to acid reflux), inflammation (e.g., eosinophilic esophagitis), previous surgery (e.g., after fundoplication), or neoplasia (often labeled "pseudoachalasia"). True paraneoplastic causes of achalasia caused by the destruction of inhibitory innervation by tumor antibodies from distant tumors (e.g., lung cancer) are much rarer than local invasion of the EGJ by tumor or external compression of the distal esophagus by metastases. A combination of endoscopy and imaging to exclude a structural cause is prudent before a diagnosis of EGJOO is made. A typical finding in functional causes (i.e., motility disorders) is increased wall thickness from muscle hypertrophy.

Diagnosis

The diagnosis of achalasia and EGJOO is suspected in patients who have long-standing dysphagia to solids and liquids with regurgitation of undigested material that can include saliva. A careful clinical history, followed by upper gastrointestinal endoscopy and appropriate radiological investigations to rule out structural lesions including underlying malignancy, is essential in the initial workup to exclude local pathology. Occult malignant infiltration of the gastroesophageal junction is a rare but important differential diagnosis that affects about 2% of patients evaluated for achalasia. These patients are generally older and have a more rapidly progressive clinical course [11].

Clinical Presentation

The annual incidence of achalasia is 1/100,000 and the prevalence is 10/100,000 [12]. Patients most commonly present between the ages of 25 and 60 years with no gender or racial preference. Dysphagia of both solids (91%) and liquids (85%) with regurgitation of saliva and undigested

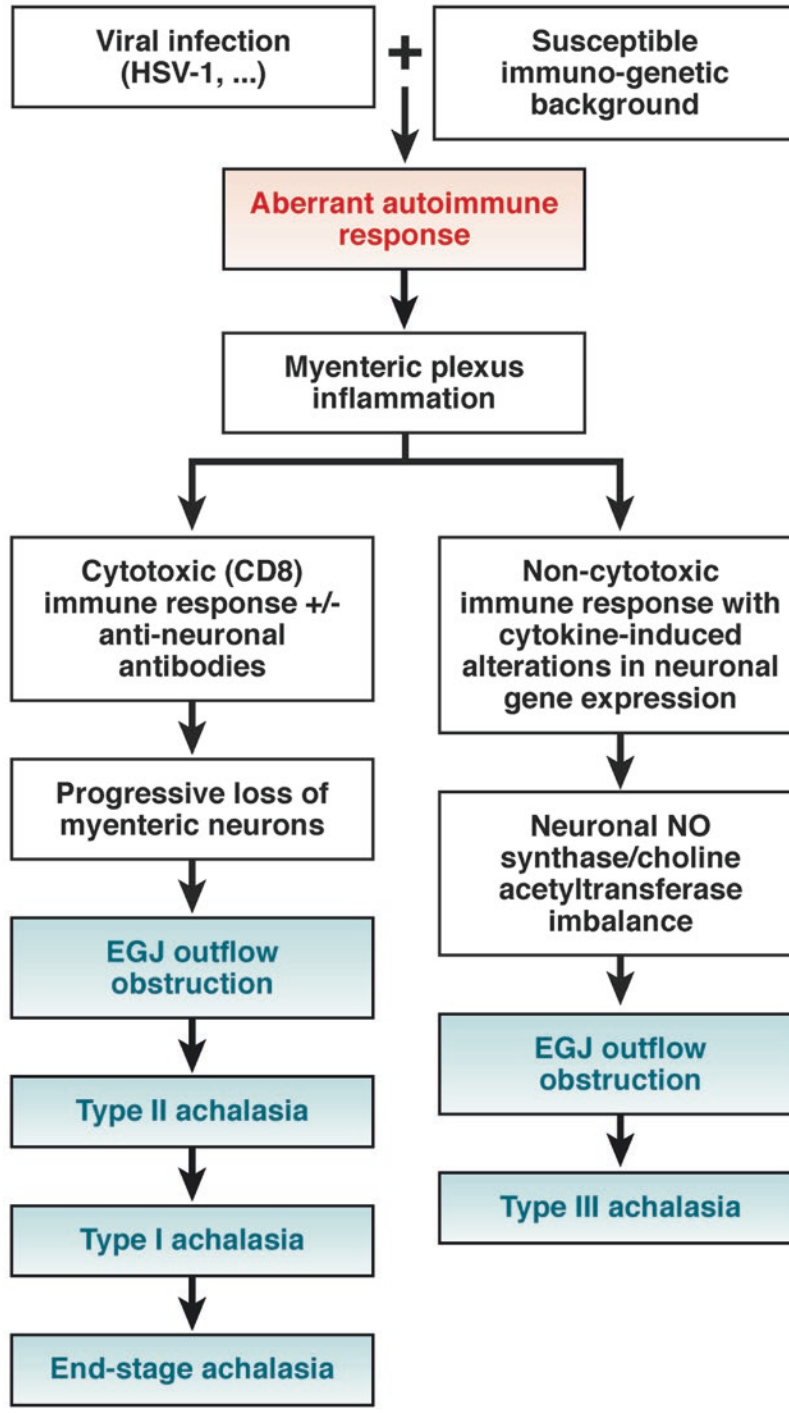


Fig. 1.1 Schematic representation of etiology proposed to underlie the different achalasia phenotypes

food (76–91%) is a frequent symptom in patients with achalasia [13–18] (Table 1.2). Other presenting symptoms include slow eating, heartburn, chest pain, and respiratory symptoms including cough [15]. Achalasia can present with symptoms that suggest gastroesophageal reflux disease [17–21] and up to 49% of patients were reported to experience heartburn in one series [20]. Heartburn can be caused by intermittent reflux with prolonged acid exposure due to

impaired clearance; however, this nonspecific symptom can also be due to mechanical distension of the esophagus and chemical irritation of the mucosal lining by food or lactate production by bacterial fermentation of retained carbohydrate [18]. Chest pain is reported in 25–63% of patients and is thought to be common in Type III achalasia [22]. Up to 41% of patients in one study experienced supraesophageal symptoms [14]. Impaired clearance of esophageal contents predisposes patients to aspiration. Abnormal radiological findings of centrilobular nodules with "tree-in-bud" pattern, septal thickening, and necrotizing pneumonia are reported [23].

The symptoms of EGJOO are similar to achalasia. Most of the patients present with dysphagia to solids, chest pain, and nonspecific reflux symptoms [24–27] (Table 1.3). As EGJOO is a manometric diagnosis, a careful evaluation to exclude a structural cause is important. Patients with a structural cause of EGJOO tend to complain more of dysphagia (62% vs. 25%, $p = 0.09$) and chest pain (75% vs. 25%, $p = 0.08$) than those with functional EGJOO [26]. A short history, weight loss, and older age at presentation may clinically be suspicious of an underlying malignancy. Patients with EGJOO should undergo further evaluation to exclude neoplastic or inflammatory changes.

Table 1.1 Causes of esophagogastric junction outflow obstruction (EGJOO)

1. Structural pathology
• Reflux-induced strictures, Schatzki's ring
• Hiatus hernia
• Eosinophilic esophagitis
• Malignancy (esophageal, cardia)
• Extrinsic compression (malignancy)
• Surgical (post-fundoplication/bariatric surgery)
2. Functional (no structural pathology)
• Impaired LES relaxation ("variant achalasia")

Endoscopy

The role of upper gastrointestinal gastroscopy is to rule out a mechanical cause with particular emphasis on the EGJ and gastric cardia. Findings may range from a normal appearing esophagus to a dilated esophagus with retained food/saliva and in advanced cases a sigmoid esophagus. Investigation should always include biopsies of the distal and mid-esophagus to exclude eosinophilic esophagitis as a cause of swallowing difficulties. Biopsies will also rule out squamous mucosal dysplasia and Barrett esophagus that can be caused due to chronic inflammation. It should be emphasized that this investigation is poorly sensitive in the early stages of achalasia prior to the occurrence of esophageal dilatation.

Endoscopic ultrasound (EUS) is requested to exclude infiltrating tumor at the EGJ or external compression of the distal esophagus due to lymph node metastases or other neoplastic pathology. This is especially appropriate in patients with

Table 1.2 Symptom patterns in patients with achalasia

Author	Dysphagia	Chest pain	Heartburn	Regurgitation	Others
Eckardt et al. [13]		64/101 (63%)			
Sinan et al. [15]	95/110 (86%)	35/110 (32%)	45/110 (41%)	70/110 (63%)	
Fisichella et al. [16]	136/145 (94%)	60/145 (41%)	75/145 (52%)	110/145 (76%)	Aspiration (18/145) 12%
Spechler et al. [18]	66/67 (99%)	35/67 (52%)	32/67 (48%)	47/67 (70%)	
Ponce et al. [19]			15/40 (38%)		
Huselmans et al. [21]	200/209 (96%)	53/209 (25%)	37/209 (18%)		Weight loss (82/209) 39%

Table 1.3 Symptom patterns in patients with functional esophagogastric junction outflow obstruction (EGJOO)

Author	Dysphagia	Chest pain	Heartburn/regurgitation	Others
Scherer et al. [24]	15/16 (94%)	4/16 (25%)	9/16 (56%)	Globus 3/16 (19%)
Van Hoeij et al. [25]	23/34 (68%)	24/34 (71%)	12/34 (35%)	Cough/globus/dyspepsia 5/34 (15%)
Perez-Fernandez et al. [26]	21/28 (75%)	13/28 (46%)	19/28 (68%)	Atypical GERD 10/28 (36%) Dyspepsia (12/28) 43%
Clayton et al. [27]	24/27 (89%)	2/27 (7%)		Cough 1/27(4%)

rapidly progressive symptoms or EGJOO in whom the etiology is uncertain. In addition, EUS serves an adjunctive role for the diagnosis of major motility disorders in which there is often evidence of thickening of the esophageal smooth muscle [28].

Barium Studies

The classic "bird's-beak" appearance at the EGJ on barium swallow arises as a result of impaired emptying of barium, esophageal dilation, and minimal LES opening. However, these features occur only in more advanced cases of achalasia, barium studies, and lack of diagnostic sensitivity (60%). Radiology serves a useful adjunctive role to rule out structural lesions, estimate esophageal diameter, and assess for the presence of epiphrenic diverticula [29]. The timed barium esophagogram (TBE) provides a standardized assessment of esophageal clearance function and can be helpful to assess treatment effect (see below).

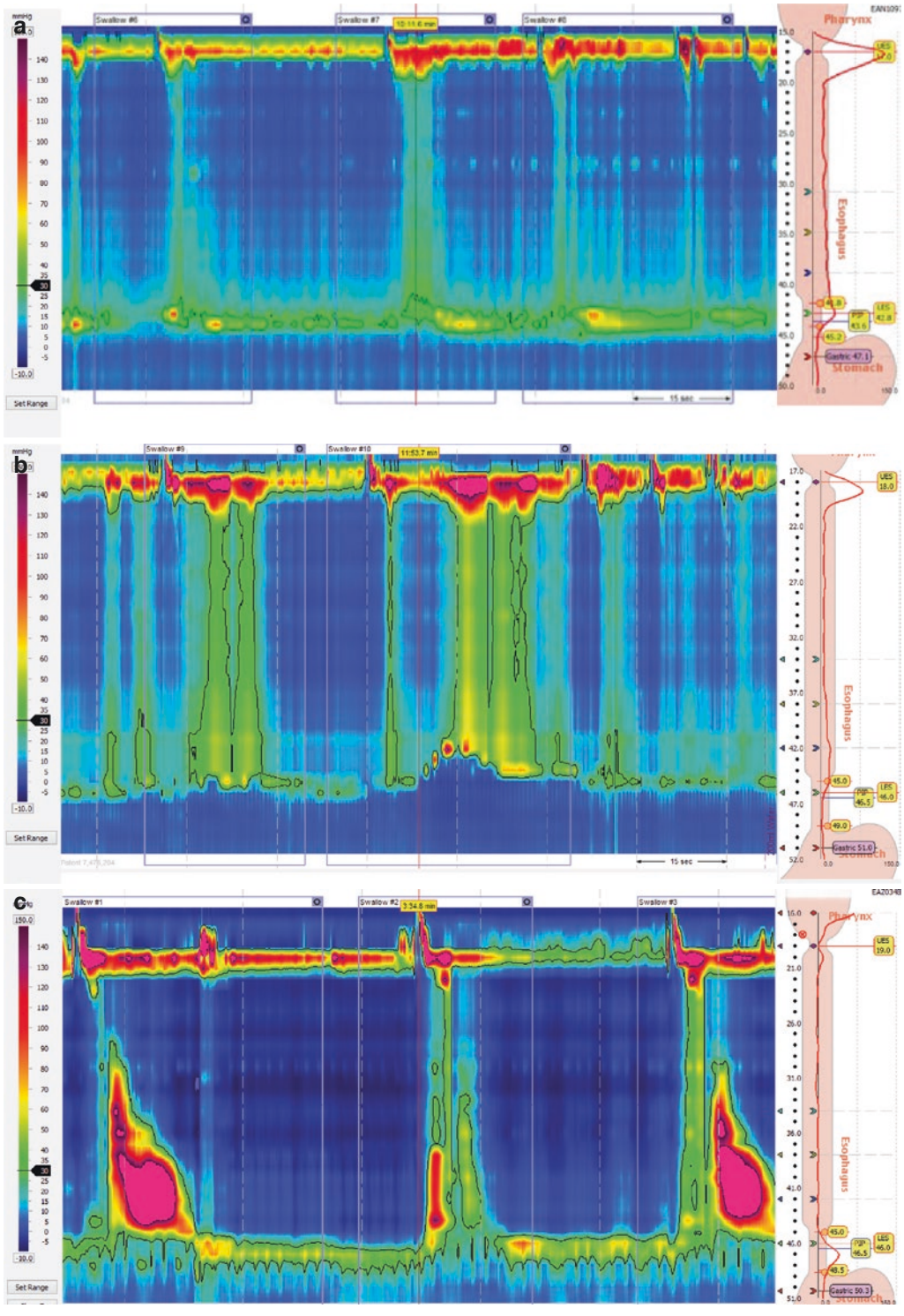
Manometry

The diagnosis of achalasia is established on manometry. Typical findings on conventional manometry with 5–8 pressure sensors including a sleeve sensor at the LES were the absence of peristalsis and incomplete relaxation of the LES during deglutition [30]. The current reference standard is high-resolution manometry (HRM) with up to 36 closely spaced pressure sensors [31]. HRM data is displayed as esophageal pressure topography (EPT) plots, also known as Clouse plots, a continuous representation of motility and function from the pharynx to the stomach [32]. Analysis of this data calculates metrics that provide an objective assessment of esophageal and EGJ/LES function. Based on these HRM metrics the Chicago Cassification provides a diagnosis of esophageal motility disorders. This stepwise, hierarchical algorithm places most emphasis on EGJ disorders (i.e., achalasia, EGJOO) since these have the greatest impact on bolus transport and symptoms [33]. HRM increases interobserver agreement [34] and diagnostic accuracy compared to conventional manometry [35] and provides definitive diagnosis.

The integrated relaxation pressure (IRP) is a metric that was developed to quantify EGJ relaxation and opening [36]. An electronic sleeve sensor compensates for any movement of the LES during respiration [37]. The IRP is calculated from the electronic sleeve as the mean value during 4 s of maximal EGJ relaxation after pharyngeal contraction. Validation studies have shown that this provides a more accurate diagnosis of achalasia than previous metrics based on conventional manometry (e.g., nadir LES pressure, percentage LES relaxation) [36, 37]. The diagnosis of achalasia is based on an elevated IRP > 15 mm Hg in the absence of peristaltic contractions in the esophageal body. The diagnosis of EGJOO also requires an elevated IRP > 15 mm Hg but with preserved esophageal contractility [2] (Fig. 1.2).

Three subtypes of achalasia have been described [37] based on the presence of raised IRP and the pattern of contractility in the esophageal body during HRM studies: Type I "classic" achalasia (without evidence of

Fig. 1.2 HRM findings in achalasia and EGJOO. HRM findings relevant to the Chicago Classification are highlighted by application of a 30 mm Hg isobaric contour plot (*black*). The condition is diagnosed by the presence of impaired EGJ relaxation as defined by raised IRP > 15 mm Hg. (**a**) Type I achalasia: elevated IRP with absent peristalsis and minimal contractile activity between the upper esophageal sphincter and EGJ junction. (**b**) Type II achalasia: elevated IRP with pan-esophageal pressurization to ≥30 mm Hg in ≥20% of wet swallows. Note also significant esophageal shortening (swallow #10). This can lead to false-negative diagnosis due to "pseudo-relaxation" (movement of LES above sleeve sensor) in patients with conventional manometry even in the presence of a sleeve sensor [123]. (**c**) Type III achalasia: elevated IRP with ≥20% of wet swallows associated with spastic (premature) contractions. Note esophageal shortening during spasm. (**d**) EGJOO: elevated IRP with ≥20% of wet swallows associated with compartmentalized pressurization between peristaltic contractions and the EGJ. Repeat endoscopy to reassess the local anatomy showed no obvious inflammation; however, biopsies from the mid- and distal esophagus revealed eosinophilic esophagitis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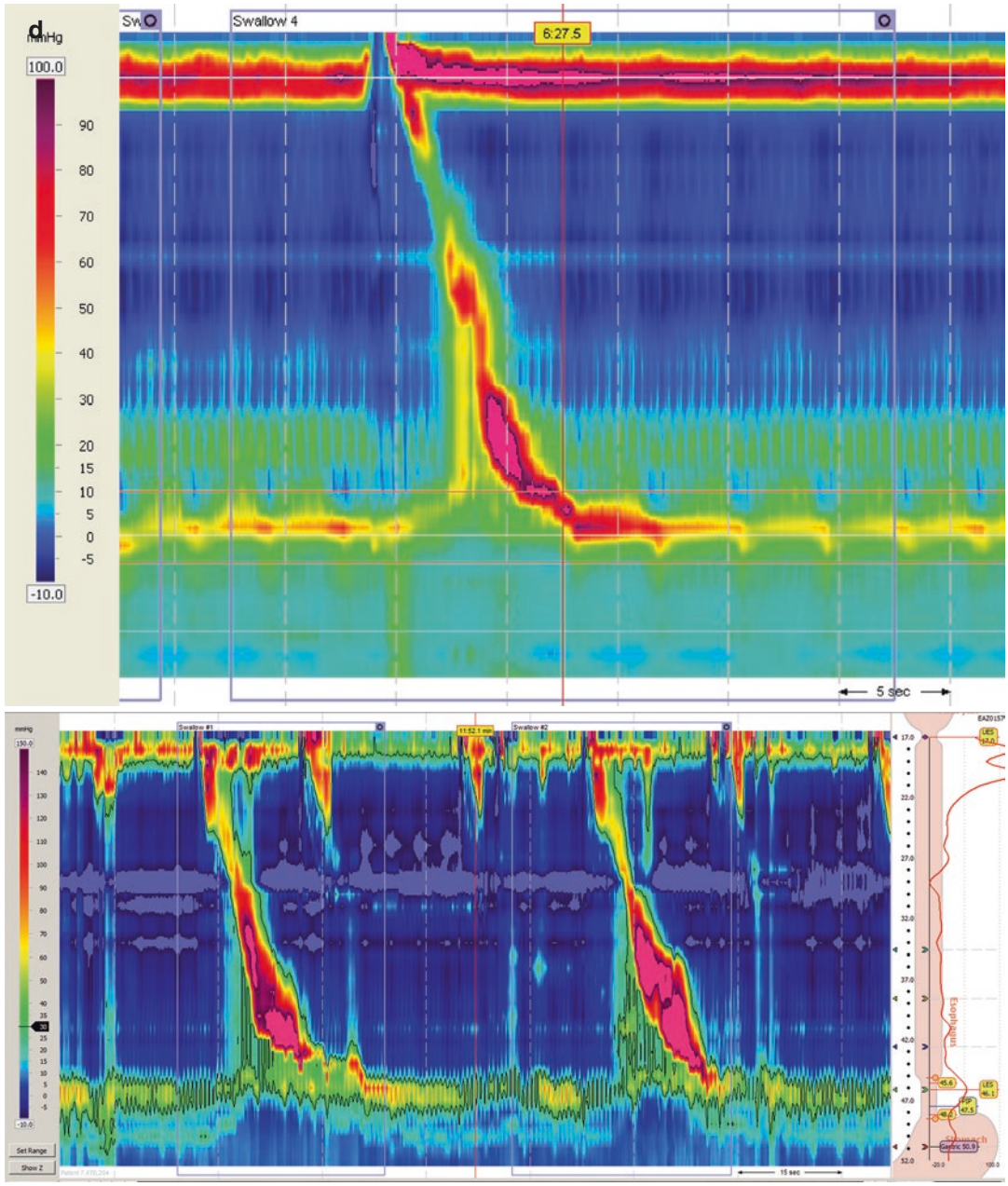


Fig. 1.2 (continued)

pressurization or contractility); Type II achalasia (with pan-esophageal pressurization); and Type III "vigorous" achalasia (with ≥2 spastic contractions in the distal esophagus). This classification is clinically relevant since the subtype of achalasia guides treatment decisions and predicts outcome (Fig. 1.2a, b, and c).

The Chicago Classification identifies esophagogastric junction outflow obstruction (EGJOO) as a major motility disorder [33]. The diagnosis is applied to any pathological process, whether functional or structural, that affects esophageal transit across the EGJ in which effective peristaltic contractions are observed. It is the presence of effective esophageal body peristalsis that distinguishes EGJOO from achalasia (Fig. 1.2d). There are diverse structural and functional causes of EGJOO (Table 1.1).

HRM with Adjunctive Tests/ Physiological Challenge

The current Chicago Classification is based on the analysis of ten 5 mL water swallows in the supine position. This approach is nonphysiological as eating and drinking is a continuous process performed in the upright position. Studies have shown that, also in healthy volunteers, multiple swallows are often necessary to clear a solid bolus as not every single swallow is effective [38, 39]. In addition, esophageal symptoms almost never occur with water swallows but during normal eating and drinking [40].

Adjunctive tests with rapid drink challenge (RDC; 100–200 mL water) and/or a solid test meal may improve diagnostic sensitivity (Fig. 1.3d) [41, 42]. In particular, EGJOO may not be evident with water swallows because the resistance to bolus passage is minimal. Increasing the physiological load by increasing fluid volume or bolus viscosity can highlight functional or structural obstruction to bolus transport. For example, whereas most patients show a decreased IRP during repeated swallowing due to profound EGJ relaxation, patients with achalasia showed a higher IRP during 200 mL RDC (Fig. 1.3a, b, and c) [41]. Similarly application of HRM with a standardized test meal highlights EGJ obstruction in patients with persistent dysphagia after fundoplication (Fig. 1.3d) [43]. This finding identified patients that responded to pneumatic dilatation of the EGJ in whom other investigations

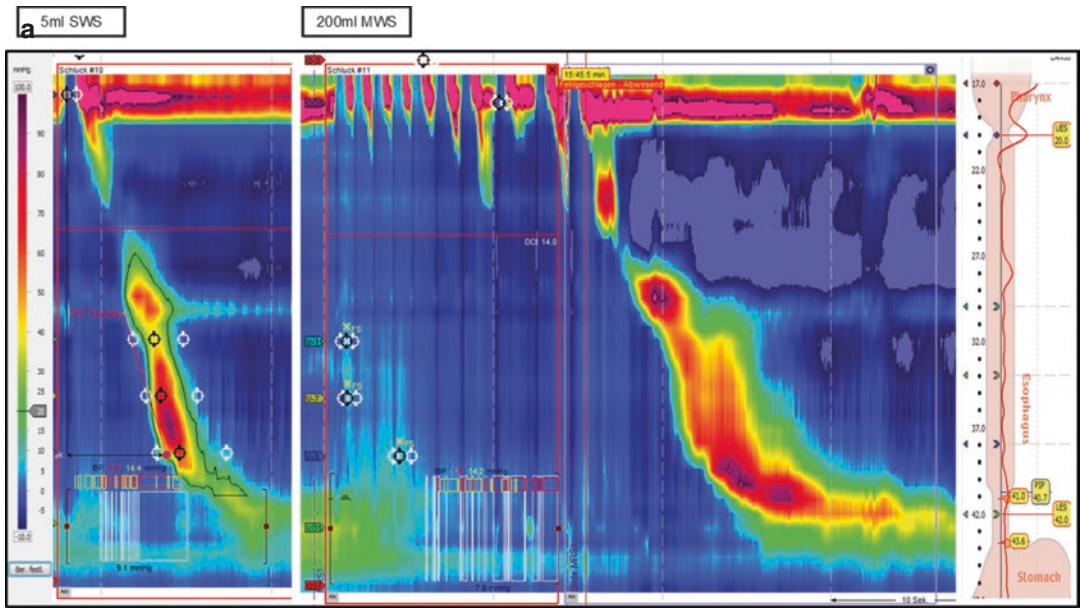
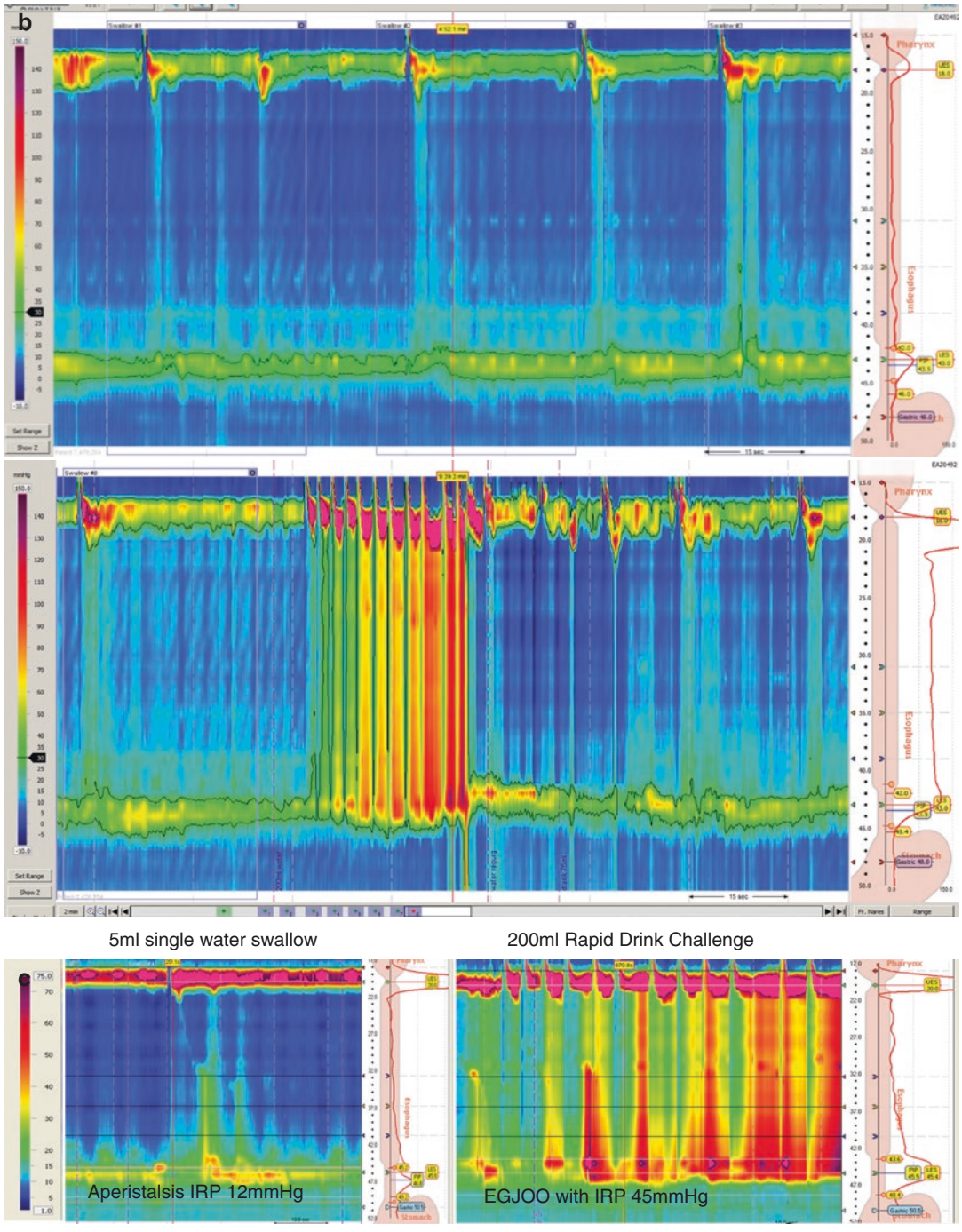


Fig. 1.3 Use of adjunctive tests with HRM in investigation of achalasia and EGJOO. (**a**) Example of a single water swallow (SWS) followed by rapid drink challenge (RDC) in normal subject. There is complete esophagogastric junction (EGJ) relaxation and suppression of contractility during RDC. IRP is lower during RDC than SWS (6 mm Hg vs. mean 9 mm Hg). RDC is followed by an effective clearance contraction. (**b**) Typical findings of SWS and RDC in achalasia. SWS is associated with aperistalsis and an elevated integrated relaxation pressure. With RDC pan-esophageal pressurization was observed and IRP is increased further (mean IRP 31 mm Hg vs. IRP-RDC 37 mm Hg). This effect is observed only in achalasia and functional EGJ/LES outlet obstruction [41]. (**c**) Increased sensitivity of HRM study with adjunctive RDC. SWS is associated with aperistalsis and IRP within normal levels (12 mm Hg) for single water swallows (SWS). The criteria for pan-esophageal pressurization (>20 mm Hg) were not fulfilled. With RDC functional obstruction at the EGJ is obvious. IRP increased to 45 mm Hg and pan-esophageal pressurization was obvious. These findings identify impaired EGJ relaxation in achalasia type I with low baseline LES pressure. (**d**) Increased sensitivity of HRM study with adjunctive test meal. HRM during SWS (*top panel*) and during solid test meal (*lower panel*) in patient with persistent dysphagia after fundoplication surgery. SWS is associated with normal peristalsis; however, with solids, there is compartmentalized pressurization above the EGJ indicative of obstruction due to a slipped or twisted fundoplication wrap (confirmed at redo surgery)



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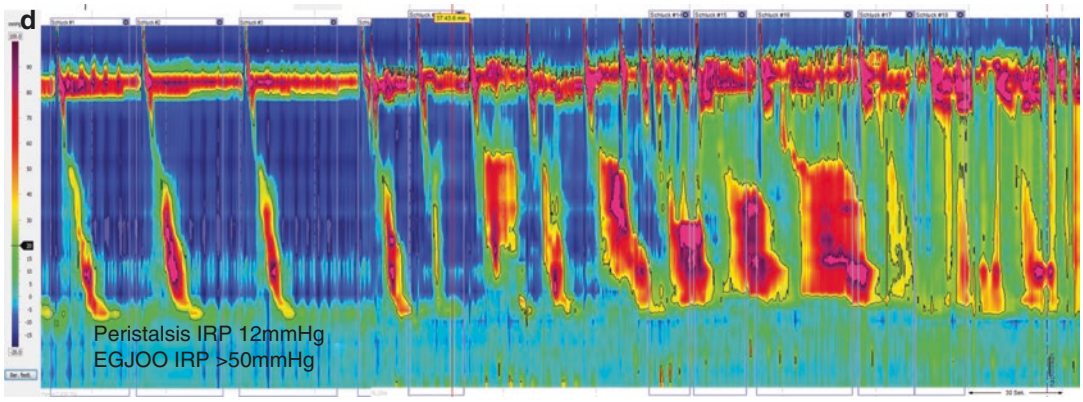

Fig. 1.3 (continued)

were nondiagnostic. In the future the use of concurrent, high-resolution intraluminal impedance with HRM will clarify the impact of motility on esophageal function. The combined technique highlights the presence of food and fluid (and gas) in the esophagus. This is important as, in most cases, it is not motility disorders per se but bolus retention that leads to symptoms.

Endoluminal Functional Lumen Imaging Probe (Endo-FLIP)

The endoluminal functional lumen imaging probe (Endo-FLIP) is a recently described technique that uses impedance planimetry to determine multiple cross-sectional areas (CSA) within a cylindrical bag during volume-controlled distension [44]. This approach provides a measure of esophagogastric junction (EGJ) distensibility (CSA/intrabag pressure). EGJ distensibility has been evaluated in patients before and after treatment for achalasia. The results correlated well with esophageal emptying on timed barium esophagogram and clinical response based on Eckardt score < 3 [44–46]. More recently, FLIP topography demonstrated esophageal contractility in Type I and Type II achalasic patients who did not show any contractions on manometry. In addition, a unique feature of repetitive retrograde contractions was observed in Type III achalasic patients [47]. These findings suggest a potential novel method of Endo-FLIP technique to evaluate EGJ distensibility and eosphageal contractility. This could increase diagnostic sensitivity to motility disorders; however, its clinical utility is not proven.

Treatment

The aim of all therapeutic options for achalasia and EGJOO is to reduce the resistance to bolus passage across the EGJ. The available methods include pharmacotherapy, botulinum toxin injections, endoscopic dilatation, and myotomy which can be performed either surgically or by endoscopy (per-oral endoscopic myotomy [POEM]) [48]. The following section considers each of these options and then reviews studies that assessed the relative efficacy of pharmacologic, endoscopic, and surgical treatment.

Pharmacology Including Botulinum Toxin

In achalasia and functional causes of EGJOO calcium channel blockers and nitrates relax gastrointestinal smooth muscle and reduce LES pressure. Data from randomized controlled studies is lacking; however, this effect appears to improve dysphagia in some cases [49]. Sublingual nifedipine (10–30 mg, 30–45 min before meals) or isosorbide dinitrate (ISDN 5–10 mg, 15 min before meals) can be useful as short-term measures in patients who are poor candidates for myotomy or endoscopic dilatation. However, these drugs are often associated with

side effects including headache, orthostatic hypotension, and edema and do not retard disease progression. The 5′-phosphodiesterase inhibitors, such as sildenafil (Viagra®), reduce LES pressure and can attenuate distal esophageal contractions. This medication works by blocking the enzyme that degrades nitric oxide and increasing local concentration of this inhibitory neurotransmitter in the smooth muscle [50]. The lack of long-term data and cost issues have largely restricted the off-label use of sildenafil in achalasia.

Injection of botulinum toxin into the lower esophageal sphincter blocks the release of acetylcholine from nerve endings and reduces LES pressure in achalasia [51]. In one study up to 66% of achalasia patients achieved improvement in dysphagia after 6 months [52]. However, the therapeutic effect wears off due to axonal regeneration, with a meta-analysis reporting symptomatic response rates after one injection of 78%, 70%, 53%, and 41% at 1 months, 3 months, 6 months, and 12 months, respectively [53]. Repeated treatments with Botox have been associated with inferior response rates compared to subsequent Heller myotomy [54]. Based on the above findings, botulinum toxin injection is generally applied only in elderly patients with multiple comorbidities that are unfit for more definitive treatments [29].

Endoscopic Dilation

Endoscopic dilation aims to improve bolus transport by mechanically disrupting the EGJ/LES. In cases of structural EGJOO due to tight peptic or inflammatory strictures Savary bougie dilatation of the EGJ is most appropriate since the risk of esophageal perforation by a large balloon is high. In achalasia, functional EGJOO and other causes of structural EGJOO (e.g., post-fundoplication) pneumatic dilatation are performed. A noncompliant balloon (e.g., Rigiflex, Boston Scientific, USA) is positioned across the EGJ over an endoscopically inserted guidewire. The position of the balloon is confirmed fluoroscopically and controlled dilation is performed according to the manufacturer's instructions until the balloon is fully expanded [55]. A graded approach is recommended with increasing balloon diameters (3.0, 3.5, and 4.0 cm) spaced 2–4 weeks apart depending on symptom relief [21, 56], residual LES pressures [21, 57] or improvement in timed barium esophageal (TBE) emptying [58–60].

Pneumatic dilatation is safe and effective in the majority of patients; however, response rates are lower in patients that are young (<40 years) and male gender [61], and those with elevated LES pressure and in Type I achalasia (with gross dilatation) and Type III achalasia (with spasm) [13, 22, 62]. Further, a gradual loss of remission occurs with time in many patients [21, 63, 64]. A study from the Cleveland clinic [55] reported a 62% success rate at 6 months and 28% success rate at 6 years in patients who had undergone a single pneumatic dilatation, whereas serial dilation improved symptom response to 90% at 6 months and 44% at 6 years. Overall, approximately one-third of patients experience symptom relapse after 4–6-year follow-up but are often responsive to repeat pneumatic dilatation [21].

The most important complication of pneumatic dilation is esophageal perforation. A systematic review reported a risk of 1% which was comparable to the risk of unrecognized perforation during Heller myotomy [65]. In general, these perforations can be managed conservatively, although there is an associated mortality [63]. Risk factors for perforation include a large balloon diameter, old age, and Type III achalasia [21, 57, 66].

Surgical Heller Myotomy

Surgical treatment of achalasia by Heller myotomy was first reported by Ernst Heller in 1914 and is considered the most definitive treatment. In current practice laparoscopic Heller myotomy (LHM) is preferred because it provides an enhanced view of the muscle layer and allows a meticulous dissection of the transverse fiber bundles. The laparoscopic approach has a lower morbidity and comparable long-term outcome compared to the thoracoscopic or transabdominal approach [67]. The reported perforation rate occurring from LHM is 3.1% with the majority occurring during surgery and repaired immediately [68]. An antireflux procedure [69] performed in the same operation decreases the risk of postoperative gastroesophageal reflux after LES

disruption [70]. A recent large-scale study [71] reported a prevalence of GERD of 8.6% at 6 months using 24-h esophageal pH evaluation in patients who had undergone prior LHM with a Dor fundoplication.

The LHM procedure has efficacy rates between 88 and 95% [62, 72, 73]. Predictors of a good outcome include younger age (<40 years) and a high resting LES pressure (>30 mm Hg) [74–76]. A large sigmoid shaped esophagus as seen in achalasia type I carries a worse prognosis [74–76]; however, surgery is still the preferred modality in this situation since the efficacy of pneumatic dilatation is very poor in this situation.

Per-Oral Endoscopic Myotomy (POEM)

POEM is an endoscopic technique that applies the principles of natural orifice transluminal endoscopic surgery (NOTES) to perform LES myotomy in achalasia. The technique was initially described by Pasricha [77] and further developed by Inoue [78]. It involves creating a submucosal tunnel from the mid-esophagus and dissecting the mucosa downwards to reach the cardia. This is followed by selective myotomy of the circular muscle fibers for a minimum length of 6 cm up the esophagus and 2 cm distal to the squamocolumnar junction onto the gastric cardia. Success rates of POEM [79–82] are high in the short term but efficacy decreases with time from 97% at 3 months to 82% at 1 year [83]. The major side effect of POEM is the development of gastroesophageal reflux disease (GERD). A systematic review of five studies that have used esophageal pH monitoring to evaluate patients after POEM reported a 43% prevalence of pathological acid exposure [84]. This was confirmed in a recent series of 103 patients with a prevalence of 51% abnormal pH studies with esophagitis in 29% [85]. Although POEM is now performed in many centers, there is a lack of long-term outcome data comparing its efficacy with conventional techniques of endoscopic dilatation and surgical myotomy.

Appropriate patient selection for POEM has not been established. Advocates of the technique have treated patients with all forms of achalasia, prior treatment with Botox [86], prior treatment with pneumatic dilation [86, 87], and who have failed surgical myotomy [88–90]. In a recent multicentre retrospective analysis of the 2-year outcome after POEM, the overall success rate was 80% [91]. Analysis by achalasia subgroups showed similar efficacy in Type I achalasia (75%), Type II achalasia (79.2%), and Type III achalasia (75%) [91]. Most experts do not use POEM in patients with gross dilatation or other, anatomical abnormalities of the distal esophagus (e.g., diverticulum). However successful POEM in patients with sigmoid achalasia has been reported [92].

The most common complication of POEM is GERD. Reflux symptoms and reflux esophagitis occur frequently and are a logical consequence of LES disruption without an antireflux procedure [82]. The frequency of endoscopic features of reflux esophagitis (Grade A/B) was 38% at 2-year follow-up [91]. One case has been reported of severe reflux esophagitis with resultant peptic stricture that required endoscopic dilatation [82]. It seems likely that the risk of postprocedural reflux is higher in patients with central adiposity and this could explain the increased risk of GERD in American and European case series compared to original reports from Japan. Proton pump inhibitors (PPIs) should be used routinely in all patients with symptoms and are prescribed routinely by many experts [82].

Esophagectomy for End-Stage Achalasia

Between 2 and 5% of patients will develop end-stage achalasia, defined as a massive dilation of the esophagus (diameter > 6 cm) with retention of food, persistent reflux disease, or presence of preneoplastic lesions [93]. Pneumatic dilation is less effective in this situation but studies have shown symptomatic improvement in 72–92% [94, 95] of patients with a megaesophagus who undergo Heller myotomy. Nevertheless esophagectomy is an option in patients with severe symptoms and objective evidence of very poor clearance after other treatments. It is also appropriate in patients with severe squamous dysplasia or Barrett esophagus with high-grade dysplasia to reduce the risk of invasive carcinoma [96].

Table 1.4 Comparison of treatment outcome with pneumatic dilation compared to intrasphincteric application of botulinum toxin A at endoscopy

Reference	No. of patients (PD)	No. of patients (Botox)	Follow-up (months)	Outcome
Annese et al. [99]	8	8	12	Symptom score 0.8 ± 0.4 (PD) vs. 1.5 ± 0.6 (Btx), $p = 0.215$
Vaezi et al. [100]	20	22	12	14/20 (70%) PD vs. 7/22 (32%) Btx in remission, $p = 0.02$
Muehidorfer et al. [101]	12	12	30	Recurrence of symptoms in 9/9 (Btx) vs. 4/10 PD patients
Prakash et al. [102]	26	42	24	No difference in survival analysis curves between Botox and PD groups at 2 years ($p = 0.4$)
Mikaeli et al. [103]	20	20	12	Relapse/retreatment 2.69× higher in Btx vs. PD group
Ghoshal et al. [104]	10	7	8	Cumulative dysphagia-free rate by Kaplan-Meier analysis significantly reduced in Btx vs. PD group ($p = 0.027$)
Allescher et al. [105]	14	23	48	PD and Btx similar efficacy at 12 months PD superior at 24 and 48 months
Bansal et al. [106]	18	16	12	16/18(PD) vs. 6/16 (Btx) remission at 12 months

Comparison of Treatment Modalities

Botulinum Toxin vs. Pneumatic Dilatation and Laparoscopic Heller Myotomy

A meta-analysis of controlled studies comparing outcomes at 1 year showed superior response rates from pneumatic dilation compared to botulinum toxin (66% vs. 36% [RR 2.0 (95% CI 1.51–3.20), $p < 0.0001$]) [97]. Similarly, a Cochrane review [98] that compared the outcome of patients who had undergone PD versus Botox showed no significant difference in remission at 4 weeks, but at 6-month follow-up, 46/57 PD patients achieved remission compared to 29/56 in the Botox. This benefit was maintained at 12 months in the PD group (55/75 in remission) compared to the Botox group (27/72 in remission) giving a risk ratio of 1.88 (95% CI 1.35–2.61, $p = 0.0002$) [98]. Table 1.4 summarizes studies [99–106] which compared botulinum toxin injection to pneumatic dilation. Comparison of response rates of Heller myotomy compared to botulinum toxin therapy at 1 year also showed superior response rates for surgery (83% vs. 65% [RR 1.28, CI 1.02–1.59, $p < 0.0001$]) [97].

Pneumatic Dilatation vs. Laparoscopic Heller Myotomy

A meta-analysis showed superior effects of LHM compared to pneumatic dilatation [107, 108]; however, the majority of trials included in the analysis performed only one endoscopic procedure. This does not reflect normal clinical practice. Table 1.5 summarizes studies [62, 63, 73, 109–114] which compared pneumatic dilation with LHM. A European multicenter RCT compared laparoscopic Heller myotomy (LHM) with Dor fundoplication with a pragmatic protocol for pneumatic dilation. This involved a series of dilatations with increasing balloon diameter until clinical remission was achieved followed by dilatation for recurrent symptoms. The endoscopic approach was considered to have failed if more than three dilatations were required within the 5-year follow-up period.

Table 1.5 Comparison of treatment outcome with pneumatic dilation (PD) compared to laparoscopic Heller myotomy (LHM)

Reference	No. of patients (PD)	No. of patients (laparoscopic Heller myotomy)	Follow-up (months)	Primary outcome variable	Secondary outcome
Boeckxstaens et al. [62] Prospective	95	106	43	Eckardt score ≤ 3 LHM 90% vs. PD 86% (pNS)	No difference in LES pressure, height of barium column, SF 36 scores between PD and LHM patients at 5 years
Moonen et al. [109] Prospective	96	105	LHM 6.6 (range 9–10.1 PD 0.6(range 0–10.1)	Eckardt score (≤3) LHM 84% vs. PD 82% at 5 years (pNS)	No difference in LES pressure, height of barium column, SF 36 scores between PD and LHM patients at 5 years
Novais et al. [110] Prospective	42	43	3	Absence of dysphagia or dysphagia < 1/week LHM 38/43 (88%) vs. PD 31/42 (74%), $p = 0.08$	Higher acid exposure in PD group (13/42 [31%]) vs. LHM (2/43 [5%]) $p = 0.0001$ LES pressure in PD (14.7 ± 8.0) vs. LHM (15.2 ± 5.7), pNS
Kostic et al. [111] Prospective	26	25	12	Treatment failure PD 6/26 [23%] vs. LHM 1/25 [4%] $p = 0.04$	Similar improvement in dysphagia scores and GSRS scores in PD and LHM groups
Persson et al. [73] Prospective	28	25	60	Treatment failure PD 10/28 (36%) vs. LHM 2/25 (12%) $p = 0.016$	Similar improvement in dysphagia scores and GSRS scores in PD and LHM groups
Lopushinsky et al. [112] Retrospective	1181	280 (either open myotomy or laparoscopic myotomy)	120	Cumulative risk of subsequent intervention after initial PD (63.5%) vs. initial myotomy (37.5%), $p < 0.001$	No difference in physician visits, use of reflux medication in both groups
Vela et al. [63] Retrospective	106	73	72	Dysphagia/regurgitation <3/week or need for additional treatment PD 90% vs. HM89% at 6 months; PD 44% vs. HM 57% at 6 years	
Suarez et al. [113] Retrospective	16	14	LHM 17.5 months [range 2–48] PD 22.7 months [range 2–60]	Similar improvement in symptom scores for dysphagia, heartburn, regurgitation, chest pain in both PD and LHM groups	
Borges et al. [114] Prospective	48	44	24	Absence of dysphagia PD 54% vs. LHM 60% (pNS)	Higher reflux rates in PD group (28%) vs. LHM (4.7%), $p = 0.003$ Age > 40 years, LES pressure ≤ 32 mm Hg before treatment and decrease of LES > 50% responded better to surgery

The results of this study indicated similar efficacy for surgical and endoscopic management (82% vs. 91%; p = not significant) [109]. Detailed examination of outcome data confirmed that surgery was superior in certain groups including patients under 40 years or with Type III achalasia [22].

POEM vs. Laparoscopic Heller Myotomy

A recent meta-analysis of four nonrandomized studies comparing short-term outcomes of POEM with laparoscopic Heller myotomy reported comparable postoperative Eckardt scores [115]. Controlled randomized studies comparing the outcome of POEM with conventional therapies of pneumatic dilation and Heller myotomy are under way and such long-term outcome data are awaited.

Therapeutic for EGJ Outflow Obstruction

Therapies aimed at reducing EGJ outflow obstruction are similar to those for achalasia. In a cohort of 15 patients with EGJOO, [24] follow-up data was available in 9 patients over a mean duration of 16 months. The overall success rate of 33% was confined to patients who had undergone Heller myotomy (n = 3) with poor response rates observed in patients who had undergone pneumatic dilation (n = 3), standard dilation (n = 1), and Botox (n = 2). In a group of patients with symptomatic EGJOO after fundoplication, a median of two sessions of pneumatic dilatation achieved satisfactory symptom relief in 7 of 12 patients at 6-month follow-up [43]. In the absence of a structural cause, patients with functional obstruction responded well to either botulinum toxin injection or pneumatic dilation [27] although two recent series [25, 26] have reported favorable response to conservative measures in patients with preserved peristalsis and absence of a structural lesion (possibly false-positive diagnosis). However, close follow-up is recommended of this patient group as experience is limited and some cases do represent early achalasia [25, 27].

Posttreatment Follow-Up

Clinical Symptoms

The aim of achalasia treatment is symptom relief. In patients with a good symptomatic response to therapy the value of objective measurements that confirm improvement in esophageal function (i.e., bolus transport) is not proven, although it may predict the need for repeated therapy. All treatment options described above are noncurative and an estimated 20% of patients will require further treatment within 5 years [76, 116, 117]. The development of megaesophagus is estimated to occur in approximately 6–20% of treated patients [118].

Timed Barium Esophagogram (TBE)

A posttreatment evaluation of symptom response and objective assessment of esophageal retention and EGJ outflow obstruction is considered useful in predicting treatment success and the need for further intervention [59]. TBE measures esophageal emptying in the upright position [60]. The subject drinks 250 mL of low-density barium sulfate, in some cases followed by ingestion of a 13 mm tablet. Images are obtained at 1, 2, and 5 min. The height of the barium column serves as an objective measure of bolus retention [59]. The presence of more than 1 cm of residual liquid barium in the esophagus at 1 and 5 min is abnormal, and retention of the pill at 5 min is similarly regarded as abnormal. Vaezi et al. reported a significant association between the results of the TBE and symptom resolution [59, 60]. In addition, they identified patients who had poor esophageal emptying despite reporting complete symptom resolution. Although long-term outcome and quality-of-life data is lacking this suggests the need to assess efficacy of treatment by objective evaluation.

Esophageal Manometry

Assessment of residual LES pressures can be useful in the posttreatment follow-up of patients.

Patients who recorded low posttreatment LES pressures (IRP < 10 mm Hg) are more likely to remain in remission at 10 years (100% vs. 23%) [21, 56]. In patients who have undergone prior pneumatic dilation or myotomy, a posttreatment LES pressure (IRP < 15 mm Hg) was associated with lower Eckardt score (i.e., less dysphagia) and less esophageal retention on TBE [119].

Endoscopic Surveillance for Cancer

The risk of esophageal squamous cell carcinoma is increased in achalasia likely due to the stasis of esophageal contents from impaired LES relaxation. The approximate incidence of cancer is 1 per 300 patient years [103]. In view of the low prevalence of achalasia and the poor survival of patients following a diagnosis of esophageal malignancy, there is no data to support the routine endoscopic surveillance for patients with achalasia [120, 121].

Conclusion and Future Developments

Achalasia is an uncommon disorder; however, developments in high-resolution manometry (HRM) have improved the diagnostic sensitivity of clinical investigation. As a result many experts report an increase in the prevalence of this condition. The application of new technologies such as Endo-FLIP and HR impedance manometry with new adjunctive tests (e.g., test meals) will further increase diagnostic accuracy also for patients with EGJOO.

At the same time, the minimally invasive POEM has provided a new option for the treatment of achalasia. However, notwithstanding this innovation, current treatment options in achalasia are all palliative and not curative. Disruption or myotomy of the LES reduces resistance to bolus passage across the EGJ; however, this does not address the underlying disease process. A definitive cure should address the underlying pathogenesis. This could include immune therapy that reverses the immune-mediated loss of myenteric neurons in early achalasia (i.e., in patients that still have a substantial number of neurons). Even more radical is the possibility of neural stem cell transplantation that could replace lost neurons and restore function even in patients with complete aganglionosis [10, 122].

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Esophageal Chest Pain: Esophageal Spasm

2

Dustin A. Carlson and John E. Pandolfino

Introduction

Chest pain often delivers a frightening patient experience due to its connection with life-threatening cardiovascular disease. Once cardiovascular disease and other life-threatening entities are excluded as an etiology, an esophageal origin of the *noncardiac chest pain* is often considered. Although gastroesophageal reflux and functional chest pain are the most common causes of esophageal chest pain, spastic esophageal motility disorders, such as distal esophageal spasm (DES), nutcracker esophagus, or hypercontractile (jackhammer), are also sometimes considered as a possible etiology [1, 2]. However, these spastic esophageal motility disorders can be associated with diagnostic and therapeutic challenges related to their overall rarity and clinical heterogeneity.

Patient question: I was worried I was having a heart attack, but I wasn't. I was told esophageal spasms could be causing my chest pain—what is esophageal spasm?

Suggested response to the patient:

Esophageal spasm means that abnormal contractions of your esophageal muscles may be causing your pain. Normally, your esophageal muscles squeeze in a coordinated fashion to push food down into your stomach: peristalsis. If those contractions become uncoordinated (i.e., *spastic*) *or too strong* (i.e., *hypercontractile*)*, which may be related to dysfunction of the nerves or muscles of the esophagus, they can cause chest pain often associated with trouble swallowing.*

Because esophageal spasm is a disorder of esophageal motility, an esophageal motility test, an esophageal manometry, will be necessary to diagnosis esophageal spasm. However, your symptoms may be related to a different and more common esophageal disorder, such as reflux or esophageal obstruction. Therefore, other tests such as an upper endoscopy and a trial of reflux therapy (i.e., *stomach acid suppression*) *may be tried prior to completing an esophageal manometry.*

Esophageal spasm: definition(s) and diagnosis.

The concept of esophageal spasm has fluctuated over time from being nearly synonymous with noncardiac chest pain (and thus overused) in the 1980s to present day being recognized as a specific esophageal motility disorder associated with dysphagia and chest pain [3–7]. While radiographic or endoscopic findings of frequent tertiary contractions or a "corkscrew" esophagus can be suggestive of a spastic motility disorder,

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definitions and diagnostic criteria of the spectrum of spastic esophageal motility disorders (DES, nutcracker, and jackhammer esophagus) are based on esophageal manometry (Table 2.1) [5, 7]. However, diagnostic criteria have varied among reports which limits a consistent description of specific disease characteristics or response to treatments among historic reports.

Esophageal symptoms, including chest pain, can be nonspecific when it comes to identifying the underlying pathology. Therefore, an initial evaluation should include a careful upper endoscopy to evaluate for a potential mechanical obstruction (e.g., stricture, hiatal hernia), as well as esophageal biopsies to evaluate for eosinophilic esophagitis (especially with coexisting dysphagia). Supplementary imaging, such as barium esophagram, may also be helpful to exclude an esophageal mechanical obstruction and may provide suggestive evidence for a spastic motility disorder, i.e., tertiary contractions, or rarely a corkscrew appearance [8, 9]. Additionally, gastroesophageal reflux disease is a common cause of esophageal chest pain and thus empiric trial of reflux therapy (i.e., proton pump inhibitor, PPI) or objective testing for reflux (esophageal pH testing) should be considered [10].

Esophageal manometry is the primary test to establish a diagnosis of a spastic esophageal motility disorder [5, 7]. Achalasia (particularly *spastic, vigorous,* or *type* III achalasia) could be considered within a spectrum of spastic motility disorders and may share some clinical features, such as an association with esophageal chest pain. Nonetheless, the spastic motility disorders described in the remainder of this chapter (DES, nutcracker esophagus, and jackhammer) should be considered differentiated from achalasia primarily based on normal deglutitive lower esophageal sphincter (LES) pressures on manometry.

With conventional, line-tracing manometry, simultaneous contraction (often defined by a rapid propagation velocity) was the typical diagnostic criterion for DES (Fig. 2.1) though (a) repetitive, (b) multi-peaked, (c) high-amplitude, (d) prolonged-duration, or (e) spontaneous contractions, in addition to required intermittent normal peristalsis, were also occasionally incorporated [3, 5]. Some overlap can be appreciated with the criteria for *nutcracker esophagus*, which is characterized by high-amplitude contractions, but also sometimes repetitive or long-duration contractions [5].

Table 2.1 Manometric criteria for esophageal spastic motility disorders

Motility disorder	Contractility pattern	Associated features
Conventional manometry [5]		
Distal esophageal spasm	>10% simultaneous contractions	• Intermittent normal peristalsis
		• Spontaneous contractions
		• Repetitive contractions
		• Multi-peaked contractions
Nutcracker esophagus	Elevated mean distal wave amplitude	
High-resolution manometry [7]		
Distal esophageal spasm	≥20% premature (abnormal distal latency) contractions	• Some normal peristalsis may be present
Hypercontractile ("jackhammer") esophagus	≥20% Hypercontractile (elevated distal contractile integral) swallows	• Multi-peaked contractions
		• Can co-occur with an EGJ outflow obstruction, if not meeting criteria for an achalasia subtype

All of the listed diagnoses are associated with normal deglutitive lower esophageal sphincter pressures

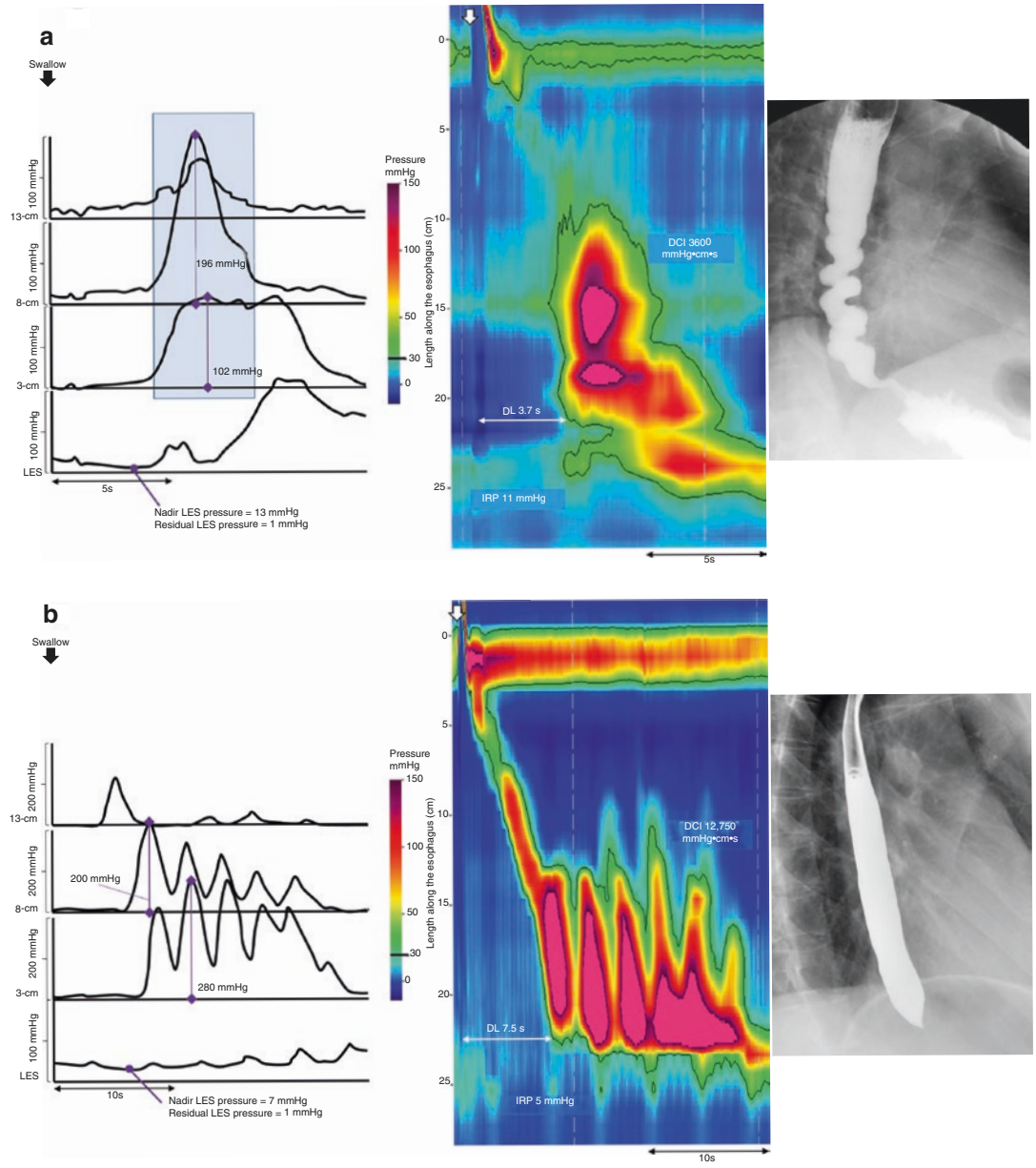

Fig. 2.1 Spastic esophageal motility disorders. Conventional line tracings (*left*) and high-resolution manometry/esophageal pressure topography (EPT; *center*) of the same swallow as well as a barium esophagram (*right*) from patients with (**a**) distal esophageal spasm (DES) and (**b**) jackhammer esophagus are displayed. Deglutitive esophagogastric junction pressures were normal (residual pressure < 8 mm Hg; integrated relaxation pressure, IRP, <15 mm Hg) in both cases. (**a**) DES is diagnosed on line tracings by simultaneous contractions (*blue box*); the abnormal, reduced distal latency (DL < 4.5 s), indicating a premature contraction, can be appreciated on the EPT. The corkscrew appearance of the esophagus is apparent on the esophagram. (**b**) Jackhammer esophagus is diagnosed based upon the elevated distal contractile integral (DCI > 8000 mm Hg s cm) on EPT. On the line tracings, the repetitive, high-amplitude, simultaneous contractions could be classified as DES. The esophagram in this patient was normal. Figure used with permission from the Esophageal Center at Northwestern

More recently, high-resolution manometry (HRM) and associated esophageal pressure topography (EPT) have provided enhanced depiction of esophageal motility characteristics and subsequently revised concepts (and subsequently diagnostic criteria) for esophageal motility disorders. Thus, utilizing the improved spatial resolution of HRM, rapidly propagating (*simultaneous*) esophageal contractions were identified as a nonspecific finding often found in patients with otherwise weak or normal peristalsis [11]. Alternatively, premature swallows, which were defined by a reduced distal latency (the time interval from the onset of swallow to the contractile deceleration point, i.e., end of the fast component of esophageal peristalsis, Fig. 2.1) appeared to represent a distinct pathophysiologic manifestation of abnormal inhibitory innervation [11, 12] and now entail a chief criterion for DES.

Additionally, contractile vigor can be assessed with HRM as a composite measure of pressure amplitude (mm Hg) × contraction duration (s) × contractile length (cm): the distal contractile integral (DCI). Thus, the extreme clinical phenotype of esophageal hypercontractility is defined by swallows of a greater vigor (as defined by elevated DCI) than those observed in asymptomatic controls [7, 13]. Sometimes associated with repetitive or multi-peaked contractions this motility pattern was termed *jackhammer esophagus*; thus, it appears possible that this entity may have been represented in former studies describing DES by repetitive, high-amplitude, repetitive and/or long-duration contractions on conventional manometry.

It is worth noting that studies that described DES or nutcracker esophagus using conventional manometry with a single LES pressure sensor (i.e., without the use of an LES pressure sleeve, which was most of them) were susceptible to misidentifying achalasia patients due to the manometric measurement phenomenon known as LES "pseudorelaxation" (Fig. 2.2): the erroneous but

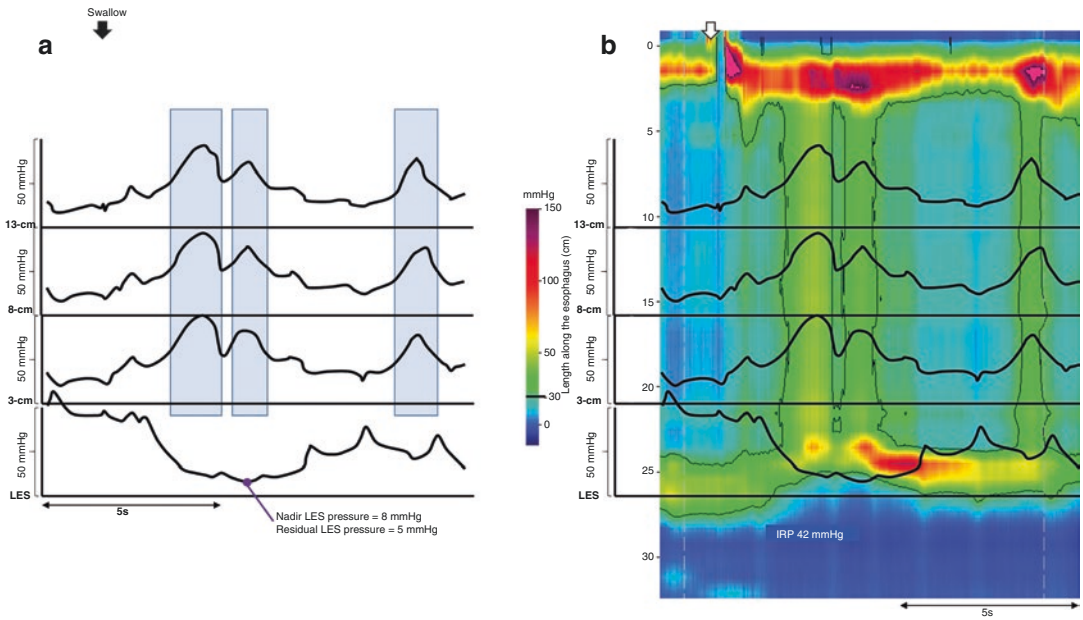

Fig. 2.2 Lower esophageal sphincter "pseudorelaxation." Conventional, line-tracing manometry (**a**) and high-resolution manometry/esophageal pressure topography (EPT), with overlaid line tracings (**b**), of a patient with achalasia. The line tracing (**a**) could be interpreted as distal esophageal spasm based on the simultaneous, repetitive esophageal contractions (*blue boxes*) with normal lower esophageal sphincter (LES) relaxation pressure. However, on EPT (**b**), the pan-esophageal pressurization and abnormal deglutitive LES pressure (integrated relaxation pressure, IRP, >15 mm Hg) can be easily appreciated. The swallow-associated esophageal shortening pulled the LES proximal to the single LES pressure sensor and resulted in "pseudorelaxation" of the LES. Figure used with permission from the Esophageal Center at Northwestern

apparent decrease in "LES" pressure related to proximal migration of the LES during swallow-associated esophageal shortening, which can be profound in patients with achalasia.

Finally, while the diagnosis of spastic motility disorders is typically defined by stationary esophageal manometry, symptom-associated or abnormal spastic esophageal contractions may occur infrequently and thus outside a 10–15 swallow manometry study. Consequently, an increased diagnostic yield has been reported for DES by increasing the manometric testing period, and even prolonged, ambulatory manometry (Fig. 2.3) [14–16]. A recent study evaluating stationary HRM and 24-h ambulatory manometry with pH impedance identified esophageal spasm (symptom-associated, simultaneous, and often multi-peaked or repetitive contractions of at least >100 mm Hg and lasting at least 3 s) on ambulatory manometry in 7% (4/59) of patients [16]. None of the 59 patients met the diagnostic criteria for a spastic motility disorder on stationary HRM, though three of the four patients with DES on ambulatory manometry had subtle contractile abnormalities on stationary HRM. However, patient tolerance to prolonged manometry catheter placement and limited availability remain limitations of utilizing ambulatory manometry in typical clinical practice.

Epidemiology of Esophageal Spasm

Noncardiac chest pain, often attributed to chest pain of an esophageal origin, is a common entity with an approximately 13% worldwide prevalence [17]. The majority of esophageal chest pain is related to gastroesophageal reflux or functional chest pain [1, 2]. On the other hand, primary manometric diagnoses of spastic esophageal motility disorders make up only a small proportion of noncardiac chest pain patients, though

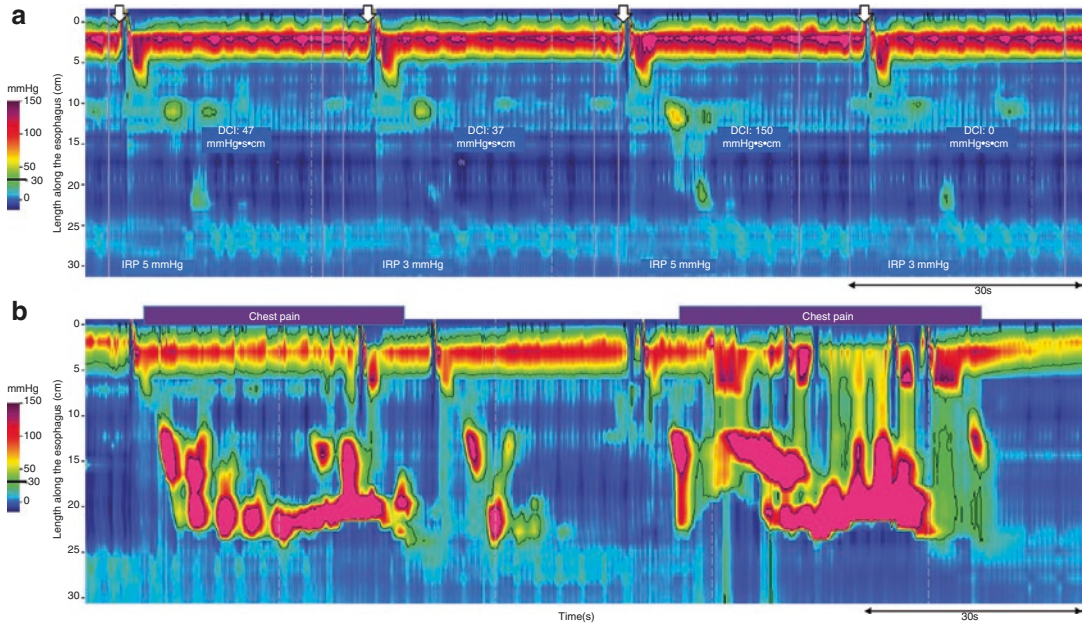

Fig. 2.3 Symptom association with manometric findings. (**a**) Four representative swallows (*white arrows*), three failed and one weak, from the standard ten-swallow high-resolution manometry (HRM) study protocol from a patient evaluated for severe episodic chest pain with rare dysphagia. The esophageal motility diagnosis was ineffective esophageal motility. (**b**) During prolongation of the HRM recording for 2 h, multiple episodes of chest pain occurred that were associated with repetitive, vigorous contractions associated with esophageal shortening; the *purple boxes* indicate when chest pain was present. Figure used with permission from the Esophageal Center at Northwestern. *DCI* distal contractile integral, *IRP* integrated relaxation pressure

information regarding the epidemiology of spastic esophageal motility disorders relates to the diagnostic criteria applied, and thus may fluctuate over the course of evolving diagnostics definitions.

Using conventional manometry criteria, a recent study of 350 consecutive patients undergoing manometry from 2012 to 2013 found DES (defined by simultaneous contractions) in 3% and nutcracker esophagus (defined by mean distal wave amplitude >220 mm Hg) in 3% [18]. As a reference, achalasia, which has an estimated incidence rate of about 1/100,000 person-years, was found in 8% of the 350 patients [18, 19].

With HRM evaluation and criteria, DES with premature contractions (reduced distal latency) in ≥20% of swallows was found in 0.5% ($n = 6$) of 1070 patients without previous foregut surgery [11]. Among the same HRM cohort, 44/1070 (4.1%) had at least one hypercontractile (DCI > 8000 mm Hg s cm) swallow; [13] thus under the current HRM diagnostic criteria requiring ≥20% of hypercontractile swallows, hypercontractile esophagus would be expected to be diagnosed even more infrequently [7]. Again for reference, incident achalasia was diagnosed in 99/1000 (10%) of consecutive HRMs from the same center [20].

Therefore, spastic esophageal motility disorders ultimately reflect rare disorders encompassing even a small portion (<5%) of all patients undergoing esophageal manometry. Reports of higher rates should raise questions about diagnostic interpretation (particularly with DES and correct identification of the contractile deceleration point and subsequent measurement of the distal latency).

Pathophysiology

The pathophysiologic mechanism(s) behind spastic or hypercontractile esophageal motility disorders remain incompletely understood though multiple hypotheses have been suggested. In addition to esophageal neuromuscular dysfunction or imbalance, associations of spastic motility disorders to esophageal obstruction or gastroesophageal reflux are reported. Thus a fundamental question is posed when spastic manometric features are identified: primary esophageal motility disorder or secondary response to another (potentially subtle) esophageal stimuli?

Neuromuscular dysregulation is thought to be the pathologic foundation of primary esophageal motility disorders (e.g., achalasia) and is also hypothesized to be a pathologic mechanism of DES and hypercontractile esophageal disorders. Impaired inhibitory innervation among patients with simultaneous contractions (DES) was supported by an elegant study demonstrating abnormalities of distal contractile latency and in the expected deglutitive inhibition with paired swallows [12]. Further, spontaneous contractions were induced by cholinergic (excitatory) stimulation in both DES and patients with normal motility and spontaneous contractions were inhibited by cholinergic blockade in DES patients [12]. Another study evaluating esophageal muscle specimens of patients with nutcracker esophagus found an increased ratio of cholinergic (excitatory) to nitronergic (inhibitory) protein immunostaining compared with patients with normal manometries, thus supporting a role of neural signaling imbalance within nutcracker esophagus as well [21]. However, another study evaluating esophagectomy specimens for refractory esophageal chest pain found normal esophageal ganglion among patients with DES ($n = 2$) and nutcracker esophagus ($n = 4$) [22].

Abnormal muscular function has also been proposed as a pathologic mechanism in spastic motility disorders. Thickened circular esophageal muscle has been observed in patients with DES, nutcracker, and jackhammer esophagus [23, 24]. Additionally, asynchrony between circular and longitudinal muscle contraction was reported in patients with nutcracker esophagus using a sophisticated simultaneous manometry with high-frequency intraluminal ultrasound technique [25]; further, this muscular asynchrony was able to be induced with cholinergic stimulation (edrophonium) and reversed with cholinergic inhibition (atropine). Therefore, a contribution of reduced esophageal inhibitory and/or excess excitatory innervation appears to be related to the underlying mechanism of spastic motility disorders.

Additionally, simultaneous, repetitive, and hypertensive esophageal contractions have been reported in both animal models and humans with esophageal obstruction. In cats and opossum, simultaneous, repetitive, multi-peaked, and increased wave amplitude contractions were induced following creation of a distal esophageal obstruction [26–28]. In humans, an intriguing study utilizing HRM on patients with laparoscopic adjustable gastric bands (LABG) reported inducing repetitive and hypertensive contractions when inducing an esophageal obstruction by overfilling the gastric band [29].

The association of spastic motility features with reflux has also been reported. Objective evidence of reflux (esophagitis or abnormal esophageal pH testing) or a symptomatic response to reflux-targeted therapy (PPI or fundoplication) was reported among patients with DES, nutcracker, and jackhammer esophagus [13, 30, 31]. Further, a previous study utilizing combined manometry and acid perfusion reported provocation of chest pain and spastic motility patterns (simultaneous and repetitive contractions) among patients with a normal manometry at baseline [32]. Thus, the demonstration that the typical manometric features of spastic motility disorders can be *induced* by esophageal obstruction and esophageal acid exposure supports the notion that these spastic manometric features can also represent a secondary esophageal response.

Beyond the mechanisms behind spastic esophageal contractions, the generation of symptoms, particularly chest pain, among these spastic motility disorders also remains incompletely understood, particularly as esophageal symptoms are not consistently associated with objectively measured abnormal esophageal contractions [33]. Esophageal tissue ischemia was proposed as a mechanism of symptom generation based on a sophisticated study that demonstrated reduced esophageal wall blood perfusion in patients with nutcracker esophagus compared with asymptomatic controls [34]; further, controls had an increase in esophageal blood perfusion during meals which appeared to be blunted in the nutcracker patients.

Esophageal hypersensitivity also appears to be a contributing factor to symptom generation. Patients with nutcracker esophageal showed a lower pain threshold to intraesophageal balloon distension than in healthy controls [35]. Additionally, symptomatic improvement without changes in spastic manometric findings following therapy with trazodone, an antidepressant without effects on esophageal motor function (e.g., anticholinergic properties), supports a component of hypersensitivity [36].

Ultimately, the mechanisms behind spastic and hypertensive esophageal contractions are complex and likely multifactorial. Therefore multimodal *management* strategies may need to be applied.

Patient question: How is esophageal spasm treated?

Suggested response to the patient:

The treatment of esophageal spasm typically targets the abnormal esophageal contractions, and thus begins with medications to relax the esophageal muscles. However, esophageal targeted smooth muscle relaxants are limited; thus the medications are used off-label for esophageal symptoms. Therefore the symptomatic benefits need to be gauged against potential side effects, such as lightheadedness and drops in blood pressure. Sometimes injection of botulinum toxin or esophageal surgery is used to diminish the abnormal esophageal contractions. However, given the association of these spastic motility disorders with other causes, for example esophageal obstruction or even esophageal hypersensitivity, further diagnostic evaluation, a trial of esophageal dilation with endoscopy, or trials of medications to treat esophageal sensitivity (antidepressants) might be considered before pursuing more aggressive endoscopic or surgical therapy.

Treatment of Spastic Esophageal Motility Disorders

Following a thorough diagnostic evaluation and consideration for empiric treatment trials, e.g., acid suppression or even empiric dilation, given the potential for an alternate (or secondary) cause of esophageal symptoms and manometric findings, the treatment of primary spastic esophageal

Table 2.2 Therapeutic options for spastic esophageal motility disorders

	Therapeutic options
Pharmacologic	Nitrates
	Calcium-channel blockers
	Anticholinergic (hyoscyamine)
	PDE-5 inhibitors
	Peppermint oil
	Proton pump inhibitor
	Antidepressants
Endoscopic	Dilation
	Botulinum toxin injection
Surgical	POEM
	Laparoscopic or thoracoscopic myotomy

PDE phosphodiesterase, *PPI* proton pump inhibitor, *POEM* per-oral endoscopic myotomy

motility disorders aims to reduce the spastic or vigorous esophageal contractions. Multiple pharmacologic, endoscopic, or surgical therapies (Table 2.2) are available; thus the typical approach should be to start with less invasive options (i.e., medical therapy) and reserve more invasive endoscopic or surgical approaches for patients with medical-refractory and severely life-altering symptoms. It is worth noting that the majority of clinical studies reported have included only patients defined by conventional manometry criteria; thus generalization of these reports to HRM-defined spastic motility disorders carries potential limitations.

Pharmacologic Therapies

Smooth muscle relaxants are the mainstay of medical therapy for primary spastic motility disorders. These include medications that reduce both LES pressure and contractile amplitude through an attempt to mimic esophageal inhibitory (nitronergic) signaling (e.g., nitrates and phosphodiesterase-5, PDE-5, inhibitors), diminish esophageal excitatory (cholinergic) stimulation (e.g., anticholinergics), or directly relax smooth muscle (calcium channel blockers, CCBs). Unfortunately, there are no presently available medications that specifically target esophageal smooth muscle; thus these medications are used off-label for esophageal symptoms and their use can be limited due to the systemic side effects.

Nitrate use in patients with DES and nutcracker esophagus was associated with symptomatic and manometric improvement (including increased distal latency in DES) in several small, open-label studies [37–39]. A placebo-controlled crossover study using diltiazem in patients with DES reported no significant difference in chest pain or dysphagia scores with therapy (however, chest pain and dysphagia did improve in 6/8 and 4/6 patients, respectively) [40]. A reduction in contractile wave amplitude on manometry with CCBs was demonstrated in two placebo-controlled crossover studies with nutcracker; however symptomatic improvement was inconsistent [41, 42]. Sildenafil (a PDE-5 inhibitor) also demonstrated manometric improvement in patients with DES and nutcracker esophagus as well as some symptomatic improvement with open-label, on-demand use [43, 44]. Peppermint oil was also reported to reduce simultaneous contractions in one small study of patients with DES, including symptom resolution during manometry in 2/8 patients [45]. Clinical studies of anticholinergic agents in spastic motility disorders are lacking, though studies of healthy controls have demonstrated reduced contractile pressures with atropine and hyoscyamine [46, 47]. In addition, atropine was demonstrated to reduce wave amplitude and esophageal circular and longitudinal muscle asynchrony [25]. Thus, given the apparent contribution of cholinergic excess in spastic motility disorders, anticholinergic therapy carries some potential benefit.

Smooth muscle relaxants are available in various formulations which can be tailored to the frequency and pattern of patient symptoms. For patients with only infrequent or spontaneous symptoms, on-demand use of sublingual or immediate-release agents can be employed, e.g nitroglycerin, isosorbide, or hyoscyamine. Due to safety concerns observed in the treatment of hypertensive crises, immediate-release nifedipine should be avoided. Therapeutic trials for more frequent symptoms typically start with a low-dose immediate-release formulation with a

plan to escalate the dosage every 2–3 days while monitoring tolerance (Table 2.3). The medications are typically dosed prior to meals to facilitate eating. Finally, an effective smooth muscle relaxant should alleviate symptoms shortly after achieving a therapeutic dose; therefore the duration of a therapeutic trial for frequent symptoms should be completed within 1–2 weeks. If the medication is ineffective or poorly tolerated, it should be abandoned. If the medication is effective, converting the dosing to an extended-release formation can be considered for patient convenience.

Finally, treatment with low-dose antidepressants may be beneficial in spastic motility disorders as well. A randomized controlled trial that administered trazodone (a selective serotonin reuptake inhibitor) or placebo for 6 weeks in patients with manometric contractile abnormalities (typically spastic features) demonstrated improvements in esophageal and global symptoms without changes in motility [36]. In addition to supporting the notion that esophageal hypersensitivity may play a role in symptom generation in spastic motility disorders, this produces some appeal for treatment with an antidepressant with

Table 2.3 Examples of dosing and medication titration schedules for esophageal smooth muscle relaxants

Medication	Initial dosing/uptitration schedule	Typical adverse effects
Isosorbide dinitrate	1. 5 mg SL or PO BID prior to meals × 2 days	• **Avoid use with sildenafil or other PDE-5 inhibitors**
	2. 5 mg SL or PO TID prior to meals × 2 days	• Headache
	3. 10 mg SL or PO TID prior to meals × 3+ days	• Flushing
	4. Consider converting lowest effective and tolerated dosing to extended release formulation	• Low blood pressure • Lightheadedness/orthostasis
Hyoscyamine[a]	1. 0.125 mg SL or PO TID prior to meals × 3+ days	• Dry mouth or eyes
	2. 0.25 mg SL prior to meals or PO	• Lightheadedness/orthostasis
Diltiazem	1. 30 mg PO TID prior to meals × 3+ days	• Low blood pressure • Bradycardia
	2. 60 mg PO TID prior to meals	• Lightheadedness/orthostasis
	3. 90 mg PO TID prior to meals	• Headache • Edema
	4. Consider converting lowest effective and tolerable dosing to extended release formulation	• Constipation
Sildenafil	1. 25 mg PO daily prior to worst meal	• **Avoid use with isosorbide or other nitrates
	2. 25 mg PO BID—TID prior to meals	• Headache
	3. 50 mg PO daily—TID	• Flushing • Low blood pressure • Priapism (rare) • Cost

Treatment of esophageal chest pain or dysphagia is off-label use for the listed medications. Dose escalation can be done as needed based on symptomatic response while assessing for side effect tolerance

[a]Hyoscyamine can also be used concurrently with nitrates or calcium channel blockers

PDE phosphodiesterase

more anticholinergic activity (e.g., a tricyclic) to a potential multifactorial benefit. However, clinical study of other antidepressants in esophageal spastic motility disorders is lacking.

Endoscopic Therapy

Endoscopic therapies for spastic motility disorder include esophageal dilation and botulinum toxin injection. Given the potential association of esophageal obstruction with spastic esophageal motility, a trial of esophageal dilation may be considered. However, a crossover study of patients with nutcracker esophagus demonstrated neither symptomatic nor significant manometric improvement following 54-french therapeutic bougie dilation compared with a sham (24-french) dilation [48]. Benefit was reported following 30-mm (sometimes followed by 35 mm) pneumatic dilation in 14/20 patients with DES; however an esophageal perforation also occurred [49]. Therefore while a therapeutic trial of dilation may be reasonable, particularly if an esophageal outflow obstruction is suspected, a small, but real, risk of perforation needs to be considered prior to advancing to pneumatic dilation.

Botulinum toxin injection, which exhibits its inhibitory neuromuscular effect via cholinergic blockade, is also a therapeutic option. Injection of botulinum toxin into the LES or LES and distal esophageal wall demonstrated symptomatic improvement in open-label use among patients with DES [50, 51]. Further, a sham-controlled, crossover study of botulinum toxin injection (into the LES and distal esophageal wall) in patients with DES or nutcracker esophagus demonstrated a symptomatic improvement, but not significant manometric improvement, following botulinum toxin injection [52]. A recent retrospective study of HRM-defined DES and jackhammer patients also reported a symptomatic response in most (5/7 jackhammer and 4/6 DES) patients at ≥6 months; however, a patient death due to botulinum toxin injection-related mediastinitis was reported [53]. Further multicentered, retrospective study of the safety of esophageal botulinum toxin injection found mild complications in 16% of 141 botulinum toxin injections among patients with nonachalasia spastic motility disorders; chest pain was the most common [54]. The death following mediastinitis, which was also included in this study, was the only major complication among 657 total botulinum toxin injections for all esophageal motility disorders [54]. Therefore, botulinum injection appears to be another reasonable endoscopic treatment option for spastic motility disorders.

Surgical Therapy

Surgical esophageal myotomy remains a therapeutic option for symptoms that are refractory to medical or endoscopic (i.e., less invasive) therapies. Symptomatic benefit following an extended esophageal myotomy via thoracoscopic or laparoscopic approach in patients with DES and nutcracker esophagus has been described in numerous uncontrolled reports [55–57].

Recently per-oral endoscopic myotomy (POEM), an application of natural-orifice surgery initially utilized for therapy in achalasia, appears to provide a promising therapeutic option for spastic esophageal motility disorders [58, 59]. Endoscopic creation of a submucosal tunnel in the esophageal wall allows minimally invasive access to perform a myotomy at the LES that can also be extended proximally along the esophageal body. An international multicenter report of POEM in patients with HRM-defined DES and jackhammer esophagus that were refractory to medical therapy demonstrated symptomatic improvement in 9/9 DES patients and 7/10 jackhammer patients [60]. Thus while greater experience remains needed with POEM for nonachalasia spastic motility disorders, it represents a promising therapeutic option for patients that are refractory to other therapies.

Patient question: What will happen to me in the long run? What type of follow-up and monitoring do I need?

Suggested response to the patient:

Although the course of esophageal spasm is generally not well understood, it likely carries a stable but overall benign course. Hypothetically, there may be a small chance of progression to

another esophageal motility disorder (*achalasia*). *Therefore, the primary aim of long-term follow-up will be to ensure that symptoms are adequately managed, though repeating diagnostic testing* (*endoscopy, manometry, barium esophagram*) *every several years may be considered.*

The Natural History of Spastic Esophageal Motility Disorders

The natural history of spastic motility disorders is generally not well understood. Based on the potentially shared pathologic mechanism with achalasia (impaired inhibitory innervation), a continuum of esophageal disease resulting in progression from spastic motility disorders to achalasia has been suggested. A study that repeated conventional manometry at a mean +/− SD 4.8+/−3.4 years after a diagnosis of DES reported achalasia in 8% (1/12 patients) [61]. Another study that repeat conventional manometry at 1–4 years (mean 2.1) following an initial diagnosis of DES reported "progression" to achalasia in 14% (5/35 patients) [62]. In these two studies, 58% (7/12) and 74% (26/35) of patients maintained a diagnosis of DES, while 25% (3/12) and 11% (4/35) had normal manometry, at follow-up manometry [61, 62]. There are only case reports of nutcracker esophagus "progressing" to both DES and achalasia [63–65]. However, the possibility that instead of rare progression these studies report initially missed diagnoses of achalasia that was detected on repeat manometric testing (e.g., Fig. 2.2) needs to be considered.

Evidence of progression of HRM-defined spastic motility disorders (DES and jackhammer) remains primarily limited to case reports. Additionally, while only presented to date in abstract form, one retrospective study of patients that previously completed multiple HRMs reported type III achalasia in 1/8 patients with jackhammer esophagus on initial HRM 14 months earlier [66].

Ultimately, the risk of progression from DES, nutcracker, or jackhammer esophagus to achalasia appears to be low. However, so does normalization of manometric findings. Therefore, surveillance should primarily focus on symptom control and necessary therapeutic adjustments. However, due to the potential for spastic motility features representing a reactive motility finding (particularly to reflux or esophageal obstruction), repeat diagnostic testing with endoscopy, barium radiography, as well as manometry may be considered intermittently (i.e., every 3–5 years) or as directed by therapeutic ineffectiveness in symptomatic management.

Conclusions

Spastic esophageal motility disorders, DES, nutcracker, and jackhammer esophagus are rare esophageal motility disorders associated with esophageal chest pain and dysphagia. Manometric criteria (previously simultaneous, now premature contractions for DES; high-amplitude contractions for nutcracker; hypercontractile contractions for jackhammer) form the basis for diagnosis. However diagnostic challenges arise as the associated motility findings may reflect a secondary reaction to reflux or esophageal obstruction and further intermittent symptoms and motility patterns may not occur during the timeframe of the standard stationary manometry. Therefore, a comprehensive diagnostic approach is often required to accurately define the esophageal disease process(es) contributing to symptoms. While disease-targeted therapy is ideal, therapeutic management often requires a sequential series of therapeutic trials to optimally achieve symptom relief, typically beginning with least invasive (pharmacologic) to more invasive (endoscopic then surgical) options. Hopefully, advances in esophageal diagnostics, beginning with increased application of HRM, will continue to enhance our understanding of spastic esophageal motility disorders and help improve future management paradigms.

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Chest Pain of Esophageal Origin and Reflux Hypersensitivity

3

Wojciech Blonski and Joel E. Richter

Chest Pain Due to Gastroesophageal Reflux

Why Does Acid Reflux Cause Chest Pain Rather Than Heartburn?

Response to the patient: In gastroesophageal reflux disease (GERD), the acid present within stomach comes back up to the swallowing tube (esophagus) due to weakened muscle ring separating the swallowing tube from the stomach. In the majority of patients, acid reflux causes a burning sensation arising from the stomach and spreading up towards the patient's neck along the swallowing tube. However, in some patients acid irritates nerve endings (called receptors) within esophagus causing chest pain.

Brief Review of Literature

According to a recent meta-analysis of 16 population-based studies reporting the prevalence of non-cardiac chest pain in 14 separate populations encompassing nearly 25,000 subjects, the pooled prevalence of non-cardiac chest pain was 13% (95% CI 9–16) [1]. There was no difference in the prevalence of non-cardiac chest pain between women and men (pooled OR 0.99, 95% CI 0.82–1.20) [1]. Subjects with GERD were nearly fivefold more likely to experience non-cardiac chest pain than those without GERD (pooled OR 4.71, 95% CI 3.32–6.70) [1]. Furthermore, individuals with frequent typical GERD symptoms (heartburn, regurgitation) were sixfold more likely (pooled OR 6.37, 95% CI 4.08–9.96) and individuals with occasional typical GERD symptoms were fourfold more likely (pooled OR 4.20, 95% CI 2.59–6.82) to have non-cardiac chest pain than those without typical GERD symptoms [1]. Therefore, there is a strong association between the presence of typical GERD symptoms and non-cardiac chest pain suggesting a common pathophysiological mechanism [1].

The exact mechanism by which acid causes esophageal chest pain is not known.

Chest pain of esophageal origin represents visceral chest pain. Visceral pain is diffuse, poorly localized, referred to other locations, accompanied by motor and autonomic reflexes and may occur without visceral injury [2]. Esophageal mucosa, serosa, and longitudinal and circular muscles are innervated by sensory afferent fibers from the vagus nerve and spinal

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nerves [3]. Afferent fibers innervating esophageal mucosa are sensitive to the light touch of the mucosa, low pH, and chemicals [3]. In addition, afferent fibers innervating the esophageal muscle are sensitive to intraluminal distension [3]. The innervation of the esophagus was well described based on the multiple animal studies including rats, dogs, cats, guinea pigs, and rhesus monkey [4–10].

Several animal studies have investigated the pathophysiology of acid-induced esophageal pain. Acid-induced esophageal pain may be mediated by two esophageal chemoreceptors, vanilloid receptor (VR1) and anion-sensing channels (ASICs) that are upregulated under inflammatory conditions [11, 12]. Transient receptors potential ion channel of the vanilloid type 1 (TRPV1) expressed by primary afferent neurons innervating the gut and other organs are stimulated by various agents such as capsaicin, noxious heat, or acidosis that leads to activation of various pro-algesic pathways in animal model studies [13, 14]. ASIC chemoreceptors are expressed in the dorsal root ganglia and brain and shown to induce an amiloride-sensitive cation channel which is transiently activated by rapid extracellular acidification [15]. In addition, spinal *N*-methyl-D-aspartate (NMDA) receptors are postulated as another mediator in prolonged chemical nociception based on the studies with rats [16, 17]. A guinea pig model furthermore suggested that mast cell activation increases esophageal epithelium permeability to acid which may increase activation of esophageal vagal nociceptive C fibers [18]. A study in cats observed a convergent input from the heart and somatic fields in response to intracardiac bradykinin injection and somatic stimuli within spinal neurons that received input from the distal esophagus [19]. Therefore, the authors postulated that activation of spinal neurons by visceral and somatic input caused referred pain from the distal esophagus [19]. In addition, viscerosomatic and visceroviscerel convergence onto the same spinal neurons may be responsible for difficulties in differentiating between pain of esophageal and cardiac origin [19].

Data from animal studies are further supported by human studies. It has been shown that blocking NMDA receptors by ketamine reversed acid-induced esophageal pain [20]. A study of epithelial innervation of the esophagus based on esophageal biopsies obtained from esophagitis patients and healthy controls showed that the innervation of the esophageal mucosa is not changed within non-inflamed tissue, but it is altered within inflamed tissue with a selective 3–4-fold increase in vasoactive intestinal peptide-containing nerves [21]. Study by Matthews et al. found increased TRPV1 expression in the inflamed esophagus of seven patients with erosive esophagitis suggesting that acid-induced inflammation causes an upregulation of acid-sensitive receptors such as TRPV1 and may contribute to the visceral hypersensitivity seen in patients with GERD and chest pain [22].

Several functional studies have evaluated the role of gastric acid in causing esophageal chest pain. Bernstein et al. developed an esophageal perfusion test with 0.1 N hydrochloric acid to elicit the symptoms of esophagitis such as midline pain and burning extending above the level of the xiphoid [23]. The authors claimed that the esophageal acid perfusion test allowed for unequivocal differentiation between esophageal pain and anginal pain [23]. Smith et al. found that time to onset of pain associated with the intraesophageal infusion of acid was longer with increasing pH and that all patients had pain with pH 1–1.5, 80% with pH of 2.0, and 50% with pH between 2.5 and 6.0 [24]. A study by Hewson et al. assessed the usefulness of the esophageal acid perfusion as a diagnostic tool for GERD in patients with non-cardiac chest pain finding that the acid perfusion test elicited chest pain in only 46% of patients [25]. The authors determined that the esophageal acid infusion test was a poor tool for diagnosing GERD in non-cardiac chest pain with 59% sensitivity and specificity, 57% positive predictive value, and 61% negative predictive value [25]. Subsequently, ambulatory esophageal pH testing has replaced this test. Mehta et al. observed that acid perfusion caused a decrease in pain threshold to balloon distension in patients with negative results of the esophageal

provocation tests (intravenous edrophonium chloride or intraesophageal acid infusion) and healthy controls but not in patients with positive results of esophageal tests [26]. This phenomenon suggested possible sensitization of esophageal pain receptors to esophageal provocation tests; hence, these receptors did not respond to further stimulation with acid perfusion [26]. Similarly, Hu et al. found reduced pain threshold to mechanical intraluminal balloon distension following acute exposure to acid in healthy volunteers [27]. On the other hand, Fass et al. suggested that chronic acid reflux affects only chemosensitivity within the esophagus and does not affect esophageal hypersensitivity to mechanical distension in patients with non-cardiac chest pain [28]. Sarkar et al. found that esophageal electrical pain thresholds in GERD patients after PPI therapy were still lower than those in healthy volunteers and reduction in symptoms occurred only in 50% of GERD patients [29]. It was proposed that GERD patients with chest pain have PPI-responsive esophageal pain hypersensitivity [29]. The authors suggested that persistently reduced pain threshold after PPI therapy in GERD patients might be not only due to acid exposure but also due to inflammation by bile reflux, infections, or irreversible central sensitization [29].

Several studies have assessed the association between GERD and non-cardiac chest pain. DeMeester et al. observed that 46% of patients with chest pain and normal cardiac function by coronary arteriography had abnormal distal esophageal acid exposure confirmed by 24-h esophageal pH monitoring [30]. Another group observed that GERD was a cause of chest pain in 67% of patients with coronary artery disease with refractory chest pain despite optimal antianginal therapy who underwent 24-h pH study [31]. Although the presence of esophagitis, esophageal stricture, Barrett's esophagus, and hiatal hernia is more frequently encountered in patients with heartburn and regurgitation than those with non-cardiac chest pain, these conditions are not uncommon in non-cardiac chest pain. According to data from Clinical Outcomes Research Initiative (32,981 patients with classic GERD symptoms and 3688 patients with non-cardiac chest pain), a greater proportion of patients with non-cardiac chest pain had normal upper endoscopy than those with classic GERD symptoms (44.1% vs. 38.8%, $p < 0.0001$) [32]. Prevalence of hiatal hernia (44.8% vs. 28.8%, $p < 0.0001$), erosive esophagitis (27.8% vs. 19.4%, $p < 0.0001$), and Barrett's esophagus (9.1% vs. 4.4%, $p < 0.0001$) was statistically significantly greater among patients with classic GERD symptoms than those with non-cardiac chest pain [32]. Conversely, prevalence of any peptic ulcer (1.5% vs. 2.0%, $p = 0.01$) and duodenal ulcer (0.35% vs. 0.57%, $p = 0.03$) was greater among patients with non-cardiac chest pain than those with classic GERD symptoms [32]. The aforementioned data emphasizes the importance of performing an upper endoscopy in patients presenting with non-cardiac chest pain to identify not only esophageal disease but also possible peptic ulcer disease.

How Can We Distinguish Chest Pain Due to Acid Reflux from Cardiac Chest Pain?

Response to the patient: It is impossible to differentiate with certainty between chest pain from acid reflux and cardiac chest pain based on the description of the pain. If you experience chest pain, the first and most important step is to go to the emergency room where an appropriate evaluation can be performed to exclude life-threatening causes of chest pain like a heart attack, clots in your lungs, rapid accumulation of fluid around your heart, or a tear in one of your big blood vessels that carries the blood from your heart. After these conditions are excluded then you can be referred to a gastroenterologist (specialist in diseases of swallowing tube, stomach, and bowels) to evaluate whether your chest pain is caused by an acid reflux.

Brief Review of the Literature

In a Swedish study comparing 208 patients with unexplained chest pain and 40 patients with chest pain due to ischemic heart disease, there were too many symptom similarities between these two

entities to reliably determine by history alone the cause of chest pain [33]. The most significant distinguishing features of unexplained chest pain were sensory descriptors such as "dull pain, stabbing pain, or sore pain" and affective descriptors such as "annoying pain, troublesome pain, or worrying pain" [33]. On the other hand, the most significant sensory descriptor of chest pain due to ischemic heart disease was "stinging pain" [33]. Overall, patients with unexplained chest pain had greater pain intensity and used more sensory and affective words to describe their pain when compared with those with chest pain due to ischemic heart disease ($p < 0.01$) [33]. On the other hand, more patients with ischemic chest pain complained of central chest pain (33%) than patients with unexplained chest pain (33% vs. 12%, $p = 0.04$) [33]. In another study, relief of chest pain by nitroglycerin was not a reliable predictor distinguishing between cardiac and non-cardiac chest pain with a positive likelihood ratio for coronary artery disease of 1.1 (95% CI 0.96–1.34) [34]. Mousavi et al. found that relief of non-cardiac chest pain by antacids and concomitant presence of heartburn and regurgitation were the only characteristics more frequently seen in patients with non-cardiac chest pain due to gastroesophageal reflux disease [35]. Similarly, data from a Korean study of 58 patients with non-cardiac chest pain found the presence of heartburn or regurgitation was associated with a greater likelihood ratio (2.83, 95% CI 1.52–5.18) and absence of heartburn or regurgitation was associated with significantly lower likelihood ratio (0.44, 95% CI 0.25–0.73) of GERD-related chest pain [36].

How Do You Diagnose Chest Pain Caused by Acid Reflux?

Response to the patient: The easiest method is to give you medication that decreases acid production in your stomach for 8 weeks. This medication is called a proton pump inhibitor (PPI) and should be taken by mouth twice a day, 30 min before breakfast and dinner on an empty stomach. If your chest pain resolves with treatment, then your chest pain is caused by acid reflux.

The other method is to check your esophagus for evidence of acid reflux. This can be done by a simple upper endoscopy. The doctor inserts a thin, flexible tube with a light and camera on the end through your mouth and advances to see your swallowing tube, stomach, and the first part of small bowel called the duodenum. The doctor will assess whether there is any inflammation in your swallowing tube and may obtain small samples of the lining for examination. If there are no visible erosions in your swallowing tube, then the doctor can actually measure the amount of acid reflux by either placing a small wire down your nose for 24 h or attaching a small capsule to your esophagus for 48 h. In either test, you will be asked to follow your daily routine, complete a diary in which you will record all your meals, beverages, and timing and type of symptoms. Whenever you have a chest pain, you will press the button on the receiver box. The doctor then will analyze the recordings with the aid of a computer to determine whether your chest pain is related to acid reflux.

Brief Review of Literature

After a cardiac cause of chest pain has been excluded, a short-term PPI trial is the most cost-effective method for assessing whether non-cardiac chest pain is due to GERD [37]. A meta-analysis of eight studies including 321 patients who received various PPIs for one to 8 weeks found that the PPI test had a pooled sensitivity of 80%, specificity of 74%, and diagnostic odds ratio of 13.83 (95% CI 5.48–34.91) for diagnosing GERD in patients with non-cardiac chest pain when compared with 24-h pH monitoring and upper endoscopy [38]. Another meta-analysis of five randomized placebo controlled clinical trials showed that patients with objectively confirmed GERD (either abnormal esophageal acid exposure on pH test or reflux esophagitis on upper endoscopy) treated with PPIs were fourfold more likely to achieve at least 50% improvement in their chest pain when compared to placebo (pooled RR = 4.3 (95% CI 2.8–6.7; $p < 0.0001$) [39]. However, it should be noted that PPIs tend to improve but not completely resolve chest pain due to GERD [39]. On the other hand, there was no difference between PPIs and placebo in achieving chest pain improvement in patients without objective evidence of GERD (pooled RR = 0.4 (95% CI 0.3–0.7). In addition, the mean therapeutic gain of

PPI therapy over placebo was greater for chest pain patients with GERD (62%) than without GERD (5%) [39]. Therefore, patients with chest pain who do not respond to twice daily PPI therapy are highly unlikely to have acid reflux as a cause of their chest pain. In patients who respond to high-dose PPI therapy, it is recommended to taper the dose down to the lowest dose controlling their symptoms [40].

In patients with persistent chest pain despite PPIs for up to 8 weeks, the next step is to perform 24-h distal esophageal pH monitoring or 48-h wireless distal esophageal pH monitoring off PPI therapy to provide objective evidence whether acid reflux is present. Charbel et al. showed that 93% of patients with typical GERD symptoms (heartburn, regurgitation) and 99% of patients with extraesophageal GERD symptoms had normal distal esophageal pH monitoring while studied on PPI BID [41]. Therefore, it is important to document that patients with suspected GERD symptoms not responding to PPIs have excessive acid reflux while off PPIs. A suggested diagnostic approach to these patients is shown in Fig. 3.1 [42]. The management of patients with noncardiac chest pain depends on the results of their

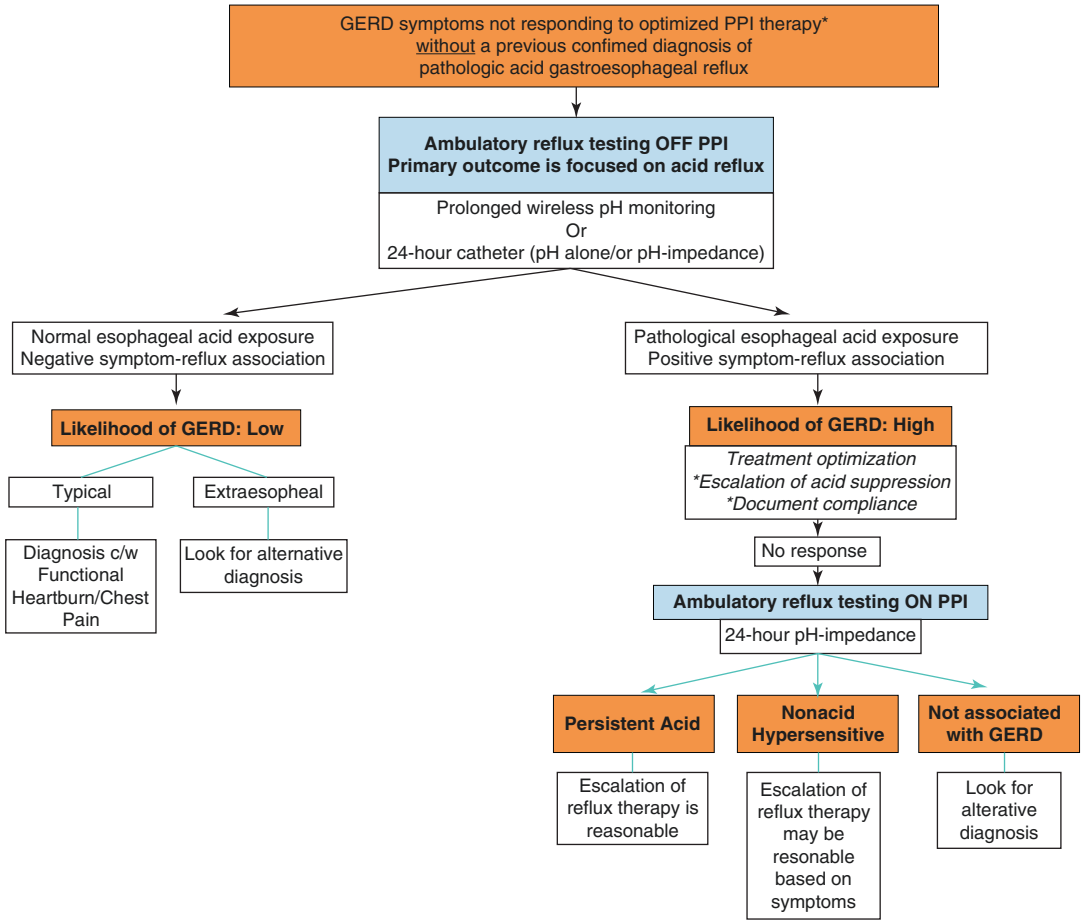

Fig. 3.1 The approach to patients with GERD symptoms not responding to medical therapy. *The optimal proton pump inhibitor (PPI) dose threshold to define failure of acid suppression is unknown. Based on the data from Charbel et al. [41], a dose that is either twice the Food and Drug Administration (FDA)-approved dose or a twice daily dose of the FDA indicated dose are the default regimens for defining PPI nonresponders.

distal esophageal pH monitoring. Patients with pathological esophageal acid exposure and/or positive symptom-reflux association have a high likelihood of GERD and their management strategies include treatment optimization with PPIs (escalation of the dose, ensuring compliance with PPI) [42]. Patients with normal acid exposure with negative symptom-reflux association have a low likelihood of GERD, may stop their PPI [42] and a search made for other causes.

How Do You Treat Chest Pain Caused by Acid Reflux?

Response to the patient: Chest pain due to acid reflux is treated by taking medication that stops acid production in your stomach. The medication is called a proton pump inhibitor (PPI). If you have chest pain related to acid reflux that has been confirmed by abnormal pH testings in your swallowing tube and you do not wish to take medications, then an alternative is to undergo surgery. During this procedure done laparoscopically (small incision in your belly), a surgeon will wrap the upper part of your stomach around the distal part of your swallowing tube to tighten your weak lower valve.

Brief Review of the Literature

PPIs are the mainstay therapy for suspected GERD-related chest pain. According to a meta-analysis of seven trials including 232 patients, there was a significantly decreased risk of chest pain continuation after PPI therapy (pooled RR = 0.54, 95% CI 0.41–0.71) when compared to placebo [38]. The overall number needed to treat was 3 to achieve symptomatic response [38]. Patients treated with PPIs were more likely to achieve at least a 50% response than placebo recipients with a statistically significantly lower risk of continued chest pain (pooled RR 0.60, 95% CI 0.44–0.81) [38]. On the other hand, no difference was observed between PPI and placebo in achieving complete resolution of non-cardiac chest pain (pooled RR 0.83, 95% CI 0.66–1.05) [38] indicating that PPIs substantially improve but do not completely resolve chest pain due to GERD. Another systematic review of the literature suggested that non-cardiac chest pain due to GERD should be treated with double-dose PPI for at least 2 months [43].

However, no studies have been done comparing the efficacy between once daily PPI to twice daily PPI in patients with non-cardiac chest pain. Based on cost analysis, Fass et al. recommended PPI BID for 8 weeks and in the responders then decreasing the dose to once daily [44].

Due to the growing concern within the community about possible PPI-related side effects such as dementia or chronic kidney disease, it was recently suggested that PPIs for GERD be discontinued after symptom resolution for longer than 2 weeks. The suggested options are to use H2 receptor antagonists or antacids for infrequent symptoms or intermittent 2–4 week courses of PPIs for symptom recurrence (at least two episodes a week) [45]. Patients who require daily PPIs to control their symptoms should continue them only if the gain in quality-adjusted-life-years with long-term symptom control far exceeds any decrease due to possible rare, serious adverse events [45]. Patients worried about side effects and those whose quality of life is affected should either seek other therapies (surgery) or accept their symptoms [45].

Several open-label trials have evaluated the efficacy of surgery in patient with non-cardiac chest pain due to GERD [46]. Improvement in chest pain was observed among 58–96% of patients who underwent laparoscopic Nissen fundoplication. Patients with a confirmed association between chest pain and acid reflux by esophageal pH testing had higher response rates to surgery (up to 96%) than those without such an association (up to 65%) [46]. Importantly, the response to PPIs was an important predictor of response to surgery [46].

There is only one small study that evaluated the efficacy of endoscopic antireflux treatment with endoluminal gastroplication (Endocinch) in patients with atypical GERD symptoms [47]. Improvement in chest pain was observed in 13 of 18 of patients (72%) at 6 months when compared with baseline [47].

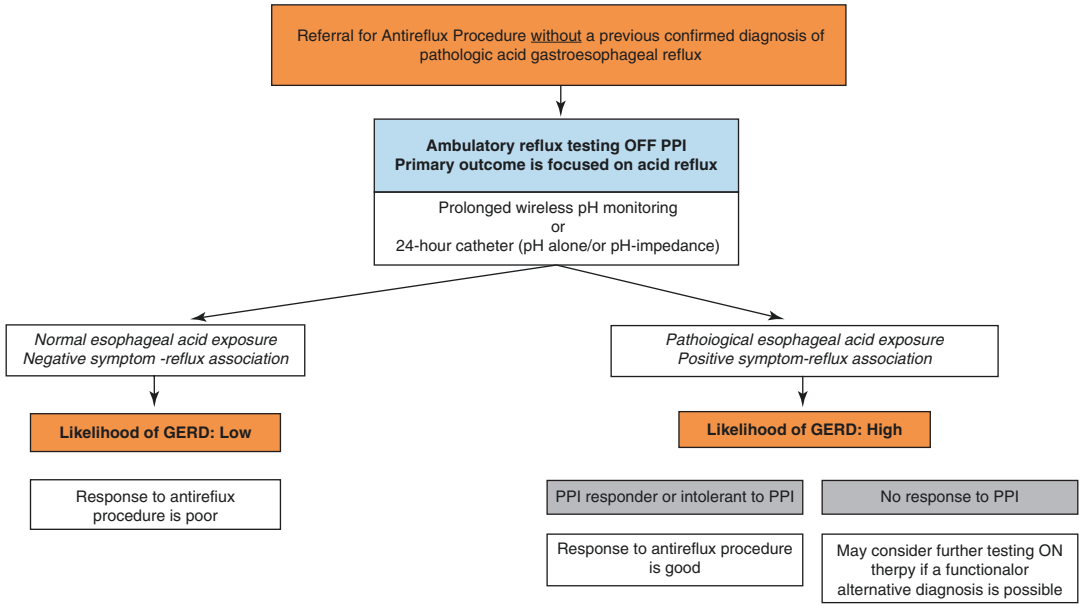

Fig. 3.2 The approach to patients referred for antireflux procedures without a previous confirmed diagnosis of GERD [42]. Reprinted from Dis Esophagus 2013; 26 (8). Richter JE, Pandolfino JE, Vela MF, Kahrilas PJ, Lacy BE, Ganz R, Dengler W, Oelschlager BK, Peters J, DeVault KR, Fass R, Gyawali CP, Conklin J, DeMeester T; Esophageal Diagnostic Working Group. Utilization of wireless pH monitoring technologies: a summary of the proceedings from the esophageal diagnostic working group. pp. 755–65. Copyright 2012 with permission from John Wiley & Sons, Inc.

The 2013 consensus of the Esophageal Diagnostic Advisory Panel clearly recommends objective confirmation that GERD is the cause of patients' symptoms before consideration of surgery (Fig. 3.2) [42, 48]. Required preoperative workup should include upper endoscopy, barium esophagram, pH testing off PPI therapy for at least 7 days, and esophageal manometry [48]. Patients with normal distal esophageal acid exposure on esophageal pH testing have a low likelihood of GERD and poor response to antireflux surgery [48]. A positive symptom index or symptom association probability alone is not sufficient indications for anti-reflux surgery as chest pain is likely due to esophageal hypersensitivity and not GERD [48]. According to recent guidelines by the Society of American Gastrointestinal and Endoscopic Surgeons, objective confirmation of GERD is required before consideration of antireflux surgery and surgical therapy should be considered if patients have inadequate control of symptoms on PPIs, severe regurgitation on PPIs, or side effects of PPIs, prefer surgery due to quality of life issues, developed GERD complications such as peptic stricture or Barrett's esophagus, or have extra esophageal manifestations of GERD such as asthma, hoarseness, cough, and chest pain [49].

Chest Pain Due to Esophageal Hypersensitivity

What Is Esophageal Hypersensitivity and Why Does It Cause Chest Pain?

Response to the patient: Some patients experience chest pain due to sensitivity of the nerve fibers within their swallowing tube to repetitive mechanical stimuli, prior tissue injury, or inflammation. The esophagus with such sensitive nerve fibers is called the "hypersensitive esophagus." Some patients may also experience chest pain due to increased stimuli coming from the brain itself due to anxiety, panic attacks, or depression.

Brief Review of the Literature

Non-cardiac chest pain without evidence of acid reflux, esophageal motility disorders, or eosinophilic esophagitis may be due to visceral hypersensitivity, i.e., "functional chest pain." This type of chest pain is typically associated with irritable bowel syndrome or other functional disorders in up to 80% of patients [50]. Sensitization of visceral afferents may occur during mucosal injury causing hyperalgesia [51]. The animal and human studies investigating the pathophysiology of esophageal pain in response to various stimuli are described in the section on chest pain due to acid reflux (answer to question 1).

Two mechanisms of esophageal hypersensitivity are proposed: (1) increased esophageal afferent pathway sensitivity and (2) increased secondary cortical processing due to psychological factors such as hypervigilance with normal afferent transmission [52]. Both mechanisms lead to reduced pain thresholds [52].

Various studies have identified abnormal pain perception via peripheral and central mechanisms in patients with non-cardiac chest pain in response to electrical, mechanical, and chemical stimulus.

Electrical Stimulus

Hobson et al. observed that patients with non-cardiac chest pain were characterized by reduced pain thresholds and increased latencies of esophageal evoked potentials in response to electric stimulation when compared to healthy controls [52]. Furthermore, patients with non-cardiac chest pain were divided into three separate phenotypic categories: (1) normal or reduced esophageal evoked potential latencies and reduced pain thresholds, (2) increased esophageal evoked potential latencies with reduced pain thresholds, and (3) normal or increased esophageal evoked potential latencies and normal pain thresholds [52]. Therefore, the authors hypothesized that either increased esophageal afferent pathway sensitivity or abnormality in the secondary cortical processing of esophageal sensory information (central mechanisms of esophageal hypersensitivity) were mechanisms responsible for non-cardiac chest pain [52]. In another study, patients with non-cardiac chest pain were found to experience pain at a twofold lower esophageal electrical stimulation intensities (3.6 ± 1 vs. 7.8 ± 2 mA, $p < 0.05$) than healthy controls suggesting hypersensitivity (allodynia) to esophageal electrical stimulation [53].

Mechanical Stimulus

In their landmark study, Richter et al. observed in 1986 that patients referred by their cardiologists with non-cardiac chest pain were more sensitive to smaller volumes of balloon distension than healthy controls who experienced chest pain at greater distension volumes [54]. In that study, 15 of 18 patients experienced chest pain with balloon volumes of less than 8 mL and all healthy controls with pain (6 of 30 subjects) noted it after balloon volumes of at least 9 mL [54]. There was no difference in balloon pressures or esophageal contractions above the balloon during pain episodes between patients and healthy controls [54]. Therefore it was proposed that esophageal balloon distension triggers esophageal chest pain in susceptible patients due to a lower pain threshold rather than abnormal esophageal contractions [54]. These data were further supported by Rao et al. who showed greater reactivity of the esophagus to balloon distension and a less distensible esophageal wall among patients with non-cardiac chest pain compared to healthy controls evaluated by impedance planimetry [55]. It was suggested that excessive reaction to luminal distension in patients with non-cardiac chest pain might be due to a stiffer esophageal wall [55]. Furthermore, another study by Rao et al. observed that chest pain induced by esophageal balloon distension was not reduced by atropine indicating that the major mechanism responsible for eliciting functional chest pain was hyperalgesia and not motor dysfunction [56].

Chemical Stimulus

A study by Sarkar et al. among 19 healthy volunteers and 7 patients with non-cardiac chest pain found that patients with non-cardiac chest pain had lower baseline electrical pain threshold in the upper esophagus which further decreased and lasted longer after infusion of hydrochloric acid into the distal esophagus when compared with healthy volunteers [57]. In addition, infusion of acid into the lower esophagus decreased the pain threshold to electrical stimulation within the upper esophagus and anterior chest wall in healthy volunteers [57]. The authors postulated that central sensitization may play a role in concurrent visceral and somatic pain hypersensitivity [57]. Another study of ten healthy volunteers found reduced electrical evoked potential latency and electrical pain threshold within nonacid-exposed proximal esophagus suggesting a central increase in afferent pathway velocity [58]. It was postulated that hypersensitivity within the proximal, nonacid-exposed esophagus was due to hyperexcitability within the central visceral pain pathway [58].

How Can We Distinguish Chest Pain Due to Esophageal Hypersensitivity from Cardiac Chest Pain?

Response to the patient: It is difficult to distinguish between cardiac chest pain and chest pain due to esophageal hypersensitivity based on the description of your pain. If you experience chest pain you should always go to the emergency room to undergo proper evaluation to exclude life-threatening conditions of heart and lungs. After life-threatening conditions have been ruled out you will be referred to the gastroenterologist for further workup.

Brief Review of the Literature

Please refer to answer to question number 2 in the section on chest pain due to acid reflux.

How Do You Diagnose Chest Pain Due to Esophageal Hypersensitivity?

Response to the patient: Please refer to the answer to question number 3 in the section on chest pain due to acid reflux. If your chest pain does not respond to PPIs, your upper endoscopy is normal, the biopsies of samples taken from your esophagus are normal, your pH study is normal, then your chest pain is not due to acid reflux. The doctor will determine next whether you have an abnormal esophageal motility (muscle contractions) that could cause your chest pain. A thin catheter will be inserted through your nose and advanced into your esophagus. You will be asked to swallow sips of water several times and the doctor will check the pressures within your esophagus. If this test is normal, then your chest pain is most likely due to esophageal hypersensitivity.

Brief Review of the Literature

Chest pain due to esophageal hypersensitivity is a diagnosis of exclusion. There is no single gold standard test that allows for the diagnosis of this condition. Recently published Rome IV criteria clearly define the diagnostic criteria for chest pain due to esophageal hypersensitivity (i.e., functional chest pain) [51]. Functional chest pain may be diagnosed if chest pain started at least 6 months before diagnosis, is present at least once a week, and has been present within the last 3 months [51]. It is described as retrosternal pain or discomfort, cardiac causes must be excluded, associated symptoms such as heartburn and dysphagia are absent, and there is no evidence of gastroesophageal reflux, eosinophilic esophagitis, or major esophageal motility disorders [51].

An esophageal workup should be initiated only after cardiac causes of chest pain (especially coronary artery disease) have been eliminated [51]. Due to the high prevalence of GERD in patients with non-cardiac chest pain, the most cost-effective step is to prescribe high-dose PPI therapy for 8 weeks [38, 44]. Upper endoscopy with biopsies of the esophagus are

recommended to exclude erosive or eosinophilic esophagitis as possible causes of chest pain [44]. Nonresponders to high-dose PPI therapy should be offered esophageal pH monitoring off PPIs [44].

It should be noted that Rome IV classification has proposed a more strict definition of GERD in which only abnormal esophageal acid exposure confirms the diagnosis [51]. Patients with normal esophageal acid exposure but positive chest pain-reflux association (acid-sensitive esophagus) are now classified as having "reflux hypersensitivity" and belong to the functional chest pain group (Fig. 3.3) [51]. Previously, Rome III criteria included acid-sensitive esophagus within non-erosive reflux disease spectrum [59]. The Rome IV classification change evolved from the observation that reflux-symptom association measured only by a positive symptom index or symptom association probability with normal distal esophageal acid exposure often can occur by chance alone [60]. Response to PPIs does not preclude the diagnosis of chest pain due to reflux hypersensitivity [51].

After excluding GERD, the next step is to perform esophageal manometry to determine whether a major esophageal motility abnormality may be causing the chest pain [44]. These would include achalasia, esophagogastric junction outflow obstruction, jackhammer esophagus, diffuse esophageal spasm, or absent peristalsis. If esophageal manometry is normal, then one approach is to perform an esophageal balloon distension test which can reproduce esophageal chest pain in up to 75% of patients with chest pain due to esophageal hypersensitivity [61]. However, the balloon distension test in academic and clinical practice is rarely done. Figure 3.4 presents an algorithm for establishing the diagnosis of chest pain due to esophageal hypersensitivity [62].

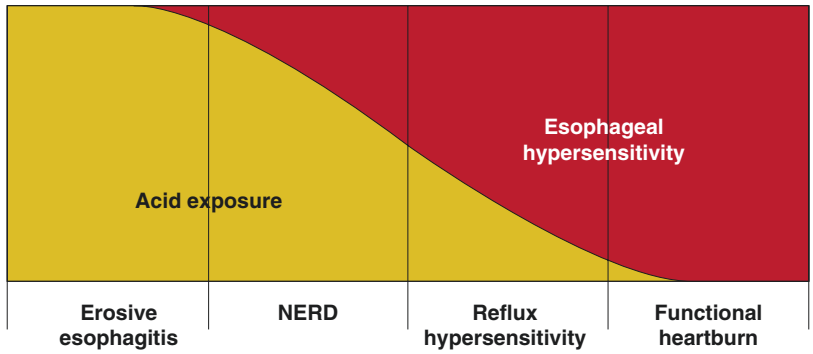

Fig. 3.3 The association between acid exposure and esophageal hypersensitivity in GERD, reflux hypersensitivity, and functional heartburn [51]. Reprinted from Gastroenterology 2016; 150 (6). Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional Esophageal Disorders. pp. 1368–1379. Copyright 2016 with permission from Elsevier

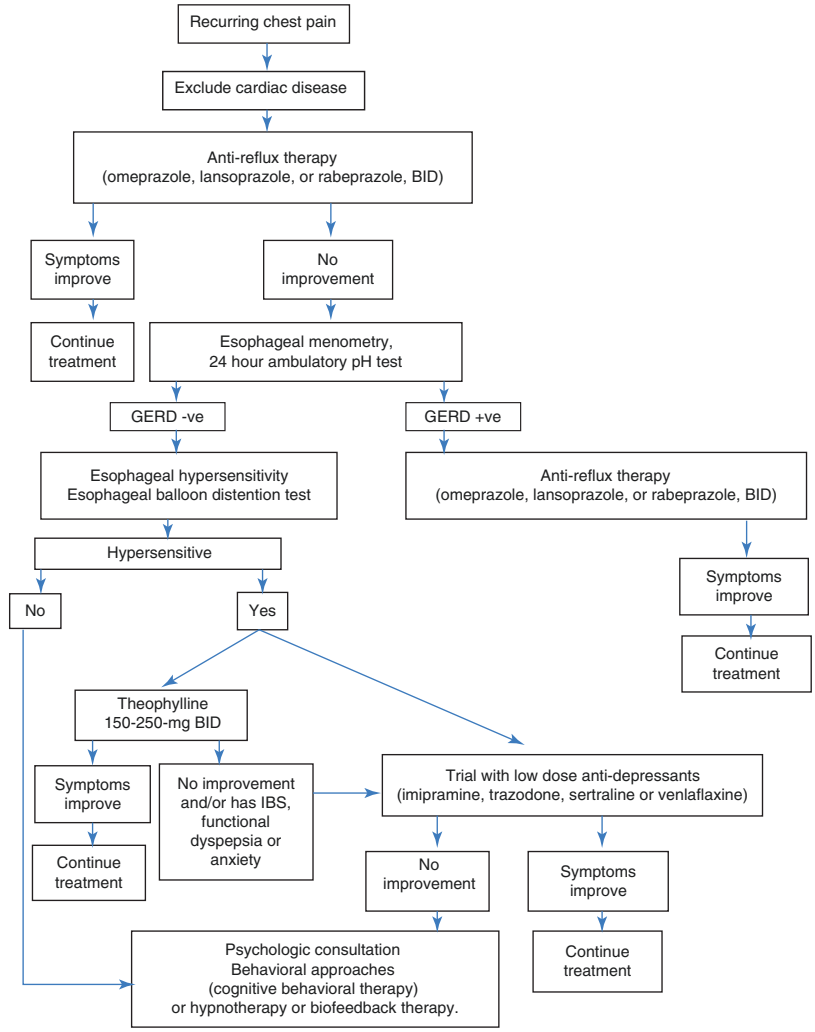

Fig. 3.4 Algorithm for management of esophageal chest pain [62]. Reprinted from Clin Gastroenterol Hepatol. 2014; 12 (8). Coss-Adame E, Erdogan A, Rao SS. Treatment of esophageal (non-cardiac) chest pain: an expert review. pp. 1224–45. Copyright 2014 with permission from Elsevier

How Do You Treat Chest Pain Due to Esophageal Hypersensitivity?

Response to patient: If your chest pain is caused by reflux hypersensitivity, then you may respond to PPIs. In patients not responding to PPI, the recommended treatment for chest pain due to esophageal hypersensitivity includes a variety of antidepressants (tricyclic antidepressants (TCA), serotonin reuptake inhibitors (SSRIs)) or psychological interventions such as cognitive behavioral therapy, coping skills, or hypnosis to decrease pain hypersensitivity.

Brief Review of Literature

It has been suggested that patients with an acid-sensitive esophagus may respond to PPI therapy. Among patients with normal upper endoscopy and reflux symptoms responding to PPIs, 26% in one study were found to have a hypersensitive esophagus [63]. However, that study evaluated patients with typical reflux symptoms and it is uncertain whether these findings can be also applied to patients with chest pain due to an acid-sensitive esophagus [63].

In patients not responding to PPIs, the first line treatment are medications targeting neuromodulation of pain [64]. These include antidepressants such as tricyclic antidepressants (imipramine, amitriptyline), serotonin reuptake inhibitors (sertraline, paroxetine, citalopram), trazodone, or serotonin noradrenergic reuptake inhibitors (venlafaxine) (Table 3.1) [64]. According to a recent systematic review of six randomized placebo controlled trials, venlafaxine (50% vs. 10%; $P < 0.001$), sertraline (63% vs. 15%; $P = 0.02$), and imipramine (52% vs. 1%; $P = 0.03$) but not paroxetine showed statistically significant superiority over placebo in reduction of non-cardiac chest pain [65]. On the other hand, a recent meta-analysis of four randomized placebo controlled trials including 184 patients assessing the efficacy of selective serotonin reuptake inhibitors for non-cardiac chest pain found no difference between active drug and placebo in improving chest pain (standardized mean difference = −0.17; 95% CI = −0.46–0.12) [66].

It has been proposed that adenosine and ATP play a role in the development of visceral chest pain [67, 68] by A1 receptor activation [69]. Several studies have shown that angina-like chest pain can occur after the intravenous infusion of adenosine [70–72]. Theophylline, an adenosine receptor antagonist and smooth muscle relaxant, was evaluated in two small randomized placebo controlled trials in patients with non-cardiac chest pain [73]. Both trials assessed the efficacy of intravenous and oral formulations of theophylline in patients with chest pain due to esophageal hypersensitivity [73]. An analysis of the sensory and biomechanical properties of the esophagus by balloon distension in 16 patients found a statistically significant greater increase in chest pain thresholds, esophageal cross-sectional area, and esophageal distensibility in patients receiving IV theophylline compared with placebo [73]. An

Table 3.1 A pain modulators for the treatment of functional esophageal disorders [64]

Class of drug	Dose	Disorder	RCT	Side effects	Response
TCAs					
Imipramine	50 mg/day	NCCP	+	+/–	57%
Amitriptyline	10–20 mg/day	NCCP, globus	+	+/–	52%
SSRIs					
Sertraline	50–200 mg/day	NCCP	+	+	57%
Paroxetine	50–75 mg/day	NCCP	+	+/–	Modest
Citalopram	20 mg/day	ES	+	+/–	Significant
Trazodone					
Vs clomipramine	50/25 mg/day	NCCP	–	+	Modest
Trazodone alone	100–150 mg/day	Dysmotility	+	+/–	29–41%
SNRIs					
Venlafaxine	75 mg/day	NCCP	+	++	52%
Other					
Theophylline	200 mg twice/day	NCCP	+	+/–	58%
Gabapentin	300 mg 3 times/day	globus	+	+/–	66%

ES esophageal hypersensitivity, *RCT* randomized control trial, *SNRI* serotonin norepinephrine reuptake inhibitor
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oral formulation of theophylline (200 mg PO BID) was more efficacious than placebo in the reduction of chest pain episodes, duration and severity and the number of days with chest pain during a 4 week crossover trial of 24 patients [73]. Overall, there was improvement in chest pain in patients treated with oral theophylline versus placebo (58% vs. 6%, $p < 0.02$) [73].

A recent Cochrane meta-analysis of 17 randomized controlled trials including 1006 patients with non-cardiac chest pain analyzed the efficacy of psychological interventions such as cognitive behavioral therapy (CBT), hypnotherapy, autogenic training, group support, brief intervention by a nurse, relaxation training, and breathing retraining [74]. Psychological interventions were associated with a significant reduction in reports of chest pain (RR 0.70, 95% CI 0.53–0.92), a significant increase in the number of chest pain-free days (mean difference = 3.00, 95% CI 0.23–5.77), and reduced chest pain frequency (mean difference = −2.26, 95% CI −4.41 to −0.12) over the 3 months of intervention [74]. Studies suggested that maintenance therapy for 3–12 months was also associated with significant reduction of chest pain (RR = 0.59, 95% CI 0.45–0.76). On the other hand, psychological interventions did not influence chest pain frequency after 3–12 months (mean difference = −0.81, 95% CI −2.35 to 0.74) [74]. The authors concluded that there was a modest to moderate benefit in treating non-cardiac chest pain with psychological interventions, especially with CBT or hypnotherapy; however, the effect was limited to the first 3 months on therapy [74]. The limitations of available data include high heterogeneity of the results and low numbers of participants in individual studies [74]. Further clinical trials of psychological interventions in patients with non-cardiac chest pain with at least 12 months follow-up are warranted to evaluate their long-term efficacy [74].

The proposed treatment algorithm of esophageal chest pain is presented in Fig. 3.4 [62]. After failure to respond to a PPI trial and exclusion of GERD, major esophageal motility abnormalities or eosinophilic esophagitis by appropriate testing (esophageal pH, esophageal manometry, and upper endoscopy with esophageal biopsies), it is reasonable to obtain an esophageal balloon distension test [51, 62]. Treatment options include theophylline 150–250 mg PO BID, low-dose antidepressants (imipramine, trazodone, sertraline, or venlafaxine), or psychological interventions such as CBT or hypnotherapy [62].

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Nonspecific Esophageal Motility Disorders

4

C. Prakash Gyawali

The first high-fidelity, water-based conventional esophageal manometry systems were developed in the mid-1970s, but pressure-recording sites were limited along the esophagus, and measurements were often cumbersome and inconsistent [1]. When these conventional manometry catheters were utilized, certain motor patterns could not be characterized further, and were termed "nonspecific" motor disorders. With modern solid-state catheters containing up to 36 pressure sensors reliably measuring pressure data, high-resolution manometry (HRM) provides accurate, sensitive, and reproducible measurements of esophageal pressure phenomena [1, 2]. Use of software tools has made the process of esophageal motor evaluation more specific, with clear criteria under the Chicago Classification for disorders with an obstructive element at the esophagogastric junction (EGJ), major disorders (not seen in health), and minor disorders that imply a bolus transit abnormality [3]. Nevertheless, there are esophageal body contraction wave abnormalities and EGJ motor findings that are not captured by the software tools utilized for modern motor diagnoses using the Chicago Classification. Therefore, the implications of a "nonspecific" motor disorder have changed in the past two decades.

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My Manometry Findings Do Not Fit into Specific Disorders. What's Wrong with My Esophagus?

To understand nonspecific motor disorders, their counterpart, "specific" motor disorders need to be recognized. While the criteria and nomenclature for specific motor disorders have changed in the current era of HRM, diagnostic standards carried over from conventional manometry include achalasia, extreme hypomotility disorders (so-called scleroderma esophagus), diffuse esophageal spasm, and ineffective esophageal motility (Table 4.1). When conventional manometry was utilized for diagnosis of motor disorders, metrics used for designation of esophageal body abnormalities included amplitude of the contraction wave, propagation velocity, and wave morphology. At the LES, while post-swallow residual pressures constituted the main metric assessed, resting LES pressures were also characterized, with designations of hypotensive, normal, and hypertensive LES.

High-resolution manometry (HRM) has allowed improved identification, understanding, and management of motor disorders of the esophagus and anorectum [1, 4, 5]. HRM data is

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Table 4.1 Characterization of specific and nonspecific motor disorders

Specific motor disorders[a]
Esophageal outflow obstruction
Achalasia, subtypes 1, 2, and 3
Esophagogastric junction outflow obstruction: motor or structural
Major motor disorders
Hypercontractile disorder (jackhammer esophagus)
Diffuse esophageal spasm
Absent contractility
Minor motor disorders
Ineffective esophageal motility
Fragmented peristalsis
Nonspecific motor disorders
Esophageal body disorders
Contraction wave abnormalities
High contraction amplitudes
Double and multiple peaked waves
Rapid or simultaneous contractions
Broad peristaltic wave duration
Distal shift in contraction vigor
Breaks in peristaltic integrity
Transition-zone defects
EGJ disorders
Hypotensive EGJ
Hypertensive EGJ
Abnormal EGJ morphology: hiatus hernia
Other nonspecific disorders
Supragastric belching
Rumination

[a]Described in the Chicago Classification, v 3.0 [3]

displayed in a three-dimensional topographic "Clouse plot" of time, distance, and pressure representation as a color scale. With the initial reports of HRM in normal volunteers, it became evident that esophageal peristalsis relies on contracting segments, the proximal skeletal muscle segment (segment 1), and the distal two smooth muscle contraction segments (segments 2 and 3) [6]. Peristalsis is therefore visualized as a chain of contracting segments and relaxing sphincters, assessed using measurements of smooth muscle contraction vigor (distal contractile integral, DCI), peristaltic timing (distal latency, DL), and nadir residual pressures at the esophagogastric junction during swallows (integrated relaxation pressure, IRP) [1, 7, 8]. Changes in individual contraction segments can result in motor abnormalities, and the most profound of these are identified within the Chicago Classification v. 3.0 [9] (Table 4.1). A progressive gradient of decreasing cholinergic and increasing non-cholinergic, non-adrenergic influence in smooth muscle segments has been reported in animal models, and this is supported by observing the cholinergic effects of cisapride in enhancing more cephalad smooth muscle contraction [10, 11]. Therefore, many of the esophageal body motor disorders can be explained on the basis of incomplete contractile function (with cholinergic neurotransmission), or abnormal esophageal inhibition (where non-cholinergic, non-adrenergic influences dominate, mediated by nitric oxide).

With HRM, achalasia diagnosis has become more precise and detailed, with three achalasia subtypes now recognized [12]. Abnormal relaxation of the lower esophageal sphincter (LES) remains the hallmark for the diagnosis of achalasia, now identified when the IRP is elevated above the upper limit of normal for the particular HRM system being utilized. Incomplete achalasia patterns with retained esophageal body peristalsis have been characterized (EGJ outflow obstruction), which need to be differentiated from structural mechanical processes at the EGJ with alternate complementary tests [3]. Diffuse esophageal spasm is now diagnosed based on a shortened latency (DL < 4.5 s) between initiation of the swallow (relaxation of the upper esophageal sphincter or UES) and the arrival of the contraction sequence in the distal esophagus. Esophageal body contraction vigor, assessed using DCI, is further characterized into ineffective (DCI < 450 mm Hg cm s) and hypercontractile peristalsis (DCI > 8000 mm Hg cm s); DCI also defines a failed sequence (DCI < 100 mm Hg cm s) from a weak sequence within the ineffective realm. Motor patterns not meeting the criteria for esophageal outflow obstruction (achalasia spectrum, mechanical EGJ obstruction), major motor disorders (diffuse esophageal spasm, hypercontractile disorder, absent contractility), and minor motor disorders (ineffective esophageal motility, fragmented peristalsis) are considered normal.

What Are Nonspecific Motor Disorders and Why Do They Develop?

In the current HRM era, motor disorders are therefore specific. However, abnormal contraction wave patterns exist within the "normal" realm that do not fulfil the criteria for a named HRM abnormality, but are nevertheless abnormal patterns. Many of these have origins within conventional manometry, with abnormalities in peristaltic wave pattern (double and multiple peaked waves), wave duration, propagation velocity, and wave amplitude (Table 4.1). Others have evolved from HRM, especially breaks in the peristaltic contour. Abnormal sphincter metrics are not defined within the HRM classifications of motor disorders, and could be considered nonspecific abnormalities. Finally, motor abnormalities have also been described with rumination and supragastric belching.

Contraction Wave Abnormalities

Normal smooth muscle contraction in the esophagus requires a balance between excitatory and inhibitory influences on esophageal motor function [13]. When control of smooth muscle contraction is abnormal, the contraction wave can be premature, non-peristaltic, and exaggerated (Fig. 4.1). The duration of the contraction wave can be prolonged, and the contraction at individual amplitudes can be double peaked or multiple peaked [13]. The correlate for multiple peaked waves on HRM consists of overlapping smooth muscle contraction segments (Fig. 4.1), rather than the normal sequential segmental architecture where the third

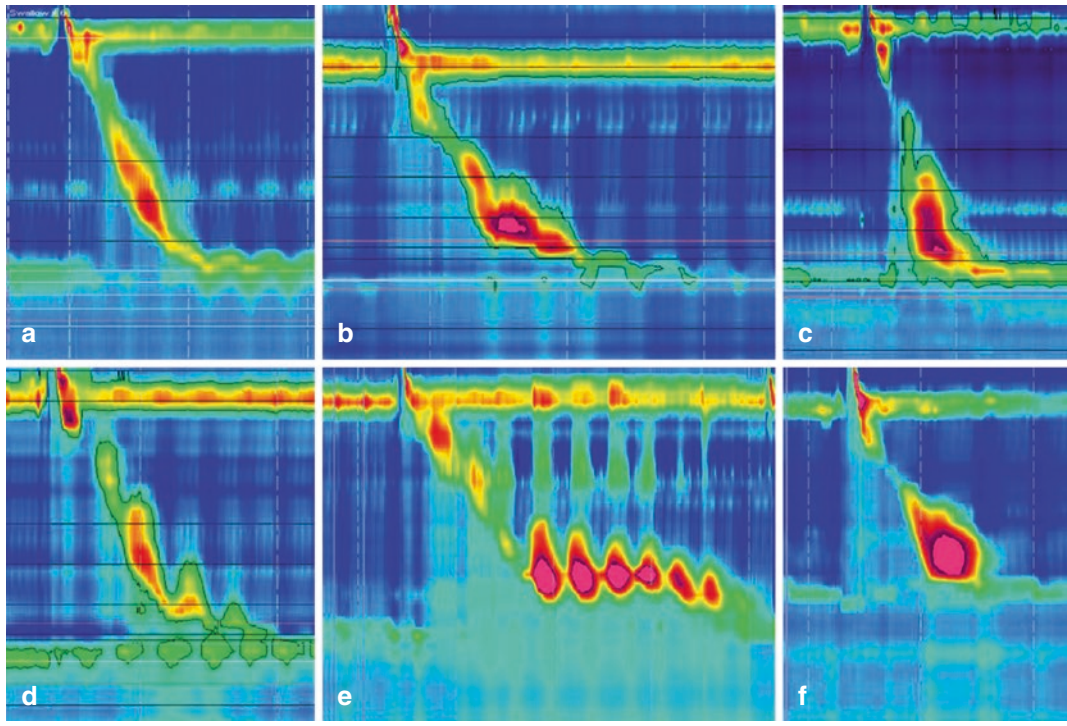

Fig. 4.1 Contraction wave abnormalities with normal Chicago Classification parameters. In all instances, distal contractile integral (DCI) and distal latency (DL) were within normal limits described for these parameters. (**a**) Normal esophageal body peristaltic sequence for comparison purposes. (**b**) Broad duration of the peristaltic sequence, >5.7 s. (**c**) Rapid contraction sequence, with normal DL. (**d**) Double-peaked peristaltic sequence, with overlapping third contraction segment. (**e**) Multiple peaked peristaltic sequence, with multiple repetitive contraction of the third contraction segment. (**f**) Exaggerated contraction vigor in the third segment

contraction segment follows the second segment [14]. Using balloon distension in conjunction with pressure measurements, Sifrim et al. demonstrated abnormal esophageal inhibition in patients with contraction wave abnormalities (CWA) and simultaneous contractions fulfilling criteria for diffuse esophageal spasm (DES) [15]. In these studies, there was an inverse relationship between the degree of inhibition and the propagation velocity of deglutitive contraction, as well as an absence of inhibition in simultaneous contractions [13]. With HRM, however, individual smooth muscle contraction segments are not separately evaluated; instead, vigor of the entire smooth muscle contraction is evaluated using DCI, thereby overriding specific contraction abnormalities to obtain an overview of adequacy of smooth muscle contraction [16]. Similarly, timing of peristalsis is assessed using DL, which measures timing of contraction in relationship to initiation of peristalsis, but does not assess simultaneity in the smooth muscle contraction [17]. Use of these two HRM metrics identifies motor disorders that are well developed (i.e., hypercontractile disorder, diffuse esophageal spasm), but may miss individual contraction wave abnormalities (CWA) if DCI or DL is normal [9].

There is increasing evidence suggesting a relationship between esophageal perception and CWA. For instance, Borjesson et al. demonstrated using intraesophageal balloon distension that increased visceral perception (i.e., lowered thresholds for esophageal pain perception) correlated with higher amplitude and duration of esophageal peristaltic waves [18]. Further evidence for increased esophageal perception is provided by the fact that patients with these nonspecific changes in the contraction wave are more likely to have residual perceptive esophageal symptoms such as heartburn, and an increased need for medication usage following adequate antireflux therapy, when compared with patients without these abnormalities [19]. There is a higher likelihood of acid sensitivity (where esophageal acid exposure time is physiologic, but a statistical correlation is identified between symptoms and reflux events) in patients with exaggerated contraction patterns in the esophageal smooth muscle [20].

Provocative study of nonobstructive dysphagia and noncardiac chest pain has provided insights into the relevance of contraction wave abnormalities. Some CWA can be induced by provocative balloon testing in patients with nonobstructive dysphagia [21, 22]. While normal volunteers are not symptomatic and only develop secondary peristalsis during sustained balloon distension in the esophagus, patients with nonobstructive dysphagia develop simultaneous contractions and other CWA during balloon distension, and the majority develop their characteristic symptom [21, 23]. Further, automated impedance manometry (AIM) analysis has suggested that nadir esophageal impedance (indicating peak bolus content) is closer to peak contraction pressures with nonobstructive dysphagia in contrast to healthy controls, where nadir impedance and peak contraction are further apart [24]. While the exact pathophysiology is not known, asynchrony between contraction of the esophageal circular and longitudinal muscles may explain these findings. This has been demonstrated in patients with noncardiac chest pain, which could provide insights into how CWA might be associated with perceptive symptoms. In a normal patient, circular muscle contraction, as assessed by increase in intraluminal pressure, is synchronized with longitudinal muscle contraction, as measured by cross-sectional area on high-frequency ultrasound images [25]. In contrast, in patients with nutcracker esophagus, the pressure peak follows increase in cross-sectional area, suggesting that the two muscle groups are not in synchrony with exaggerated contraction, which represents a CWA.

In fact, these abnormal perception concepts are borne out on functional magnetoencephalography [26]. Normal subjects demonstrate symmetrical activation of the sensorimotor cortex with swallowing. Patients with functional dysphagia not only have abnormal activation of these areas, but also demonstrate activation of areas depicting vigilance and self-monitoring. These in turn may interfere with downstream sensorimotor control of deglutition [26]. Therefore, both abnormal motor function and abnormal perception or increased vigilance may participate in functional esophageal symptoms. It is possible

that abnormal peristalsis, possibly in the form of contraction wave abnormalities, could be epiphenomena of the increased vigilance that is seen with these disorders. There is limited data suggesting that contraction wave abnormalities can also be seen as a consequence of distal esophageal obstruction [27], or from respiration-induced motion artifact in esophageal pressure phenomena [28]. In assessing symptom burden in the context of contraction wave abnormalities, these different CWA may have similar relationships to esophageal symptom burden.

Characteristics of contraction wave abnormalities:

Contraction wave abnormalities not identified with HRM software tools include the following (Fig. 4.1):

(a) Exaggerated contraction amplitudes: With conventional manometry, mean distal esophageal contraction amplitudes >180 mm Hg identified "nutcracker esophagus." With Chicago Classification v 2.0, DCI > 5000 mm Hg cm s was designated "hypertensive peristalsis" [4] but this was eliminated from Chicago Classification v 3.0, mainly because healthy controls sometimes have contraction amplitudes within this range [3]. Only contraction amplitudes >8000 mm Hg cm s are currently recognized as hypercontractile (jackhammer esophagus), when two or more sequences demonstrate this abnormality. However, contraction amplitudes that do not meet this threshold in the esophageal body may have clinical manifestations similar to hypercontractile disorder, and as discussed above may associate with lowered thresholds for esophageal perception [9, 18]. This may manifest on HRM as merging together of the two smooth muscle contraction segments, with obscuring of the trough between these two segments [9, 29].
(b) Simultaneous contractions: While premature contractions are identified using DL (<4.5 s), simultaneous contractions limited to the smooth muscle esophagus without a shortened DL are not captured by Chicago Classification v 3.0. Simultaneous contractions are identified by evaluating contraction front velocity 3, 8, and 11 cm above the lower esophageal sphincter; velocity >8 cm/s is diagnostic of simultaneous contractions, and >20% simultaneous contractions are abnormal. Simultaneous contractions with normal DL can manifest esophageal motor and symptomatic features similar to DES [30].
(c) Double and multiple peaked waves: On conventional manometry, these manifest as double or multiple peaks of contraction, with at least 10 mm Hg difference between the peaks. On high-resolution manometry, contraction segments are identified as overlapping, with the third segment sometimes simultaneous or even retrograde [14].
(d) Prolonged wave duration: This can be associated with exaggerated contraction amplitudes and multiple peaked waves. Normal duration of the esophageal contraction wave is <5.7 s. In many instances, prolonged wave duration may be associated with DCI in the hypercontractile range.
(e) Distal shift in contraction vigor: This is another abnormality that may not been captured using DCI, and represents a more prominent third smooth muscle contraction segment compared to the second segment [20]. A surrogate marker for distal shift in contraction vigor consists of distal esophageal contraction amplitudes in the 150–180 mm Hg range. This finding has been associated with acid sensitivity, suggesting increased esophageal perception [20, 27].

How Are Contraction Wave Abnormalities Relevant to My Symptoms?

Existing data in the literature suggest that CWA may be clinically relevant, especially when dysphagia is a presenting symptom. In past studies evaluating patients with nonobstructive dysphagia, CWA, especially simultaneous contractions, were more evident compared to normal volunteers, both with routine conventional manometry and with provocative studies using esophageal air or fluid

infusion [31, 32]. Simultaneous and retrograde contractions have been induced by balloon distension studies, both using conventional manometry where typical symptoms were reproduced with balloon distension [21], and more recently, using the functional luminal imaging probe and evaluating esophageal luminal diameter changes in response to balloon distension [33]. In some symptomatic patients, limited data suggests that asynchrony between esophageal circular and longitudinal muscle contraction can potentially explain bolus transit abnormalities [25].

Alternatively, increased esophageal sensitivity and hypervigilance are reported in conjunction with contraction wave abnormalities, especially in the setting of perceptive symptoms like heartburn and chest pain [18, 19, 34]. Esophageal perceptive thresholds are lower in the presence of CWA [18, 22], CWA may participate in esophageal acid sensitivity [20], and the presence of CWA contributes to persisting esophageal symptoms following successful antireflux surgery [19]. Further, exaggerated esophageal body contraction patterns (distal shift in contraction vigor, merged esophageal body contraction segments) represent a continuum in terms of esophageal symptoms, and only the most extreme of these patterns are identified by Chicago Classification designations [9]. Many of the CWA have been linked to abnormal esophageal inhibitory function [13], with an inverse relationship between the degree of inhibition and the propagation velocity of deglutitive contraction, as well as an absence of inhibition in simultaneous contractions [13]. Finally, functional magneto-electroencephalographic studies demonstrate activation of cortical areas depicting vigilance and self-monitoring in perceptive esophageal symptoms like dysphagia, which in turn may interfere with downstream sensorimotor control of deglutition and generation of abnormal motor patterns [26]. These data suggest that CWA could represent a minor motor disorder which may not be pathognomonic for a defined motor diagnosis, but one which can potentially explain esophageal symptoms, particularly transit symptoms like dysphagia.

Breaks in Peristaltic Integrity

Integrity of the peristaltic wave relies on adequate formation of esophageal body contraction segments. In particular, the second segment, which is the proximal of the two smooth muscle contraction segments, can form poorly in hypomotility disorders, resulting in prominence of the trough between skeletal and smooth muscle contraction segments [35, 36]. This trough, which has been termed intersegmental trough or a transition-zone defect, has been linked to dysphagia, and indeed, bolus retention has been identified at this location using HRM with impedance [35, 37–39]. Studies using HRM with impedance suggests that breaks of >2 cm in the 20 mm Hg isobaric contour may be variably associated with impaired bolus clearance, while breaks >5 cm are uniformly associated with bolus escape [38, 40]. However, the association with dysphagia is not perfect, and the trough can be identified in healthy normal individuals, suggesting that the mere presence of a trough is not abnormal [38]. For this reason, focus has shifted to measurement of vigor of remaining contraction segments when such troughs are present, using DCI. The Chicago Classification v 3.0 currently recognizes >5 cm breaks as abnormal, if DCI is within the "intact" range (i.e., >450 mm Hg cm s)—these sequences are termed "fragmented."

The two symptoms linked to the presence of breaks are dysphagia and chronic cough. In the presence of proximal breaks (transition-zone defects), dysphagia was noted in approximately a third of patients, significantly higher than in the absence of such breaks [37]. However, breaks only account for <4% of dysphagia. Limited studies have also suggested that the presence of a break is more likely in patients who present with cough as a presenting symptom, typically within the realm of reflux [41]. The pathophysiologic mechanism is thought to be related to proximal migration, bolus retention, and stimulation of the proximal esophagus. While these have not been demonstrated in the setting of chronic cough, proximal migration of refluxate has been associated with higher perception of typical reflux symptoms [42, 43], and bolus retention as well as

esophagitis have been identified at higher proportions when compared to absence of breaks [39].

An extended trough between the skeletal and smooth muscle contraction segments has also been associated with prolongation of latency between initiation of peristalsis, and transfer of contraction between skeletal and smooth muscle contraction segments [35]. Termed proximal latency of smooth muscle contraction, this was noted to be prolonged in gastroesophageal reflux disease, and correlated with length of the intersegmental trough.

The second contraction segment has dominant cholinergic influences. For instance, when cisapride, a cholinomimetic agent, was administered to healthy volunteers, selective enhancement of contraction vigor of the second segment was demonstrated [11]. This is supported by older studies that have suggested a gradient of cholinergic and non-cholinergic influences in the smooth muscle esophagus, with cholinergic influences dominating in the proximal smooth muscle. The second segment is noted to be hypomotile with lower contraction vigor in patients with gastroesophageal reflux disease and especially Barrett's esophagus, where esophageal clearance can be compromised [36]. Additionally, distal obstruction can result in augmentation of the second segment, which can be interpreted as recruitment of the second segment to overcome the obstructive process [27]. Therefore, the importance of the second contraction segment lies in its role as a "pump" of sorts, such that failure of this segment can be associated with suboptimal esophageal clearance of bolus, potentially leading to the sensation of dysphagia or more profound reflux changes. The presence of a break, therefore, may need to be taken into account as a nonspecific disorder that can sometimes participate in esophageal symptoms and bolus clearance, but the true significance of a break <5 cm is unclear at the present.

Can LES and EGJ Abnormalities Contribute to My Problems?

The barrier against reflux at the esophagogastric junction (EGJ) consists of the intrinsic LES, and the muscle fibers of the crural diaphragm (CD) that enclose the LES. When the LES and CD are superimposed, intrinsic LES tone is bolstered by CD contraction during inspiration (Fig. 4.2). A hypotensive intrinsic LES with a reduced resting tone can be associated with reflux, especially from increased intra-abdominal pressure (strain) promoting pressure differential across the EGJ [35, 44]. Axial separation of the intrinsic LES and CD results in a hiatus hernia, which also compromises the EGJ barrier and promotes reflux [44, 45]. The presence of a hiatus hernia can further reduce LES pressure and esophageal body contraction vigor, promoting swallow-induced reflux, strain, and delayed acid clearance from the esophagus [45, 46].

Motor and morphologic deficiencies at the EGJ have not been incorporated as well into modern esophageal motor classification schemes as have esophageal outflow obstruction and motor dysfunction of the esophageal body [3]. HRM software tools have been recently developed to interrogate the EGJ barrier, using a similar concept as DCI to describe vigor of the EGJ barrier. The metric used to report EGJ vigor is termed EGJ contractile integral (EGJ-CI), and measures both expiratory and inspiratory pressures across the EGJ over the duration of three respiratory cycles; the metric (reported in mm Hg cm) is rendered independent of the duration of respiration by dividing the recorded value by the duration of the three respiratory cycles [47, 48]. Normative values have been described in healthy controls, and a hypotensive EGJ by EGJ-CI has been reported to be associated with higher esophageal reflux burden [48–50]. On the other hand, EGJ morphology is well characterized based on the degree of separation between the pressure profiles of the intrinsic LES and CD [44], and has been reported in the context with esophageal motor disorders, but is not incorporated into a formal classification of EGJ abnormalities [3]. HRM is reported to be highly sensitive and specific for identification of a hiatus hernia, and more sensitive than endoscopy or radiography alone [51]; therefore, there is value to incorporation of EGJ morphology and motor deficiencies into HRM interpretation.

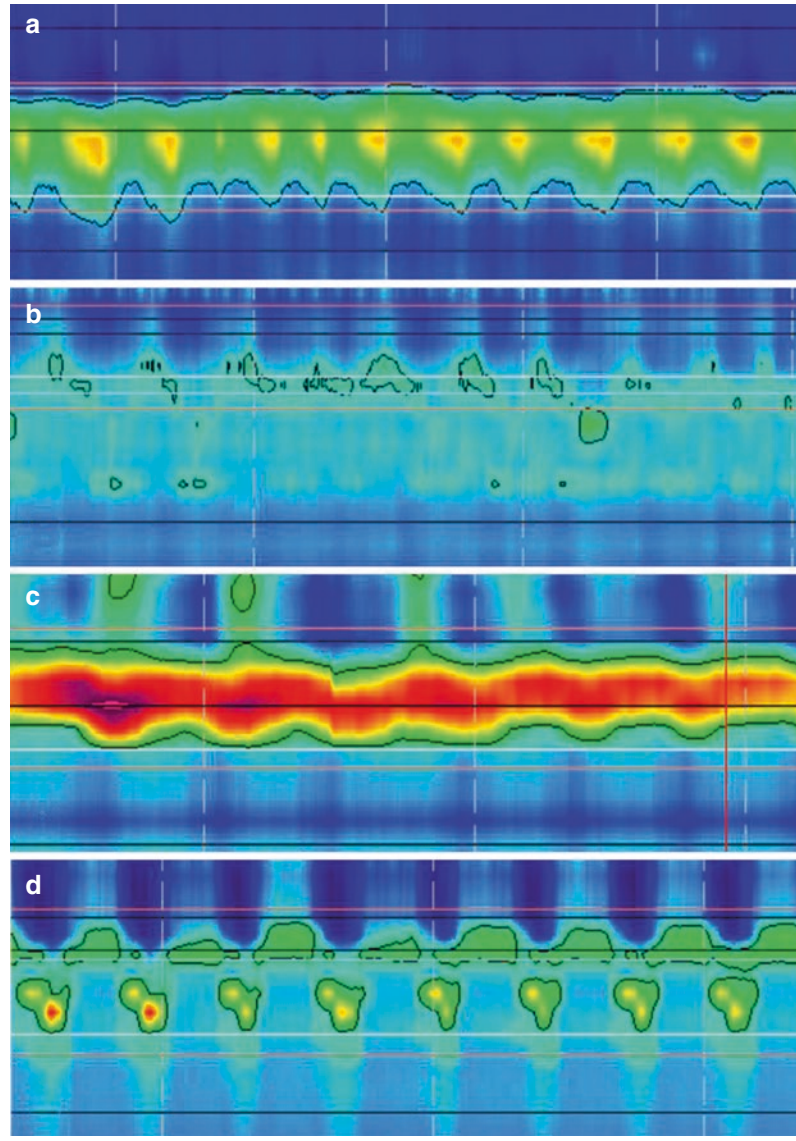

Fig. 4.2 Motor and morphologic abnormalities at the esophagogastric junction (EGJ). (**a**) Normal EGJ, with superimposed intrinsic LES and crural diaphragm, visualized as augmentation of contraction during inspiration. (**b**) Hypotensive EGJ. (**c**) Hypertensive EGJ. (**d**) Hiatus hernia, with separation between the intrinsic LES and crural diaphragm

Increased LES tone, or increased EGJ-CI in the absence of esophageal outflow obstruction (i.e., a hypertensive LES), is sometimes encountered in clinical HRM studies (Fig. 4.2). This can be seen on occasion in conjunction with exaggerated or hypercontractile esophageal body metrics (jackhammer esophagus), when the pathophysiology is expected to be similar to that of exaggerated esophageal body contraction [52]. However, this can be an isolated finding with a normal esophageal body, and with adequate relaxation of the EGJ with swallows. The true significance of a hypertensive LES is unclear; structural processes at the EGJ (e.g., intrinsic, intramural, or extrinsic compression, paraesophageal hernia) will need exclusion when this is encountered.

Other Nonspecific Disorders

Characteristic motor abnormalities can be encountered on esophageal motor testing in the setting of rumination and gastric and supragastric belching [53, 54]. These are behavioral disorders,

and can be suspected on the basis of clinical history and presentation, particularly the association with background anxiety, stressful life events, and noxious gut stimuli [55, 56]. Rumination is a learned behavior, with volitional contraction of the abdominal muscles, sharply increasing intra-abdominal pressure and forcing gastric content up the esophagus into the mouth [55]. Supragastric or gastric belching starts with influx of air into the esophagus and stomach by contracting the diaphragm, followed by contraction of the abdominal and thoracic muscles to force air back out the form of a belch [57].

Characteristic findings can be diagnostic on esophageal motor testing for both rumination and supragastric belching [57–63]. Diagnosis can be made on both conventional manometry and HRM; concurrent impedance helps by identification of direction of movement of air and gastric content with pressure events [58, 62]. Adding a postprandial measurement period to motor testing can enhance diagnosis of rumination.

A supragastric belch is identified as rapid influx of air into the esophagus, followed by immediate retrograde expulsion of the air [57]. Two patterns are described: (a) negative intrathoracic pressure from diaphragmatic contraction creating air movement into the esophagus, followed by rapid and repeated belches, and (b) air swallowing, followed by volitional increase in intra-abdominal pressure triggering less frequent belching, similar to rumination [62]. Rumination is diagnosed on the basis of simultaneous increase in intra-abdominal pressure (*r* wave), manifest during diaphragmatic relaxation and immediately prior to retrograde flow of gastric content into the esophagus. Rumination can occur following the onset of a reflux event or following a supragastric belch, in which instance rumination is termed secondary.

Summary

While extreme motor disorders of the esophageal body and EGJ are well characterized and classified under the current version of the Chicago Classification, several other "nonspecific" patterns are not well described. These patterns may have implications on symptoms, but are not pathognomonic of disease in many instances. Therefore, further study is needed to determine the true clinical significance of nonspecific disorders, but it is essential to report these disorders in the context of clinical and research studies.

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Scleroderma Esophagus

5

David A. Katzka

I Have Just Been Told That I Have Scleroderma and It Can Affect the Esophagus. What Should I Expect?

Review of the Literature

Scleroderma is a complex autoimmune disease of unclear etiology [1]. It consists of an autoimmune-driven chronic inflammatory response that leads to collagen deposition and tissue fibrosis. Environmental factors such as silica, solvents, and other chemicals have been implicated in the pathogenesis but it is likely a genetic predisposition is also present. For example, multiple abnormalities of specific human leukocyte antigen loci have been associated with scleroderma. Although abnormalities in genes that regulate fibrosis have been found in animal models of scleroderma, these have not been consistently found in human studies. More convincing evidence exists for abnormalities in type 1 interferon and genes that are involved in antigen presentation to T and B cells in patients with the disease. STAT4, which plays a major role in an inflammatory model of fibrosis, may also be abnormally expressed. This pathway in coordination with other areas of inflammatory dysregulation leads to fibrosis of skin, tendons, heart, and organs with smooth muscle such as blood vessels, lungs, and gut. It is particularly the hyperreactivity of vasculature with subsequent ischemia and oxidative stress that leads to end-organ injury.

Scleroderma is more common in women than men and more prominent in middle age. Scleroderma may be classified into disorders of limited skin involvement (lSSC), skin and esophageal involvement (calcinosis, Raynaud's, esophagus, skin, telangiectasias), and diffuse involvement of skin and internal organs (dSSc). The diagnosis is made by the finding of compatible clinical findings in association with Raynaud's phenomenon and positive antinuclear antibody, Anti-Scl 70 (antitopoisomerase-1), and anti-centromere antibodies in up to 95% of patients. As the distal two-thirds of the esophagus are composed of smooth muscle (as is the remainder of the luminal gastrointestinal tract), esophageal involvement is common.

How Commonly Does It Involve the Esophagus?

The likelihood of scleroderma affecting the esophagus varies by the type of assessment used to define esophageal involvement. In a recent study combining newly and previously diagnosed patients with scleroderma, esophageal

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symptoms were present in 39 cases (69.6%), reflux esophagitis in 17 cases (32.7%), manometric abnormalities in 32 cases (68.1%), and abnormal reflux in 33 cases (80.5%) on ambulatory pH monitoring [2]. In another study using high-resolution manometry, esophageal body dysmotility was present in 33 patients (67.3%) while symptoms were present in 87.5% [3]. Interestingly, correlation between the presence of symptoms and manometric abnormalities was poor. On biopsy, atrophy in the circular smooth muscle was found in 93% of cases [4]. Diffuse esophageal skin involvement, presence of Scl70, and absence of ACA are associated with esophageal involvement.

What Are the Symptoms of Scleroderma When It Involves the Esophagus?

Scleroderma specifically affects esophageal function by reducing and often eliminating esophageal peristalsis and by decreasing lower esophageal sphincter pressure. As a result, patients most commonly develop symptoms of heartburn and regurgitation due to an incompetent lower esophageal sphincter and poor esophageal clearance. Dysphagia is due to poor esophageal transit and sometimes peptic strictures developing as a result of acid reflux.

How Is Esophageal Involvement Diagnosed, What Tests Should Be Done?

The tests used to diagnose esophageal involvement are those used to typically evaluate esophageal symptoms in general. In contrast to most patients, however, scleroderma patients commonly undergo a staging esophageal manometry to determine the presence of gut involvement even without esophageal symptoms. Endoscopy is routinely performed to assess for the high prevalence of erosive esophagitis. Barium esophagography is helpful to better assess the degree of esophageal dilation-associated global esophageal hypokinesis as an adjunct to high-resolution esophageal impedance manometry. Ambulatory pH/impedance monitoring is not as often needed in scleroderma patients due to the high prevalence of esophagitis and the common baseline of esophageal involvement compared to patients with suspected idiopathic gastroesophageal reflux.

How Is Scleroderma Esophagus Treated?

Scleroderma esophagus is treated similarly to gastroesophageal reflux with one caveat in mind: symptoms can be severe and persistent due to the functional equivalent of a common cavity between the stomach and esophagus. As a result, high doses of proton pump inhibitors are commonly needed well beyond those used in routine GERD. Even in the presence of complete gastric acid suppression, these patients may still suffer from reflux due to the severe dysfunction of the lower esophageal sphincter that becomes indiscriminate to preventing the reflux of all gastric content whether acid or not. Unfortunately, scleroderma esophagus has always been considered a contraindication to fundoplication because of the high likelihood of unmanageable postoperative dysphagia. A study from 2007 challenged this concept to some degree with some success with fundoplication but greater efficacy from laparoscopic Roux-En-Y gastric bypass [5].

What Will Happen in the Long Run (If Treated and if Not Treated?)

Most patients with scleroderma can be managed with effective gastric acid control and lifestyle changes such as taking small frequent meals and avoiding meals before sleep. Nevertheless, the disease appears progressive with worsening dysmotility in time [6].

Two sequelae of chronic severe reflux that can occur in patients with scleroderma esophagus are Barrett's esophagus and pulmonary interstitial fibrosis. One study determined a

12.7% prevalence of Barrett's metaplasia in scleroderma patients [7] supporting prior literature. A follow-up study from this same group documented a 3% incidence of esophageal adenocarcinoma in scleroderma patients with Barrett's [8]. Interstitial pulmonary fibrosis is also a potential complication of gastroesophageal reflux in scleroderma [9] and worsens with increasing amounts of measured reflux [10].

Do I Need Special Follow-Up?

Patients with scleroderma and symptoms of gastroesophageal reflux need follow-up given the progressive nature of esophageal involvement and the need to control reflux for prevention of esophageal complications and lung disease. They will require endoscopic follow-up if Barrett's esophagus is present at baseline endoscopy.

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Globus Sensation

6

Ram Dickman and Doron Boltin

Question 1: What Is Globus Sensation and Why Did This Happen to Me?

Answer: First of all, you should know that globus sensation is a benign functional esophageal problem, not associated with severe life-threatening conditions. Globus sensation is a recurring or persistent feeling of a lump or foreign body in the throat. This sensation can come and go and it does not interfere with your eating and drinking that typically relieve your disturbing sensation. Globus sensation is a common problem and it is estimated that it accounts for almost 4% of patient visits to an ENT specialist. In one study it was found that globus sensation was reported, at least once in a lifetime, by up to 46% of otherwise healthy individuals. Globus affects women and men equally and can affect anyone of any age even though it is much more common in people of middle age. The cause of globus is uncertain, meaning we do not completely understand the cause of this condition. Furthermore, it is not completely understood why in someone with globus sensation, when trying to swallow saliva, swallowing is felt to be disordered (to the point they feel a sensation of a lump in the throat) and, when food is swallowed, swallowing occurs without any problem. The proposed mechanisms that may cause globus sensation include visceral hypersensitivity, motor abnormalities of the upper esophageal sphincter (UES), and psychological comorbidity. Although all have been associated with globus sensation, none of these mechanisms is based on robust evidence. As a result, there are no widely accepted standard investigations or treatment strategies for this disorder.

Brief Review of Literature

Definition

Globus sensation is a recurring or persistent feeling of a lump or foreign body in the throat [1]. This may also manifest as feeling of a retained food bolus or tightness in the midline between the thyroid cartilage and sternal notch. Globus sensation is not associated with painful swallowing (odynophagia) or difficulty in swallowing food (dysphagia). It should be noted that patients with globus sensation report that symptoms occur primarily when swallowing saliva (dry swallow) or in between meals.

According to the most recent diagnostic criteria for functional esophageal disorders (Rome IV, 2016) globus requires the absence of an underlying structural lesion, GERD, mucosal abnormalities such as a gastric inlet patch (heterotropic gastric mucosa in the upper esophagus), or an esophageal motility disorder [2].

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Epidemiology

Globus sensation is considered to be quite common but there are not enough reliable clinical studies to estimate the actual prevalence of this disorder. It is estimated that globus accounts for almost 4% of visits to ENT specialists. In one study, globus sensation was reported (at least once) by up to 46% of 147 apparently healthy individuals [3]. Globus sensation is prevalent equally in men and women; however women are more likely to seek health care for this sensation. It is most common in individuals of middle age but it can affect anyone of any age. It is more common in urban dwellers compared to those who live in a rural environment. Globus sensation is a chronic condition as symptoms persist for more than 3 years in most of the patients (75%) and even after 7 years in almost half of them.

Pathophysiology

Although the pathophysiology is unclear, there are several theories including visceral hypersensitivity, gastroesophageal reflux, esophageal motor disorder, and psychological comorbidity.

Visceral Hypersensitivity

This refers to a phenomenon whereby normal stimuli or signals which are derived from the throat and transmitted to the brain undergo pathological processing in the central nervous system (CNS) during which the input is abnormally amplified. This information is translated into an unpleasant sensation such as globus (lump or tightness in the throat). Evidence for the mechanism of visceral hypersensitivity in patients with globus sensation is derived from well-designed clinical studies that assessed the response to esophageal balloon distention. From these studies it was demonstrated that compared with healthy controls, patients with globus sensation reported of symptoms at lower distending thresholds, suggesting the presence of esophageal hypersensitivity [4]. In another study, as compared with healthy controls, only patients with globus reported that during esophageal balloon distention they felt globus sensation in the suprasternal notch, suggesting that globus may represent an aberrant central processing of esophageal stimuli.

Esophageal Dysmotility

Patients with globus sensation have been assessed by stationary esophageal manometry in an attempt to find clues for a possible motoric dysfunction which might explain the occurrence of symptoms. Thus far, however, results have not shown any consistent evidence which attributes globus to malfunction of the upper esophageal sphincter (UES). There have been some reports of abnormal UES function such as hypercontractility of the UES (hypertensive UES). However, in more recent studies that employ high-resolution manometry (HRM), these findings were not confirmed, and researchers found no difference in UES mechanics between controls and those with globus sensation [5]. Recently, high-resolution manometry has revealed a number of patterns of UES pathology, including hyperdynamic upper esophageal sphincter inspiratory pressure and high upper esophageal sphincter post-swallow residual pressure among patients with globus. Although these might correlate with symptoms, there is no evidence that these findings are related to disease pathogenesis. Furthermore, in the face of a completely normal food-induced oropharyngeal swallowing process, the issue of a major esophageal motor disorder does not seem to be likely. The same holds true for an anatomic abnormality, including the cricopharyngeal bar, as the anatomy of the oropharyngeal cavity in patients with globus sensation is completely normal.

Gastroesophageal Reflux

Globus may itself represent an atypical manifestation of the GERD spectrum and as a result more patients with globus sensation report also of reflux symptoms. For this reason GERD must be thoroughly excluded prior to establishing a diagnosis of globus sensation. According to the recent Rome IV consensus for the diagnosis of globus sensation (described below) even a potentially acid-producing esophageal inlet patch of heterotropic gastric mucosa precludes a diagnosis of globus sensation. Thus far a strong causal relationship between GERD and globus has not been established [6]. In fact, the response rate of globus sensation to PPI therapy is low and there is only anecdotal evidence that patients with globus

are more likely than controls to have abnormal pH studies. Overall, it seems that GERD plays a minor role in the pathophysiology of globus meaning that if a PPI trial succeeds the diagnosis is GERD with globus and if not one should evaluate for other etiologies, mainly major esophageal motor disorder and psychological comorbidity that induces globus sensation.

Psychiatric Comorbidity

Psychiatric illness, particularly anxiety and depression, is common in patients with globus sensation and may predispose, precipitate, exacerbate, or perpetuate symptoms. By using self-reported questionnaires that evaluate for neuroticism, introversion, anxiety, and depression, it was found that patients with globus sensation score higher than healthy controls [7, 8]. In addition, women with globus sensation demonstrated a higher prevalence of anxiety and somatic concerns [9–11]. However, despite the aforementioned observations, no specific psychological characteristic or specific "hysterical" personality traits have been identified in patients with globus. Thus, the commonly used term "globus hystericus" is a misnomer and should no longer be applied [12]. Stressful life events that preceded the onset of globus have been reported in the literature, suggesting stress as a risk factor in globus generation or exacerbation [9]. In fact, acute stress has been reported in the majority (97%) of sufferers as a precipitating factor of globus exacerbation.

Other Associations

An association between chronic thyroiditis and globus sensation has been described in many observational studies. In a recent cohort of 92 subjects attending a thyroid clinic, 35% reported globus sensation and 39% had ultrasonographic evidence of chronic thyroiditis [13]. Overall, the risk of globus sensation was calculated as 3.7-fold higher in patients with chronic thyroiditis. Secondly, sleep disorders are associated with globus sensation. In a cohort of 3360 healthy volunteers, sleep disorders were present in a significantly higher proportion of those reporting globus sensation (23.7%), compared to 13.6% among those with globus sensation [14]. Thirdly, globus sensation can occasionally be a result of pharyngeal, laryngeal, or upper esophageal pathology, including cysts and benign or malignant neoplasms. For this reason a thorough examination by an ENT surgeon is the recommended first step for the investigation of globus sensation.

Question 2: How Is Globus Diagnosed, What Tests Should Be Done?

Answer: Investigation includes as first steps a careful history taking and naso-oral inspection, performed by an ENT specialist, preferably using a laryngoscope. Globus sensation is considered a "diagnosis of exclusion." This means that there is no specific test which confirms this condition. Instead, the diagnosis is made after having tests to be sure that you do not have a more serious condition.

If there is no finding in your examination by the ENT specialist, the next step is to start treatment with PPIs, twice daily, half an hour before a meal, and on empty stomach. Treatment should be continued for a period of 1–2 months. In the case your symptoms improved, your diagnosis is GERD with globus and you should continue PPI therapy with the lower effective dose. In the case of treatment failure, it is recommended to perform an upper endoscopy and esophageal manometry to rule out structural and motility disorders of the esophagus.

Brief Review of Literature: Clinical Management

History and Physical Examination

Diagnosis is made primarily by a careful history taking and by excluding structural lesion, esophageal dysmotility, and GERD. In clinical practice, globus is highly suspected in patients with a sensation of a lump or foreign body in the throat and the absence of heartburn, regurgitation, dysphagia, and odynophagia (symptoms which suggest GERD and dysmotility). It is crucial to differentiate between globus sensation and dysphagia,

since dysphagia may implicate a more severe condition and consequently requires an invasive approach, early in the investigation stage. The diagnoses of odynophagia or weight loss need to be excluded as well. Examination by an ENT specialist is recommended as the first step. This should include physical examination of the neck (thyroid neck/tonsillar mass, cervical adenopathy) and examination of the pharynx by laryngoscope. Globus sensation can occur in association with other symptoms of laryngeal dysfunction such as hoarseness (especially in smokers that are at risk for laryngeal cancer) which should prompt ENT evaluation. The clinician should be alert for any risk factors of laryngeal malignancy, including a past history of neck or head radiation, smoking, and alcohol abuse. If present, a thorough ENT examination should be expedited.

The most widely accepted diagnostic criteria for globus sensation are the Rome IV (2016). Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least once a week [2]. All of the following three criteria must be fulfilled: (1) Persistent or intermittent, nonpainful, sensation of a lump or foreign body in the throat with no structural lesion identified on physical examination, laryngoscopy, or endoscopy. The sensation occurs between meals, and is not associated with dysphagia, odynophagia, or an esophageal inlet patch. (2) Gastroesophageal reflux or eosinophilic esophagitis is not the cause of the symptom. (3) Major esophageal motor disorders are not present (such as achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis).

Additional symptom assessment tools exist, such as the Glasgow-Edinburgh Throat Scale (GETS) [15]. The GETS is a ten-item questionnaire using terminologies such as "feeling of something stuck in the throat," "discomfort or irritation in the throat," and "wanting to swallow all the time." This tool may be useful for assessing patients who are unable to clearly express their symptoms, and also to track the magnitude of symptoms over time. The GETS has been validated in several languages and has a high internal consistency.

Investigation of Globus Sensation

Following a thorough history and examination, in the absence of pharyngeal structural or inflammatory lesions, the next step is to commence a PPI therapeutic trial. It is recommended to start with a double-dose PPI trial for 4–8 weeks, and according to the response, the next step will be treating GERD in the case your patient responds. Once a satisfactory treatment response has been established, the dose of PPI should then be reduced to the minimal dose still associated with a satisfactory treatment response. In the case the patient does not respond the next step is to order an upper GI endoscopy for the evaluation of mucosal lesions such as esophageal gastric inlet patch or other mucosal finding in the esophagus. In a recent cohort of patients with symptoms suggestive of globus, 52% had coexisting GERD-related symptoms and 44% ultimately responded to a PPI trial. Following upper GI endoscopy and 48-h wireless ambulatory pH monitoring, ultimately 70% were diagnosed with GERD and 30% fulfilled the diagnostic criteria for globus sensation [16].

At this stage, it is also advised to complete the evaluation with esophageal manometry in order to exclude a major esophageal motor disorder, which may manifest with globus-like symptoms. Recently, high-resolution manometry has been used to identify certain abnormal patterns of upper esophageal sphincter relaxation which seem to be unique to patients with globus sensation [17]. In one study, 24 patients with globus were compared to patients with nonobstructive dysphagia and to health controls. Upper esophageal sphincter post-swallow residual pressures were highest in patients with globus sensation, and 66.7% had recordable upper esophageal sphincter residual pressure, in contrast to 9.5% of controls, and 37.5% of dysphagia patients. In another study, the changes in upper esophageal sphincter pressure during respiration were analyzed. The basal upper esophageal sphincter pressure normally increases during respiration in healthy subjects. In patients with globus sensation, however, this pressure spike during respiration was found to be accentuated. This so-called hyperdynamic upper esophageal sphincter inspiratory pressure was present in about 60% of

patients with globus sensation, compared to less than 15% of subjects with GERD and healthy controls. These abnormal manometric measurements, particularly a high post-swallow residual pressure, have the potential, for the first time, to allow an objective assessment of patients with globus sensation, although further studies are needed before this measure can be used in the clinical setting.

Following high-resolution manometry, endoscopy, and PPI trial, patients not responding to PPI and without an identifiable cause in the oropharynx and esophagus are diagnosed with globus [2].

Additional diagnostic tests are occasionally needed in the case of diagnostic uncertainties and make part of a more detailed gastroenterological workup. In most cases these investigations are unnecessary. Such investigations may include a 24-h ambulatory esophageal pH and impedance study to assess for abnormal esophageal exposure to nonacidic reflux or persistent acid reflux in patients who fail to respond to a PPI trial. Other tests include videofluoroscopy to identify functional or structural abnormalities of the pharynx and neck computed tomography (CT) for patients with cervical adenopathy and goiter.

Question 3: How Is Globus Treated?

For you and for many people with globus sensation, having your symptoms explained may be all that you needed. Just knowing that you do not have a serious underlying problem like cancer can be very reassuring.

For others, various treatments may be suggested. For example:

- Physiotherapy for the muscles around the throat. You may be referred to a speech and language therapist for this type of physiotherapy.
- Treatment for GERD, including antacid medicines and PPIs
- Cessation of smoking.
- Treatment for stress, if this is a problem: This might involve prescription of an antidepressant tablet or participating in therapy sessions such as cognitive behavioral therapy (CBT).

Brief Review of Literature: Therapeutic Options

Non-pharmacological

There is currently no single treatment modality for globus sensation which is effective for all patients. However, once the diagnosis of globus is confirmed, reassuring the patient that there is no serious underlying problem may be all that is needed in terms of management.

In patients with dominant symptoms suggestive of anxiety or depression, it is recommended to refer for a psychiatric consultation. The psychiatric intervention is aimed to teach coping strategies for dealing with globus sensation [18]. Several psychological therapies have been proposed for the treatment of globus sensation although clinical evidence, where available, is based upon small, retrospective cohorts rather than well-designed prospective studies. Among ten women with globus sensation who participated in hypnotically assisted relaxation (HAR) therapy over 12 sessions, nine (90%) reported a reduction in globus symptomatology following treatment. Although this study is limited by serious methodological flaws, the authors concluded that this relaxation technique may be useful in managing patients with globus sensation who fail to respond to antireflux therapy [11].

Evidence for other psychological treatment modalities such as cognitive behavior therapy can be inferred from well-designed, prospective studies of patients with unexplained medical symptoms. Such studies include a heterogeneous patient population, many of whom have globus sensation as the dominant symptom. Overall globus sensation is the fourth most common manifestation of somatization or an unexplained medical condition, after vomiting, aphonia, and limb pain [19]. Overall, 11 out of 13 randomized, controlled trials assessing cognitive behavior therapy in this context found both a clinical benefit and cost-effectiveness.

Speech therapy may be effective in improving globus sensation. In a prospective non-blinded randomized controlled study including 36 subjects with globus, speech therapy techniques

were reported to be superior to simple reassurance and education [20].

Other non-pharmacological measures commonly advocated include smoking cessation. Although this is good advice for all, there are no data to support an improvement in globus sensation following smoking cessation.

Pharmacological

Medical therapy is aimed to treat GERD and psychological comorbidities. Firstly, a PPI trial, as previously mentioned, is an integral part of the diagnostic workup for patients reporting globus sensation and should include a double-dose PPI for 6–8 weeks. It is estimated that about one-third of patients with suspected GERD will experience partial relief of globus sensation [21].

Antidepressants are indicated for patients with persistent symptoms despite a PPI therapeutic trial and without evidence for esophageal dysmotility. The most extensive evidence for using this class of drug in the treatment of globus sensation is for the tricyclic antidepressant, amitriptyline. In a prospective, non-blinded randomized controlled trial including 34 patients, amitriptyline was found to improve globus sensation independently of a mood disorder [22]. In this study patients with Rome III confirmed globus sensation were randomly assigned to receive either 25 mg amitriptyline at bedtime or 40 mg pantoprazole once daily for 4 weeks. After 4 weeks, 75% of patients receiving amitriptyline reported a significant symptom response (defined as greater than 50% reduction in Glasgow-Edinburgh Throat Scale) as compared to only 36% response group who had a greater response rate among those receiving pantoprazole. In addition, the amitriptyline group was more likely than the pantoprazole group to experience improvement in sleep and quality of life. Unfortunately, treatment is limited by adverse effects, of which dry mouth, sleepiness, dizziness, and constipation are the most common. The precise mechanism of action of amitriptyline is unknown, although it is thought that the drug works as a neuromodulator, affecting the brain-gut axis by altering neurotransmitter systems within the limbic system and other pain centers of the brain, and ultimately reducing visceral hypersensitivity. This is achieved through indirect stimulation of norepinephrine and serotonin by inhibiting their reuptake in nerve synapses.

Antidepressants are indicated especially for those with somatization, depression, and anxiety. In patients with depression and globus sensation, antidepressants have shown to improve globus symptoms, sleep quality, and quality of life [10, 23, 24].

Gabapentin is an antiepileptic drug with an unknown mechanism of action, which in addition to controlling seizures has been found to be effective for controlling neuropathic pain and neurogenic cough. Although gabapentin has been used empirically for the treatment of globus sensation, well-designed prospective studies are lacking. In a retrospective cohort of 87 patients with globus sensation following PPI therapy for at least 2 months, patients were reviewed following at least 2 weeks of gabapentin 300 mg three times daily. Overall, 68% of patients responded to gabapentin therapy [25]. Although these results seem encouraging, clinicians should be aware of serious potential side effects associated with gabapentin treatment, including leukopenia, thrombocytopenia, ataxia, and withdrawal seizures.

Invasive Therapy

Endoscopic ablation of an esophageal inlet patch has been proposed as a treatment option for subjects with globus sensation. In a small multicenter randomized controlled trial 82% of subjects reported symptom improvement following ablation of heterotropic gastric mucosa in the upper esophagus, compared to 0% of those undergoing a sham procedure [26]. It should be noted that according to the recent Rome IV consensus statement, and in deference to this study, the presence of an esophageal inlet patch should be excluded before assigning a diagnosis of globus sensation.

Surgical therapy for refractory globus sensation has been described in a small retrospective cohort. Among 13 subjects who underwent a partial epiglottectomy, 12 were completely symptom free 1 year following the procedure [27]. Further studies are needed before surgical therapy can be incorporated into the treatment algorithm for globus sensation.

Summary

- Definition—globus sensation is a disturbing and recurring benign condition, described as a sensation of a lump, tightness, or retained food

bolus in the throat. Globus is a functional esophageal disorder that is not caused by GERD, esophageal motility disorder, structural lesion, or mucosal abnormality such as a gastric inlet patch or eosinophilic esophagitis (EoE).

- Etiology—there are no clear etiologies that underlie this condition. However, several possible pathogeneses have been described: GERD, visceral hypersensitivity, hypertensive upper esophageal sphincter (UES), and psychological comorbidities.
- Diagnosis—globus sensation is suspected in patients with typical symptoms and the absence of heartburn, regurgitation, dysphagia, or odynophagia. Patients should initially undergo a complete history and physical examination by an ENT specialist (that includes examination of the oropharynx and larynx). A definitive diagnosis of globus sensation requires the fulfillment of the Rome IV criteria for functional esophageal disorders that appear in the text.
- Management—reassurance may serve as the single best and first therapeutic measure. In those with concomitant psychiatric morbidity, a consultation with a psychiatrist may be helpful. Medical therapy includes double-dose PPI empirical trial for 1–2 months. In the case of failure it is recommended to undergo upper GI endoscopy for the exclusion of mucosal lesions such as esophageal gastric inlet patch, and esophageal manometry for the exclusion of a major esophageal motor disorder. Patients not responding to PPI and without an identifiable cause in the oropharynx and esophagus are diagnosed with globus. Amitriptyline (tricyclic antidepressant) has been found to be effective in patients with persistent symptoms that are not relieved by PPIs.

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UES Restrictive Disorders

7

Ling Mei and Patrick Sanvanson

Why Do I Have Coughing and Choking Right After Eating? Epidemiology and Pathophysiology of UES Restrictive Disorders

Suggested Response to the Patients

Frequent coughing and choking right after eating could be a sign of a swallowing disorder, also called dysphagia. The swallowing process is complex and involves the following different stages: Oral phase refers to sucking, chewing, and moving food or liquid down to the throat; pharyngeal phase is the transport of the bolus down the throat and closing off the airway to prevent food or liquid from entering the airway or to prevent choking; esophageal phase involves propagation food bolus downwards through the esophagus into the stomach due to its rhythmic contraction. An important muscular structure located at the top of the esophagus, called the upper esophageal sphincter (UES), isolates the pharynx from the esophagus. The opening of this sphincter is tightly timed to open when a bolus of food and liquid reach it. The sphincter is normally closed and then relaxes during pharyngeal swallowing and then closes again as the food moves down in the esophagus towards the stomach. Disease conditions that limit adequate opening of the UES during swallowing will result in bolus residue in the pharynx and therefore increase the risk of aspiration of food and liquid into the airway as well as into the nasal passage. If this happens, individuals will experience choking or coughing right after eating or drinking. A number of intrinsic disorders of the UES can cause diminished or failed UES opening, such as Zenker's diverticulum, cricopharyngeal bar, and cricopharyngeal achalasia, causing resistance to bolus flow from the pharynx to the esophagus.

Zenker's diverticulum is an esophageal pouch that forms at the back of throat at the junction of the pharynx and esophagus typically in older patients. The cricopharyngeal bar is a frequent incidental radiologic finding, which in many cases does not cause symptoms. It is present in 5–19% of patients who undergo pharyngeal radiography. Both Zenker's diverticulum and cricopharyngeal bar are related to the fibrosis of the UES that results in diminished compliance and restricted opening of the UES. Increased flow resistance during swallow results in high pressure between the pharynx and esophagus, which facilitates the pouch formation in the area where the muscle is weak. Both conditions are almost uniformly seen in

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the elderly. The prevalence of Zenker's diverticulum in the United States ranges from 0.01 to 0.11% of the population. Cricopharyngeal achalasia is a consequence of impaired neural mediated relaxation of the UES. There are diverse causes of cricopharyngeal achalasia, such as stroke, Parkinson's disease, and Alzheimer's disease. The true incidence of the disease is unknown.

Brief Review of Literature

The UES is a complex muscle structure that is composed of the cricopharyngeus muscle (CP), the inferior pharyngeal constrictor muscle, and the proximal cervical esophagus in the pharyngo-esophageal junction [1–5]. It plays an important role in the swallowing process and marks the transition from pharyngeal deglutitive phase to the esophageal phase. Adequate UES opening is therefore essential for an effective swallow. UES opening requires coordination of several factors: UES relaxation, anterior laryngeal traction, UES distensibility, bolus propulsion, and bolus size [1–8]. Failed or diminished UES opening results in incomplete pharyngeal clearance, post-deglutitive residual, and potential post-deglutitive aspiration. Disordered UES opening can be the result of abnormal UES distensibility, such as Zenker's diverticulum, cricopharyngeal bar, or lack of neural relaxation, such as cricopharyngeal achalasia. Alternatively, it can be due to weak pharyngeal propulsion alone or in addition to failed UES relaxation. For this review, we focus on intrinsic UES restrictive disorders.

Zenker's Diverticulum

Zenker's diverticulum is protruding of the mucosa and submucosa through the posterior hypopharyngeal wall at an area of muscular weakness (Killian's dehiscence) between the lower fibers of the inferior constrictor muscle and the upper fibers of the cricopharyngeus. The first case of posterior pharyngeal diverticulum was described by Ludlow in 1767 [9]. Zenker and von Ziemssen did a systematic review of this entity one century later [10]. Since then, this kind of diverticulum was called Zenker's diverticulum. A complete understanding of the etiology of Zenker's diverticulum formation is not available yet. The disease is thought to be related to esophageal motor dysfunction.

It has been reported that the annual incidence of symptomatic Zenker's diverticulum is 2 per 100,000 people per year in the United Kingdom [11]. The prevalence of Zenker's diverticulum in the United States ranges from 0.01 to 0.11% in the population [12]. It is more common in males than females by a ratio of 1.5:1. It rarely occurs in patients younger than 40 and extremely rare under the age of 30. The median age of presentation is in the seventh to eighth decades of life [13, 14]. Congenital pharyngeal pouches have been reported, suggesting that a congenitally weakened Killian's triangle may be a contributing factor in some cases [15, 16]. There is geographic difference of the disease occurrence and it appears to be more common in North America, Northern Europe, and Australia than southern Europe and Asia [17].

Current combined videoradiographic and pharyngeal manometric data support the hypotheses that the formation of Zenker's diverticulum is due to a poorly compliant but normally relaxing UES, which cannot be fully distended during the process of sphincter opening [13, 18]. This leads to abnormal high intrabolus pressure during the phase of trans-sphincteric bolus flow. Pressure imparted to the area of relative muscle weakness (Killian's dehiscence) predisposes to posterior herniation of the pouch over many years [13]. One study compared the cricopharyngeus and inferior constrictor muscle strips in patients with Zenker's diverticulum to controls obtained at autopsy from non-dysphagic individuals. The results showed histologic changes in muscle fibers in Zenker's diverticulum, including increased collagen content, fibroadipose tissue replacement, and fiber degeneration [19, 20]. These morphologic changes in the cricopharyngeus muscle affect contractile and elastic properties of the muscle and account for its restricted opening. In vitro, isolated cricopharyngeus muscle strip from patients with Zenker's demonstrated diminished time to peak twitch, reduced

contractile velocity, and lowered amplitude contractions when compared with controls [21, 22]. The aging process might play a role because of the loss of tissue elasticity and the decrease in muscle tone.

Cricopharyngeal Bar

The cricopharyngeus muscle (CP) is a major component of the upper esophageal sphincter, where it spans between 2.5 and 4.5 cm in length to prevent reflux of gastric contents and allows bolus passage during swallowing [23]. Dynamic function and coordinated relaxation of CP muscle are essential for successful bolus transfer from pharynx to esophagus. Dysfunction of CP muscle encompasses a broad spectrum of clinical manifestations and pathologies. The spectrum of presentation ranges from asymptomatic to severe dysphagia. CP bar refers to the radiographic appearance of a posterior indentation of the esophageal lumen between cervical vertebrae 3 and 6 during barium swallow, partially occluding the lumen of the upper esophageal inlet, and is best visualized in the lateral view [24–26]. It mostly represents an incidental finding on radiographic study and usually does not cause symptom. It is rarely a cause for dysphagia.

A CP bar is present in 5–19% of patients who undergo dynamic pharyngeal radiography [27]. Approximately 13% of these patients have dysphagia [28]. It is almost always seen in elderly subjects [24].

The pathophysiology of the CP bar is not completely understood and several etiological factors have been implicated. CP bar can occur secondary to decreased compliance of CP muscle by fibrosis, incoordination, or congenital weakness of CP muscle [4, 25, 27, 29]. Recent studies of inflammatory myopathy and dysphagia noted increased prevalence of a CP bar and stenosis in patients with dysphagia due to polymyositis or dermatomyositis [30, 31]. CP bar, seen mostly in the elderly, is not a direct result of the aging process, but may be a consequence of the increased prevalence of the neuromuscular disorders or systemic and degenerative processes in the elderly [32, 33]. Investigation by manometry and videofluoroscopy showed normal UES relaxation, normal flow rate across the UES, normal UES resting tone, and hyoid and laryngeal movement in the subjects with CP bar [25, 34]. The major abnormalities in the patients with CP bar are reduced maximal dimensions of UES during the trans-sphincteric flow secondary to decreased passive compliance of UES, and increased intrabolus pressure in the hypopharynx. Thus, the increase in intrabolus pressure preserves normal trans-sphincteric flow rates even though the UES does not open normally [35]. This situation may contribute to the development of Zenker's diverticulum in some patients. Histologic alteration of CP bar from patients undergoing myotomy includes degeneration and regeneration in the muscle fibers of CP with interstitial fibrosis [36].

Cricopharyngeal Achalasia

Cricopharyngeal achalasia (CA) or UES achalasia is a condition characterized by incomplete relaxation of the UES, or by a lack of coordination of the UES opening with pharyngeal contraction. It can arise from intrinsic problems confined to the muscle or from underlying neurologic dysfunction causing high UES tone. The term of CA is somewhat a confusing entity and has been inappropriately used in many instances to describe the radiologic abnormality of incomplete UES opening, such as seen in CP bar. Indeed, manometric studies from pharyngoesophageal segment in CP bar have demonstrated normal UES resting tone and normal relaxation in response to deglutition. There is also no specific finding to correlate with failed UES relaxation in radiography.

The exact incidence of CA is unknown. The lack of epidemiologic data results from the significant controversy regarding the diagnostic criteria required for proper use of the term cricopharyngeal achalasia. The literature reports CA as the primary cause of or as a contributor to dysphagia in 5–25% of patients being evaluated for clinical symptoms of dysphagia [37].

The UES is a skeletal muscle structure and is innervated by excitatory neurons residing in the nucleus ambiguous. The activation of motor

neurons is through the neurotransmitter acetylcholine, by acting on nicotinic receptors at the neuromuscular junction. Resting tone in UES is dependent on tonic input from excitatory neurons. Inhibition of tonic firing of excitatory neurons results in UES relaxation during deglutition. The central generator of swallowing resides within the medulla of the brain stem [38]. During deglutition, normal relaxation of the UES depends on complete and adequate inhibition of muscle tone and accurate coordination with pharyngeal activity in a swallow event. UES relaxation has to occur at a correct time, which is during superior laryngeal excursion and before opening by an average 0.1 s [39]. The UES relaxes during the apogee of UES movement, facilitating the entry of bolus into the UES. Destruction of the neuronal circuit of swallowing, which could involve any of the followings, medullary interneurons, efferent pathways carrying signals away from cortical swallowing centers, and afferent pathways transmitting sensory information to the central generator, may result in UES spasm and impairment of relaxation [3, 5, 39].

Primary CA refers to the abnormality that leads to the persistent spasm or failure of relaxation of the cricopharyngeus muscle that is confined to the muscle, with no underlying neurologic or systemic cause. In many instances, failed UES relaxation is secondary to neurologic disorders such as cortical stroke, lateral medullary stroke, Parkinson's disease, cerebral palsy, amyotrophic lateral sclerosis, myasthenia gravis, Arnold-Chiari malformation, multiple sclerosis, inclusion body myositis, and post-polio syndrome.

Four abnormal patterns of CP activities during deglutition have been observed: (1) incomplete relaxation that blocks the passage of the food bolus into the cervical esophagus; (2) abnormally short duration of complete relaxation; (3) abnormal hypertonic cricopharyngeus during the normal interval of inhibition; and (4) lack of coordination between the pharyngeal propulsion and the cricopharyngeal relaxation [39].

Histologic analysis of surgical specimens in CA patients has shown both striated muscle fibrosis and hypertrophy in the cricopharyngeus muscle [40].

What Are the Symptoms If My UES Does Not Open Normally During Swallowing and How Do You Diagnose It? Clinical Features and Diagnosis of UES Restrictive Disorders

Suggested Response to the Patients

Clinical symptoms for individuals with impaired UES opening vary. Depending on the level of UES restriction and whether or not other contributing factors to dysphagia coexist, e.g., weak pharynx, individuals may be totally asymptomatic to varying degree of difficulty swallowing. Common complaints may include coughing or choking right after eating or drinking, gurgling sound or voice after eating, and extra effort or time needed to chew or swallow. Other symptoms may include regurgitation of undigested food, feeling a lump in the throat, or recurrent pneumonia. As a result, individuals may have poor nutrition, dehydration, risk of aspiration, and chronic lung disease.

The major diagnostic tool is the barium swallow with videofluoroscopy. Individual eats or drinks food or liquid with barium in it, and then the swallowing process is viewed on an X-ray. Endoscopic evaluation of the pharynx and esophagus is to rule out complications and other intraluminal etiologies that may count for or contribute to dysphagia. Esophageal manometry is a tool to evaluate pressure changes that occur during swallowing. It is also used to assess the function of the UES.

Brief Review of Literature

Zenker's Diverticulum

Classical symptoms of Zenker's diverticulum are progressive oropharyngeal dysphagia, and regurgitation (often hours after ingestion) of undigested food debris due to food entrapment in the diverticulum. Eighty percent of the patients have complained of regurgitation of undigested food [22, 41]. Patients may present with chronic cough, chronic aspiration, foul breath, audible gurgling in the throat, sensation of a lump in the

throat, and hoarseness. Weight loss can happen in patients with long-standing dysphagia. The duration of symptoms prior to presentation varies from weeks to many years.

Squamous cell carcinoma complicating a pouch has been reported with an incidence between 0.4 and 1.5% [42, 43]. Chronic inflammation due to food stasis may attribute to the malignant changes. Malignancy should be suspected if there is a sudden change in the severity of symptoms or development of alarm symptoms (hemoptysis, hematemesis, or local pain). Other rare complications include bleeding [44, 45], benign ulceration of the mucosa within the pouch probably secondary to acid reflux or aspirin use [46], bezoar formation, and fistula formation. Due to the risk of perforation during endoscopy or passage of nasogastric tube in patients with known Zenker's diverticulum, it is advisable to intubate the esophagus under direct visualization.

The mainstay diagnosis is the barium swallow with videofluoroscopy. This dynamic study provides information about the size and location of the Zenker's diverticulum. In addition, it can help to detect pharyngeal dysfunction that might contribute to the patient's dysphagia. The esophagus should also be carefully examined in the radiographic study since coexistent pathology might account for the patient's dysphagia or regurgitation. Endoscopic techniques have limited diagnostic capability, as the opening of the pouch is not always apparent endoscopically. If a constant filling defect is seen radiographically, endoscopy is needed to rule out malignancy. Esophageal manometry is usually not required.

Cricopharyngeal Bar

Most of the time, CP bar is an incidental finding on pharyngeal radiography. It usually does not cause any symptoms, but when it becomes symptomatic, oropharyngeal dysphagia is the most frequent complaint. Depending on the swallow function, symptoms can vary from diet modification and/or prolonged mealtime to cough, aspiration, weight loss, or non-oral feeding. The CP bar is more frequently associated with dysphagia when there is a marked obstructive bar with narrowing of the UES lumen [47], when a Zenker's diverticulum is present, or when the patient has current pharyngeal weakness [25].

The diagnosis of CP bar includes videofluoroscopic, endoscopic, and manometric evaluation. CP bar is seen in the barium swallow as a posterior indentation in the barium column between cervical vertebrae 3 and 6 that persists throughout the swallow [24]. Recent interest in high-resolution manometric study of the UES and pharynx has improved our understanding of the motility alteration in CP bar. Manometry is not an essential for diagnosis, but will show an increase in intrabolus pressure suggesting increased flow resistance [48]. The UES relaxation and pharyngeal contraction are normal. A CP bar is difficult to appreciate on endoscopic examination; however, endoscopic evaluation is essential to rule out malignancy or other causes of dysphagia.

Cricopharyngeal Achalasia

The clinical presentation of CA is nonspecific and quite variable. Symptoms may have an abrupt or gradually progressive onset going on for months or years. Most patients complain of food sticking or catching in the lower part of the neck. Solid dysphagia seems more common than liquid dysphagia. "Stringy" foods like noodles or vegetable leaves seem to be particularly challenging [39]. Patients may also experience heartburn, choking, and odynophagia. Less common symptoms include dysphonia, globus sensation, and pressure in the neck during deglutition. Pulmonary symptoms like aspiration pneumonia usually result from aspiration of ingested food retained in the hypopharynx above a non-relaxing UES. In severe dysphagia, weight loss, starvation, and dehydration could occur.

Videofluoroscopic swallow remains the mainstay for diagnosis in the patients with symptoms suggestive of CA. It can demonstrate reduced opening of the pharyngoesophageal segment and dilated pharynx with holdup of the contrast bolus. Videofluoroscopy can also detect other disturbances in function, such as abnormal tongue strength or movement, impaired hypolaryngeal elevation, nasopharyngeal regurgitation, or aspiration. However, as mentioned before, there is no

specific radiologic finding indicative of failed UES relaxation. Besides CP relaxation, UES opening also relies on anterior laryngeal elevation, UES distensibility, bolus propulsion, and bolus size. Any or combined abnormalities of these conditions can result in impaired UES opening and hypopharyngeal bolus retention.

When appropriately utilized, esophageal manometry can be helpful in the diagnosis of CA by demonstrating impaired UES deglutitive relaxation and inappropriate contraction during the normal period of motor quiescence [49]. It can assess the coordination of UES relaxation with hypopharyngeal contraction during swallow. Typical manometric findings in CA include elevated deglutitive UES nadir pressure, reduced interval of UES relaxation, and elevated hypopharyngeal intrabolus pressure. One shortcoming of the manometric study is that it cannot assess for the presence of many other conditions that can cause symptoms similar to CA; therefore, it is not sufficient for diagnosis of CA by itself without additional information from radiologic study to rule out other causes.

Endoscopic evaluation is generally not helpful in the diagnosis of CA. In some occasions, tight entrance to the esophagus at the level of UES may raise the suspicion of CA; however, this finding is nonspecific. The main role of endoscopy is to rule out other conditions that may cause similar symptoms.

What Are the Treatment Options Available? Therapy for UES Restrictive Disorders

Suggested Response to the Patients

Treatment depends on the symptom and cause of the swallowing problems. There is no treatment required for asymptomatic patients. Mild dysphagia could be managed by modifying diet, avoiding food that causes problems, or changing the consistency of the diet. In individuals with Zenker's diverticulum, management depends on the local expertise, patient's age, and size of the diverticulum. Intervention could be open surgical repair or endoscopic repair. The latter has been increasingly adopted as a main treatment option among otolaryngology specialists in the United States since it is proven to be less invasive and has similar efficacy compared to surgery. Other treatment options for UES restrictive disorders include endoscopic dilation, botulinum toxin injection, and surgical myotomy. The purpose of these treatments is to relieve the UES obstruction. Endoscopic dilation and botulinum toxin injection are effective treatment options, but may need to be repeated at different intervals to achieve long-term effect.

Brief Review of Literature

Zenker's Diverticulum

Zenker's diverticula require intervention only if they produce symptoms. Small asymptomatic diverticula do not need treatment, as the risk of severe adverse complications, cancer, and aspiration is low. Open surgeries, which include CP myotomy alone, diverticulectomy, diverticulopexy, or diverticular inversion, all with or without current CP myotomy, have long been the conventional treatments with a high success rate, but are associated with high morbidity and mortality [50–54]. Since Zenker's diverticulum mainly affects elderly patients accompanied by multiple comorbidities, less invasive treatments are favored. In recent years, endoscopic repair of Zenker's diverticulum has been found to be a viable safe and effective alternative to surgery and gained widespread acceptance. When compared to open stapler-assisted diverticulectomy and CP myotomy, endoscopic staple-assisted diverticulostomy (ESAD) are associated with shorter operative times, shorter postoperative hospital stays, quick resumption of oral intake, and few complications, such as recurrent laryngeal nerve injury and bleeding [54, 55]. In many centers, EASD is performed as an outpatient procedure in appropriately selected patients. Flexible endoscopic approach consists of cutting

the septum between the diverticulum and the esophageal lumen, as the septum contains part of the cricopharyngeal mask [56–58]. The objective is to create a common room between the sac of the diverticulum and the esophagus, so that food can pass more easily into the esophagus. In the meanwhile, it helps to reduce the local pressure of the cricopharyngeal muscle. It has been reported that symptom relief or improvement was achieved in 89–96% of patients under EASD with recurrence ranging from 0 to 9% [55]. Factors that most often precluded a successful endoscopic approach were a patient's inability to open their mouth fully, extend their neck completely, or a shallow diverticula sac (<3 cm) that precludes full engagement of the entire CP muscle in the common wall by the stapler [55].

Cricopharyngeal Bar

The goal for treatment of a symptomatic CP bar is to increase the UES diameter during swallowing. If the CP bar does not cause symptoms or the bar is not the culprit for dysphagia, there is no need to treat it. Treatment options include endoscopic dilation, botulinum toxin injection, and surgical myotomy. Since this patient population is usually elderly with multiple comorbidities and high risk for perioperative complications, nonsurgical interventions are more preferred than surgical treatments. Though botulinum injection and CP dilation have been reported to be highly effective and safe, CP myotomy has remained as the gold standard treatment of CP bar.

Botulinum toxin A injection to the cricopharyngeus muscle under direct vision has been utilized since 1994 with success rate ranging from 43 to 100% [59]. Repeated injections are often necessary to achieve or maintain a good effect. Botulinum toxin injection works best in patients with impaired relaxation of the CP muscle, and is partially or not effective in structural stenosis of UES caused by persistent hypertrophy or restricting fibrosis, which is usually the case in patients with CP bar [25]. Diffusion of the toxin to adjacent muscle may worsen dysphagia or cause vocal cord dysfunction. Controlled trials are needed to determine the safety and efficacy of the use of botulinum toxin.

Dilatation of the cricopharyngeus muscle may be performed using either a balloon dilator or bougie dilator (Savary–Gilliard dilator). Both techniques have been broadly used clinically and proved to be safe and effective, although half of the patients experienced short-term recurrence and required repeated dilation over many years in order to maintain symptomatic improvement [34, 60–62]. It has thus been suggested that dilatation might be used as a first-line intervention, prior to more definitive management. Balloon dilation of the UES is a low-risk option that serves best in patients with fibrosis of the CP, which is usually the case in patients with CP bar.

CP myotomy has been a traditional treatment option for CP dysfunction. It helps to normalize UES opening and may improve pharyngeal contraction [63, 64]. It serves best in patients with structural UES disorders that constrict its opening, such as CP bar and Zenker's diverticulum. UES opening showed better improvement with CP myotomy than with dilation or botulinum toxin [64]. The success rates range from 50% in patients with dysphagia secondary to neurogenic etiologies to 98% in Zenker's diverticulum [65, 66]. In a report by Dauer et al., including 14 patients that underwent CP myotomy, 5 of 7 with idiopathic CP bar were completely asymptomatic postoperatively, while all of the 3 patients with concomitant systematic neurologic disorders had postoperative Functional Outcome Swallowing Scale (FOSS) score greater than 3 [67]. CP myotomy can be performed as open or endoscopic approach. The two techniques have a similar success rate, but endoscopic CP myotomy is associated with shorter operative times, more rapid postoperative recovery, and lower risk of major complications.

Cricopharyngeal Achalasia

Dietary modifications are usually the initial step if the symptoms are provoked by certain foods. These foods should be avoided or their consistency modified. For patients with solid and pill

dysphagia, liberal use of liquid wash may stimulate sensory input that drives the swallow central pattern generator toward more normal function.

Various forms of therapies have been employed for CA. Mechanical dilation of the CP muscle through balloon or tapered bougies has been proven to be safe and effective in all age groups. Objective responses to such therapy include improved pharyngoesophageal segment opening on videofluoroscopy and reduction in basal UES pressure. In adults, dilation diameters 16–20 mm usually result in immediate symptom improvement, though some require repeated dilation at varying intervals [39]. Potential risks of dilation include perforation or bleeding in the pharynx or esophagus; however, these risks can be minimized by appropriate videofluoroscopy or endoscopic pre-dilation assessment.

Botulinum toxin injection was reported to provide temporary relief of symptoms. By diminishing acetylcholine levels, the toxin interferes with nerve impulse transmission and causes flaccid paralysis of muscles [68]. The injection into the cricopharyngeus muscle can be via endoscopy or percutaneous EMG-guided needles. Onset of subjective benefit is usually by day 7, with duration of benefit varying by 3–4 months [39]. Repeated injection is usually required to maintain the effect. Botulinum toxin injection has better symptomatic response in isolated cricopharyngeal dysfunction without other impairment in the swallowing mechanism. Complications from botulinum toxin injection are low, but there is a risk of spreading the toxin into adjacent muscles, which could result in paradoxical worsening of dysphagia or aspiration.

Surgical treatment with cricopharyngeal myotomy is the curative care of CA. Mechanical division of the cricopharyngeus muscle essentially alleviates the symptoms caused by tonic contraction of the UES. The procedure can be performed via an open (transcervical) or endoscopic approach. The potential risk for complications is higher than that of nonsurgical approaches, including infection, hemorrhages, inadequate myotomy, recurrent laryngeal nerve injury, and pneumonia. Outcomes of cricopharyngeal myotomy tend to be poor when significant pharyngeal weakness is also present.

What Are the Other Conditions That Could Be Confused with UES Opening Dysfunction? Disorders That Need to Be Distinguished from UES Opening Dysfunction

Suggested Response to the Patients

Structural abnormalities of the esophagus just below the level of the UES or in the proximal esophagus, such as esophageal webs or rings, may cause dysphagia that needs to be distinguished from impaired UES opening. Barium swallow and endoscopic evaluation can help to differentiate the diagnosis. Treatment option for proximal esophageal webs and rings is mechanical dilation.

Brief Review of Literature

An esophageal web is a thin, non-circumferential membranous tissue covered with squamous epithelium that protrudes into the lumen. Esophageal webs could be congenital or acquired. The congenital webs are usually located in the middle or distal esophagus, while acquired esophageal webs most commonly occur anteriorly in the cervical esophagus below the cricoid, causing narrowing of the esophageal lumen. The prevalence of cervical webs in patients undergoing barium swallow studies is reported to be 5.5–8% [69, 70]. It appears to predominantly affect white individuals and mostly in female patients [71]. It can occur in all age groups. Esophageal webs associated with iron-deficiency anemia, glossitis, koilonychia, and esophageal or pharyngeal carcinoma are known as Plummer-Vinson syndrome or Paterson-Kelly syndrome [71]. Esophageal webs have also been reported to be associated with extracutaneous manifestations of bullous dermatologic disorders such as epidermolysis bullosa [72], bullous pemphigoid [73], pemphigus vulgaris [74], and immunologic disorders in chronic graft-versus-host disease [75], as well as Zenker's diverticulum [76] and gastroesophageal reflux disease [77].

Most patients with cervical webs are asymptomatic. In symptomatic patients, the characteristic complaint is solid food dysphagia. The

severity of dysphagia is directly related to the luminal obstruction. Some patients may even present with acute food impaction. Other complaints include nasopharyngeal reflux, aspiration, and spontaneous perforation. The esophageal webs are usually diagnosed by barium swallow and upper endoscopy. A frequent videofluoroscopic finding is that impaired transit of a swallowed tablet or marshmallow at a subtle narrowing site of the post-cricoid region coincides with subjective experience of dysphagia. Endoscopic diagnosis of esophageal webs can be difficult because the proximal location of a web makes it difficult to detect. An esophageal web appears as a smooth, thin membrane that is eccentric under endoscopic examination [71].

Asymptomatic esophageal webs do not require any intervention. For patients with mild dysphagia, the initial step is diet modification to avoid certain foods that can trigger symptoms. Lifestyle modification including cutting food into small pieces and chewing carefully can help to eliminate symptoms. Mechanical dilation with through-the-scope balloon dilator or a large bougie dilator can be used to rupture the ring. In patients with underlying medical conditions such as iron-deficiency anemia or chronic graft-versus-host disease, treatment should be aimed at the underlying medical condition after dilatation.

An esophageal ring is defined as a concentric, smooth, thin extension of mucosa or muscular structure. It can be found anywhere along the esophagus, but the most common location is in the distal esophagus, such as Schatzki ring. The pathogenesis of esophageal ring is related to acid exposure and eosinophilic esophagitis (EoE) [78, 79]. The clinical presentation is typically solid food dysphagia. The diagnosis can be made with barium esophagram and endoscopy. The treatment is mechanical dilation combined with acid-suppressive treatment. One of the differential diagnoses of proximal esophageal rings is eosinophilic esophagitis (EoE). Endoscopic findings that suggest EoE include stacked circular rings, linear furrows, whitish papules, and small-caliber esophagus [80, 81]. Esophageal biopsies should be obtained to confirm the diagnosis. The treatment of EoE involves dietary, acid suppression, tropical steroid, and mechanical dilation. The details of EoE are presented in a separate chapter in this book.

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Erosive Esophagitis

8

Frank Zerbib

Abbreviations

GERD	Gastroesophageal reflux disease
PPIs	Proton pump inhibitors
H_2RAs	H_2-receptor antagonists

What Causes Erosive Esophagitis? Is It Frequent?

Response to the Patient

Erosive esophagitis is diagnosed by endoscopy and is defined by "mucosal breaks" at the level of esophageal mucosa, which corresponds to the presence of "ulcers" of the esophagus. These ulcers are most frequently superficial; that's why the term "erosion" is preferred. Erosive esophagitis is also called "reflux esophagitis" since these inflammatory lesions of the mucosa are related to the noxious effects of the gastric content in case of gastroesophageal reflux. The damage of esophageal mucosa is essentially caused by the acid component of the gastric juice: indeed, if the gastric mucosa is very well protected against gastric acid, esophageal mucosa is not, and if acid reflux is prolonged and/or frequent, erosions may occur. Bile acids, coming up from the duodenum through the stomach, may also be deleterious for esophageal mucosa. Erosive esophagitis is a frequent condition: its prevalence is considered to be approximately 2–5% in the general population, but 20–40% of patients with gastroesophageal reflux symptoms have erosive esophagitis.

Brief Review of the Literature

Diagnosis: Erosive esophagitis is defined by the presence of mucosal breaks at endoscopy (Fig. 8.1), as defined by the Los Angeles classification [1] which differentiates low-grade (A and B) and high-grade (C and D) esophagitis (Table 8.1). Gastroesophageal reflux disease (GERD) is the main etiologic factor of erosive esophagitis ("reflux esophagitis"). Differential diagnosis of reflux-related esophagitis can be easily ruled out. Pill-induced esophagitis, infectious esophagitis (herpes, CMV), Crohn's disease, and skin diseases with esophageal involvement are usually easily differentiated from peptic ulcer-

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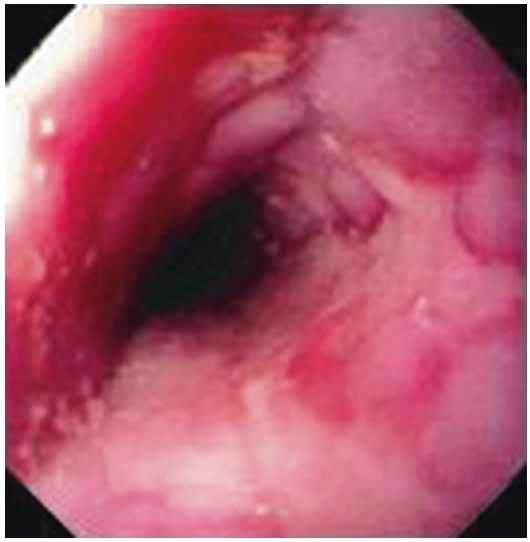

Fig. 8.1 Example of grade C esophagitis

Table 8.1 Los Angeles classification of reflux esophagitis [1]

Grade A	One or more mucosal breaks no longer than 5 mm, not bridging the tops of mucosal folds
Grade B	One or more mucosal breaks longer than 5 mm, not bridging the tops of mucosal folds
Grade C	One or more mucosal breaks bridging the tops of mucosal folds, involving <75% of the circumference
Grade D	One or more mucosal breaks bridging the tops of mucosal folds, involving >75% of the circumference

ations located at the lower third of the esophagus [2]. The presence of mucosal breaks despite PPI therapy may reflect poorly controlled acid reflux, which could be in some rare cases related to a Zollinger-Ellison syndrome.

Epidemiology: Overall, the prevalence of erosive esophagitis is approximately 5%, but varies widely among countries, continents, and studies. In patients without reflux symptoms, a recent literature review reported a prevalence of 12.1% in Sweden, 8.6% in Italy, 6.1% in China, and from 1.6 to 22.8% in health-check programs in six Asian countries [3]. In many of these studies, most "asymptomatic" patients probably have dyspepsia [4], a condition where the prevalence of esophagitis is more than 13% in some studies [5]. The prevalence of erosive esophagitis in patients with GER symptoms is considered to be less than 50% [6], and probably even less since, nowadays, most patients with upper gastrointestinal (GI) symptoms are prescribed proton pump inhibitors (PPIs) as first-line empirical therapy. Indeed, most patients referred for upper GI endoscopy have previously received one or more PPI treatment course, and therefore, the current prevalence of erosive esophagitis in patients with GER symptoms is probably much lower. It has been reported that 6–30% of patients with persisting symptoms on PPIs have erosive esophagitis [7, 8].

Pathophysiology: In erosive esophagitis related to GERD, mucosal damage results from the effects of aggressive factors of the refluxate (mainly acid, pepsin, and bile acids) that overcome the protective factors of the esophageal mucosa (mainly effective esophageal peristalsis to decrease acid-mucosa contact time, efficient epithelial and postepithelial defense [9]). The results of a recent study have challenged the concept of "caustic" acid injury of the esophageal mucosa, by showing that refluxed gastric juice may initiate a cytokine-mediated inflammatory process and ultimately erosions [10]. In patients with GERD, the factors associated with the development of erosive esophagitis are male gender, increased esophageal acid exposure, presence of a hiatal hernia, esophageal dysmotility, and older age [11, 12]. Data on the association between erosive esophagitis and obesity are inconsistent because of variations in study populations and methods used to determine obesity but recent studies have shown that abdominal visceral adipose tissue volume is associated with an increased risk of erosive esophagitis in both males and female [13].

Symptoms: Symptoms of erosive esophagitis are not different from symptomatic gastroesophageal reflux, i.e., mainly heartburn, acid regurgitation, and chest pain. Dysphagia may be present in one-third of patients whatever the severity of endoscopic lesions, and even in the absence of esophageal stricture [14]. The diagnosis of erosive esophagitis requires upper gastrointestinal endoscopy. If most patients with reflux symptoms may be treated empirically with PPIs, and

will not be investigated by endoscopy, this procedure is indicated in patients with alarm symptoms (dysphagia, bleeding, anemia, weight loss, and recurrent vomiting) or when GERD symptoms persist despite a therapeutic trial of 4–8 weeks of twice-daily PPI therapy [15, 16].

How Is Erosive Esophagitis Treated?

Response to the Patient

Most erosive esophagitis will be successfully treated by antisecretory drugs, such as proton pump inhibitors ("PPIs") which significantly decrease (but not completely abolish) gastric acid secretion. Antisecretory drugs can't avoid the reflux of the gastric content into the esophagus but make the refluxate less acidic and therefore less harmful for the esophageal mucosa. Most erosive esophagitis (90%) will be healed by a 4- to 8-week course of PPI treatment. Only very severe esophagitis may be refractory to PPIs and need surgery, which is a rare situation. Most patients with erosive esophagitis have reflux symptoms such as heartburn and regurgitation, which will also resolve with PPIs. However, in some cases, esophagitis can heal and symptoms persist. In patients with refractory esophagitis and/or symptoms, an anti-reflux surgery may be indicated. This surgery, called "fundoplication," consists in creating a wrap around the lower esophagus with the upper part of the stomach. By creating an efficient anti-reflux barrier, the procedure is effective to achieve mucosal healing and symptom resolution in patients with gastroesophageal reflux refractory to medical therapy.

Review of the Literature

Medical treatment: The treatment of erosive esophagitis is based on anti-reflux therapy, with the aims of symptom relief, mucosal healing, and prevention of relapse. If lifestyle modifications, weight loss, and topics (antacids, alginates) may help to reduce gastroesophageal reflux symptoms, there is to date no data supporting their efficacy to heal erosive esophagitis. Antisecretory agents are the medications of choice for pharmacologic therapy of GERD, especially when erosive esophagitis is considered. H_2-receptor antagonists (H_2RAs) and PPIs both decrease gastric acid secretion but PPIs provide a superior control of intragastric pH over a 24-h period. Indeed, by inhibiting the H^+/K^+-ATPase at the level of the parietal cells, PPIs suppress to a significantly greater degree daytime-, nighttime-, and meal-stimulated acid secretion [17]. As a consequence, it has been clearly established that both esophagitis healing and symptom relief were more complete and occurred faster with PPIs compared to H_2RAs [18]. All PPIs provide excellent healing rates at 8 weeks, ranging from 85 to 95% [17]. Healing rates of high-grade esophagitis are slightly lower and longer to be achieved [19]. There is no perfect correlation between mucosal healing and symptom relief: indeed, if most patients with symptom relief will have a complete esophageal mucosal healing, approximately 30% of patients whose esophagitis has healed on PPIs will still experience reflux symptoms [20]. In patients with persisting symptoms, only 30% will have persisting mucosal breaks at endoscopy [8]. In clinical practice, it is not recommended to check for esophageal mucosal healing if the patient is asymptomatic. By contrast, a follow-up endoscopy is mandatory for severe esophagitis not only for mucosal healing but also to verify whether underlying Barret's esophagus is present once the mucosa has healed (see below). A small proportion of patients may have refractory esophagitis, mainly those presenting initially with the most severe lesions (i.e., grade C and D esophagitis). These refractory esophagitis are related to insufficient acid secretion inhibition. In this situation, physicians should check for compliance which is frequently suboptimal in GERD patients [21, 22]. In addition to compliance, dosing time should also be checked since taking PPIs 15 min before a meal results in a better gastric pH control [23] although it has not been clearly demonstrated that it was associated with an improved clinical efficacy. Zollinger-Ellison syndrome should also be ruled out by appropriate investigations. Once adherence and dosing time are optimal, anti-reflux surgery may be indicated for refractory esophagitis.

Surgery: Laparoscopic fundoplication has become the gold standard procedure for anti-reflux surgery [24]. Whatever the type of wrap, i.e., complete (Nissen procedure) or partial (Toupet procedure), fundoplication provides excellent results in terms of symptom relief and esophagitis healing rates at 1 and 5 years [25]. A meta-analysis of randomized controlled trials has shown that, compared to the Nissen procedure, laparoscopic Toupet fundoplication is associated with less dysphagia, gas-related symptoms, and reoperation rates, with a similar reflux control [26]. Recurrence of symptoms may occur in approximately 10% of patients at 5–10 years postoperatively [27]. Mortality is approximately 0.05% in patients younger than 70 years [28]. Fundoplication may have significant side effects such as dysphagia (less than 5%), bloating, early satiety, and flatulence, which may significantly alter the quality of life. However, despite these side effects, patient satisfaction is generally over 90% in most studies coming from academic centers [29]. Functional outcome after fundoplication is probably related to the quality of surgery, which should ideally be restricted to units with experience and high-volume activity [27]. Selection of good candidates for surgery is a crucial issue, especially when symptoms persist despite PPI therapy. Most of these patients don't have overt persisting and uncontrolled acid GERD, and the challenge for physicians is to establish a relationship between symptoms and gastroesophageal reflux, which is the key for a successful operation [20, 30]. By contrast, when refractory esophagitis is present despite adequate medical treatment, there is little doubt that esophagitis is related to insufficient acid control and the indication for surgery is much easier.

What Will Happen in the Long Run?

Response to the Patient

Gastroesophageal reflux disease is a chronic condition which requires long-term treatment. After an initial 4–8 weeks of treatment, most esophagitis and reflux symptoms relapse over a 6-month period. According to the frequency and severity of relapse, intermittent or continuous treatment is indicated. Some patients may need a daily maintenance treatment while others will manage their treatment on an "on-demand" basis. Patients with severe esophagitis often require permanent treatment and/or anti-reflux surgery. The use of PPIs on the long term as maintenance therapy is safe: side effects are rare (less than 10%, mainly headache and diarrhea), and if potential risks related to PPI use have been suggested (infectious diarrhea, pneumonia, bone fracture), none has been yet clearly confirmed by appropriate studies. The alternative of long-term PPI treatment is surgery (fundoplication) which has been shown to provide excellent results in terms of symptom control, but may have significant side effects such as dysphagia (swallowing problems), pain, bloating, or flatulence. Whatever the treatment, if the reflux is adequately controlled, the overall prognosis is very good. By contrast, if the treatment is not taken or inefficient, patients may develop complications of erosive esophagitis, especially when severe lesions are present initially. The most frequent complications are peptic stricture and Barrett's esophagus. Peptic stricture is caused by inflammation and fibrosis of the esophageal wall and is defined by a narrowing of the esophagus lumen. This will result in swallowing difficulties ("dysphagia") especially for solid food and may need endoscopic esophageal dilation in addition to antisecretory treatment. Barrett's esophagus does not cause symptoms per se. It is defined as a change in esophageal mucosa's structure ("metaplasia") that may lead, in the long term, to esophageal cancer. If Barrett's esophagus is clearly a preneoplastic condition, the occurrence of cancer is a long-term process with intermediate stages (low-grade and high-grade dysplasia). In the absence of dysplasia the risk of cancer is low, approximately 0.2% per year. Even if the overall risk of cancer is low, the presence of Barrett's esophagus should be detected in patients with severe esophagitis and if present the patient should be included in a screening program with regular endoscopic surveillance of esophageal mucosa.

Review of the Literature

Long-term PPI therapy: GERD is a chronic condition which requires a long-term treatment since healing of mucosal injury is not sufficient to change the natural history of the disease. Indeed, randomized controlled trials have shown that 70–90% of patients with erosive esophagitis experience symptomatic and endoscopic relapse over a 6-month period after initial treatment has been stopped [31–33]. Asymptomatic relapse of esophagitis is uncommon. The pretreatment severity of erosive esophagitis is consistently associated with higher relapse rates. As a consequence, long-term antisecretory therapy is mandatory in most patients with esophagitis, the optimal approach being based mainly on symptom relief and pretreatment esophagitis severity. Patients with low-grade esophagitis and intermittent symptoms may be treated "on demand," while patients with severe esophagitis and frequent symptoms should continue with a daily treatment as a maintenance therapy [24]. Both H_2RAs and PPIs could theoretically be used as maintenance therapy but PPIs are much more popular among patients and physicians, considering the more potent acid inhibition with PPIs which are more effective, especially in patients with severe esophagitis [17, 19]. At 5 years, remission rates on maintenance PPI therapy are approximately 90% [19], although some dose escalation may be mandatory in 1 out of 4 patients as shown in the Lotus study [29].

Tolerability and safety of PPIs: As a class, PPIs are very well tolerated and can be considered as very safe on the long term, especially when compared with alternative treatments such as surgery (see above). Side effects such as diarrhea and headache occur in less than 10% of patients and can be managed by switching to another PPI molecule. During the past years, several concerns have arisen regarding the long-term use of PPIs. Case-control studies and retrospective reviews have reported an increased risk for *Clostridium difficile*-associated diarrhea, community-acquired pneumonia, and bone fracture, but conflicting data have been reported and appropriate prospective data are reassuring [17, 19]. Decreased absorption of vitamin B12 has also been reported with limited impact on vitamin B12 plasma levels and in clinical practice vitamin B12 testing is not necessary [19, 34]. There are some controversies regarding the potential interaction between esomeprazole and clopidogrel but appropriate studies did not show any significant clinical impact of this association [35]. More recently, an association between PPI use and chronic kidney disease has been reported that requires further evaluation for confirmation [36]. The potential risk of gastric neoplasm in patients taking long-term PPIs has been a matter of debate for many years, since PPI may increase the incidence of gastric atrophy and intestinal metaplasia—a pre-neoplastic condition—in patients with *Helicobacter pylori* infection. Hence, it is now recommended by international guidelines to eradicate *Helicobacter pylori* in patients treated with PPIs on the long term [37]. Since PPI therapy increases gastric pH, patients on maintenance therapy may have elevated gastrin plasma levels which may increase the density of enterochromaffin-like cells (ECL) in gastric mucosa [38]. However, long-term follow-up (at 5 and 12 years) of two cohorts of patients included in prospective randomized trials did not raise any safety concern associated with long-term PPI use regarding laboratory results and incidence of neoplasms [34]. Data on the effects of very-long-term PPI use (more than 10–20 years) are mandatory but overall most available data available to date are reassuring. This information should be given to the patients when anti-reflux surgery is considered to avoid long-term PPI therapy.

Anti-reflux surgery: Regarding symptomatic outcome, the Lotus study, a large multicentric randomized study, showed that both laparoscopic fundoplication and esomeprazole had remission rate above 90% at 5 years, provided that the dose of PPI could be increased if needed [29]. There was a statistically significant superiority of medical therapy for the primary outcome which was an overall assessment of symptom control by the patient. If each individual reflux symptom was better controlled by the fundoplication (especially regurgitation), the overall assessment was probably hampered by the greater occurrence of

side effects in the surgical arm. Therefore, both medical and surgical treatments are valid options for the long-term treatment of GERD, and the decision should be adapted to each individual situation. It is of note that these comparative studies have been conducted in patients whose symptoms were adequately controlled by PPIs. Patients with refractory symptoms represent a different situation which requires an extensive workup to ensure that the persisting symptoms are indeed reflux related, which is usually the case in patients with refractory esophagitis, but much more difficult and challenging in patient with nonerosive reflux disease [20].

Long-term prognosis: Whatever the treatment, if the reflux is adequately controlled, the overall prognosis is very good, and the incidence of complication is low. On the other hand, if the treatment is not able to adequately control the gastroesophageal reflux (because of poor adherence or insufficient acid secretion inhibition), the patient is exposed to esophagitis relapse and complications.

Peptic stricture: Thanks to the efficacy of PPI therapy, peptic stricture (Fig. 8.2) is a rare event whose incidence has declined since the beginning of 1990s [39, 40]. Most patients can be treated efficiently by PPIs and sometimes endoscopic esophageal dilation. Patients with peptic strictures should be maintained on long-term PPI therapy to reduce the risk of relapse and the need for subsequent dilation.

Barrett's esophagus and esophageal adenocarcinoma: Compared to patients with nonerosive reflux disease, patients with erosive esophagitis have an increased risk of esophageal adenocarcinoma [41]. This cancer risk is related to the development of Barrett's mucosa since erosive esophagitis is associated with a fivefold increased risk for Barrett's esophagus after 5 years [42], especially when severe esophagitis is present. Barrett's esophagus is an acquired condition defined as a metaplastic change at the level of the esophageal mucosa, where the squamocolumnar junction is displaced proximal to the gastroesophageal junction, identified endoscopically as the most proximal extend of the gastric folds. Columnar mucosa appears as a salmon-colored mucosa which proximal extent will differentiate short- (<3 cm) and long-segment Barrett's esophagus (Fig. 8.3). Biopsy samples will further confirm the diagnosis by showing that squamous cells are replaced by mucus-secreting columnar cells. For most experts, the definition of Barrett's esophagus requires the presence of intestinal metaplasia in the columnar mucosa [43]. The prevalence of Barrett's esophagus is 1–5% in the general adult population [44, 45], and 5–15% in patients with GERD symptoms [46]. In addition to GERD symptoms and erosive esophagitis, several factors have been associated with the development of Barrett's esophagus, mainly white

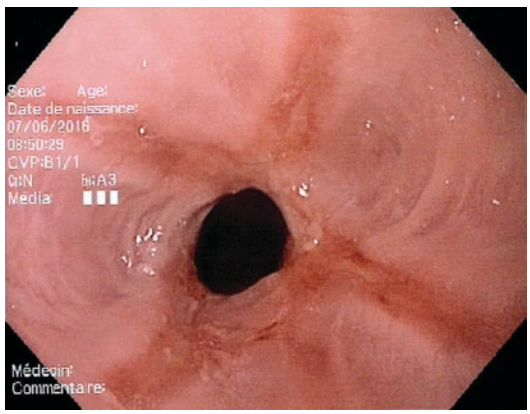

Fig. 8.2 Example of peptic stricture associated with erosive esophagitis

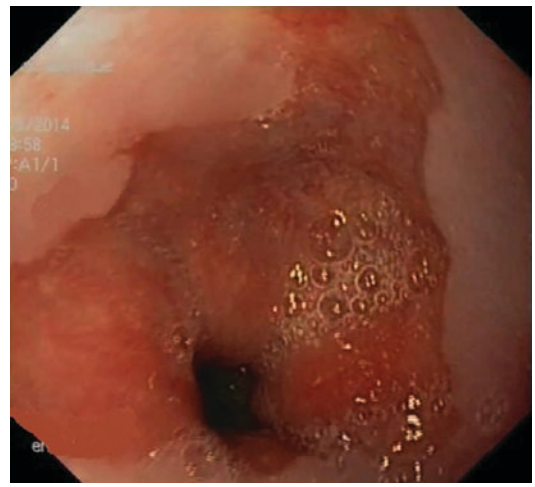

Fig. 8.3 Example of Barrett's esophagus

race, male gender, older age, and hiatal hernia, while *Helicobacter pylori* infection, NSAIDs, and statins are considered to be protective factors [43]. In patients with GERD symptoms and who have one of these risk factors, an endoscopic screening for Barrett's esophagus is recommended [43]. Barrett's esophagus is a clearly recognized risk factor for the development of esophageal adenocarcinoma, with an annual incidence of 0.1–0.3% in patients with nondysplastic mucosa [43, 47, 48]. Risk factors for cancer development are mainly white race, male gender, older age, and length of Barrett's mucosa [47]. The progression from nondysplatic Barrett's esophagus to esophageal adenocarcinoma is a long process, which classically goes through different stages, i.e., low- and high-grade dysplasia. The annual incidence of cancer in patients with high-grade dysplasia is approximately 10% [49], or even more in some studies with selected patients [50]. The data are more difficult to interpret for low-grade dysplasia, with annual incidence rates varying from less than 1 to 9%. These discrepancies between studies are probably related to the poorly reproducible diagnosis of low-grade dysplasia. In a recent study, the annual risk of patients with downstaged low-grade dysplasia to no dysplasia after expert review was 0.6%, while those with confirmed dysplasia had a much higher progression risk of 9% [51]. These data highlight the need of an expert histological review for adequate risk stratification.

Esophageal adenocarcinoma is a lethal disease with a 5-year survival of less than 15%. The aim of surveillance programs in patients with Barrett's esophagus is to detect early/superficial neoplasms who have a better prognosis. Even better is to detect low/high-grade dysplasia before the development of an actual adenocarcinoma. Some studies suggest that patients with tumors detected by endoscopic surveillance have earlier stage tumors and an overall better prognosis, but these studies may have overestimated the benefit of this strategy [43]. Nevertheless, despite the lack of solid evidence to support the practice of endoscopic surveillance, scientific societies around the world recommend endoscopic surveillance of patients with Barrett's esophagus, at intervals of 3–5 years [43]. This holds true also for patients with reflux treated medically or surgically, since neither PPIs nor anti-reflux surgery have proven efficacy to prevent the development of adenocarcinoma [52]. Most patients with high-grade dysplasia and/or superficial adenocarcinoma should be treated endoscopically, by endoscopic mucosal resection and/or ablation by radiofrequency. Recent data suggest that radiofrequency ablation of Barrett's mucosa with low-grade dysplasia may be beneficial [53] but this remains a matter of debate [43].

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Regurgitation

9

Kenneth R. DeVault

Question: Food and Liquid Are Coming Up in My Throat. What Is Causing This?

This sounds like regurgitation but asking the patient several other questions can better characterize the situation:

- *Is there associated heartburn?* If the patient is on an acid blocker, you may have to ask if they used to have heartburn but do not anymore. Another way to ask this question is "do your symptoms worsen when you miss a dose of medication?" Some have argued that stopping PPI may exacerbate symptoms due to rebound acid production. While this may happen, the question and maneuver are still helpful, especially when the patient has no worsening after stopping the medication. The combination of heartburn and regurgitation is fairly specific for gastroesophageal reflux (GER) [1]. Reflux-related regurgitation typically is not associated with nausea, retching, or abdominal pain, although reflux can overlap with any of those symptoms.
- *When this happens, does food come up?* If food comes up during a meal, it is less likely reflux and could be due to an esophageal motility disorder or perhaps rumination. If it happens in the immediate postprandial period, it could still be from esophageal stasis but also may be reflux from the stomach. If it is 2 or more hours after a meal, then delayed stomach emptying is more likely.
- *Do you actually spit the material out or does it feel like it is coming up but does not and do you ever have it come back up into your mouth and then reswallow it?* Regurgitation associated with GER usually does not come all the way into the mouth or is spit out. If that is happening, an esophageal disorder like achalasia should be considered. In fact, in patients with primary regurgitation and no heartburn, the GERD diagnosis can be erroneous in a number of patients who actually have achalasia [2]. The concept of regurgitating into the mouth and then reswallowing is suggestive of rumination. Like regurgitation, rumination is not usually preceded by retching (which is seen with vomiting) [3]. Water brash is often confused with regurgitation, but is a feeling of a large amount of bicarbonate-rich material appearing in the mouth, often as a reflex response to acid in the esophagus [4].

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Question: I Have Reflux and Used to Have Heartburn, but It Doesn't Happen When I am on My Acid Blocker. I Still Have Liquid Coming Up, Particularly at Night and It Makes Me Cough? What Is Causing This and What Can I Do?

Heartburn and regurgitation are more sensitive and specific symptoms for GER compared to all other symptoms [5]. On the other hand, even combining these symptoms with response to PPI only results in a sensitivity of 78% and specificity of 54% [6]. It has also been estimated that between 10 and 40% of patients with GERD do not respond completely to PPI therapy [7]. There is substantial overlap between GERD and functional dyspepsia. Symptoms such as postprandial fullness, nausea, vomiting, and early satiety can be misinterpreted as or coexist with regurgitation. Patients with those symptoms tend to not respond as well to reflux therapy [8]. Since drugs that address the underlying motility problem in GERD have, for the most part, not been successfully developed, most patients with GER are treated with acid blockers. These agents relieve heartburn and despite the fact that they really do not change the underlying physiology actually do improve regurgitation, but improve it less than they do for the symptom of heartburn. In a systematic review of the response of regurgitation to PPI therapy, there was an overall 17% improvement compared to placebo but heartburn showed an improvement of 37% compared to placebo [9]. Refractory heartburn, regurgitation, or both can be seen in up to 32–45% of GERD patients treated with PPI [10]. There is incomplete consensus on what is required before declaring a patient "refractory" but most commonly these patients are initially treated with once-daily PPI and then increased to twice daily before declaring failure [11]. Regurgitation is considered by some to be the major contributor to unsatisfactory response in many patients [12]. When impedance testing was compared to symptom production, episodes that led to the symptom of regurgitation were more likely to extend further up the esophagus (proximal) than those leading to "heartburn" [13]. These interesting data make sense, since a small amount of acid could activate mucosal, acid-sensitive receptors, but one would think that regurgitation would require a sufficient volume to perhaps distend the esophagus.

When a patient presents with refractory regurgitation felt to be GERD-related, reflux surgery is often considered. It is critical that the diagnosis is very clear prior to that decision. The clinical history is key but not sufficient. Large hernias are well diagnosed on barium testing and can lead to surgery, but the demonstration of reflux on barium swallow is neither specific nor sensitive for pathologic GERD [14]. Likewise, endoscopy can be suggestive and at times confirmatory. Esophagitis is specific with LA-B or greater. Redness, LA-A, or less is less specific. Barrett's esophagus can also confirm pathologic reflux, but using this "diagnosis" is challenging since many patients are labeled as such have irregular squamocolumnar junctions and even normal anatomy due to the widespread practice of biopsy of this area. These patients may or may not have pathologic reflux.

While it would seem to make sense that refractory reflux-related regurgitation is caused by reflux of large amounts of neutralized gastric content into the esophagus, there are other possibilities. These include esophageal hypersensitivity (the experience of symptoms with normal or physiological volumes of reflux), poor esophageal clearance, or perhaps both. So, prior to considering anything beyond medical therapy, most patients will need their reflux confirmed with ambulatory reflux testing. How should this testing be performed? Tube or probe based? On or off therapy? With or without impedance? The question here is whether or not the patient has reflux, so an off-therapy test is most appropriate [15]. For heartburn and regurgitation, the method of the test (tube or probe based) is not that important (assuming that the patient is not on acid-blocking medications) nor does impedance add a great deal. Dual-channel and impedance-based tests do have an advantage of faster sampling

rates and the ability to estimate the height of reflux episodes, which may be helpful in some patients particularly those with proximal symptoms. As above noted, reflux episodes leading to the symptom of regurgitation tend to reach the proximal esophagus more often than those producing heartburn. The outcome of pH testing provides a guide to future therapy. Patients with abnormal acid exposure (>5%) and particularly those with severe acid exposure (>10%) have confirmed reflux and do not need additional testing. Another group will have normal esophageal acid exposure but a positive symptom association between their reflux events and symptoms. There are little data on the use of symptom association with the symptom of regurgitation, so care should be taken in interpreting those studies. Finally, some patients will have a normal study with a negative symptom association. They likely do not have reflux as a cause of their symptoms, although there is a small, but real false-negative rate with pH testing. There are some suggestions that refractory symptoms, including regurgitation, can be caused by a mixture of liquid and gas reflux [16]. This may be due to distention of the esophagus rather than activation of chemoreceptors. These events can be seen with impedance testing and are missed with testing that only looks at esophageal pH.

The indication for on-therapy testing is much less clear. There are some patients who have abnormal acid exposure despite BID PPI therapy, but more often the overall exposure is normal [17]. Another group of patients will have normal acid exposure but have symptoms that temporally relate to either acid or nonacid reflux events. There are even less data on how to deal with a positive symptom association when the patient is on reflux medications. Personally, I do not consider reflux proven based on symptom association in patients with normal acid exposure whether on- or off-reflux medications. It is important to remember that both the SI and SAP are best characterized when used to measure acid events and not nearly so well accepted when measuring nonacid events identified with impedance testing, especially on medication.

Are there medical approaches to reflux-related regurgitation beyond acid suppression?

In 2005, the first American College of Gastroenterology guidelines for treatment of GERD [18] stated:

> "The pathogenesis of GERD is related to defects in esophagogastric motility. Ideal pharmacological therapy would correct these defects, making suppression of normal amounts of gastric acid unnecessary. Results with the available drugs have been disappointing."

Unfortunately, little has changed in the past 20 years, although there have been a number of studies looking at nonacid-suppressing methods of reflux/regurgitation control. For example, although not directly targeting regurgitation, a trial of baclofen demonstrated an improvement of both acid and nonacid reflux events measured during impedance/pH monitoring [19]. An additional trial suggested an improvement in postprandial retrograde events in patients with rumination or supragastric belching [20]. Lesogaberan is a GABA receptor agonist under study as a gastrointestinal agent. In a trial of adding this medication to PPI therapy, there was an improvement in both heartburn and regurgitation [21]. Many other agents have been studied with the goal of reducing reflux without necessarily blocking acid or as an "add-on" therapy in patients with refractory reflux including arbaclofen placarbil (a prodrug with perhaps a better side effect profile) [22]. Alginates are suggested to form a pH-neutral "raft" in the proximal stomach and hence prevent reflux. In a randomized trial of patients on once-daily PPI with ongoing symptoms, alginate improved the severity and frequency of heartburn but also decreased the frequency of regurgitation [23]. European formulations have a higher concentration of alginate making comparisons difficult. Despite a large investment from pharmaceutical companies and many clinical studies, there are really no safe and effective prokinetic agents widely available for GERD patients.

How does reflux-related regurgitation that is refractory to PPI therapy respond to reflux surgery?

There have been several studies looking at the prevalence of regurgitation before and after laparoscopic fundoplication. There were two studies reporting baseline prevalence of 71.4% and 93.3%, which decreased to 3.6% and 13.3%, respectively [24, 25]. A longer term study suggested some recurrence of regurgitation over time reporting 29.1% at 10 years [26]. Some patients with abnormal motility may experience regurgitation and blame it on GERD when they are really experiencing esophageal stasis, especially after fundoplication. An additional small study compared patients who responded to PPI to those who did not and who eventually underwent a fundoplication [27]. Regurgitation resolved in 96% of the PPI responders and in 84% of the PPI nonresponders. It seems to be clear that refractory regurgitation responds to reflux surgery in well-selected patients.

There have been several nonsurgical, endoscopic methods developed to help control reflux. In a 5-year study of radiofrequency application to the LES, all reflux symptoms including regurgitation were improved over baseline [28]. A study of 696 patients who had troublesome regurgitation despite daily PPI use were randomized to either omeprazole of transoral esophageal fundoplication (TF). The regurgitation was eliminated in 67% after TF compared to 45% on omeprazole [29]. The newly developed magnetic sphincter device showed outstanding control of regurgitation with moderate or severe regurgitation present prior to implant in 57% of patients but only in 1.2% at 5 years postimplant [30]. Fundoplication remains the gold standard, but some of these other approaches may, in time, prove to be an alternative in patients requiring mechanical control of esophageal reflux.

Overview of the Symptom of Regurgitation

Regurgitation is a symptom most often described as the effortless return of material from the stomach to esophagus. It can simply be the feeling of material coming into the chest but also can come all the way into the mouth and is often accompanied by a sour or burning sensation. There remains some controversy in even defining the symptom. The Montreal Conference was an attempt to provide clear definitions in GERD. There was nearly a 50–50 split among international specialists; one contingent defined regurgitation as gastric contents entering the mouth or hypopharynx evidenced by a sour or bitter taste, and the other contingent included in the definition the perception of gastric contents entering the esophagus, without requirement of a taste sensation [31].

As above noted, it is most common in gastroesophageal reflux disease with a prevalence of up to 80% in some series. Despite that association, it is not perfectly specific for GERD, especially when not accompanied by heartburn. If food, swallowed fluid, or both do not empty from the esophagus, usually related to esophageal motility disorders such as achalasia, a very similar symptom can occur. The type of material can help distinguish (bland and often containing food with achalasia) in some but not all cases. Another possibility is rumination. This was briefly discussed above, but probably deserves additional comment. Traditionally, this was thought to be associated with delayed or impaired mental development, but recently has been reported more frequently in older patients without cognitive issues [32]. The Rome Criteria for rumination requires persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing that is not preceded by retching. Supportive criteria include lack of preceding nausea, cessation of the process when material becomes acidic, and finding of a "pleasant taste" in the regurgitant material [33]. Given that achalasia can present similarly, testing to exclude that diagnosis and perhaps to look for manometric signs of rumination is critical. It is important to understand that ambulatory pH testing can be misleading in these patients since rumination and reflux can look very similar.

Mechanical issues can also lead to symptoms of regurgitation. Zenker's diverticula often collect fluid, food, or both and that collection can be regurgitated and confused with gastroesophageal

reflux or esophageal stasis. Obstruction in the esophagus due to rings, strictures, or eosinophilic esophagitis can produce a symptom that is confused with more common causes of regurgitation. Hiatal hernias are associated with gastroesophageal reflux, but if complicated or paraesophageal can result in regurgitation related to esophageal stasis rather than gastroesophageal reflux.

Recently, many patients are being referred to gastroenterologists with pulmonary and laryngeal symptoms. In some cases, this symptom complex includes the buildup of fluid material in the upper aerodigestive tract. While this can be due to esophageal or even gastroesophageal reflux, postnasal drip, sinusitis, and pulmonary disease such as bronchiectasis should be considered in the differential diagnosis of this type of "regurgitation."

Regurgitation as a functional illness is not well described (with the exception of rumination). That having been said, there are many studies that suggest that stress can heighten esophageal sensation and it is not a real leap of faith to assume that some patients describe the symptom of regurgitation during normal, physiological activity within the esophagus. Esophageal motility and sensation are altered by various forms of stress [34]. Likewise, some patients with nonerosive reflux disease will sense liquid in their esophagus regardless of the pH [35]. Finally, both auditory stress and lack of sleep can result in an increased sensitivity to esophageal acid infusion in patients with nonerosive reflux disease [36, 37]. All of this suggests that functional regurgitation may indeed be an issue in some patients.

What Is the Evaluation for Regurgitation?

As above noted, a carefully taken history can usually lead toward more likely etiologies, but selected testing will usually be needed to confirm the diagnosis and help to plan for therapy.

- *Barium testing*: A carefully performed barium examination can screen for esophageal obstruction and major disorders such as achalasia and esophageal diverticula. Symptoms cannot always be correlated with hiatal hernia, but large or complicated hernia can certainly be implicated as the cause of regurgitation. Reflux should not be definitively diagnosed based on barium testing [38]. Proximal diverticula (Zenker's) may also be diagnosed. In patients with dysphagia and perhaps in patients with atypical sounding regurgitation, adding a solid bolus to the barium test may increase the sensitivity for stenosis, including most importantly lower esophageal (Schatzki) rings, which are easily missed on liquid-only testing. Changes of eosinophilic esophagitis can also be suggested, especially when a solid bolus becomes lodged.
- *Esophageal manometry*: In patients with regurgitation associated with heartburn, manometry is not needed unless reflux surgery is being considered. In patients with symptoms or barium results suggestive of achalasia it is confirmatory. High-resolution manometry has expanded the diagnosis of achalasia and other motility disorders [39]. If a manometry is normal or shows aperistalsis then it can be very helpful and often diagnostic. Unfortunately, many patients will have nonspecific disorders particularly disorders of esophagogastric junction relaxation. The provider is often left questioning if the findings have anything to do with the symptoms being evaluated. It has become increasingly clear that narcotics produce changes in esophageal motility and testing on those medications should be avoided if possible [40]. Sildenafil and other agents that treat erectile dysfunction also interfere with esophageal peristalsis in some patients [41]. There are now criteria for the diagnosis of rumination based on manometry [42]. Basically a marked increase in intra-abdominal pressure associated with a reflux event is suggestive of rumination. This, of course, requires an event to occur during monitoring (which has to be protracted compared to a routine esophageal test) and requires visual review of the tracing since analysis software would not identify such an event.
- *Testing of gastric emptying*: In patients with regurgitation several hours after meals, delayed

gastric emptying should be considered. Nuclear medicine testing is the gold standard. It is important to note that accurate testing requires scanning at least 4 h after meal ingestion [43]. Older studies which attempt to determine emptying by extrapolating data from the first 1–2 h are much less accurate. Agents that delay gastric emptying (most importantly narcotics and anticholinergics) should be discontinued prior to testing.

– *Endoscopy*: Endoscopy in GERD has been extensively discussed and probably yields little beyond screening for Barrett's esophagus [44]. Likewise, endoscopy in an uninvestigated regurgitator may not be that helpful. If there is suggestion of an obstruction or a significant dysphagia then endoscopy is indeed reasonable. It is especially useful for both diagnosis and therapy when an obstruction has been suggested by barium testing. Biopsies to assess for eosinophilic esophagitis should be performed if there are suggestive endoscopic signs, but in the case of dysphagia and perhaps with regurgitation, it may be reasonable to biopsy normal-appearing esophagus [45].

Regurgitation: A Stepwise Approach

Step 1: Is this reflux-related regurgitation? As above noted, history and selected testing can usually sort this out. Testing may include endoscopy, pH testing (off-acid-blocking medications), or both. It is important to recognize that refractory regurgitation in a patient with well-proven gastroesophageal reflux may respond to mechanical augmentation of the lower esophageal sphincter using surgical or perhaps endoscopic methods.

Step 2: Once reflux is reasonably excluded, then is there a primary esophageal motility disorder? Testing for this should include a barium examination, esophageal manometry, or at times both. Achalasia and aperistalsis (either related to connective tissue disease or idiopathic) are findings that usually produce symptoms, which are likely to improve with treatment. Other, less specific findings such as distal spasm, high-pressure (jackhammer) esophagus, and poor EG junction relaxation may be diagnosed, but are not always the cause of symptoms and respond less completely to intervention.

Step 3: Once reflux and a specific motility disorder have been ruled out, the diagnosis becomes more difficult. Rumination may have been suspected at step 1 and if not should be considered. Gastric motility issues and other gastric causes can be considered. The possibility of the disorder being functional, perhaps related to abnormalities in esophageal sensation, can be considered. In some patients, assuming that they are maintaining their weight and not aspirating, encouragement and support may be all we have to offer.

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Nonerosive Reflux Disease (NERD) 10

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What is the role of pain modulators in NERD patients?

Adding a pain modulator in NERD patients who failed PPI once daily is a possible therapeutic strategy, because esophageal hypersensitivity plays an important role in symptom generation of this patient population. Although there are few studies demonstrating the value of pain modulators in NERD patients who failed PPI once daily, these medications have been shown to improve esophageal pain in patients with functional esophageal disorders where esophageal hypersensitivity is also an important underlying mechanism [139–141].

What is the likelihood that NERD patients will progress over time to develop erosive esophagitis, Barrett's esophagus, or adenocarcinoma of the esophagus?

Progression of NERD patients to erosive esophagitis is very uncommon. The vast majority of NERD and erosive esophagitis patients remain within their respective GERD group throughout their lifetime. In addition, there is no evidence that NERD patients progress over time to develop Barrett's esophagus or adenocarcinoma of the esophagus [30–34].

Introduction

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach content causes troublesome reflux-associated symptoms [1]. GERD is a chronic and highly prevalent disorder; population-based studies have demonstrated that 44% of the US adult population report GERD-related symptoms (heartburn and acid regurgitation) at least once a month and 20% once a week [2–4]. GERD is also emerging as a leading digestive disorder in Asian countries with 2.5–7.1% of the population suffering from at least weekly GERD-related symptoms [5]. The disease has a significant impact on patients' quality of life and contributes substantially to health care expenditures [6].

Patients with GERD symptoms have been divided into three phenotypes: Barrett's esophagus, erosive esophagitis, and nonerosive reflux disease (NERD). NERD has been commonly defined as the presence of classic GERD-related symptoms in the absence of esophageal mucosal injury during upper endoscopy. The Genval workshop suggested that the diagnosis of

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NERD should be reserved for individuals who satisfy the definition of GERD, but without Barrett's esophagus or definite mucosal breaks in the distal esophagus (erosions or ulcerations) [7]. The Montreal consensus meeting defined NERD as the presence of typical GERD-related symptoms caused by intraesophageal reflux, in the absence of visible esophageal mucosal injury during endoscopy [1]. Erosive esophagitis and NERD have different pathophysiological and clinical characteristics and clearly diverge when it comes to response to antireflux treatment [8, 9].

Studies have shown that about 30–50% of NERD patients demonstrate esophageal acid exposure within the physiological range [10]. The Rome III Committee for Functional Esophageal Disorders suggested that NERD encompasses patients with GERD symptoms who demonstrated normal mucosa on white light endoscopy and had one of the following: (1) abnormal pH testing, (2) normal pH testing but positive symptom indices, or (3) normal pH testing, negative symptom indices, but positive response to PPI therapy [11]. What is unique about Rome III is that as compared with Rome II or I an abnormal pH test was not required for the diagnosis of NERD. The most recent Rome IV Committee for Functional Esophageal Disorders classified patients with NERD as having increased esophageal acid exposure on impedance + pH monitoring and no endoscopic evidence of erosive disease (Figs. 10.1 and 10.2) [12]. Rome IV stressed that patients who have normal endoscopy, normal esophageal acid exposure, and positive symptom indices represent a functional esophageal disorder termed reflux hypersensitivity. Also, Rome IV did not support the inclusion under NERD of patients with abnormal weakly acidic reflux in the background of normal esophageal acid exposure and normal endoscopy. Rome IV did not see any value in testing patients off PPI treatment with impedance + pH.

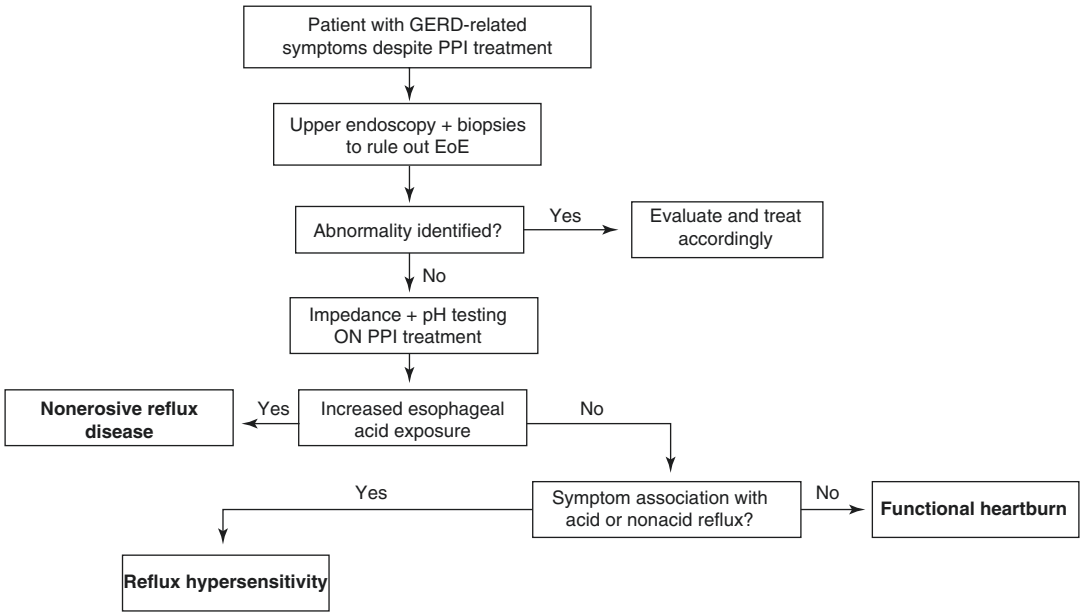

Fig. 10.1 A diagnostic algorithm for NERD in patients on PPI treatment based on Rome IV criteria (adapted from [12])

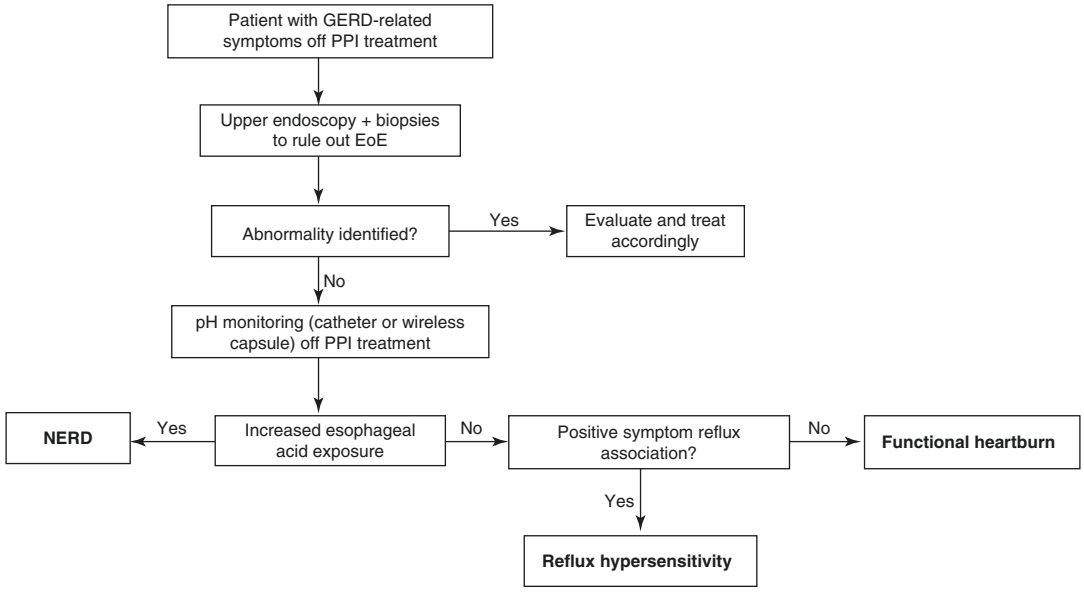

Fig. 10.2 A diagnostic algorithm for NERD in patients off PPI treatment based on Rome IV criteria (adapted from [12])

Epidemiology

There are limitations to epidemiologic estimates of the prevalence of NERD due to the spectrum of symptoms, low sensitivity of low grades of erosive esophagitis (especially Los Angeles Grade A), widespread use of proton pump inhibitors, and evolving definitions. Early studies reported that about 50% of patients with heartburn were found to exhibit normal esophageal mucosa during endoscopy [13, 14]. However, several European community-based studies found a much higher prevalence of up to 70% [15, 16]. Robinson et al. evaluated subjects who used antacids for symptomatic relief of heartburn. Of 165 patients enrolled in this study, 53% had normal esophageal mucosa on upper endoscopy [17]. In a population-based study, 1000 subjects with or without GERD-related symptoms were randomly selected to undergo an upper endoscopy. Of the patients with gastroesophageal reflux symptoms, only 24.5% were found to have erosive esophagitis [18]. Zagari et al. performed a similar large epidemiologic study in the general population in northern Italy. Of the patients with reflux symptoms, 75.9% were found to have a negative endoscopy [19]. Based on a review of two population-based studies, one non-community study, and several endoscopy-based studies, 50–85% of patients with typical reflux symptoms have NERD [20]. It was also estimated from this review that 11–12% of the general population and considerably higher proportions of patients presenting to endoscopy (37–87%) may have NERD. In Asia, NERD is the most common presentation of GERD, affecting up to 65% of Indians, 72% of Malaysians, and over 90% of Chinese in studies from Malaysia, Singapore, China, and Hong Kong [21]. In a cross-sectional study analyzing 10,837 healthy Japanese subjects who underwent upper gastrointestinal endoscopy, 733 (6.8%) had reflux esophagitis and 1722

(15.9%) had NERD. In a recent retrospective study including 3382 patients with heartburn symptoms, 59% had NERD and 41% had erosive esophagitis [22]. Overall, based on old and recent epidemiologic studies investigating patients with GERD-related symptoms, the prevalence of NERD in the general population is between 50 to 70%.

Natural History

The pathophysiological relationship between NERD and erosive esophagitis or Barrett's esophagus remains the subject of protracted debate [23], with most studies demonstrating a low, if any, rate of progression from NERD to erosive esophagitis and Barrett's esophagus. Most of the studies are limited because of retrospective design, irregular follow-up, and common use of antireflux medication in GERD patients.

Pace et al. followed 33 patients with NERD retrospectively for a period of 3–6 months while on therapy with antacids, prokinetics, or both [24]. Five (15%) of the patients that remained symptomatic during therapy developed erosive esophagitis of unknown grading. However, there were several limitations to this study. Patients were treated from the time of admittance into the study, suggesting that some may not have been true NERD patients. Furthermore, since it was noted that NERD patients rapidly progressed to develop erosive esophagitis after only a very short duration of follow-up (3–6 months), this may indicate that those who developed erosive esophagitis during the study period were likely healed erosive esophagitis patients that were labeled incorrectly as having NERD from the beginning.

Kuster et al. followed 109 patients with GERD, of whom 33 had endoscopically documented erosive esophagitis for 6 years [25]. Only 2.7% of the NERD patients developed erosive esophagitis after 3 years and 3% after 6 years of follow-up. This study provided longer duration of follow-up, and despite its limitations (i.e., high dropout rate) very few NERD patients progressed to develop erosive esophagitis. Isolauri et al. conducted a longer duration follow-up (17–22 years, mean 19.5 years) of 60 patients with documented GERD [26]. Patients received medical (N = 50) or surgical (N = 10) antireflux therapy as needed (no standardization). Of the subjects who received only medical therapy, 30 had NERD and 20 had erosive esophagitis at baseline. At follow-up, only five (17%) of the NERD patients progressed to erosive esophagitis (all to grade 1 Savary-Miller).

McDougall et al. performed a prospective follow-up of 101 GERD patients for a period of at least 32 months after initial assessment with pH testing and an upper endoscopy [27]. During follow-up more than half of the patients were on a PPI or H_2 blocker. Of the 17 subjects with NERD and abnormal pH testing, 4 (24%) developed erosive esophagitis while on an H_2 blocker. In a 5-year follow-up investigation including patients with NERD (N = 113) and erosive esophagitis (N = 90) at baseline, progression from NERD to erosive esophagitis occurred in 11 patients and 2 developed Barrett's esophagus [28].

One study stands out in their findings about the natural course of NERD. In a publication by Pace et al., which was a long-term follow-up of a previously published short-term follow-up study, the authors claimed that 94% of NERD patients progressed to develop erosive esophagitis after 5 years [29]. The authors concluded that GERD is a chronic disease characterized by increasing severity over time, requiring protracted medical therapy, and that almost all NERD patients are destined to progress to erosive esophagitis, regardless of the extent of their esophageal acid exposure. However, in their original study, Pace et al. included a large number of patients with healed erosive esophagitis [24], who were erroneously considered as having NERD. Their original article lacks any information on how the diagnosis of NERD was made, what grading system was used to describe esophageal mucosal involvement, and whether patients were receiving any antireflux treatment prior to first endoscopy.

Labenz et al. have proposed a highly complex model to describe the natural course of GERD

[30]. The authors evaluated progression or regression in GERD using the ProGERD (progression of gastroesophageal reflux disease) database. After a 2-year follow-up, 24.9% of the NERD patients progressed to develop low-grade erosive esophagitis (Los Angeles classification grades A and B), and 0.6% developed severe erosive esophagitis (Los Angeles classification grades C and D). Interestingly, 50.4% of the subjects with grades C and D and 61.3% with grades A and B regressed to NERD. The study provides findings from only two endoscopic studies (index and follow-up). This is the first study that suggests that patients may move freely and in large numbers from NERD to erosive esophagitis and back again.

Serrano et al. followed 692 GERD patients over a period of 6 years and prospectively assessed progression or regression along the spectrum [31]. Patients with NERD did not develop erosive esophagitis and those with erosive esophagitis remained within the grading of the initial diagnosis. Sontag et al. performed a retrospective study of 2306 GERD patients having at least two separate upper endoscopies during a mean follow-up of 7.6 years. The authors reported that the endoscopic findings of 67% of the patients remained unchanged, 21% improved, and 11% worsened [32]. Bardhan et al. provided the longest and largest natural history data evaluating 12,374 GERD patients over a period of 24 years [33]. The authors documented only 4.4% progression to erosive esophagitis among the NERD patients with the mean time for the development of this change being 5.3 years. In a separate study, male sex, smoking, and presence of metabolic syndrome independently increased the likelihood of progression from NERD to erosive esophagitis [34].

Thus far, there is no evidence to suggest that patients with NERD progress to adenocarcinoma of the esophagus. In a recent large population-based cohort study of 33,849 patients, only erosive esophagitis was associated with an increased risk of adenocarcinoma of the esophagus [35]. Of the 7655 patients with NERD, only 1 was diagnosed with adenocarcinoma of the esophagus after 4.5 years of follow-up.

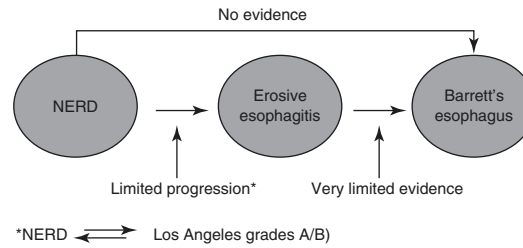

Fig. 10.3 The current understanding of the natural course of NERD (adapted from [36])

Overall, these studies suggest that lack of progression is much more common than progression along the spectrum of patients with NERD. The vast majority of NERD and erosive esophagitis patients remain within their respective GERD group throughout their lifetime (Fig. 10.3) [36]. Most importantly, there is no evidence that NERD patients progress over time to develop Barrett's esophagus or adenocarcinoma of the esophagus.

Pathophysiology

Current concepts in the pathophysiology of NERD involve peripheral factors (luminal, mucosal, and sensory afferents) as well as central (psychological, stress, sleep, etc.).

Overall, there is no difference in gastric acid output between NERD patients and those with erosive esophagitis [37]. The degree of esophageal acid exposure in patients with NERD is significantly lower as compared to that measured in patients with erosive esophagitis or Barrett's esophagus. In one study, the mean recorded number of acid reflux events was 95.3 in NERD versus 139.7 in those with erosive esophagitis [10]. Furthermore, patients with NERD have the lowest esophageal acid exposure profile (pH < 4) in % total, recumbent, and upright time as compared to the other GERD groups. Unlike patients with erosive esophagitis and Barrett's esophagus who demonstrate a very high acid exposure in the very distal portion of the esophagus that tapers down proximally, NERD patients have very little variation in esophageal acid exposure distribution throughout the esophagus (total and

Table 10.1 The extent of the overlap of esophageal acid exposure (% total time pH < 4) among the different GERD phenotypes (adapted from [39])

Group compared	Total (%)	Upright (%)	Recumbent (%)
BE, EE	47.8	40.7	24
BE, NERD	31.6	37.5	20.8
EE, NERD	47.4	64.7	81.8

BE Barrett's esophagus, *EE* erosive esophagitis

recumbent) [38]. Shapiro et al. have shown a marked overlap in esophageal acid exposure between NERD patients and those with erosive esophagitis and even those with Barrett's esophagus (Table 10.1) [39]. The study suggests that other factors, possibly genetic and environmental, determine disease presentation.

Recently, Sano et al. evaluated the mechanisms of acid reflux episodes in patients with NERD as compared to healthy controls and patients with mild esophagitis [40]. Transient lower esophageal sphincter (LES) relaxation (TLESR) was found to be the major mechanism of acid reflux in all three groups. There were no differences in the rate of TLESRs per hour among the three groups. At 7 cm above the LES, patients with NERD had significantly more frequent episodes of acid reflux during TLESRs (mean ± SEM 42.3 ± 4.8 per hour) as compared to those with mild reflux esophagitis (28.0 ± 3.8 per hour) and healthy subjects (10.8 ± 2.5 per hour) suggesting that acid extends proximally more readily in patients with NERD than in the other two groups. Furthermore, total acid and weakly acidic reflux is greater in erosive esophagitis and Barrett's esophagus than in NERD [41], but NERD patients demonstrate greater proximal migration of any type of reflux [38]. NERD patients are also more sensitive to weakly acid reflux than those with erosive esophagitis [42].

Adachi et al. have demonstrated that NERD patients had significantly lower nighttime esophageal acid exposure as compared to patients with grade C and D erosive esophagitis [43]. Dickman et al. have shown that the esophageal acid exposure pattern during sleep is similar among the different GERD groups [44]. NERD patients with abnormal pH test had similar level of esophageal acid exposure during sleep as patients with erosive esophagitis. Esophageal acid exposure was the highest at the beginning of sleep and markedly dropped toward the middle of the sleep period.

Several luminal factors were found to be predictive of a sensed acid reflux event as compared to a non-sensed acid reflux event (using impedance + pH sensor), and they include proximal migration of an acid reflux event, larger pH drops, lower pH nadir, larger volume and longer acid clearance time, preceding higher esophageal cumulative acid exposure time, and presence of gas in the refluxate [42, 45]. Schey et al. have shown that NERD patients demonstrated the highest number of acid reflux events before a sensed reflux event as compared with other heartburn groups [46]. This suggests that prior sensitization is needed for an acid reflux to be perceived in NERD patients who demonstrated a lower esophageal acid exposure compared with erosive esophagitis patients. Proximal esophageal migration of a reflux event has been shown to be an important predictor of symptom generation in NERD patients as well as other GERD groups, regardless of whether the reflux is acidic or weakly acidic [47]. The underlying mechanism for this phenomenon is unknown. Some have stipulated that it is likely due to summation effect (the higher in the esophagus the reflux migrates, the more esophageal pain receptors are sensitized) or increased sensitivity of the proximal portion of the esophagus to either chemical or mechanical stimuli.

The role of nonacid reflux in NERD was assessed by esophageal impedance-pH monitoring in 150 NERD patients [48]. NERD patients had more reflux episodes (acid and nonacid) as compared to controls. A study that was conducted in a small group of normal subjects has demonstrated that acidic or weakly acidic solutions can result in the development of dilated intercellular space (DIS) [49]. The study suggests that NERD patients are likely to develop similar mucosal abnormalities from both types of gastroesophageal reflux. DIS in NERD patients have been associated with impaired esophageal mucosal resistance [49, 50]. Farre et al. found baseline

impedance as a sensitive marker of esophageal mucosal integrity in a rabbit model [51]. In a systematic review of patients with GERD who are on a PPI, 80% of reflux episodes were weakly acidic or weakly alkaline and 83% of symptom episodes were associated with weakly acidic or weakly alkaline reflux. The study concluded that weakly acidic reflux underlies the majority of reflux episodes in patients with GERD on PPI therapy, and is the main cause of symptoms occurring on PPI therapy [52]. A recent study demonstrated that symptomatic weakly acidic refluxes were preceded and sensitized by acid reflux episodes [53].

Gas reflux episodes can be perceived as heartburn and regurgitation [45] by triggering mechanoreceptors during esophageal luminal distention [54]. Emerenziani et al. demonstrated that the presence of gas in the refluxate significantly increases the probability of reflux perception in NERD patients [42]. Moreover, a recent study showed that some patients with GERD symptoms refractory to PPI therapy have increased number of prandial air swallows and postprandial, mixed gas-liquid reflux than those who responded to PPI therapy [55].

There are very limited data concerning the role of bile reflux in symptom generation of patients with NERD. The mean fasting gastric bile acid concentration in NERD patients is similar to healthy controls. Additionally, combined acid and duodenogastroesophageal reflux, which correlates with severity of mucosal involvement in GERD, has been documented in only 50% of NERD patients compared with 79% of erosive esophagitis patients [56].

Physiological studies in patients with NERD have revealed minimal esophageal abnormalities. These patients have a slightly higher rate of primary peristalsis failure, defined by non-transmitted contractions or peristaltic contractions that do not traverse the entire esophageal body as compared to normal controls [57]. The rate of triggering secondary peristalsis in patients with NERD is significantly lower than normal controls. However, when secondary peristalsis does occur in NERD patients, there is no difference in amplitude and velocity when compared to normal controls [57]. The abnormality in secondary peristalsis may explain the overall homogeneous distribution of acid reflux that was observed by Dickman et al. [38]. NERD patients demonstrate mildly reduced mean lower esophageal sphincter resting pressure and distal amplitude contractions as compared with normal subjects [58]. Resting lower esophageal sphincter pressure is rarely below 10 mm Hg [23]. In contrast, 25% of patients with mild erosive esophagitis and 48% of those with severe erosive esophagitis demonstrate peristaltic dysfunction. The mean resting lower esophageal sphincter pressure is significantly lower in patients with erosive esophagitis as compared to those with NERD [23, 37].

Hiatal hernia occurs in only a minority of NERD patients. Cameron et al. compared hiatal hernia rates in patients with NERD versus those with erosive esophagitis and demonstrated that 29% of the NERD patients had hiatal hernia as compared with 71% of those with erosive esophagitis [59]. A recent study showed hiatal hernia in 34.5% of patients with erosive esophagitis as compared to 17.4% of NERD patients [60]. The absence of diaphragmatic hernia suggests that transient lower esophageal sphincter relaxation is likely the predominant mechanism for gastroesophageal reflux in most of the NERD patients [40, 61].

The main underlying mechanism for heartburn is sensitization of esophageal chemoreceptors either directly by gastroesophageal reflux or indirectly by inflammatory mediators [62]. Dilated intercellular space (DIS) has been suggested to be an indicator of early diagnosis of GERD [63, 64]. It has been proposed that this physiologic event is possible related to the presence of marked DISs in the esophageal mucosa of NERD patients, as documented by electron microscopy. The presence of DISs results in an increase in paracellular permeability, allowing acid and other reflux components to diffuse into the intercellular spaces and reach nerve endings that are located within the esophageal mucosa, leading to a heartburn sensation [65].

It still remains to be elucidated why most acid reflux events (95%) that occur during a 24-h pH test are not associated with symptoms. It has been substantiated that acid is not the only stimulus

responsible for heartburn sensation, but rather one of a host of different intraesophageal stimuli (non-acidic reflux, a motor event, distension etc.).

Visceral hypersensitivity has also been considered to be an important pathophysiological mechanism in NERD. Three broad mechanisms are believed to underlie visceral hypersensitivity: peripheral sensitization, central sensitization, and psychoneuroimmune interactions [66]. In general, assessment of esophageal sensitivity in NERD patients has yielded evidence for reduced perception thresholds for painful stimuli. However, results are difficult to compare due to different sensory testing protocols as well as differences in stimuli. Furthermore, many studies evaluated so-called NERD patients without excluding the functional heartburn group.

Miwa and colleagues have specifically evaluated stimulus response functions to acid in patients with NERD, as compared to other GERD groups, using an acid perfusion paradigm [67]. The authors demonstrated that NERD patients had lower perception thresholds for pain, especially as compared to normal controls, but also as compared to those with erosive esophagitis and Barrett's esophagus. In a subsequent study, the authors confirmed their previous results but also noted that NERD patients were more sensitive to saline than subjects with erosive esophagitis [68]. The authors concluded that NERD patients display a more general esophageal hypersensitivity that is not limited to acidic stimuli only. Even when compared to functional heartburn, NERD patients with abnormal pH testing demonstrated lower perception thresholds for pain using a similar acid perfusion paradigm [39]. It has been proposed that the functional heartburn group, as compared to NERD patients, is a heterogeneous group composed of patients with esophageal hypersensitivity in which some are sensitive to chemical stimuli (acid) and others to different stimuli (thermal or mechanical).

Mechanical and thermal stimulation of the esophagus was also assessed in NERD patients. In a study by Reddy et al., the authors used a multimodal stimulation probe to assess pain evoked by either thermal or mechanical stimuli [69]. NERD patients demonstrated increased esophageal sensitivity only to heat stimuli but not to cold or mechanical stimuli when compared to normal controls. However, other studies have also demonstrated an increased sensitivity to mechanical stimuli (balloon distention) in NERD patients when compared to the other GERD groups [70]. Various central mechanisms have also been shown to influence processing of afferent signals at the brain level [71]. Psychological stress and emotional perturbation have been demonstrated to potentiate perception of intraesophageal stimuli [72].

Several receptors have been identified as mediating esophageal hypersensitivity due to acid, including acid-sensing ion channels, TRPV1 receptors (transient receptor potential vanilloid type 1), TRPV4- and the TRPA1-receptor, purinergic (P2X) receptors, and prostaglandin E-2 receptor (EP-1) [54, 73, 74]. Ma et al. demonstrated that TRPV1 activation causes ATP release from esophageal epithelial cells which results in release of substance P and calcitonin gene-related peptide from esophageal submucosal neurons and upregulation of platelet-activating factor (PAF) by the epithelial cells [75]. Release of PAF induces production of inflammatory mediators in the circular muscle layer which decrease muscle contraction, possibly leading to a self-sustaining cycle of motor abnormalities, resulting in enhanced exposure of the mucosa to acid and further inflammation. Furthermore, both PAF and substance P are important inflammatory mediators which could lead to an increased mucosal permeability and further peripheral sensitization [75].

Clinical Characteristics

Currently there are no clinical features that can distinguish patients with NERD from those with erosive esophagitis, Barrett's esophagus, reflux hypersensitivity, or functional heartburn. Studies have consistently demonstrated that the severity, frequency, or intensity (severity × frequency) of symptoms is similar among the different GERD phenotypes and heartburn-related functional

esophageal disorders [76]. The impact of heartburn severity on patients' quality of life was similar in patients with NERD and those with erosive esophagitis [76, 77].

Several studies evaluated the clinical characteristics of NERD patients. Lind et al. conducted a large study consisting of 424 patients with troublesome heartburn associated with NERD [15]. The mean age of the population was 50 years; 58% were female; 21% were smokers; 45% were active alcohol users; 53% had more than a 5-year history of heartburn; and 37% had hiatal hernia documented during upper endoscopy. Carlsson et al. compared the clinical characteristics of patients with NERD and those with erosive esophagitis [77]. In the NERD group, 60% were female; the mean age was 49 years; mean weight was 80.5 kg for males and 69.5 kg for females; 23% were smokers; 59% were alcohol consumers; 80% had symptom duration longer than 12 months; 29% had hiatal hernia; and 34% were positive for *Helicobacter pylori*. The erosive esophagitis group was similar to the NERD group when comparing mean age, smoking, alcohol consumption, prevalence and duration of heartburn, and *Helicobacter pylori* status. However, there were more males (59%), increased prevalence of hiatal hernia (56%), and increased weight of both males and females (86 kg and 76 kg, respectively) in the erosive esophagitis group. Lee et al. also compared symptom presentation and risk factors for NERD and erosive esophagitis in 261 Chinese patients [60]. The erosive esophagitis group was significantly older (mean 48.94 vs. 43.34 years) predominately male (58.6 vs. 39.5%), had more hiatal hernia (34.5 vs. 17.4%), greater body weight (67.57 vs. 61.06 kg), and higher BMI (24.09 vs. 22.68) than patients with NERD. Both erosive esophagitis and NERD groups had similar rates of severity and frequency of heartburn and acid regurgitation and lifestyle habits (such as tea, coffee, alcohol consumption, and cigarette smoking). While the frequency of regurgitation was significantly greater in the female NERD patients than in the male NERD patients, this was not noted with heartburn symptoms. GERD symptoms and quality of life for the erosive esophagitis and the NERD groups were similar and both groups had lower quality-of-life scores when compared with the control group. The female patients with NERD had a higher frequency of GERD symptoms and lower quality-of-life score as compared with the NERD male patient. Gender had no effect on symptom scores or quality-of-life scores in the erosive esophagitis group. A recent study evaluating risk factors for erosive esophagitis and NERD demonstrated that a hiatal hernia increased the risk for both erosive esophagitis and NERD. *Helicobacter pylori* infection was significantly more common among those with NERD. Logistic regression analysis showed that female gender was a significant risk factor for NERD [22].

Increase in body mass index (BMI) has been associated with an increased risk for having erosive esophagitis or other complications of GERD [78]. However, a recent study has demonstrated that being overweight is an important risk factor for having NERD but not reflux hypersensitivity or functional heartburn [79].

Psychological comorbidities in GERD patients have been shown to predict the presence of GERD-related symptoms regardless of the presence or absence of esophageal mucosal injury [80–82]. Patients with higher emotional sensitivity or neuroticism complain more frequently of GERD symptoms such as heartburn. However, studies did not find a specific correlation between psychological comorbidity and esophageal mucosal damage or extent of esophageal acid exposure [83].

Wu et al. evaluated the clinical characteristics of patients with NERD in comparison to those with erosive esophagitis [84]. Each patient underwent endoscopy, esophageal manometry, acid perfusion test, and ambulatory 24-h esophageal pH monitoring. The authors found that NERD patients had a significantly higher prevalence of functional bowel disorders such as functional dyspepsia and irritable bowel syndrome. In addition, NERD patients were more likely to have psychological disorders and

positive acid perfusion test. In contrast, patients with erosive esophagitis were characterized by higher prevalence of hiatal hernia, greater esophageal acid exposure, and more esophageal dysmotility [85].

Irritable bowel syndrome (IBS) and dyspepsia-like symptoms are commonly reported by NERD patients [84, 86]. However, the association or overlap with functional bowel disorders is not unique to NERD and is also very common in erosive esophagitis patients. These symptoms were demonstrated to independently determine reflux symptom severity in NERD patients as compared with normal controls [87]. A recent study evaluated upper gastrointestinal symptoms (GERD and dyspepsia-like) in patients on maintenance PPI therapy for erosive esophagitis or NERD [88]. NERD patients had significantly higher symptom scores than the erosive esophagitis group. In a study comparing NERD and functional heartburn patients by assessing bowel symptoms, heartburn was scored higher in patients with NERD as compared to those with functional heartburn, while bowel symptoms were similarly scored in the two groups. In both functional heartburn and NERD, bowel symptoms were the strongest predictors of heartburn severity [89].

Several studies have reported that GERD is commonly associated with sleep disturbances resulting in considerable economic burden and reduction in health-related quality of life [90, 91]. Sleep dysfunction has been shown to be similar in patients with NERD and those with erosive esophagitis [92]. Although the causative relationship between GERD and OSA remains a subject of debate, a recent study conducted by You et al. found that there was an increased risk for OSA in patients with NERD as compared to patients with erosive esophagitis and healthy controls [93]. Furthermore, subjects with nocturnal GERD-related symptoms in the NERD group were more commonly at risk for OSA than those in the erosive esophagitis group.

Comparison of clinical and physiologic characteristics of NERD and erosive esophagitis is summarized in Table 10.2.

Table 10.2 Clinical and physiologic characteristics of nonerosive reflux disease (NERD) patients as compared to patients with erosive esophagitis (EE) (adapted from [36])

Parameter	NERD versus EE
Gender	More female
Age	Younger
Weight	Leaner
Smoking	ND
Alcohol consumption	ND
Symptoms duration	Shorter
Hiatal hernia	Less common
Helicobacter pylori infection	ND
Lower esophageal sphincter resting pressure	Normal
Distal amplitude contractions	Slightly reduced
Motility abnormalities	Slightly reduced
Distal esophageal acid exposure (total, supine, and upright)	Slightly increased
Duodenogastroesophageal reflux	Slightly increased
Proximal reflux	Slightly increased

ND no difference

Diagnosis

Patients presenting with GERD-related symptoms (heartburn and acid regurgitation) in the absence of alarm symptoms are likely to be treated empirically with an antireflux medication. Empiric PPI therapy is a reasonable approach to assess for GERD when it is suspected in patients with typical symptoms. However, this approach has a sensitivity of 78% and specificity of 54% and therefore has some limitations [94].

Barium esophagrams with double contrast can detect signs of esophagitis, although the overall sensitivity of this test is extremely low [95], and therefore it is not recommended as a diagnostic test in patients with NERD without dysphagia [96].

Diagnosis of NERD requires an upper endoscopy which is the most sensitive diagnostic tool for assessing GERD-related esophageal mucosal injury such as erosions, ulceration, stricture, Barrett's esophagus, and others. A negative endoscopy may suggest the presence of NERD, although the sensitivity of diagnosing Los Angeles Grade A and even B has been relatively low, resulting in overdiagnosis of these lesions.

Endoscopy has excellent specificity for erosive esophagitis when the LA classification is used [97]. All patients suspected to have NERD on upper endoscopy should undergo biopsies of the esophagus to assess for the presence of eosinophilic esophagitis (EoE) [98, 99]. Similarly, in GERD patients refractory to PPI therapy, EoE has been identified as a potential underlying mechanism in up to 8% of cases [100]. Therefore, esophageal biopsies to assess for EoE in patients with PPI refractory GERD-related symptoms are commonly performed [12].

Several studies have evaluated the usefulness of identifying dilated intercellular spaces (DIS) in the characterization of GERD and diagnosis of NERD [65, 101]. A recent study by Kundulski et al. aimed to differentiate NERD from functional heartburn by determining the presence or absence of DISs and other microscopic inflammatory changes in the distal esophagus [102]. Basal cell hyperplasia, DIS, and total inflammatory score ($P < 0.05$–0.001) provided the required distinction between the two disorders, with the highest discrimination factor being DIS. There were no significant histomorphological abnormalities of the esophageal mucosa in patients with functional heartburn and normal controls. DIS was also correlated with acid reflux parameters by means of acid exposure time, number of acid reflux episodes, as well as acid-gas reflux episodes. However, assessment of DIS requires an electron micrograph, a tool that is not routinely used by pathologists.

The role of esophageal biopsies to differentiate patients with normal endoscopy to those with NERD, reflux hypersensitivity, and functional heartburn remains controversial. It is still unclear at what level of the esophagus biopsies should be obtained.

Studies using high-resolution magnification endoscopy, chromoendoscopy (Lugol), and narrow band imaging (NBI) have demonstrated the presence of minimal mucosal changes at the squamocolumnar junction (SCJ) of NERD patients with otherwise normal-appearing mucosa by conventional upper endoscopy. These minimal changes include vascular injection or vascular spots above the Z-line, villous mucosal surface, microerosions, increased vascularity at the SCJ, and islands of columnar cell epithelium above the Z-line [103–106]. However, thus far there is still no consensus regarding the definition of "minimal changes" and what mucosal abnormalities fall under this category.

Kiesslich et al. evaluated several endoscopic minimal changes in healthy controls compared with NERD patients, before and after treatment with 20 mg esomeprazole using high-resolution magnification endoscopy [103]. Overall, more patients with NERD had punctate erythema above the Z-line that corresponded to blood vessels shining through the mucosa. Sharma et al. have demonstrated by using narrowband imaging that dilated and increased number of intrapapillary capillary loops were the most sensitive parameters for the diagnosis of NERD with minimal changes (sensitivity of 90% and a specificity of 70%) [107].

The clinical value of identifying SCJ "minimal changes," using specialized endoscopy and other advanced visualization techniques, remains to be determined. By using pH monitoring as the gold standard, minimal changes were found to have a sensitivity for NERD that ranges from 60 to 90%, and a specificity that ranges from 64 to 83% [106].

The next step in diagnosing NERD after a negative upper endoscopy is to determine whether pathological gastroesophageal reflux is present using ambulatory reflux testing. In patients who are off treatment, a pH test should be performed. However, in patients who are on PPI treatment, there is no clear consensus whether reflux monitoring should be performed after stopping PPI therapy or while on medication [12, 108]. Overall, the approach is based on the patient's clinical presentation and pretest probability of having GERD [108]. Patients with unproven GERD (i.e., no prior documented evidence of reflux-related pathology on endoscopy or ambulatory reflux monitoring) should be studied off PPI therapy (Fig. 10.2) [12]. In contrast, patients with proven history of GERD should be studied on PPI therapy (Fig. 10.1). Reflux monitoring off

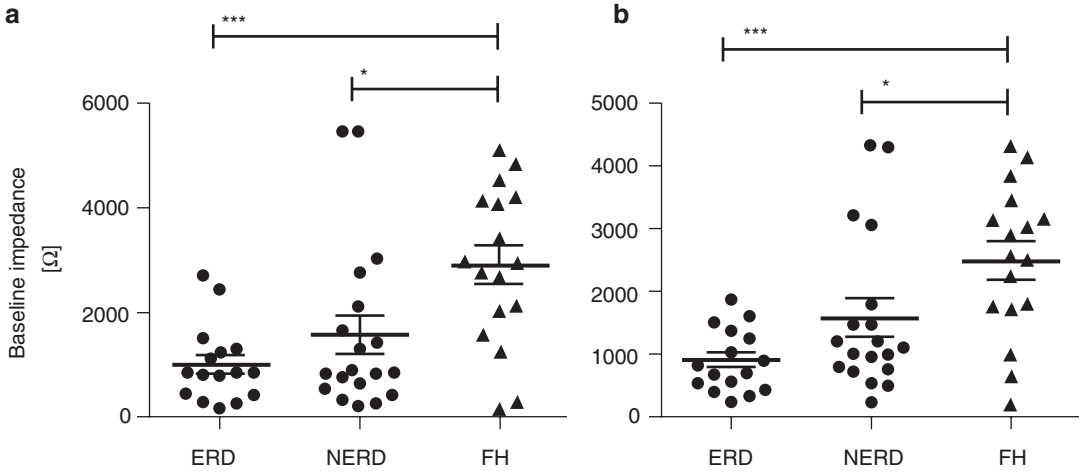

Fig. 10.4 Distal baseline impedance levels at (**a**) 3 cm and (**b**) 5 cm above the LES in patients with erosive reflux disease, nonerosive reflux disease, and functional heartburn (with permission from [110])

PPI can be performed with catheter-based or wireless pH capsule. Reflux monitoring on PPI (twice daily) should be performed with the impedance-pH technique to primarily evaluate for the presence of nonacid reflux. Diagnosis of NERD depends on the presence of abnormal esophageal acid exposure detected by either the catheter-based pH test or the wireless pH capsule [12]. However, an estimated 37–50% of patients with normal endoscopy have normal esophageal pH assessment off antireflux treatment [10]. In a recent study, Savarino et al. demonstrated that in patients with normal endoscopy undergoing impedance + pH testing, 40% had abnormal acid exposure (NERD), 36% showed symptom–reflux correlation in the absence of abnormal reflux parameters (reflux hypersensitivity), and 24% had normal pH–impedance monitoring without reflux-symptom association (functional heartburn) [48].

Esophageal manometry is of limited value in the primary diagnosis of NERD. It is recommended before consideration of antireflux surgery to rule out achalasia or scleroderma-like esophagus [108]. However, it should be considered in patients with NERD if there is any associated dysphagia. It is also commonly performed in patients with PPI-refractory GERD-related symptoms since certain motility disorders may have similar clinical presentation [109].

Baseline impedance levels have been suggested to help in distinguishing between NERD patients and those with functional heartburn. A recent study by Kandulski et al. demonstrated that baseline impedance was significantly lower in patients with erosive reflux disease or NERD than in those with functional heartburn (Fig. 10.4) [110]. By using baseline impedance, the authors observed a 78% sensitivity and 71% specificity in differentiating patients with erosive reflux disease or NERD from those with functional heartburn.

Recently, the measurement of esophageal mucosal impedance has been evaluated in the diagnosis of GERD. Mucosal impedance (MI), a minimally invasive, simple, and low-cost device, can assess esophageal mucosal impedance during an upper endoscopy [111]. In a prospective longitudinal study, median MI values were significantly lower at the site of erosive mucosa than other nonerosive regions, and were significantly lower at 2 cm above the squamocolumnar junction in patients with GERD, as compared to those without GERD [111]. The researchers then evaluated the role of MI in patients with erosive esophagitis, NERD, achalasia, eosinophilic esophagitis, and non-GERD (dyspepsia symptoms without objective evidence of GERD) using a follow-up longitudinal study [112]. Findings were compared with those from wireless pH

monitoring. MI values were found to be significantly lower in patients with GERD (erosive esophagitis or NERD) or eosinophilic esophagitis than in patients with reflux-related symptoms with nonerosive mucosa and normal pH or patients with achalasia. In addition, the recorded pattern of MI in patients with GERD differed from that in patients without GERD or those with eosinophilic esophagitis. These MI changes normalized with acid-suppressive therapy. The recorded MI patterns identified patients with erosive esophagitis with higher levels of specificity (95%) and positive predictive values (96%) than wireless pH monitoring (64% and 40%, respectively) [112].

Treatment

The goals of treatment in NERD include acute and long-term relief of symptoms, prevention of symptom relapse, and improvement in quality of life. In general, therapeutic requirements for patients with NERD are similar to those for patients with erosive esophagitis. Proton pump inhibitors are the most efficacious therapeutic modality in NERD patients. In a meta-analysis, van Pinxteren et al. demonstrated that the relative risk for heartburn remission in placebo-controlled trials of patients with NERD was 0.68 (95% CI: 0.59–0.78) for PPIs versus placebo and 0.84 (95% CI: 0.74–0.95) for H2RA versus placebo [113]. The relative risk for PPIs versus H2RAs was 0.74 (95% CI: 0.53–1.03).

A number of studies evaluated the efficacy of PPIs in NERD patients. In a multicenter, randomized, double-blind study, omeprazole 20 mg once daily was compared with placebo in controlling symptoms of 209 patients with NERD [114]. After 4 weeks of therapy, 57% of patients in the omeprazole group were free of heartburn, 75% were free of acid regurgitation, and 43% were completely asymptomatic. In another study, 509 NERD patients were randomized to omeprazole 20 mg/day, omeprazole 10 mg/day, or placebo over 4 weeks [15]. The authors found that 46% of patients treated with omeprazole 20 mg/day, 31% treated with omeprazole 10 mg/day, and 13% of those who received placebo reported complete relief of heartburn. Another 4-week study included 203 patients with NERD who were randomized to either rabeprazole 20 mg once daily or placebo [115]. At the end of the study period, 56.7% of the patients receiving rabeprazole reported satisfactory symptom relief when compared with 32.2% of those receiving placebo. A study that utilized a wireless pH capsule has demonstrated that PPIs can normalize esophageal acid exposure in patients with NERD within 48 h after initial administration [116].

Katz et al. performed two randomized, double-blind, 4-week, multicenter trials with identical methodology comparing once-daily esomeprazole (40 mg or 20 mg) with placebo in patients with NERD [117]. Patients treated with either dose of esomeprazole were 2–3 times more likely to achieve complete resolution of heartburn when compared to patients treated with placebo. The percentage of heartburn-free days was significantly higher with esomeprazole 40 or 20 mg than with placebo in each of the studies. In a 4-week, double-blind, placebo-controlled study that included 947 patients with NERD, dexlansoprazole 30 and 60 mg/day was shown to be superior to placebo in providing 24-h heartburn-free days and nights (54.9% vs. 17.5% and 80.8% vs. 51.7%, respectively) [118]. In a systematic review, indirect comparisons revealed significant difference in heartburn control of patients with NERD treated with either esomeprazole or dexlansoprazole at 4 weeks. Dexlansoprazole 30 mg was shown to be more effective than esomeprazole 20 or 40 mg (RR: 2.01, 95% CI: 1.15–3.51; RR: 2.17, 95% CI: 1.39–3.38) [119].

It has been recently proposed that the goal of achieving a complete symptom control in NERD patients is unrealistic. Unlike erosive esophagitis patients, those with NERD rarely report complete symptom resolution on PPI treatment regardless of the dose. It also appears that NERD patients are content with certain level of residual symptoms. Thus, physicians should accurately present to NERD patients the clinical goal of symptom improvement rather than complete symptom resolution [120].

Since NERD, in general, is not thought to be a progressive disorder, treatment for many patients could be symptom driven. The use of an on-demand (patient initiates PPI treatment and consumes for the duration they desire) or intermittent (patient initiates PPI treatment, but takes it for a fixed period of time) PPI therapy is more convenient and cost effective, relieves GERD-related symptoms, reduces the likelihood of acid rebound, and improves quality of life [121–126]. In addition, Nagahara et al. conducted an open-label study in Japan comparing the efficacy of continuous versus on-demand treatment with omeprazole 20 mg for 6 months. The authors demonstrated comparable efficacy between the two groups [127]. Thus, on-demand or intermittent therapy with a PPI is an attractive therapeutic strategy for NERD patients in clinical practice.

There is paucity of data regarding risk factors for PPI refractoriness in NERD patients. A recent study conducted by Shi et al. aimed to determine which factors may potentially predict PPI treatment results in 117 patients with NERD. It was demonstrated that NERD patients who failed PPI treatment had lower BMI and more commonly concomitant functional dyspepsia symptoms [128]. PPI failure patients had a higher percentage of type I esophagogastric junction (EGJ) morphology, increased EGJ augmentation, higher prevalence of esophageal motility disorders, and a higher rate of negative symptom index. Concomitant functional dyspepsia symptoms, EGJ augmentation, and negative SI were independent risk factors for PPI failure in NERD.

The proportion of NERD patients responding to a standard dose of PPI is approximately 20–30% lower than what has been documented in patients with erosive esophagitis. In a systematic review, the pooled PPI symptomatic response rate was 37% (95% CI: 34.1–39.3) in NERD patients and 56% (95% CI: 51.5–59.5) in those with erosive esophagitis [129]. Therapeutic gain was 27.5% in NERD as compared with 48.9% in erosive esophagitis (Fig. 10.5). Furthermore, patients with NERD demonstrate a close relationship between response to PPI therapy and degree of esophageal acid exposure. The greater the distal

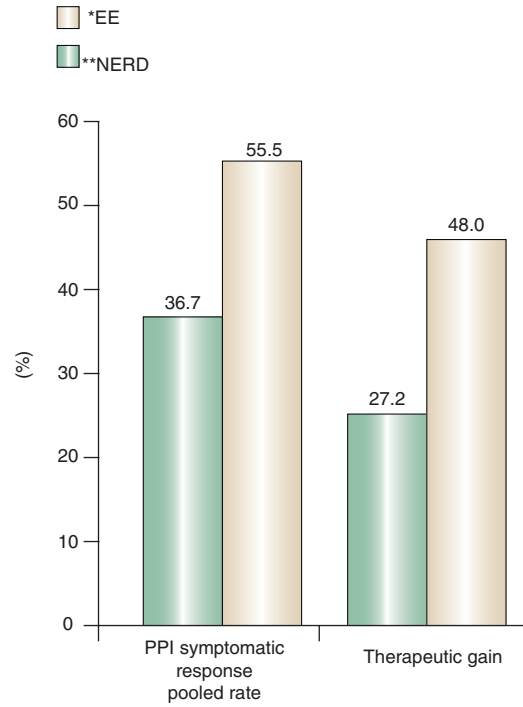

Fig. 10.5 The effectiveness of proton pump inhibitor therapy in NERD as compared to erosive esophagitis (EE) patients (adapted from [129])

esophageal acid exposure, the higher the proportion of NERD patients reporting symptom resolution [15]. This is the opposite of what has been observed in patients with erosive esophagitis, where increased esophageal inflammation and thus acid exposure have been associated with lower response rate to PPI once daily. Patients with NERD also demonstrate longer lag time to sustained symptom response when compared to patients with erosive esophagitis (two- to three-fold). In addition, patients with NERD demonstrate similar symptomatic response to half and full standard dose of PPI [130], unlike patients with erosive esophagitis who demonstrate an incremental increase in healing and symptom resolution (dose–response effect). The differences in therapeutic response parameters between NERD and erosive esophagitis are attributed to the heterogeneity of the NERD group. In some early therapeutic trials, patients with functional heartburn were not actively excluded. However, even after excluding functional heartburn patients,

the symptomatic response rate of NERD patients to PPI remains lower than what has been observed in erosive esophagitis patients. This is likely due to the fact that most NERD patients demonstrate only modest abnormal esophageal acid exposure. In addition, esophageal hypersensitivity is an important underlying mechanism in symptom generation of NERD patients.

There is limited data on the treatment of NERD patients refractory to PPI treatment. NERD patients compose the largest group of patients who failed standard-dose PPI treatment. Failure of double-dose PPI reflects more the presence of functional heartburn or reflux hypersensitivity.

Compliance, adherence, and lifestyle modifications should be considered first-line management for all patients with NERD refractory to antireflux therapy. Poor compliance and adherence to PPI treatment are common among all GERD patients. Several factors may contribute to patient compliance. These factors include knowledge about the treated disorder and the prescribed drug, perceived severity of symptoms, side effects, number of pills or additional medications, and patient's age and personality [131]. Studies have demonstrated a rapid decline in compliance from the time the antireflux medication was first prescribed and further declines with increase in dosing [132]. Moreover, poor adherence with timing of PPI consumption is rampant among both GERD and NERD patients. Gunaratnam et al. demonstrated that of the 100 patients with persistent GERD symptoms while on PPI treatment, only 46% were dosing optimally [133]. Of those who dosed suboptimally, 38.9% consumed their PPI >60 min before a meal, 29.6% after a meal, and 27.8% at bedtime. Patients should also be educated on lifestyle modifications. Heavy meals, exercise, increased alcohol consumption, and other daily activities might lead to or exacerbate symptoms in patients with NERD [134]. Consequently, it is important to recommend avoidance of specific lifestyle activities that have been identified by patients or physicians as triggering GERD-related symptoms [1]. In addition, weight loss, elevation of the head of the bed, and avoiding food consumption at least 3 h before bedtime have been shown to improve symptoms in GERD patients [135].

For patients with persistent symptoms despite these measures, treatment with transient lower esophageal sphincter relaxation (TLESR) inhibitors, endoscopic treatment for GERD, antireflux surgery, and pain modulators could be considered. Baclofen, a GABA-B agonist, was introduced as a potential add-on treatment for patients who failed PPI treatment (once or twice daily) [136]. The drug reduced TLESR rate by 40–60% and reflux episodes by 43%, increased lower esophageal sphincter basal pressure, and accelerated gastric emptying [136, 137]. Because the drug crosses the blood-brain barrier, a variety of central nervous system (CNS)-related side effects have been reported including somnolence, confusion, dizziness, light-headedness, drowsiness, weakness, and trembling. The side effects are likely an important limiting factor in the routine usage of baclofen in clinical practice [100].

Since PPI therapy has been observed to be less effective in patients with NERD when compared to patients with erosive esophagitis, alternative therapeutic options have been investigated. Sodium alginate is an antireflux agent that exerts its unique mechanism of action by rapid reaction with gastric acid and forming a raft, which floats on the top of gastric contents as an antireflux barrier [138]. Manabe et al. conducted a randomized clinical trial comparing sodium alginate plus omeprazole 20 mg daily versus omeprazole 20 mg daily alone in 73 subjects with NERD [138]. Patients randomized to sodium alginate plus omeprazole demonstrated a significantly better symptom control as compared with omeprazole alone at the end of 4-week treatment. Chiu et al. conducted a 4-week, double-blind study in NERD patients, comparing sodium alginate suspension 20 mL three times a day to omeprazole 20 mg once daily [139]. The authors demonstrated that the overall satisfaction of the group receiving sodium alginate was slightly higher than those who received omeprazole, but without significant difference. The data suggest that sodium alginate was non-inferior to omeprazole in the treatment of NERD and thus may serve as an alternative choice or an add-on when treating these patients.

Irsogladine maleate (IM), a widely used anti-ulcer treatment in Asia, protects the gastric mucosa by enhancing mucosal integrity through the facilitation of gap-junctional intercellular communication [140]. Suzuki et al. randomized 100 patients with NERD to receive either rabeprazole plus IM or rabeprazole plus placebo [141]. The presence or absence of SCJ minimal changes was documented in all patients. The addition of IM to rabeprazole significantly improved GERD-related symptoms and quality of life in patients with NERD without minimal changes.

Rikkunshito, a traditional Japanese medicine that acts as a prokinetic agent to improve gastric emptying and gastric accommodation, has been studied in NERD patients refractory to PPI treatment. In one study, NERD patients were randomly assigned to 4 weeks of either combination therapy (rikkunshito 7.5 g/day with a standard dose of rabeprazole) or double-dose rabeprazole [142]. The improvement rate of male patients in the rikkunshito group was significantly greater than that of male patients in the other group. In the rikkunshito group, the treatment was more effective in male patients with low BMI compared to those with a high BMI.

The role of antireflux surgery in patients with NERD has been scarcely evaluated. The most appropriate candidates are patients who have abnormal reflux parameters while off PPIs, report typical symptoms, and demonstrate response to PPIs [143]. Several studies compared the efficacy of Nissen fundoplication between patients with NERD and those with erosive esophagitis. The studies consistently demonstrated similar clinical outcome [144, 145]. In a more recent study, Broeders et al. evaluated the long-term outcomes of antireflux surgery in patients with NERD [144]. Nissen fundoplication was performed in 96 NERD and 117 erosive esophagitis patients demonstrating symptom improvement in 89% and 96%, respectively, 5 years post-surgery. In addition, there were no differences between the two groups in terms of PPI reduction, improvement in quality of life score, or reduction in acid exposure time. Interestingly, Omura et al. showed that laparoscopic fundoplication in patients with NERD provided excellent results even if abnormal acid reflux was not confirmed preoperatively [146].

The magnetic sphincter augmentation device (LINX Reflux Management System Thorax Medical, Shoreview, MN) is used to augment the LES [147]. The device comprises a miniature ring of interlinked titanium beads with magnetic core that are placed around the gastroesophageal junction. LINX is inserted by a simple standardized laparoscopic procedure that does not alter the anatomy of the cardia [148]. In a multicenter prospective trial, 44 participants with documented typical symptoms of GERD for at least 6 months and incomplete symptomatic response to once-daily PPI therapy as well as abnormal esophageal acid exposure while off PPI treatment underwent laparoscopic placement of LINX around the gastroesophageal junction [149]. After 3 years, 20 participants who were available for follow-up demonstrated a significant decrease in mean % total time pH < 4 from 11.9% at baseline to 3.8%, with 80% (18/20) achieving normalization of esophageal acid exposure. The mean total GERD health-related quality of life (HRQL) score of participants (off PPIs) at 4 years was significantly better (3.3 ± 3.7) as compared with baseline (25.7 ± 6.4). In another study, Ganz et al. published a 3-year follow-up of 100 participants who underwent LINX placement. Normalization of esophageal acid exposure, which was the primary endpoint, was achieved in 64% of the participants. The authors also demonstrated that the mean % total time pH < 4 had decreased from 10.9 to 3.3%, and that 87% of the participants were still off PPI at the 3-year follow-up. The median total GERD-HRQL score was 27 at baseline (off PPI) as compared with 2 at 2 years after LINX placement. In this trial, dysphagia occurred in 68% of the patients after the LINX procedure, but only 4% reported this symptom at 3 years. Two comparative studies between LINX and laparoscopic Nissen fundoplication demonstrated similar efficacy in resolving reflux symptoms and improving quality of life [150, 151]. One of the studies reported that severe dysphagia requiring endoscopic dilation was more frequent after LINX (50 vs. 0%) [150].

The other study observed higher resumption of daily PPIs (N = 24 vs. N = 12) but fewer side effects such as gas bloat in the LINX group [151].

Endoscopic techniques to treat GERD were developed more than a decade ago, but most have since been discontinued because of unacceptable side effects, modest or lack of long-term efficacy, cost, time invested, and lack of reversibility [148, 152]. Currently, there are four endoscopic techniques available in patients with GERD: Stretta, EsophyX, endoscopic stapling, and antireflux mucosectomy.

The Stretta procedure (Mederi Therapeutics Inc., Greenwich, CT), which has the best long-term data of all endoscopic techniques, uses an endolumenal approach to deliver low-power, temperature-controlled radiofrequency energy into the gastroesophageal junction. This relatively simple procedure has been observed to reduce the frequency of TLESRs and consequently reduce gastroesophageal reflux episodes and esophageal acid exposure [153]. Clinical studies have demonstrated a sustained improvement in GERD-related symptoms, quality of life, and use of antireflux medications over a period of 4 years [154]. In a 10-year follow-up, Noar et al. prospectively evaluated the long-term safety, efficacy, and durability of response to Stretta in 217 patients [155]. Normalization of GERD-HRQL of 70% or greater was achieved in 72% of patients. There was also a 50% or greater reduction in PPI use in 64% of patients, and 41% eliminating their PPIs entirely. Preexisting Barrett's metaplasia regressed in 85% of biopsied patients and no cases of esophageal cancer occurred. Concerns have been raised about the potential long-term anatomic complications of the Stretta procedure such as esophageal stricture or neurolysis. However, studies have argued against fibrosis and neurolysis as the main complications of the Stretta procedure in GERD [156].

Transoral incisionless fundoplication (TIF), using the EsophyX device (EndoGastric Solutions, Redmond, WA, USA), creates a full-thickness serosa-to-serosa plication and constructs a valve 3–5 cm in length and 200°–300° in circumference [157]. Most importantly, TIF reduces or completely eliminates PPI consumption by different GERD phenotypes, including those with NERD [158, 159]. In a multicenter trial, which included 86 patients treated with PPI (most with EE but all with hiatal hernia <2 cm in length), authors reported the results of a 12-month follow-up [160]. The study demonstrated that after 1 year, 73% of participants reported ≥50% improvement in HRQL, 85% discontinued daily PPI use, and 37% normalized esophageal acid exposure. Testoni et al. conducted a prospective, observational study evaluating the long-term effect of TIF on acid reflux and symptoms of 50 GERD patients who had daily dependence on PPI by using quality-of-life questionnaires, endoscopy, esophageal manometry, and impedance-pH monitoring, before and 6, 12, and 24 months after TIF, and subsequent yearly clinical evaluation. Patients were followed for up to 6 years. At 6, 12, 24, and 36 months after TIF, 83.7%, 79.6%, 87.8%, and 84.4% of patients, respectively, stopped or halved PPI use and remained stable for up to 6 years. Symptom scores off PPI were significantly lower. Impedance-pH monitoring indicated significantly fewer total and acid refluxes after treatment. Overall, TIF achieved lasting elimination of daily dependence on PPI in 75–80% of patients for up to 6 years.

Although the use of the TIF procedure has been limited by worrisome side effects including esophageal perforation, significant GI bleeding, and pneumothorax [161, 162], the overall reported incidence of serious adverse events associated with this procedure is 3.2% [163] and more recent studies report rare serious adverse events when compared to the sham group [164, 165].

Endoscopic stapling is a newer technique that creates an endoscopic partial fundoplication used to treat GERD patients, including those with NERD. The Endoscopic Stapling System (MUSE™, formerly called SRS, Medigus, Tel Aviv, Israel) is used to perform anterior fundoplication using a modified endoscope that incorporates a miniature camera, an ultrasound probe, and stapler at the tip [166]. The technique is yet to be approved for clinical use in the USA. A recent study compared the safety and efficacy of SRS with laparoscopic antireflux surgery

(LARS) [167]. The authors demonstrated that the procedure times for SRS and LARS were 47 min and 89 min, respectively ($P < 0.05$). However, the mean discharge time from the hospital was longer for SRS as compared with LARS (3 vs. 1.2 days, $P < 0.05$). There was no significant difference in the need for PPI consumption between the two groups at a 6-month follow-up. The mean GERD-HRQL scores significantly improved in 64% of the participants who underwent SRS. The mean score in these patients decreased from 24.8 to 8.9 ($P = 0.016$). There was one esophageal perforation in the SRS group.

Antireflux mucosectomy (ARMS) has been evaluated in ten patients with refractory GERD. ARMS of the esophagogastric junction (EGJ) mucosa was conducted using endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD), of at least 3 cm length (1 cm in the esophagus and 2 cm in the stomach) with the length of mucosal resection at the cardia measured in retroflexion from the gastric side. ARMS was conducted along the side of the lesser curve of the stomach, thus preserving a mucosal valve at the gastric cardia [168]. Post-procedure the mean heartburn score decreased from 2.7 to 0.3, regurgitation score from 2.5 to 0.3, and total score from 5.2 to 0.67. In 24-h esophageal pH monitoring, the % total time pH <4 improved from 29.1 to 3.1%. In two cases of total circumferential resection, repeat balloon dilation was necessary to control stenosis. In all cases, patients were able to discontinue their PPI without resultant symptoms.

In general, the success of any endoscopic technique for GERD depends on careful patient selection and a high level of expertise of the surgeon or endoscopist.

Adding a pain modulator in PPI-failure NERD patients is a possible therapeutic strategy, because esophageal hypersensitivity plays an important role in symptom generation of this patient population. Pain modulators, such as tricyclics, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), have been shown to be highly efficacious in patients with functional esophageal disorders, such as functional chest and functional heartburn [169–171]. Currently, there are no studies demonstrating the value of pain modulators in NERD patients who failed PPI once daily. However, adding a pain modulator to a PPI or providing a pain modulator alone to those without any improvement on a PPI is considered a possible therapeutic strategy in NERD patients who failed PPI treatment.

Psychological comorbidity is very common in GERD patients and appears to affect all GERD phenotypes. Patients with NERD, when compared with patients with erosive esophagitis, demonstrate a significantly higher prevalence of psychological disorders [172]. Patients with poor correlation of symptoms with acid reflux events display a high level of anxiety, depression, and hysteria as compared with patients who demonstrate a close correlation between symptoms and acid reflux events [173]. Patients who do not respond to PPI therapy are more likely to have psychosocial comorbidity than those who are successfully treated with a PPI [173] and response to PPI treatment may be associated with the level of psychological distress [174]. Furthermore, in a recent study increased levels of anxiety were associated with more severe retrosternal pain and burning and a reduced quality of life [175]. Therefore, alleviating anxiety or depression should be part of NERD management in these patients and NERD patients who are not responsive to treatment should be evaluated for psychological comorbidities because it is likely to play an important role in failure to respond to PPI treatment [172].

Psychological intervention can improve the general well-being and quality of life of patients with GI symptoms and also influence the outcome of medical and surgical treatment [174, 176]. Psychological modalities such as hypnotherapy, relaxation techniques, biofeedback, and cognitive behavior therapy are likely to have a therapeutic value in these patients [177–182]. In one study, muscle relaxation techniques were found to reduce heart rate, anxiety ratings, reflux symptoms, and esophageal acid exposure time in GERD patients [183].

Acupuncture has been utilized in various gastrointestinal disorders and has demonstrated a significant effect on acid secretion, gastrointestinal motility, neurohormonal levels, and

sensory perception thresholds for pain [184, 185]. Acupuncture has also been used effectively in patients with GERD who failed symptomatically on PPI once daily. In one study, adding acupuncture to PPI once daily was more effective than doubling the PPI dose for controlling GERD-related symptoms in patients who failed standard-dose PPI [186]. In a study from China, where NERD accounts for >90% of the GERD patients, acupuncture significantly inhibited intraesophageal acid and bile reflux, improved GERD-related symptoms, and was safe and well tolerated [187]. In a recent study, the authors assessed the value of electroacupuncture in 480 GERD participants [188]. The 24-h intraesophageal pH, bile reflux, endoscopic grading, and symptom score were all significantly reduced at the end of treatment.

Conclusions

NERD is the most common phenotypic presentation of GERD, accounting for 50–70% of all patients with heartburn symptoms. While separating between erosive esophagitis and NERD on a clinical basis is very difficult, there are clearly histologic, pathophysiological, and clinical characteristics that are unique to NERD separating it from the other phenotypic presentations of GERD. The vast majority of NERD patients will not progress over time to erosive esophagitis and Barrett's esophagus and appear to have a very low risk for esophageal cancer development. NERD patients as compared to those with erosive esophagitis demonstrate a highly variable and unpredictable symptomatic response to antireflux treatment. This difference in therapeutic response is attributed in part to the heterogeneity of the NERD group and the presence of esophageal hypersensitivity as an important underlying mechanism.

Future Directions

Mucosal impedance, which is not yet approved for clinical use, has the potential to be a useful diagnostic tool in patients with GERD-related symptoms including those who are refractory to PPI therapy. The technique can distinguish between NERD and functional esophageal disorders. The technique can also determine the effectiveness of PPI therapy and presence of continued reflux [112].

Further assessment of the role of pain modulators in addition to PPI treatment or as sole therapy is of major interest. The value of other therapeutic modalities, such as potassium channel blockers, new TLESR inhibitors, bile acid sequestrants, and pro-motility agents will likely be assessed as well. New endoscopic and surgical techniques (like the Endostim [189]) will be developed as growing number of NERD patients are seeking non-pharmacological alternatives to chronic PPI treatment. The role of alternative and complementary medicine will continue to be of immense interest and even be considered as a substitute to PPI treatment in NERD patients.

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Functional Heartburn

11

Pooja Lal and Michael F. Vaezi

They Can't Find Anything Wrong with My Esophagus, but I Continue to Have Heartburn

Gastroesophageal reflux disease (GERD) is a condition in which gastroduodenal contents reflux into the esophagus resulting in heartburn, difficulty in swallowing, pain, and other esophageal and extra-esophageal symptoms. This condition is increasingly prevalent, and has predefined diagnostic criteria and therapeutic options. However, frequently patients presenting with heartburn do not respond to the conventional treatment strategies and when tested for GERD do not show classic objective findings. This condition may be due to functional heartburn (FH), which behaves as GERD but is pathophysiologically distinct.

The diagnosis of functional heartburn is challenging, mainly because it is a diagnosis of exclusion with no pertinent positive findings (normal physiologic testing and lack of response to acid-suppressive therapy) [1]. The first step in fulfilling the diagnostic criteria for FH is usually a trial of proton pump inhibitors (PPIs) [2] followed by conventional reflux testing including upper GI endoscopy, prolonged pH monitoring [3] and manometric studies [4]. Endoscopy is fairly specific for GERD, as any endoscopic evidence such as mucosal erosions and inflammation excludes FH [5]. Ambulatory pH monitoring is essential to rule out reflux as the contributing factor for patients' symptoms. Manometric studies are needed to rule out achalasia and other potential motility disorders.

The exact pathophysiological mechanisms responsible for functional reflux are not fully understood but this group shares several risk factors common in other functional gastrointestinal disorders (FGIDs). For example, the prevalence of functional disorders is higher in populations with positive family history of FGIDs [6]. This familial predisposition may be due to genetic, environmental, and/or social factors. Another strong predisposing factor associated with functional heartburn is psychological stress [7]. Patients with functional gastrointestinal disorders typically show increased inclination towards somatization, anxiety, and depression.

The therapeutic options vary greatly and can be tailored according to individual cases, utilizing both pharmacologic and non-pharmacologic approaches. Different relaxation techniques, hypnotherapy, and stress-relieving exercises have shown improvement in the quality of life and

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longer symptom-free durations in FGIDs [8]. The effects of pain modulation have also shown significant results, with tegaserod (a 5-HT4 receptor partial agonist) [9], melatonin [10], nortriptyline, and AZD1386 [11] (a transient receptor potential vanilloid 1 antagonist) demonstrating benefit in this group of patients. Among patients with a history of psychological stress or depression, antidepressants, specifically fluoxetine (an SSRI), have also shown to be of benefit [12].

How Is FH Defined and What Are the Predisposing Factors?

Definition. There has been interval evolution of the diagnosis for FH. This evolution has centered on what to do with patients who have normal esophageal acid exposure but have positive symptom association. In Rome II, "acid-sensitive esophagus" with no endoscopic evidence of mucosal injury but reproducibility of symptoms with acid exposure was initially included in the FH group [13]. Subsequently in Rome III [14], functional heartburn was defined as heartburn symptoms in the absence of any endoscopic evidence of gastroesophageal reflux disease or the temporal relationship between acid reflux and heartburn. However, in Rome IV, "acid-sensitive esophagus" is now called "reflux hypersensitivity" [15], which is distinct from "functional heartburn" due to the temporal relationship between the acid reflux and the symptom.

Thus, ***based on the Rome IV criteria, FH is defined as follows*:**

Presence for at least 3 months, with onset at least 6 months before diagnosis of:

1. Burning retrosternal discomfort or pain refractory to optimal antisecretory therapy
2. Absence of GERD (abnormal acid exposure and symptom reflux association)
3. Absence of histopathologic mucosal abnormalities (normal endoscopic biopsies)
4. Absence of major esophageal motility disorders.

Potential predisposing factors in patients with FH are likely similar to those in functional gastrointestinal disorders (FGID) which include genetic and environmental influences (Table 11.1). The genetic factors involved include *lower levels of IL-10*, an anti-inflammatory cytokine modulating mucosal neural sensitivity. A study investigating the role of IL-10 in IBS demonstrated increased prevalence of genetic polymorphisms causing lower production of this anti-inflammatory cytokine in this patient population [16]. Another study suggested mutations in the serotonin reuptake pathway resulting in *increasing levels of 5-HT* as a potential contributing factor [17]. 5-HT is contained primarily in enterochromaffin (EC) cells in the epithelial lining of the gut [18, 19]. After their release, an efficient mechanism of serotonin reuptake is required to counter the overstimulation of 5-HT receptors to prevent desensitization of the gut mucosa [20]. Abnormalities are described in specific proteins involved in the reuptake mechanism of serotonin into mucosal epithelial cells and enteric neurons. These proteins include the serotonin reuptake transporter (SERT), 5-HT transporter (5-HTT), and solute carrier family 6 members 4 (SLC6A4) [21]. The genetic polymorphisms causing an increased release of serotonin are linked to diarrhea-predominant irritable bowel syndrome (dIBS) [22, 23]. It is possible that similar mechanisms may play a role in patients with FH.

Table 11.1 Factors involved in functional heartburn

• Lower levels of IL-10
• Increased production of serotonin (5-HT) from gut cells
• Family history of functional gastrointestinal disorders
• History of abuse (physical, mental, emotional, sexual)
• History of psychological illness
• Acute stressors

The *familial predisposition* may be due to the influence of genetic, environmental, social, and psychological factors. This observation is substantiated by the health-seeking behavior of children of parents with FGID who reportedly have increased prevalence of IBS as compared to children with healthy parents [6]. Similarly, there is clustering of IBS and other FGIDs among

families. Furthermore, it was revealed that the concordance for FGID was twice as likely in monozygotic twins as compared to dizygotic twins [24]. Children of adult patients with IBS make one-third more health care visits than the control children of parents without IBS [25]. Thus, there seems to be some familial causes in the development of FGID, including functional heartburn.

In addition, increased prevalence of *history of sexual, physical, and emotional abuse* is reported in patients with FGIDs. One study demonstrated that 22% of subjects suffering from FGID reported some form of abuse, with the abused patients more likely to report IBS-like symptoms as compared to subjects with no history of abuse [26, 27]. Similarly, another study reported the frequency of rape or incest near 31% among patients with FGID as compared to 18% for those with organic disorders [28]. History of abuse may be as high as 56% in female patients with FGID [29]. Patients with FGIDs not only report an increased prevalence of abuse histories as compared to normal asymptomatic controls, but also experience more severe pain, greater psychological distress, greater impairment of functioning in their daily lives, and more frequent visits to the doctor [30]. Several *psychosocial factors* are shown to play a pivotal role in exacerbating the symptoms of FH. Experiments have demonstrated acute symptom exacerbation following stress including auditory stress [31], sleep deprivation [32] and general life stress [7, 33]. Patients with functional gastrointestinal disorders show increased propensity to develop somatization, anxiety, and depression [34].

What Is the Pathophysiology of FH?

Chemical, mechanical, and neurogenic factors have all been implicated in the pathophysiology of FH (Table 11.2). Some have also suggested a role for central and peripheral neural factors. One such study demonstrated that infusion of fat into the duodenum remarkably shortened the latency to onset of heartburn and intensified the perception of heartburn in subjects with GERD [35].

Table 11.2 Pathophysiology of FH

1. *Chemical factors*
• Fat
• Cholecystokinin A
2. *Mechanical factors*
• Mechanical distension of the esophagus
• Pain receptors (TRPV1) activation
3. Neurogenic factors
• Activation of serotonergic and peptidergic nerves

This observation is attributed to the notion that fat modulates the duodenal perception during gastric distention. This effect is mediated by serotonergic [36] and peptidergic nerves which have cholecystokinin A receptors [37]. Heartburn has also been associated with mechanical stimuli such as esophageal balloon distension [38]. A study compared the cortical cerebral responses induced by esophageal balloon distension and acid perfusion (using 0.1 N HCl) between FH patients and healthy controls, using Functional magnetic resonance imaging (FMRI). The findings suggest that the chemical stimulation of the esophageal mucosa is relayed to the cerebral cortex and the response is modulated accordingly. This study also found a comparatively longer latency period in cerebral response to chemical stimulation as compared to mechanical distention, which might be explained by the time required for the stimulation of the peripheral nerve endings [39].

Patients with FH, by definition, do not have reflux. A study investigated the role of reflux-promoting factors in the pathophysiology of FH and compared the results between nonerosive reflux disease (NERD), FH, and controls. The factors taken into account were the presence of hiatal hernia, mean lower esophageal sphincter tone, and number of upright diurnal acid refluxes lasting more than 5 min. The study showed minimal difference in the prevalence of hiatal hernia between the FH and control group, while an increased prevalence was observed in patients with NERD. Similarly, LES pressure and upright acid reflux episode duration varied significantly between these groups, with values in FH being

closer to controls, while in the NERD group, the results were comparable to GERD [40].

Regardless of the inciting stimulus, the underlying pathophysiology is attributed to the conventional notion of penetrating noxious stimuli through the damaged mucosa owing to inflammatory process or increased intercellular spaces having the detrimental effect on the integrity of the esophageal barrier. This concept is substantiated by demonstration of the strong stimuli piercing through the dilated intercellular spaces to activate nociceptive receptors, such as the TRPV1 receptor or the transient receptor potential acid-sensing ion channel (ASIC), which then trigger strong vagal and spinal responses from the central nervous system [41]. TRPV1 (vanilloid receptor 1) receptor is activated when exposed to heat or any pungent stimuli. It is also activated by endogenous hydrogen ions released in tissues during inflammation [42]. The expression of TRPV1 is significantly higher in patients with painful inflammatory bowel disease (IBD). This increased expression is linked to an increased release of substance P and calcitonin gene-related peptide, which induces neurogenic inflammation resulting in pain [43]. Another study evaluating the role of TRPV1 in esophagitis found that the fraction of TRPV1-expressing nerve fibers in these cases is increased, suggesting its contribution to the visceral hypersensitivity often seen in patients with GERD and chest pain [44].

How Is FH Diagnosed?

FH poses a challenging clinical situation due to lack of any specific symptomatic picture. It is, by definition, a diagnosis of exclusion, where initial trial of PPI therapy fails to ameliorate patients' symptoms [2]. The essential tests necessary before diagnosing FH include endoscopy, ambulatory reflux monitoring, and esophageal motility testing. Upper gastrointestinal endoscopy must be performed, preferably after discontinuation of the PPIs for 2 weeks. Endoscopic evidence of esophagitis (erosions and gross inflammatory changes) favors the diagnosis of reflux and essentially rules out FH [5]. Esophageal biopsies should be obtained to rule out eosinophilic esophagitis, irrespective of the endoscopic appearance of the mucosa [45]. This will help in ruling out other potential causes of heartburn. In order to rule out GERD, testing with prolonged ambulatory pH monitoring must be undertaken [3]. Ambulatory reflux monitoring with impedance monitoring combined with pH may give a better overall diagnostic yield and may aid in describing the temporal relationship between the symptoms and reflux episodes. Finally, studies have reported association of achalasia or other esophageal motility abnormalities with heartburn. Hence manometric studies must be a part of the diagnostic workup [4].

How Is FH Treated?

Treatment of patients with FH includes both pharmacological and non-pharmacologic approaches. *Non-pharmacologic options* include cognitive-behavioral therapy (CBT), relaxation training, combined psychotherapies, dynamic psychotherapy, and hypnotherapy. CBT is shown to be effective in patients with functional bowel disorders (FBD). A study compared the clinical efficacy and safety of cognitive-behavioral therapy (CBT) against education (EDU) and desipramine (DES) against placebo (PLA) in female patients with moderate to severe FBD (irritable bowel syndrome, functional abdominal pain, painful constipation, and unspecified FBD). CBT showed statistically significant benefit when compared with EDU (composite score, $P < 0.0001$). The most notable factor that gauged the composite measure of treatment benefit was patient satisfaction with the treatment. Similarly, noticeable results were found when relaxation techniques were employed in patients with FBD [46]. Combined psychotherapies are also effective in alleviating the symptoms in FGIDs. A study compared standardized multicomponent behavioral therapy plus standard medical treatment (SMBT) to standard medical treatment alone (SMT) in the treatment of IBS. The combination therapy proved to be more potent than SMT alone resulting in better symptom

reduction and overall patient satisfaction [47]. Hypnotherapy was also found to be effective in several trials, but a methodologically strong research trial with generalizable results to assess the unbiased efficacy of this method in the treatment of FGIDs is not yet available.

Acid suppression with PPIs is among the most commonly employed *pharmacologic therapies* in FH (Table 11.3). PPI therapy not only excludes reflux disease as the cause but may also be beneficial in those with FH. One study in patients with heartburn who were not stratified based on Rome criteria showed significant symptomatic improvement following 20 and 10 mg omeprazole therapy once daily in a group of patients with heartburn. The subjects were noted to have experienced moderate to severe reflux symptoms a week prior to the inclusion in this study. Moreover, 20 mg dose proved to be more effective as compared to 10 mg, establishing a distinctive dose-response effect [2]. However, considering the pathophysiology of FH, the therapeutic benefit of acid-suppressive therapy in this group is perplexing and likely due to response by those with NERD and not FH, especially as it is being defined based on Rome IV. Similarly, a randomized controlled study demonstrated the benefit of a single dose of ranitidine in FH, but the response was likely due to those experiencing "reflux hypersensitivity" as characterized by the Rome IV definition [48].

Tegaserod, a 5-HT4 receptor partial agonist, modulates the mechanoreceptor response to painful stimuli in the GI tract. A study investigated the role of tegaserod in the management of reflux symptoms in FGID. The findings revealed that the patients taking tegaserod had a higher threshold for mechanical insult to the esophageal mucosa. However, tegaserod reportedly had no effect on the chemical stimulation of the mucosa [9]. Another study compared the efficacy of melatonin to nortriptyline and placebo in the symptomatic management of FH. Since depression and other psychological factors are known to play a role in the pathophysiology of FGID, it was not surprising that nortriptyline was more effective in alleviating symptoms as compared to placebo. Melatonin also showed efficacy and in fact had better results as compared to nortriptyline. In this study, patients receiving melatonin reported increased incidence of adverse effects like abdominal distension and diarrhea as compared to

Table 11.3 Pharmacologic options for FH

Drug	Mechanism of action	Therapeutic benefit	Side effect
Omeprazole	Proton pump inhibitor	46% of the patients had a complete relief from reflux symptoms following 20 mg omeprazole after 4 weeks	Symptoms of gastrointestinal tract, headache, and respiratory infection
Tegaserod	A 5-HT4 receptor partial agonist is shown to modulate the mechanoreceptor response to painful stimuli in the GI tract	Tegaserod increases the threshold for mechanical insult to the esophageal mucosa	Increased incidence of diarrhea
Melatonin	Regulation of multiple functions in GIT via their effect on melatonin receptors	Melatonin significantly alleviates the symptoms of heartburn	Abdominal distension and diarrhea
Fluoxetine	SSRI	Increased efficacy of fluoxetine in providing 24-h heartburn-free days as compared to omeprazole or placebo	Headache, dry mouth, and decreased libido
AZD1386	transient receptor potential vanilloid 1 antagonist (TRPV1), which is a pain receptor, activated by noxious heat	AZD1386 modulates the pain sensed by heat pain receptors; however, there is no effect on the pain thresholds caused by electrical stimulation, which suggests the receptor-specific action of AZD1286	

placebo or nortriptyline, while daytime somnolence, dry mouth, and constipation were recorded more frequently in the other two groups [10].

Similarly, the role of fluoxetine, an SSRI used to treat depression, was investigated in the treatment of heartburn. 144 adult patients with heartburn for at least 6 months but incomplete response to PPIs were randomized to fluoxetine, omeprazole, and placebo once daily for 6 months. Fluoxetine provided significantly better 24-h heartburn-free days as compared to omeprazole or placebo. The adverse effects reported with fluoxetine were headache, dry mouth, and decreased libido while dizziness, headache, and constipation were reported in the omeprazole group [11].

The theory of pain modulation in the management of heartburn was further studied with regard to transient receptor potential vanilloid 1, a nociceptor that is responsive to noxious heat and acid and may be upregulated in esophageal pain. Some studies evaluated the effects of single-dose oral AZD1386 (a transient receptor potential vanilloid 1 antagonist (TRPV1)) on esophageal pain stimulus [11]. One such study employed single-dose oral AZD1386 (30 and 95 mg) vs. placebo in 22 healthy men. The findings revealed that AZD1386 modulated the pain sensed by heat pain receptors; however, there was absence of any significant effect on the pain thresholds caused by electrical stimulation, which suggests the receptor-specific action of AZD1286. This was also evidenced by its regulatory effect on the pain perception caused by heat but not deep pressure. In the same study, it was observed that AZD3186 had no effect on pain modulation pre- and post-acid stimulation of the esophagus [49]. This is in accordance with previous animal studies, which showed the involvement of TRPV1 in pain caused by heat stimulation [50].

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12 I Am Tired of Taking Pills for My Reflux, What Else Can I Do? Surgical and Endoscopic Treatment for GERD

Jon Gould

Question: "I heard that laparoscopic Nissen fundoplication is only temporary—that the surgery eventually falls apart in most people and needs to be redone. I also heard that there are a lot of side effects and I won't be able to belch or vomit. Is that true?"

Durability, side effects, and symptomatic outcomes of laparoscopic fundoplication for GERD.

Response to a patient: It is true that a fundoplication when performed for GERD can loosen or come apart in some people. In general, only about 5–10% of people who undergo a fundoplication eventually need to have another surgical procedure because their fundoplication failed. There are some known risk factors for fundoplication failure including vomiting in the first month after surgery and severe obesity. There is also a technical component, and experienced antireflux surgeons likely have lower rates of failure than surgeons who rarely perform this procedure. A good evaluation and workup prior to surgery are important to ensure good results and limit side effects. When done properly, in a patient who has had an appropriate preoperative workup, and by an experienced surgeon, the risk of severe side effects of a fundoplication is minimal. Contrary to what you may have heard, most patients retain their ability to belch and even vomit after a properly constructed fundoplication. Most patients who undergo laparoscopic fundoplication report high rates of satisfaction and a better quality of life than they had before surgery.

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Brief Review of the Literature

Current estimates suggest that GERD affects around 10–20% of adults in Western countries on a daily or weekly basis [1]. Up to 50% of patients with GERD may require chronic pharmacologic therapy [2]. Long-term GERD pharmacotherapy is expensive with an estimated annual cost in the USA of $11 billion [3]. Proton pump inhibitors (PPIs) have been linked via retrospective studies to increased risk of enteric infections including *Clostridium difficile*-associated diarrhea, community-acquired pneumonia, bone fracture, nutritional deficiencies, kidney failure, myocardial infarction, dementia, and interference with metabolism of antiplatelet agents [4–6]. It is estimated that as many as 40% of patients with GERD suffer from persistent symptoms despite aggressive acid suppression therapy [7–9]. As a result, 20–40% of patients are dissatisfied with medical GERD treatment and might ask "I am tired of taking pills for reflux—what else can I do?" [10].

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Surgical procedures for GERD are typically considered in patients with symptoms despite optimal PPI therapy, in patients who don't tolerate or don't want to rely on medications, and in patients with severe GERD. Surgery is used, however in less than 1% of eligible GERD patients, and its usage has been decreasing over the last decade [11]. Laparoscopic Nissen fundoplication is the most commonly performed antireflux operation. The laparoscopic approach to fundoplication was introduced and popularized in the 1990s. The surgical technique involves a complete hiatal dissection with mobilization of the esophagus and fundus, re-approximation of the diaphragmatic crura, and creation of a 360-degree wrap of fundus around the distal esophagus. Laparoscopic Nissen fundoplication can be accomplished in 2 h or less for uncomplicated cases. Most patients stay in the hospital for 1–2 days. Many surgeons have their patients gradually transition from a soft or pureed diet to a more solid diet over the course of 2–8 weeks. Relief of symptoms, especially esophageal symptoms such as heartburn and regurgitation, occurs in >90% of patients and has been demonstrated to be durable beyond 10 years for the majority of patients [12, 13]. Potential surgical side effects following Nissen fundoplication include difficulty swallowing, increased flatus, bloating, early satiety, and inability to vomit or belch [14, 15]. Anatomic failure of the fundoplication with recurrent GERD can occur in 2–17% of cases [16].

The published outcomes of antireflux surgery are not always replicated in the community, especially for surgeons who perform laparoscopic antireflux surgery infrequently [17, 18]. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) has published a *Guidelines for Surgical Treatment of Gastroesophageal Reflux Disease*. According to this document "*The standardization of antireflux surgery technique is highly desirable, as it has been shown to lead to good postoperative patient outcomes (Grade A). Like any other surgical procedure, laparoscopic antireflux surgery is subject to a learning curve, which may impact patient outcomes. Therefore, surgeons with little experience in advanced laparoscopic techniques and fundoplication in particular should have expert supervision during their early experience with the procedure to minimize morbidity and improve patient outcomes (Grade B)*" [19]. Concerns related to potential side effects, recurrent GERD, and repeat surgery following laparoscopic Nissen fundoplication likely play a role in the fact that most patients who meet indications for antireflux surgery never undergo this procedure.

Future Trends

The laparoscopic fundoplication will continue to play a major role in the surgical treatment of GERD. The current high prevalence of GERD across the USA is unlikely to change anytime soon. Patients and providers alike are increasingly aware of many of the drawbacks of long-term acid suppression with PPIs and are seeking alternative treatments. An increasing array of options for addressing medically refractory GERD including gastric bypass in the obese, magnetic sphincter augmentation, and even endoscopic treatments of GERD will likely paradoxically increase the incidence of fundoplication surgery in this author's opinion. Treatment for GERD can be tailored to the patient's individual physiology, symptom profile, and treatment goals in a way that will get patients, primary care providers, and gastroenterologists to consider something other than chronic and indefinite medical therapy, as is so often the case today.

With regard to fundoplication, new technologies such as the EndoFLIP (Endoluminal Functional Lumen Imaging Probe) may help surgeons to create a more consistent fundoplication least likely to result in side effects. Fundoplication surgery in the modern era is still very much of a subjective art. A better understanding of the mechanisms of failure and the advanced technologies available prior to considering antireflux surgery in a given patient will also likely contribute to better and more durable outcomes.

Question: "What about the magnetic sphincter augmentation device for GERD? Is this a better choice than a fundoplication?

Response to Patient: Surgery to implant a magnetic sphincter augmentation device, also known as a LINX device, is an alternative to traditional antireflux surgery. The LINX device is an implantable medical device that is placed around the junction between the esophagus and the stomach to augment or increase the competence of the lower esophageal sphincter in patients with GERD. Surgery to implant the device is performed laparoscopically (small incisions) and generally takes less than an hour. Many surgeons send their patients home the same day. Compared to a Nissen fundoplication, placement of the LINX device is technically easier and less invasive. The magnetic sphincter augmentation (MSA) device has been shown to lead to very high rates of resolution of severe GERD symptoms and high rates of patient satisfaction. Compared to a Nissen fundoplication, patients who undergo placement of a MSA device preserve the ability to belch and report low rates of bloating. The LINX device has been demonstrated to be very safe as well. Since the FDA approved this device in 2012, very-long-term follow-up is still not available, although results in patients who have had the device in place for 5 years or more have been excellent. Some patients are not appropriate for the LINX device including patients with a body mass index well over 35 kg/m^2 (obese), patients with very large hiatal hernias, and patients with very poor esophageal motility. For many patients, the LINX device is a better choice than a fundoplication, especially when they are concerned about developing bloating and difficulty belching as a result of antireflux surgery. The most commonly reported side effect of MSA is dysphagia—difficulty or discomfort in swallowing. While dysphagia is common immediately after surgery, it goes away in most MSA patients.

Brief Review of Literature

The LINX® Reflux Management System (Torax Medical, Inc., Shoreview, MN, USA) is comprised of a small expandable ring of linked magnetic beads. The device is laparoscopically implanted around the esophagus at the esophagogastric junction to mechanically augment the function of the lower esophageal sphincter for the treatment of GERD. The LINX Reflux Management System is based on the premise that a device placed around the lower esophageal sphincter (LES) can assist, or augment, an incompetent LES to maintain a closed position when challenged by gastric reflux. The LINX System is indicated for patients diagnosed with GERD as defined by abnormal pH testing, and who continue to have chronic GERD symptoms despite medical therapy for the treatment of reflux. The LINX System is not intended for use in patients with suspected or known allergies to metals such as iron, nickel, titanium, or stainless steel. The current generation of the device is compatible and safe with an MRI up to 1.5 Tesla. The LINX device is currently not recommended in patients with a hiatal hernia greater than 3 cm, in patients with a body mass index greater than 35 kg/m^2, in patients with inefficient esophageal motility, or in patients with moderate to severe baseline dysphagia.

Review of published studies suggests that magnetic sphincter augmentation is safe with no reported deaths and a 0.1% rate of intra/perioperative complications [20]. Long-term efficacy of LINX appears good for typical GERD symptoms with reduced acid exposure, improved GERD symptoms, and freedom from PPI in 85–88% at 3–5 years [21–23]. The most common side effect is dysphagia, the rate of which likely differs based on definition and patient population. Early dysphagia within the first few weeks is common at about 70% [24]. Dysphagia resolves in most patients and the incidence is roughly 10% at 1 year and 4% at 3 years [24]. The need for endoscopic dilation ranges from 6 to 12% [20, 25] and the primary reason for explanation appears to be persistent dysphagia with a rate in larger series of about 3%. Erosion appears rare with one reported in the first 1000 patients [20], one additional published case report [26], and several additional reports in the FDA MAUDE dataset (true number unknown, as multiple entries in this dataset may be made for each patient). Based on limited literature, erosion can be successfully treated with explanation.

There are several publications comparing clinical outcomes of the LINX device to laparoscopic Nissen fundoplication. Perioperative outcomes, symptom control, side effects, adverse events, and pH studies were compared in 34 consecutive patients who underwent LINX to 32 consecutive patients who had laparoscopic Nissen fundoplication [27]. Operative time was longer for fundoplication. At 6 months, scores on the Gastroesophageal Reflux Disease Health Related Quality of Life scale improved from 20.6 to 5.0 for LINX vs. 22.8 to 5.1 for fundoplication. Postoperative DeMeester scores (14.2 vs. 5.1, $p = 0.0001$) and the percentage of time pH was less than 4 (4.6 vs. 1.1; $p = 0.0001$) were normalized in both groups but statistically different. LINX resulted in improved gassy and bloated feelings (1.32 vs. 2.36; $p = 0.59$) and enabled belching in 67% compared with none of the fundoplication patients. The investigators determined that LINX results in similar GERD symptom control with an improved quality of life compared to fundoplication.

An analysis of a prospective, multicenter registry of patients to undergo LINX and laparoscopic fundoplication for GERD was also reported [28]. There were 202 LINX and 47 fundoplication patients with 1-year follow-up data at the time of analysis. The fundoplication group was older with a greater frequency of large hiatal hernia and Barrett's esophagus. GERD health-related quality-of-life score improved following surgery for both procedures. Moderate or severe regurgitation improved from 58.2 to 3.1% after LINX and 60.0 to 13.0% after fundoplication ($p = 0.014$).

Proton pump inhibitor medications were discontinued in 82% of LINX and 63% of fundoplication patients ($p = 0.009$). Excessive gas and abdominal bloating were reported by 10% of LINX and 32% of fundoplication patients ($p \leq 0.001$). The authors of this study concluded that antireflux surgery should be individualized to the characteristics of each patient, taking into consideration anatomy and side effects. They felt that both LINX and fundoplication showed significant improvements in reflux control, with similar safety and reoperation rates.

In another comparative study, from a series of 62 LINX and 117 laparoscopic Nissen fundoplications, 50 patients in both groups were matched using the "best-fit" model incorporating numerous preoperative variables [29]. At 1 year after surgery, both groups had similar GERD health-related quality-of-life scores and proton pump inhibitor use. There were no patients with severe gas and bloating in the LINX group compared with 10.6% in the fundoplication group ($p = 0.022$). More fundoplication patients were unable to belch (8.5% of LINX and 25.5% of fundoplication; $p = 0.028$) or vomit (4.3% of LINX and 21.3% of fundoplication; $p = 0.004$). The incidence of postoperative dysphagia was similar between the groups. The authors concluded that analogous GERD patients had similar control of reflux symptoms with a lower incidence of gas bloat in LINX.

A comparative, multi-institutional retrospective cohort study of patients with GERD undergoing either LINX or laparoscopic Nissen fundoplication was recently published [30]. Comparisons were made at 1 year for the overall group and for a propensity-matched group. There were 201 LINX and 214 fundoplication patients that were similar preoperatively with regard to age, gender, and GERD-HRQL scores. Obesity, dysphagia, higher DeMeester scores, Barrett's esophagitis, and hiatal hernias were more prevalent in the fundoplication patients. Propensity-matched cases showed similar GERD-HRQL scores and the differences in ability to belch or vomit, and gas bloat persisted in favor of LINX. Mild dysphagia was higher for LINX (44% vs. 32%). Resumption of daily PPIs was higher for LINX (24 vs. 12, $p = 0.02$) with similar patient-reported satisfaction rates.

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Technology and Value Assessment Committee published a Safety and Efficacy analysis of the LINX device in 2013 [31]. They concluded that the device is both safe and effective, and should be an option for patients suffering from medically refractory GERD. In fact, in November of 2015, the American Medical Association awarded the LINX device a new Category 1 CPT (Current Procedural Terminology) code that will be effective from January 1, 2017. To be awarded a category 1 CPT code, a device

and associated procedure must be performed often and by many physicians across the country. The published, peer-reviewed literature must support clinical efficacy of the procedure as well.

Future Trends

As mentioned in the previous section, surgery for GERD is performed on a small portion of patients who would qualify. Magnetic sphincter augmentation is gradually becoming a more commonly performed procedure. Part of the reason for a relatively slow ramp-up of this procedure since FDA approval in 2012 (estimated 4000–5000 devices implanted worldwide by 4 years after initial FDA approval) is poor insurance coverage for the procedure. The creation of a category 1 CPT code should greatly improve access to this technology for patients with GERD. It is likely that the proportion of patients with medically refractory GERD to opt for surgery will increase overall.

Currently the LINX device has not been carefully studied in patients with hiatal hernias greater than 3 cm in size and in patients with Barrett's esophagus. It is likely that with increasing experience, the outcomes of LINX in these patients will be demonstrated to be acceptable and safe. Patients with medically refractory GERD after bariatric surgery (especially sleeve gastrectomy) may also be able to attain relief from their GERD symptoms with magnetic sphincter augmentation. Further study in these areas and for these indications is ongoing.

Question: "What proven endoscopic treatments are available to treat my reflux?"

Response to patient: Endoscopic procedures to address medically refractory GERD have been around for many years—with the FDA approving the first endoscopic device for GERD in 2000. Many different devices have come and gone over this time. There are currently two devices available on the market with some data to support their safety and efficacy. One of these devices endoscopically creates a reflux barrier similar to a fundoplication and is known as the transoral incisionless fundoplication (EsophyX; TIF, Endogastric Solutions). The other device delivers radiofrequency energy to the lower esophageal sphincter and is known as the Stretta Procedure (Mederi Therapeutics).

The Stretta procedure has been around for the longest period of time. The Stretta system delivers radiofrequency energy to the muscle between the stomach and esophagus. The procedure likely works by inducing scarring and fibrosis of the esophagus near the sphincter leading to an improved barrier function and fewer reflux events. According to the company website, Stretta has been proven safe and effective in more than 37 clinical studies and 18,000 procedures. Stretta received its initial FDA approval in 2000.

TIF or EsophyX received FDA approval in 2007. There are a number of comparative trials published with short-term outcomes demonstrating the efficacy of TIF compared to acid reduction medications or sham (fake) surgery. In the TIF procedure, endoscopic fasteners are fired through the stomach and the esophagus at the gastroesophageal junction to create a valve. According to the company website, more than 10,000 patients have been treated with few adverse events or complications.

In general, these procedures have only been evaluated in selected patients with normal anatomy, no severe esophagitis, and no Barrett's esophagus. The advantage to endoscopic therapy is GERD treatment with no incisions. The procedures currently on the market appear to be safe. The main question relates to their effectiveness and durability. To say that any one endoscopic device is proven at the current time is probably not the case. Most studies evaluating the outcomes following these procedures are plagued by arbitrary definitions of success, subjective outcomes, inconsistent study designs, poor follow-up data, and a lack of comparison data across techniques.

Brief Review of Literature

Stretta

The Stretta device delivers radiofrequency (RF) energy to a region around the LES via a balloon

with four electrode needles. The exact mechanism of action is unclear, but likely ablation, scarring, and fibrosis of the esophageal submucosal in this region may result in decreased compliance of the gastroesophageal junction and fewer reflux events. It is also possible that the ablation may disrupt neural signaling leading to modestly increased LES tone [32].

There have been four randomized controlled trials comparing Stretta to a sham procedure and to PPI therapy [33–36]. All trials are limited by small numbers of treated patients and short-term follow-up (12 months or less). In a prospective, randomized trial of radiofrequency ablation vs. placebo, Corley et al. [33] found that after 6 months there was no difference in daily medication use or in esophageal acid exposure times. Coron et al. [34] conducted a prospective randomized trial in patients with PPI-dependent reflux symptoms randomly allocated to either RF or PPI alone. Only 3 of 20 RF patients were able to completely stop PPI compared to none of the 16 PPI patients. No significant change in esophageal acid exposure was noted at 6 months in RF patients. Aziz et al. randomized 36 GERD patients into three groups: single-session RF, sham RF, and double-RF sessions for patients who did not experience a 75% improvement in GERD health-related quality of life (GERD-HRQL) [35]. RF significantly reduced GERD-HRQL, PPI medication use, esophageal acid exposure, and esophagitis compared to sham. Double RF had superior outcomes for most parameters. Patients were followed to 12 months. Arts et al. conducted the final randomized controlled trial of Stretta available at the time of this review [36]. In this study, 22 GERD patients were randomly assigned to RF or sham (11 in each group). This was a double-blind, randomized crossover study. Stretta was found to improve GERD symptoms and decrease gastroesophageal junction compliance. There were no changes observed in esophageal acid exposure or LES pressure.

Other non-randomized studies worth mentioning include a single-center series of patients to undergo Stretta with 10-year follow-up [37]. This was a prospective assessment of 217 patients with medically refractory GERD before and after Stretta. Normalization of GERD-HRQL occurred in 72% of patients. PPIs were discontinued in 41% of patients. A non-randomized, prospective evaluation of patients 5 years after fundoplication ($n = 87$) or Stretta ($n = 92$) revealed that posttreatment scores were lower in both groups at 5 years [38]. Symptomatic improvements after Stretta were significantly less than after fundoplication. After fundoplication, 91% of patients were completely off PPI therapy compared to 51% after Stretta. In a recent systematic review and meta-analysis of these four trials (153 patients), Lipka et al. [39] demonstrated that Stretta for patients with GERD does not produce significant changes compared with sham therapy in physiologic parameters, including time spent at a pH less than four, LES pressure, ability to stop PPIs, or GERD-HRQL. A recently published "Evidence Based Approach to the Treatment of GERD" opines, "Even though the procedure (Stretta) is simple and safe, there is no convincing evidence supporting its role in the treatment of GERD [40]."

Transoral Incisionless Fundoplication (TIF, EsophyX)

Transoral incisionless fundoplication creates an endoscopic fundoplication by using T-fasteners fired through the esophagus and the gastric fundus endoscopically. In this procedure, a 2–3 cm, 270-degree esophagogastric fundoplication is created. TIF is limited to patients without a hiatal hernia.

There have been five PPI or sham-controlled prospective randomized controlled trials of TIF. As is the case for the Stretta procedure, these trials are limited by short-term follow-up (6–12 months). Hunter et al. [41] screened 696 GERD patients and randomized patients with troublesome regurgitation on PPIs and hiatal hernia <2 cm to TIF and placebo ($n = 87$) vs. sham procedure and PPI ($n = 42$). TIF eliminated troublesome regurgitation in a larger proportion of patients (67%) than PPIs (45%). PH scores improved in the TIF group, but remained in the

abnormal range. Witteman et al. [42] randomized patients with chronic GERD to TIF (n = 40) or PPI (n = 20). At 6 months, GERD symptoms were more improved in the TIF group. PH normalization was 50% in the TIF group and 63% in the PPI group. All patients allocated to PPI treatment opted for crossover. At 12 months post-TIF, quality of life remained improved compared with baseline, but no improvement in esophageal acid exposure compared with baseline was found and normalization of pH was accomplished in only 29%. The fundoplication valve appeared deteriorated in many patients at the time of endoscopy and PPIs were resumed in 61%. These investigators concluded, "Although TIF resulted in an improved GERD-related quality of life and produced a short-term improvement of the antireflux barrier in a selected group of GERD patients, no long-term objective reflux control was achieved." Håkansson et al. [43] performed a double-blind, sham-controlled study in GERD patients who were chronic PPI users. Of 121 patients screened, 44 patients were randomized equally to TIF or a sham procedure. TIF patients experienced an average remission of GERD of 197 days, which was significantly longer than the sham procedure (107). After 6 months, 13/22 (59%) of the chronic GERD patients remained in clinical remission after TIF. Trad et al. [44] conducted a randomized, crossover study designed to determine if TIF could improve clinical outcomes in PPI partial responders and to evaluate durability of TIF. GERD patients were randomized to TIF (n = 40) or high-dose PPI (n = 23). At 6 months, PPI patients crossed over to the TIF group. Six months following TIF, 71% of crossover patients were off PPIs. Acid exposure decreased from 52% on PPI to 33% off PPI and after TIF. At 12 months in the original TIF group, 82% stopped PPIs and 45% normalized acid exposure. The authors concluded, "In patients with incomplete symptom control on high-dose PPI therapy, TIF may provide further elimination of symptoms and esophagitis healing. Outcomes of TIF remained stable up to 12-month follow-up." Trad et al. [45] conducted the TEMPO trial, a multicenter randomized study designed to compare the efficacy of TIF vs. PPIs in controlling GERD symptoms. Patients were randomized at seven hospitals to receive maximum standard dose of PPI (n = 21) vs. TIF (n = 39). At 6 months, troublesome regurgitation was eliminated in 97% of TIF vs. 50% of PPI patients. There was no difference in acid exposure (normalized 54% TIF vs. 52% PPI). At 6 months, 90% of TIF patients remained off PPI. A systematic review of published literature on TIF published in 2013 identified 15 studies reporting on over 550 procedures [46]. GERD-HRQL and Respiratory Symptom Index (RSI) scores were significantly decreased after TIF. Patient satisfaction was 72% overall, with 67% of patients in all studies discontinuing PPI medications at a mean follow-up of 8.3 months. PH metrics did not consistently normalize. The authors conclude, "TIF appears to provide symptomatic relief with reasonable levels of patient satisfaction at short-term follow-up."

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) published a Clinical Spotlight Review on Endoluminal Treatments for GERD in 2013 [47]. With regard to EsophyX they conclude "*Long term data is not yet available for EsophyX. In short term follow-up, from 6 months to 2 years, EsophyX may be effective in patients with a hiatal hernia <2 cm with typical and atypical GERD. Further studies are required to define optimal techniques and most appropriate patient selection criteria, and to further evaluate device and technique safety. Quality of Evidence: Low; Strength of Recommendation: Weak.*" With regard to Stretta, SAGES concludes "*Stretta is considered appropriate therapy for patients being treated for GERD who are 18 years of age or older, who have had symptoms of heartburn, regurgitation, or both for 6 months or more, who have been partially or completely responsive to anti-secretory pharmacologic therapy, and who have declined laparoscopic fundoplication. Quality of Evidence: Strong. Strength of Recommendation: Strong.*"

The ASGE (American Society for Gastrointestinal Endoscopy) Standard of Practice Committee in 2015 reviewed endoscopic GERD treatment including EsophyX and Stretta and determined "*We suggest that endoscopic antireflux therapy be considered for selected patients with uncomplicated GERD after careful*

discussion with the patient regarding potential adverse effects, benefits, and other available therapeutic options. Low Quality Evidence [48]."

The American College of Gastroenterology position in a 2013 publication [49] is "*The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy.* (*Conditional recommendation, moderate level of evidence*)."

The American Gastroenterological Association (AGA) published a Technology Coverage Statement on Minimally Invasive Surgical Options for Gastroesophageal Reflux Disease in April 2016 [50]. Regarding TIF the AGA states "… *the three-year plus evidence is sufficient to demonstrate sustainable improvement in health outcomes, symptom relief, decrease in PPI utilization and improvement in esophageal pH with transoral fundoplication. The selection criteria for transoral fundoplication includes GERD patients with BMI ≤ 35, hiatal hernia ≤2 cm, esophagitis LA grade A or B, Barrett's esophagus ≤2 cm, and absence of achalasia and esophageal ulcer. This option should be considered in patients not responding to PPI therapy (symptoms of regurgitation) who have documented objective evidence of GERD (pathologic acid exposure on pH testing (both off and on medication)) or esophagitis. Transoral fundoplication should be covered and reimbursed for appropriate patients who meet the selection criteria as described*."

It is safe to say that despite more than 15 years of experience with various endoscopic antireflux devices and treatments, a very small percentage of patients with GERD undergo an endoscopic procedure in current clinical practice. This likely relates to a variety of factors including a lack of proven long-term efficacy and a lack of insurance benefits to cover the costs associated with the procedures.

Future Trends

There exists today a large therapy gap for many patients with GERD. The vast majority of patients receiving treatment for GERD take acid suppression medications. A small percentage (<1%) undergoes antireflux surgery. It has been shown that 30–40% of patients continue to experience heartburn or regurgitation symptoms on a PPI [51]. Potential side effects and complications (osteoporosis, C. diff. infection, etc.) and significant costs associated with PPIs make alternative GERD therapy necessary. It is likely that at some point a safe, effective, and durable endoscopic option for GERD therapy will exist. This may turn out to be something currently on the market, an upgraded or enhanced version of an existing device, or something new entirely.

In the current climate of declining reimbursement and less comprehensive insurance coverage for new procedures, it will be difficult for small-device companies in the endoscopic GERD domain to survive. The need and potential market for an endoscopic GERD device are great. I suspect we are at least 5–10 years away from having an endoscopic GERD treatment as a commonly performed and accepted component of the GERD treatment armamentarium.

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13 Barrett's Esophagus: Am I Going to Get Cancer? What Should I Do to Avoid It?

Lavanya Viswanathan and Prateek Sharma

What Are My Chances of Getting Cancer?

Barrett's esophagus (BE) is a known risk factor for esophageal adenocarcinoma (EAC) , which is concerning not only for its rising incidence but also for its high mortality rate in excess of 80% at diagnosis [1]. The overall cancer incidence in BE without dysplasia was estimated to be low at 0.5% per year [2]. However, several large studies within the past 5 years have suggested that the cancer risk is even lower, between 0.12 and 0.33% per year [1, 3]. While data suggests that the majority of patients with BE do not develop cancer, the individual impact of EAC is devastating. An estimated 95% of patients with newly diagnosed EAC do not have a previous diagnosis of BE, which underscores the need for screening and recognition of BE [4]. The recommended management strategy once BE is diagnosed is surveillance and eradication of dysplastic BE to avoid progression to EAC [2]. Patients with non-dysplastic BE should be reassured of this low risk of cancer development.

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How Can I Avoid Getting Cancer?

Current management of Barrett's esophagus includes endoscopic surveillance of the disease and treatment of the underlying reflux symptoms using acid-suppressive medications (PPI). Though there are no long-term studies proving mortality benefit from surveillance, the academic consensus is to follow these patients with the goal of endoscopic eradication of high-grade dysplasia/early EAC if detected during surveillance. Endoscopic ablative therapy, which targets the neoplastic tissue and removes it, allowing for its replacement with squamous epithelium, has been shown to be effective and safe in treating, dysplasia [5]. Endoscopic mucosal resection, or EMR, is the initial and main treatment modality which provides tissue for analysis. It involves the removal of mucosal and submucosal tissue, either by submucosal fluid injection which lifts the mucosal segment or a "suck-and-cut" technique where the dysplastic tissue is sucked into a cap on the tip of the endoscope and resected using a diathermic snare [6]. The main ablative therapy used in practice is radiofrequency ablation, or RFA, by which radiofrequency energy is applied to destroy Barrett's epithelium. Current guidelines recommend endoscopic eradication therapy for high-grade dysplasia (HGD), but it is being used to treat select cases of low-grade dysplasia (LGD) as well [2].

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For reasons that are further elucidated in the course of this chapter, Barrett's metaplasia is thought to be due, in part, to chronic acid exposure in the distal esophagus. Accordingly, chronic acid exposure leads to molecular changes of the esophageal cells that potentiate carcinogenesis. Patients who are diagnosed with Barrett's metaplasia are treated medically with proton pump inhibitors (PPIs) to control acid reflux and reduce acid exposure of the esophageal mucosa. Several retrospective studies have shown that PPI use could potentially lead to a decrease in the progression risk in BE patients.

Patients should be effectively counseled when the initial diagnosis of Barrett's esophagus is made that surveillance and treatment will require close, long-term follow-up and therefore patient commitment to this process should be assessed. For example, during surveillance, patients may have to return for follow-up endoscopies with biopsies every 3–5 years. On the other hand, during endoscopic therapy of neoplasia, repeated ablative therapies may be needed every 2–3 months, depending on the extent of disease, and noncompliance may place the patient at risk of progression to esophageal adenocarcinoma. A team-based approach to care, with sufficient education by the medical team, should be employed to effectively manage this disease process.

Introduction

Barrett's esophagus is defined by the American College of Gastroenterology (ACG) as the presence of at least 1 cm of metaplastic columnar epithelium that replaces the stratified squamous epithelium normally lining the distal esophagus [7]. These histopathological changes are thought to be a consequence of gastroesophageal reflux disease (GERD). GERD is estimated to affect 20–40% of American adults and is a chronic condition which can cause inflammation in the esophageal squamous epithelium [6]. In most patients, this damaged mucosa heals with the regeneration of normal squamous cells. For others, however, healing occurs through a metaplastic process in which intestinal-type columnar cells replace esophageal squamous cells.

Pathogenesis

Metaplasia, the process by which one adult cell type replaces another, in large part appears to be a protective measure. GERD causes acid-peptic damage to tight junctions between squamous cells in the epithelium [8]. This exposes undifferentiated cells in the basal layer to acid, bile salts, and other irritants and these cells in turn start expressing factors which help protect Barrett's cells from acid. Homeobox comes from the Greek work *homeosis*, which describes a shift in structural development. Homeobox genes encode transcription factors that regulate cell differentiation during embryogenesis. Acid and bile induce expression of caudal homeobox genes (i.e., CDX1, CDX2). Bile acids, both at neutral and acidic pH levels, cause a cancer cell line to express CDX2 [9]. Barrett's cells express increased bone morphogenetic protein 4 or BMP4, which have been shown to induce the expression of cytoproteins that are characteristic of columnar cells [10]. It is proposed that GERD induces Cdx gene expression through BMP4 and this induced Cdx expression might partially lead to the development of Barrett's metaplasia [8].

Association with Reflux

Acid reflux promotes development and carcinogenesis in Barrett's metaplasia and indirect data supports that control of acid reflux interferes with carcinogenesis. However, approximately 40% of patients who have EAC report no history of chronic GERD symptoms suggesting that reflux is not the only inciting agent for BE and carcinogenesis [2]. Proton pump inhibitors (PPIs) are the mainstay of treatment; however, PPIs may not

completely eradicate acid reflux as it has been shown that even asymptomatic patients may still have chronic reflux. Several retrospective studies have shown that PPI use could potentially lead to a decrease in the progression risk in BE patients and data from a long-term randomized controlled trial is awaited. Nissen fundoplication surgery can more definitively control GERD, but antireflux surgery should not be done for the sole purpose of cancer prevention.

Dysplasia in Barrett's Esophagus

The clinical progression of BE to EAC is thought to include stages of low-grade dysplasia (LGD) and high-grade dysplasia (HGD), a process that could span several years. Recommendation for diagnosis involves taking four-quadrant esophageal biopsies from the BE segment, each 1–2 cm apart [2]; however, biopsies may not accurately diagnose dysplasia due to sampling error. Distinguishing LGD from reflux-induced reactive changes is also difficult as evidenced by the overdiagnosis of LGD in community practice. Interobserver agreement for LGD is low (kappa values <0.25) but is higher for HGD (kappa values 0.6). For this reason, it is recommended to have at least two pathologists review esophageal biopsy specimens; one of whom should preferably be an expert in esophageal histopathology, to more accurately diagnose dysplastic changes [2].

Management of LGD remains controversial as the natural history and diagnosis are not well established. An American study followed 210 patients with LGD for a mean follow-up period of 6.2 years and observed a 0.4% rate of neoplastic progression. A Dutch study, however, followed 147 patients with presumed LGD and rereviewed their biopsies and confirmed LGD in only 15% of those patients. They observed a cumulative neoplastic progression of 85% after 9 years [11]. The higher rate of progression to EAC however was suggested to be in part due to the large number of patient biopsies which were downgraded after expert pathologic analysis. The current surveillance and treatment guidelines recommend endoscopic surveillance of LGD in 6–12-month intervals and to consider endoscopic eradication therapy [2]. The primary treatment for patients with HGD and intramucosal cancer used to be esophagectomy. Now, however, several endoscopic treatment options have changed the management of BE with HGD and early cancer, which carry less risk than surgical options.

Screening for Barrett's

There is inadequate evidence to recommend endoscopic screening of the general population at this time [2]. The AGA, ASGE, and ACP recommend performing EGD only in individuals at high risk for BE. These well-established risk factors include white males over 50 years of age with chronic GERD, hiatal hernias, elevated BMI, central obesity, nocturnal reflux, or smoking history [2].

Obesity and Barrett's Esophagus

Obesity is a risk factor for both Barrett's esophagus and esophageal adenocarcinoma. Specifically, abdominal obesity decreases the anatomic antireflux barrier [12]. Though the exact relationship between obesity, Barrett's esophagus, and esophageal adenocarcinoma has not been elucidated, adipose tissues secrete inflammatory cytokines and proliferative hormones that can promote carcinogenesis. Though the overall population-based risk of cancer is low, there is an increased risk of death due to cardiovascular causes due to the known association of both cardiac disease and Barrett's esophagus with obesity [2].

NSAID's and Barrett's Esophagus

Barrett's metaplasia is considered a complication of the inflammation caused by chronic exposure to acid and bile reflux. There is extensive, ongoing

research as to whether anti-inflammatory medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may play a protective role in the neoplastic process. It has been shown that pro-inflammatory cytokine levels of IL-1β, IL-8, and IFN-γ are increased in esophagitis compared with Barrett's metaplasia [13]. Higher levels of IL-1β and IL-8 are seen in proximal areas of metaplasia, near the neo-squamocolumnar junction as opposed to higher levels of IL-10 which are seen more distally. When Barrett's metaplasia develops, the inflammatory response changes from a Th1 type found in esophagitis to a Th2 response. For example, while IL-10 levels are increased in both esophagitis and Barrett's metaplasia, IL-4 is uniquely increased in Barrett's metaplasia. The cytokine IL-6, which is also Th2 mediated, is also increased in Barrett's metaplasia, and mediates anti-apoptosis. Similarly, cyclooxygenase 2 (COX-2) is produced in response to inflammation and correlates with the level of acid reflux. It is found in all levels of acid injury to the esophagus, from esophagitis to esophageal adenocarcinoma.

The use of NSAIDs, to include aspirin, for cancer prevention in cases of Barrett's esophagus is not currently recommended [2]. Patients should be evaluated on an individual basis, as there is a harmful risk of bleeding from chronic NSAID use, and therefore aspirin should be limited to those who would benefit from its cardioprotective effects [2].

Endoscopic Imaging Techniques

Emphasis on early detection and surveillance in patients with Barrett's esophagus has led to the development of advanced endoscopic imaging technologies. The main aim of these techniques is to better identify abnormal tissue and even facilitate endoscopic diagnosis.

White Light Endoscopy (HD-WLE)

High-definition white light endoscopy has largely replaced standard definition (SD) white light endoscopy in most endoscopy centers (Fig. 13.1). HD-WLE has the capability of producing images with higher magnification and image resolution of more than one million pixels, which is at least 10× higher than SD endoscopy [14]. One study showed that detection of dysplasia using HD-WLE was improved when compared to SD examination (odds ratio 3.27, 95% confidence interval 1.27–8.40) [15].

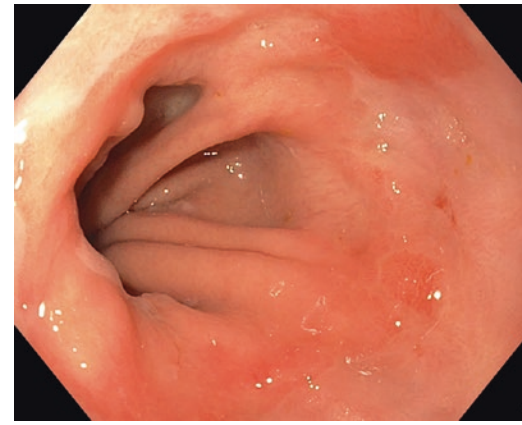

Fig. 13.1 Gastrointestinal junction under white light endoscopy (WLE) showing intestinal metaplasia consistent with Barrett's esophagus with a nodule

Chromoendoscopy

Chromoendoscopy uses the topical application of dyes or contrast agents which enhance mucosal abnormalities during endoscopic evaluation. Methylene blue chromoendoscopy studies have shown varied reports of accuracy of dysplasia detection. Indigo carmine, alternatively, is a topical coloring agent which is not absorbed by the mucosa and highlights mucosal irregularities during endoscopic evaluation. It has been used along with magnification endoscopy, which correlates villiform pit patterns and irregular mucosal patterns with the presence of intestinal metaplasia and dysplasia [14]. A recent meta-analysis showed that use of chromoendoscopy was associated with an increased rate of dysplasia detection. A total of 843 patients were included in this meta-analysis, and the use of chromoendoscopy or electronic chromoendoscopy

(i.e., NBI) increased the diagnostic yield for detection of dysplasia by 34% (95% CI, 20–56%; $P < 0.001$) when compared with WLE [16]. Acetic acid is a commonly available dye and has been used in the detection of Barrett's dysplasia. Another recent study comparing neoplasia detection rates in 982 BE patients showed statistically higher detection rates (12.5% vs. 2%; $P = 0.001$) using acetic acid vs. random biopsies. There was a 6.5-fold gain in neoplasia detection within the acetic acid cohort as compared with the biopsy cohort [17].

Electronic Chromoendoscopy

This term refers to imaging techniques that enhance the contrast between the squamous and columnar mucosa in the esophagus and allows for a detailed examination of the surface mucosa and vasculature. Narrowband imaging (NBI) manipulates light wavelengths which highlight the superficial capillary network and subepithelial vessels, allowing for identification of subtle mucosal abnormalities. In a recent meta-analysis of eight studies including 446 patients and 2194 lesions, NBI demonstrated a pooled sensitivity and specificity of 95% and 65%, respectively, for the detection of Barrett's esophagus [18]. Additionally, the sensitivity and specificity of NBI in detection of high-grade dysplasia were 96% and 94%, respectively. Particular attention should be paid to microvascular or pit patterns, as NBI pit pattern classification schemes for Barrett's esophagus have a high sensitivity and specificity for detection of dysplastic Barrett's [18]. Recently a universal classification system for the vascular and mucosal patterns seen with NBI has been standardized by the Barrett's International NBI Group (BING) [19]. High-confidence readings, or when dysplasia was identified with a high level of confidence, had a 92% overall accuracy, 91% sensitivity, 93% specificity, 89% positive predictive value, and 95% negative predictive value and lends promise to identifying high-grade dysplasia and esophageal adenocarcinoma more accurately [19]. Electronic chromoendoscopy techniques including FICE and I-Scan have also been evaluated in patients with BE with promising results. A subgroup analysis comparing chromoendoscopy to electronic chromoendoscopy showed that both techniques increased the diagnostic yield of dysplasia detection when compared to WLD, though there was no significant difference between the two chromoendoscopic techniques [16]. From a practical standpoint, however, electronic chromoendoscopy may be an easier tool to use, as it does not require the topical application of a chemical substance.

Microscopic Endoscopy

Confocal laser endomicroscopy (CLE) allows for histologic evaluation of GI mucosa during endoscopy using magnification up to 1000-fold and up to 250 μm below the mucosal surface [14]. This level of magnification enables visualization of goblet cells and specialized intestinal metaplasia. Two platforms have been evaluated, an endoscope-based system (eCLE) which is integrated into the tip of a standard endoscope and a probe-based system (pCLE) which is passed through the accessory channel of the endoscope. Both use blue laser light and require intravenous fluorescein as a contrast agent. A prospective, multicenter, international study using pCLE in conjunction with HD-WLE and NBI-enabled identification of additional high-grade dysplasia/esophageal adenocarcinoma patients compared to HD-WLE or NBI demonstrated a sensitivity and specificity of identification of neoplasia with pCLE of 68.3% and 87.8%, respectively, compared to 34.2% and 92.7% with HD-WLE [20]. Another study found that eCLE with targeted biopsies almost doubled the diagnostic yield for neoplasia (33%) compared to the standard biopsy protocol for BE (17%) [21]. With the use of eCLE, there was a 59% statistically significant decrease in mucosal biopsies needed for diagnosis and avoidance of mucosal biopsies by patients undergoing surveillance endoscopies [21]. While the advantages of CLE are apparent, such as real-time diagnostic capability with more accurate, targeted biopsies, there is an associated increase

in procedure length, cost of procedure and equipment, and additional training involved to correctly interpret images.

Endoscopic Therapies for Barrett's Esophagus

The AGA recommends endoscopic eradication therapy in cases of high-grade dysplasia, though it can be used in selected cases of low-grade dysplasia, as well [2]. There is no recommendation to endoscopically treat non-dysplastic Barrett's mucosa at this time. Although several therapeutic endoscopic techniques for eradication of dysplasia exist, as of yet, there are no head-to-head trials comparing the efficacy of each method. These techniques can be broadly categorized into those that provide tissue and those that ablate tissue. EMR and ESD provide viable tissue for histologic review, which can provide information about length and depth of dysplasia.

Endoscopic Mucosal Resection (EMR)

EMR (Fig. 13.2) removes the mucosal and submucosal layers of tissue by raising the targeted segment with submucosal injection followed by resection (cap EMR) or the suction, banding, and cut method (multi-band ligation). The band ligation technique has the advantage of allowing for multiple resections within a single endoscopic session and does not always require submucosal fluid injection. Both EMR techniques have been compared, showing that the cap EMR technique provides larger tissue samples, while band ligation is faster and less expensive when performing multiple resections [22].

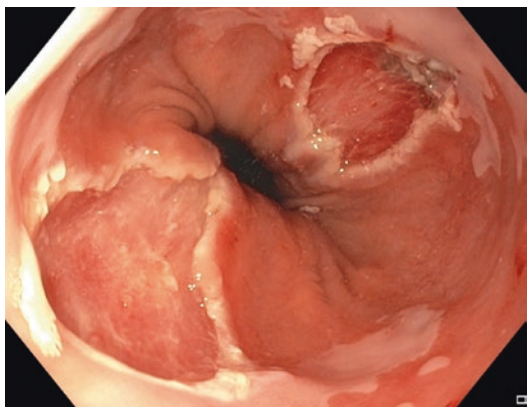

Fig. 13.2 Post-resection view of nodular lesions removed by endoscopic mucosal resection (EMR)

Use of EMR may be applied in the definitive therapy of dysplastic and early-stage (T1 N0) neoplasias with limited submucosal invasion and can be used for staging prior to endoscopic resection [23]. In a prospective study of 107 patients with suspected HGD or adenocarcinoma who underwent complete EMR with a mean follow-up time of 40.6 months, BE was eradicated completely in 80.4% of patients with 71.6% of patients with clearance of intestinal metaplasia and 100% in complete remission from HGD [24]. Recurrence rates for both HGD and cancer were 1.4%.

EMR has been shown to be relatively safe, as well. The rate of significant bleeding post-EMR in a single-center study of 681 patients who underwent 2513 EMRs was 1.2% [25]. In physicians experienced in performing EMR, reported perforation rates are less than 0.5% [23].

EMR and RFA can be combined, and recent data suggest that this can be done safely within a single session. A recent retrospective analysis of 40 patients with short-segment (median C1M2), early BE neoplasia, of which 68% of patients had invasive carcinoma, who were treated with combined EMR followed by RFA in a single session demonstrated complete remission of all neoplasia and intestinal metaplasia in an intention-to-treat analysis of 95% [26]. Most patients underwent subsequent focal RFA sessions every 2–3 months until a median follow-up of 19 months but one single-session treatment resulted in complete histologic remission intestinal metaplasia in 43% of patients. Esophageal stricture occurred in 33% of cases and was successfully treated with a median of two dilations.

Endoscopic Submucosal Dissection (ESD)

Endoscopic submucosal dissection is a technique mostly used in Japan for the treatment of gastric neoplasia. It involves submucosal injection of

fluid, followed by an incision using various cutting devices, and finally submucosal dissection of the segment [27]. The theoretical advantage of this method is that it allows the opportunity to remove a large area of cancerous mucosa en bloc with determination of lateral and vertical margins. However, this is technically difficult, especially in the esophagus, requiring several hours to complete with the potential for serious complications such as perforation.

EMR vs. ESD

A recent randomized controlled trial looking at efficacy and safety in patients with HGD or early esophageal adenocarcinoma who underwent EMR or ESD observed high rates of complete resection in those in the ESD group (58%, $P = 0.01$) than in the EMR group (11%) [28]. Though no difference in complete remission of intestinal metaplasia (CRIM) was seen in either arm at 3 months, recurrent EAC was seen in one case in the ESD group during a mean follow-up of 23.1 ± 6.4 months [28]. Two esophageal perforations were noted in the ESD group (11%) while none were observed in the EMR group [28]. This study showed that EMR is both safe and effective in eradicating dysplasia without any significant clinical advantage over ESD [28].

Radiofrequency Ablation (RFA)

RFA employs radiofrequency energy that is delivered either by an endoscopic balloon catheter or a focal ablation device (Fig. 13.3) to eradicate intestinal metaplasia. The balloon catheter spans 3 cm and the focal ablation device can ablate non-circumferential segments up to 2 cm at a time. A study comparing RFA vs. sham over 1 year showed high rates of complete eradication in both high- (81%) and low-grade dysplasia (90.5%) patients in the ablation group [29]. Results from the US registry and UK registry have shown improved clearance of dysplasia (CRD) and CRIM in patients undergoing EMR/RFA as well as efficacy and safety of using both

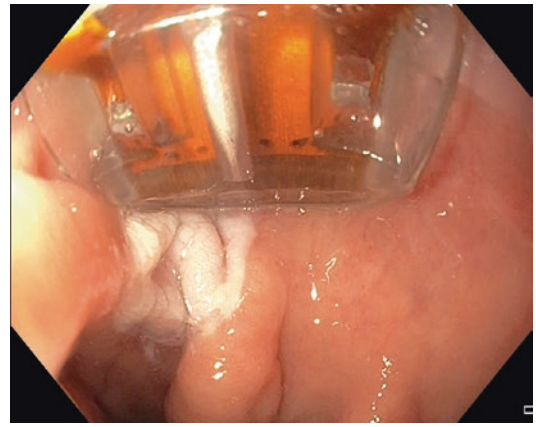

Fig. 13.3 Endoscopic application of focal radio frequency ablation (RFA) with probe shown

treatments in tandem. The US patient registry study treated patients with nodular BE with EMR before RFA and patients with non-nodular BE with RFA alone. Between the two groups, complication rates (i.e., bleeding, stricture, and hospitalizations) were not significantly different (8.4% in the EMR/RFA group vs. 7.2% in the RFA-only group) [30]. CRIM was achieved in 84% of patients treated in both groups ($P = 0.96$) and CRD was achieved in 94% and 92% of patients in the EMR/RFA and RFA-only group, respectively ($P = 0.17$) [30]. In the UK patient registry study, HGD was eradicated in 86% of patients, all dysplasia in 81%, and BE in 62% by 12 months after a mean of 2.5 RFA sessions [31]. After 19 months of therapy, 94% of these patients did not experience recurrence [31]. It was also noted that shorter segments of BE responded better to RFA and complete reversal of dysplasia was 15% less likely per each 1 cm increment of BE [31].

More commonly, EMR and RFA are used in concert to initially treat the visible and/or nodular lesions followed by the flat BE mucosa, respectively. In a retrospective study evaluating patients with nodular Barrett's esophagus with HGD or intramucosal carcinoma, EMR followed by RFA achieved CRD and CRIM at higher rates (94% and 84%, respectively) than with RFA alone (82.7% and 77.6%, respectively) without higher complication rates [32]. The complication rates between the EMR with RFA and RFA-only

groups were similar (7.7% vs. 9.6%, $P = 0.79$) [32]. Strictures occurred in 4.6% of patients in the EMR and RFA group vs. 7.7% of patients in the RFA-only group ($P = 0.53$) [32].

A recent meta-analysis of adverse event rates associated with RFA with and without EMR found a pooled rate of adverse events from RFA with or without EMR of 8.8% (95% CI, 6.5–11.9%) [33]. Strictures were the most common complication (5.6%) followed by a lower risk of bleeding (1%) and perforation (0.6%) [33]. RFA with EMR was associated with a 4.4% higher relative risk for adverse events [33].

The goal of endoscopic eradication therapy (EET) is to achieve complete remission of intestinal metaplasia (CRIM). A 7-year, multicenter retrospective analysis of recurrence rates of intestinal metaplasia after EMR and RFA demonstrated that continued surveillance after RFA is needed [34]. Though CRIM was achieved in 56% of patients after 24 months, 33% of these patients developed recurrence within the next 2 years [32]. Most recurrences were nondysplastic and endoscopically treatable (78%) [34].

Conclusions

The management of Barrett's esophagus has come a long way since 1950, with the establishment of more specific criteria for its diagnosis, greater insight into the pathogenesis, and more aggressive guidelines with the aim of cancer prevention. The goal of cancer prevention can potentially be achieved by early, accurate diagnosis and more effective and efficient surveillance methods. An accurate diagnosis of early dysplastic disease is the first hurdle and can be helped by seeking histologic confirmation by a second pathologist. Studies have also shown that use of advanced imaging techniques including narrowband imaging and chromoendoscopy can be effective in the endoscopic inspection of intestinal metaplasia and neoplasia.

Endoscopic eradication therapy, which was initially reserved for a smaller subset of patients, is now being applied more judiciously and has shown excellent results. However, it is important to explain to patients that the treatment of dysplastic Barrett's requires commitment to several endoscopic procedures and many follow-up visits until eradication is achieved. Advances in the treatment of Barrett's offer hope and optimism to both gastroenterologists and patients and, with ongoing research in this field, will eventually eradicate this complex disease.

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Supraesophageal Reflux Disease (SERD)

14

Timna Naftali

How Can My Hoarse Voice Be Caused by Stomach Content or Acid?

Gastroesophageal reflux disease is a common problem, affecting between 20 and 40% of the population in various studies [1]. Some patients suffer predominantly of heart burn, but many others complain of atypical symptoms including chest pain, asthma, and chronic cough. A particular problem is presented by those patients who complain of ear-, nose-, and throat-associated symptoms such as hoarseness, globus sensation, frequent throat clearing, choking sensation, dysphagia, dysphonia, and recurrent sore throat. These symptoms can be caused by reflux of acid that reaches the throat, the so-called supraesophageal reflux disease (SERD), but may also be caused by many other mechanisms, unrelated to reflux, hence the difficulty in diagnosing and treating those patients with the so-called atypical reflux.

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Pathophysiology

Normally, the larynx is protected from exposure to gastric refluxate by several mechanisms. Upper esophageal sphincter pressure is increased by distal esophageal reflux; furthermore, the esophagoglottic closure reflex, swallowing, and cough protect the pharynx and larynx from contact with gastric refluxate. Two mechanisms for the etiology of supraesophageal manifestations of reflux have been suggested. The reflux theory assumes that supraesophageal reflux is caused by direct laryngeal exposure to gastric contents. Since laryngeal and pharyngeal epithelia are significantly more vulnerable to damage, even short exposure to gastric contents can lead to laryngopharyngeal damage. In a study of 632 patients with supraesophageal symptoms who underwent endoscopy, esophageal manometry, and ambulatory 24-h pH monitoring, there was no difference between those with normal esophageal motility and those with ineffective motility in any of the reflux parameters. The conclusion is that esophageal dysmotility does not seem to play a role in the pathogenesis of SERD [2]. However when looking at upper esophageal sphincter pressure, Lin et al. found that reduced pressure is associated with SERD and increased pressure can be protective [3].

The reflex theory assumes that direct acid exposure occurs only in the lower esophagus. This exposure results in an activation of a reflex mechanism either by stimulation of the superior

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laryngeal nerve or the vagus. This stimulation results in supralaryngeal symptoms. In a study that compared patients with SERD, patients with gastroesophageal reflux (GERD), and healthy controls, a significantly smaller proportion of patients with SERD had UES contractile reflexes in response to slow esophageal infusion of acid. Only patients with SERD had abnormal UES relaxation responses to rapid distension with saline [4].

Diagnosis

Belfasky et al. developed the Reflux Symptom Index (RSI), a clinical score that evaluates the severity of SERD (Table 14.1) [5] and may be used to identify patients who need further investigation.

Endoscopic laryngeal examination may reveal signs suggestive of SERD. This can vary from completely normal appearance to slight vocal cord erythema and edema, erythema of both arytenoids and posterior commissure, or increased mucosal secretion. In some advanced cases, the interarytenoid mucosa may be hypertrophic and laryngeal granulations may be present. These findings are, however, not specific and poorly correlated with other findings or with response to treatment [6]. Belfasky et al. developed the reflux finding score (RFS), an eight-item clinical severity scale based on findings during fiber-optic laryngoscopy [7] (Table 14.2). When evaluated in 40 patients with SERD confirmed by double-probe pH monitoring before and after treatment, the score showed excellent interobserver reproducibility and successfully documented treatment efficacy. Photographic evaluation of the larynx seems to correlate well with the RFS score and can be a useful diagnostic tool [8].

Twenty-four-hour ambulatory esophageal pH monitoring is accepted as the clinical "gold standard" for the diagnosis of GERD. In this test, a single pH probe is placed 5 cm above the lower esophageal sphincter (LES), and the exposure of the lower esophagus to acid is monitored over 24 h. It is less clear whether the technique is sensitive enough to establish an association between reflux and supraesophageal symptoms. It was

Table 14.1 Reflux symptom index

Within the last month, how did the following problems affect you?	0 = No problem 5 = severe problem
1. Hoarseness or a problem with your voice	
2. Clearing your throat	
3. Excess throat mucus or postnasal drip	
4. Difficulty swallowing food, liquids, or pills	
5. Coughing after you ate or after lying down	
6. Breathing difficulties or choking episodes	
7. Troublesome or annoying cough	
8. Sensation of something sticking in your throat or a lump in your throat	
9. Heartburn, chest pain, indigestion, or stomach acid coming up	

Table 14.2 The reflux finding score (RFS)

Item	Score
Subglottic edema	0 = Absent
	2 = Present
Ventricular	2 = Partial
	4 = Complete
Erythema/hyperemia	2 = Arytenoids only
	4 = Diffuse
Vocal fold edema	1 = Mild
	2 = Moderate
	3 = Severe
	4 = Polypoid
Diffuse laryngeal edema	1 = Mild
	2 = Moderate
	3 = Severe
	4 = Obstructing
Posterior commissure hypertrophy	1 = Mild
	2 = Moderate
	3 = Severe
	4 = Obstructing
Granuloma/granulation tissue	0 = Absent
	2 = Present
Thick endolaryngeal mucus	0 = Absent
	2 = Present

hoped that dual-probe 24-h pH esophageal monitoring, using a distal and proximal site to look for the association between proximal reflux and pharyngolaryngeal manifestations, would be more sensitive to diagnose SERD. However, proximal pH recording has very good specificity (91%) but poor sensitivity (55%) for identifying abnormal proximal acid reflux, and a negative test does not exclude proximal reflux [9]. Another option is pharyngeal pH monitoring, in which the sensor is placed above the UES. Although some exposure of the pharynx to acid occurs in normal individuals, exposure time of more than 18% is considered pathological [10]. The poor correlation of proximal and distal acid events detected by dual-probe monitoring may be partly explained by the refluxate becoming less acidic by the time it reaches the proximal esophagus. These so-called weekly acidic events cannot be detected by a conventional pH monitoring but they are detected by a combination of pH and impedance monitoring.

Impedance monitoring (MII) uses the change in electrical conductivity to measure passage of refluxate near the probe, as well as the proximal extent of the refluxate. Simultaneous intraesophageal MII-pH detects reflux by impedance and characterizes it by pH (i.e., acid if pH below 4 and nonacid if pH above 4) [11].

When comparing a combination of RSI and RFS to 24-h multichannel intraluminal impedance (MII) pH monitoring in 58 patients with symptoms suggestive of SERD, Wan et al. found a better response to treatment in the group that was diagnosed by (MII) pH monitoring, reflecting the better diagnostic accuracy of the impedance monitoring over clinical scores [12].

The traditional cutoff of pH <4 for SERD could actually underestimate the presence of clinically significant reflux. Indeed if the cutoff is changed to pH 5.5 the correlation between distal and proximal reflux events improves [13]. In a study of 27 patients refractory to treatment with symptoms of SERD, pH impedance was measured before and after treatment, along with a symptom score, and there was no difference between the study and control groups. Pharyngeal reflux episodes detected by pH impedance were very rare and their presence did not predict the response to an 8-week double-dose PPI therapy. The conclusion was that in a population of patients refractory to full-dose PPI treatment the likelihood of SERD is low and other causes of the symptoms should be searched [14].

Another diagnostic method is the pH device for detection of liquid and aerosolized droplets in the oropharynx (the Dx–pH Measurement System [Dx–pH]). The probe is located in the oropharynx, behind the uvula, and is able to measure pH in either liquid or aerosolized droplets. In 7.8% of 660 episodes of pH <4 at the distal esophagus there was also a Dx–pH event. All events were preceded by and sequential to esophageal pH events. The investigators suggested using pH drops of >3 standard deviation from a baseline to define an event of SERD, rather than looking only at events of pH <4 [15]. In another study, however, Dx–pH Measurement results did not predict response to PPI treatment [16].

Salivary pepsin has been suggested as a marker of reflux but it had a sensitivity of 78% and specificity of 53% for predicting a high RFS [17].

What Are My Treatment Options?

Lifestyle Modifications

Lifestyle modification may enable patients to control their symptoms without the need for medical therapy; however there is very little data on lifestyle modification in SERD, and most recommendations are parallel to those given to patients with GERD [1]. Table 14.3 enlists the

Table 14.3 Recommendations for lifestyle modifications

Weight loss
Avoiding fatty, spicy, acidic food, chocolate, caffeine, mint, and carbonated drinks
Cessation of smoking
Elevation of head of bed
Avoiding heavy fatty meals
Avoiding tight cloths
Refraining from lying after meals
Avoiding alcohol

most common recommendations. However, most patients continue to be symptomatic and need medical therapy.

Over-the-counter antacids such as sodium bicarbonate, magnesium, and aluminum provide rapid but only transient relief of heartburn and their role in SERD is uncertain.

Alginates are polysaccharides found in algae that convert to a gel when in contact with cations, thus forming a physical barrier for gastroduodenal refluxate. Their effectiveness was shown in several studies and they can be used either as an addition to PPI or as a sole therapy [18].

Acid suppression is the backbone of therapy in SERD. However, whereas patients with esophagitis respond well, response among patients with SERD is unpredictable. Evidence-based data is lacking and most recommendations are derived from the common practice in GERD. Histamine receptor antagonists (H2RAs) seem less effective than proton pump inhibitors (PPI), but there is no advantage to one PPI over the other as reflected by similar esophagitis healing rate using different PPIs [19]. In patients with chronic cough, large-dose omeprazole (40 mg twice daily) as an empirical trial resulted in symptom relief and was more cost effective than tailoring treatment after manometry and 24-h pH testing [20]. PPIs were also shown to be effective in the treatment of laryngeal granuloma caused by reflux, but not in granulomas caused by other reasons [21]. The use of PPI in patients with laryngeal symptoms is less convincing, with most studies not showing a beneficial effect over placebo [22]. This absence of good-quality evidence regarding treatment has prompted a study currently looking into the response of laryngeal symptoms to PPI treatment [23]. Until further results are available, it seems reasonable to treat those patients empirically for a limited time. Response in the first month seems to predict the overall therapy results and patients who do not respond in the first month are not likely to respond at all [24]. Failure to respond to aggressive PPI therapy, confirmed by good acid control shown on pH testing, suggests another nonacid etiology for these complaints.

Anti-reflux surgery is commonly recommended to patients suffering from GERD, but the efficacy in SERD is less certain. In a study comparing 41 GERD patients predominantly with laryngeal symptoms and 26 GERD patients without laryngeal symptoms Shin et al. found that anti-reflux surgery significantly lowered RSI and RFS scores in the SERD group 24 months later [25]. Surgical success is best predicted by the patient's response to PPI therapy and should not be tried in patients who do not respond to a properly administered PPI [26]. Surgery is also a good option in patients suffering predominantly of regurgitation, a symptom that does not respond well to medical treatment.

In summary, the current common approach to patients with SERD, adopted by both gestroenterologists and otolaryngologists, is empirical PPI treatment twice daily for no more than 2 months. In patients who respond it is reasonable to taper the dose down to the minimal effective dose. Patients who do not respond after 2 months of full-dose PPI are most likely not suffering from SERD and other causes for their symptoms should be searched.

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Chronic Cough and Throat Clearing

15

J. Mark Madison and Richard S. Irwin

Common Questions Asked by Patients

Question 1. **My coughing and constant throat clearing are so embarrassing. Am I the only one who feels like this?**

Answer 1. You are not the only person to feel like this. Coughing and throat symptoms, such as excessive throat clearing, are the two most common reasons that people seek medical attention the world over [1, 2]. These symptoms have been shown to have profound negative impacts on a person's sense of well-being, self-image, and psychosocial interactions [3, 4].

Question 2. **My doctor said that I don't have allergies and gave me the newest antihistamine for my postnasal drip. Why are my chronic cough and excessive throat clearing not getting any better?**

Answer 2. The newer generation of antihistamine medications (selective H1 antagonists) is too selective to treat nonallergic rhinitis and sinusitis effectively and that is why your symptoms are not improving. The newer antihistamines are mainly useful for treating allergic rhinitis and sinusitis. For nonallergic disorders, the older antihistamine medications (e.g., dexbrompheniramine) are more effective, probably because they are less selective for histamine receptors and have significant anticholinergic effects [5–7]. Of course, the less selective antihistamines also cause more drowsiness, a side effect that some patients tolerate poorly. Nasal ipratropium bromide, a muscarinic cholinergic antagonist that does not cause drowsiness, is often helpful in controlling nonallergic upper airway disorders, especially vasomotor rhinitis.

Question 3. **My doctor said that my cough and throat clearing were caused by the same gastric reflux causing my heartburn. Why didn't my chronic cough and excessive throat clearing go away with treatment just like my heartburn did?**

Answer 3. When chronic cough is caused by GERD, it is not uncommon for the chronic cough to take longer to resolve than the symptom of heartburn [8, 9]. In fact, it is common for physicians to stop an empiric treatment trial for chronic cough due to GERD prematurely, mistakenly thinking that the cough should have resolved at the same time as the heartburn symptoms [10]. The suppression of reflux with medications, diet, and lifestyle changes is usually effective at eliminating chronic cough due to GERD but it may take 2–3 months of intensive treatment before cough begins to show signs of improvement and 5–6 months before the chronic cough resolves completely [9]. Lastly, because it has been shown

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that treating cough due to reflux with acid-suppression medicines only will fail to control coughing, it is important that dietary measures be added to your treatment regimen [11].

Introduction

The method of diagnosing and treating chronic cough is well established by widely accepted international, evidence-based guidelines [12]. In general, the diagnostic approach to chronic cough, defined as cough present for more than 8 weeks, is to identify the cause(s) of the cough and then employ specific treatment strategies that target them, thereby avoiding nonspecific cough suppressants in the greatest majority of cases. Less well established, however, is the proper diagnostic approach to the subgroup of patients with chronic cough who also have the symptom of chronic or excessive throat clearing as a dominant complaint. The purpose of this chapter is to discuss the approach to chronic cough when there is an accompanying, predominant complaint of throat clearing. Although there are no clinical trials specifically addressing the optimal diagnostic approach to such patients, the etiologies of these two different symptoms overlap sufficiently to make many of the strategies for evaluating chronic cough applicable when throat clearing is a predominant complaint.

Coughing and Throat Clearing

There is no well-established definition of throat clearing. Usually, it is a symptom included among other voice and laryngeal symptoms such as chronic sore throat or burning throat, excessive phlegm/mucus, globus pharyngeus, hoarseness, and dysphonia [13]. Throat clearing aims to clear the upper airway of perceived secretions, but is different than true coughing. The sound of throat clearing can sometimes be confused with coughing, but throat clearing is usually less forceful than coughing and clinical studies have been able to distinguish the two symptoms using acoustic recordings [14, 15]. Usually, an attentive listener can readily distinguish the two symptoms [16].

Cough and throat clearing are two distinct symptoms. It is well established that cough is a neural reflex that can be modified by cortical input [17], but it is not well established that throat clearing is a neural reflex. Throat clearing appears to have much more cortical control than cough and some have suggested that throat clearing may fall best under the category of a learned, self-perpetuating habit [16]. However, physiologists do distinguish between the cough reflex and another neural reflex termed the "expiration reflex" and some have suggested that throat clearing may be a mild manifestation of the expiration reflex when it is triggered by a relatively weak stimulus, one that is therefore especially susceptible to modulation by cortical input [18]. The cough reflex, mediated by sensory fibers of the vagus nerve, consists of an inspiratory phase, a compressive phase against a closed glottis, and then an expulsive phase that starts when the glottis opens. The expiration reflex, in contrast, usually does not have an inspiratory phase, but instead begins with compression against a closed glottis followed by an expulsive phase that aims to clear mucus or debris from the larynx and vocal cords. The expiration reflex can be elicited by chemical or mechanical stimulation of the either the larynx, vocal cords, or tracheobronchial tree [19], although the neural underpinnings of the reflex are not defined. Consistent with a fundamental difference between the two reflexes, it has been suggested that codeine does not suppress throat clearing at doses effectively suppressing cough [18]. Regardless of the neural underpinnings, many have suggested that the act of throat clearing itself may mechanically irritate the mucosa and its neural sensory fibers to cause a self-perpetuating, self-reinforcing symptom cycle [16].

Symptoms referable to the throat, such as throat clearing, are among the most common reasons patients seek medical care in an office setting in the United States, second only to the symptom of cough itself in frequency [1, 2]. Because the etiologies of these two different

symptoms overlap, because both symptoms are a result of expiratory maneuvers that aim to clear material from the airway, and because both are very common symptoms, it is not surprising that throat clearing is sometimes associated with the complaint of chronic coughing. In one study of 112 patients with chronic cough, throat clearing was present in 73 (65%) of them, although throat clearing was not necessarily the dominant complaint [20]. Neither of these two different symptoms is trivial to patients and that is what compels patients to so commonly seek medical attention for them. Like chronic cough [3], voice and speech symptoms such as throat clearing can have profound negative effects on a patient's sense of well-being, self-image, and psychosocial interactions [4].

Approach to Differential Diagnosis and Management

For a patient with chronic cough and an associated, predominant complaint of excessive throat clearing, it is best to review the well-established clinical approach to chronic cough.

The differential diagnosis for chronic cough is broad and the diagnosis is best approached in a systematic fashion, focusing first on common causes [1, 12] (Table 15.1). Causes can be mechanical or chemical stimuli that originate from the upper airway, including the sinuses; from the environment; from the lower airways and lungs; from the upper GI tract; or from stimulation by the central nervous system. For an adult patient who does not smoke and does not take an angiotensin-converting enzyme inhibitor (ACEI) or sitagliptin and has a normal chest radiograph, the four most common causes of chronic cough, in order, are upper airway cough syndrome (UACS) due to any disease of the nasal passages and/or sinuses; lower airway inflammation due to the inflammatory diseases asthma or nonasthmatic eosinophilic bronchitis (NAEB); and gastroesophageal reflux disease (GERD) due to reflux of gastric acid or nonacid into the esophagus [1, 12, 21]. Numerous clinical studies have

Table 15.1 Etiologies of chronic cough in adults

Intrathoracic etiologies
Airways
Asthma
Nonasthmatic eosinophilic bronchitis (NAEB)
Chronic bronchitis
Bronchiectasis
Tracheobronchial malacia
Obstructive sleep apnea
Drug induced: ACEI, sitagliptin
Inhaled medications
Chronic exposure to environmental and occupational irritants
Bronchogenic and metastatic carcinoma
Bronchial carcinoid
Foreign body or endobronchial suture
Broncholith
Bronchiolitis
Infectious tracheobronchitis (e.g., tuberculosis, Aspergillus)
Infectious pneumonias (e.g., bacterial, tuberculous, fungal, parasitic)
Sjogren's syndrome with xerotrachea
Relapsing polychondritis
Tracheobronchopathia osteochondroplastica
Lungs
Chronic interstitial lung disease (e.g., sarcoidosis, HSP, asbestosis, drugs)
Idiopathic interstitial pneumonias (e.g., IPF, NSIP, DIP, LIP, RB-ILD, OP)
Pulmonary vasculitis (e.g., granulomatosis with polyangiitis)
Pleura
Chronic effusion
Diaphragm
Transvenous pacemaker stimulation
Mediastinum
Neural tumors
Thymoma
Teratoma
Lymphoma
Metastatic lymphadenopathy
Intrathoracic goiter
Bronchogenic cyst
Cardiovascular
Mitral stenosis
Left ventricular failure
Premature ventricular complexes

(continued)

Table 15.1 (continued)

Pulmonary thromboembolism
Enlarged left atrium
Vascular ring
Aberrant innominate artery
Aortic aneurysm
Pericardial stimulation by transvenous pacemaker
Extrathoracic etiologies
Head and neck
Rhinitis and sinusitis (UACS)
Nasal polyps
Rhinolith
Oropharyngeal dysphagia
Laryngeal disorders (e.g., vocal fold dysfunction, laryngomalacia)
Postviral vagal neuropathy
Recurrent aspiration
Elongated uvula
Chronic tonsillitis
Neurilemmoma of vagus nerve
Neuroma of internal laryngeal nerve
Ascending palatine artery aneurysm
Osteophytes of cervical spine
Syngamus laryngeus infection
Thyroiditis
Gastrointestinal
Gastroesophageal reflux disease (GERD)
Esophageal cyst or diverticulum
Tracheoesophageal fistula
Celiac disease (and other organ-specific or systemic autoimmune diseases)
CNS
Somatic disorders
Tic disorders (e.g., Gilles de la Tourette's syndrome)

ACEI angiotensin-converting enzyme inhibitor, *CNS* central nervous system, *HSP* hypersensitivity pneumonitis; *IPF* idiopathic pulmonary fibrosis, *NSIP* nonspecific interstitial pneumonia, *DIP* desquamative interstitial pneumonitis, *LIP* lymphocytic interstitial pneumonitis, *RB-ILD* respiratory bronchiolitis and interstitial lung disease, *OP* organizing pneumonia
See Ref. [1] for a more extensive list of etiologic causes of chronic cough

shown that chronic cough frequently (up to 25% of cases) is due to multiple, concurrent diagnoses and that all must be treated in order to successfully resolve the chronic cough [21].

The general approach to the evaluation of chronic cough begins with a medical history and physical examination that defines the duration of cough, smoking status, and current use of angiotensin-converting enzyme inhibitors (ACEI) or sitagliptin. If the patient is a smoker, chronic bronchitis and irritant effects of cigarette smoke are the most likely diagnoses and further diagnostic studies and empiric therapy should not be attempted until the patient has ceased smoking for at least 4 weeks. Similarly, if the patient is taking an ACEI or sitagliptin, the medication should be discontinued for 4 weeks before attempting further diagnostic studies.

The next important step in the evaluation of chronic cough is a chest radiograph. If the chest radiograph is abnormal, the radiographic findings should be pursued as a possible cause of the cough. However, if the chest radiograph is normal, or near normal, then most cases of chronic cough are due to upper airway cough syndrome (UACS; formerly called postnasal drip syndrome or PNDS), asthma/NAEB, and/or gastroesophageal reflux disease (GERD). Confirmation of one or more of these diagnoses then depends on whether or not the cough resolves during sequential, empiric treatment trials that are specifically aimed at each suspected diagnosis. Depending on the response to empiric treatments, additional diagnostic studies may be helpful and these include sinus imaging, spirometry, methacholine inhalation challenge (MIC) testing, allergy evaluations, barium esophagography, 24-h esophageal pH/impedance monitoring, sputum for microbiology and/or cytology, flexible bronchoscopy, chest computed tomography (CT) scan, and noninvasive cardiac studies [5, 6, 21].

The goal of a systematic, medical evaluation, focusing on the most common causes of chronic cough, is to identify and confirm the underlying cause by observing the complete resolution of cough while on specific therapy. In most cases, and depending on the clinical setting, a systematic approach that faithfully follows a trustworthy, evidence-based guideline (such as the American College of Chest Physicians cough guidelines of 2006 with subsequent updates) will identify the causes of cough more than 90% of the time [12, 22]. When the cough has completely resolved on specific therapy, the cause of chronic cough may be considered "explained."

Broadly categorizing the causes of chronic cough with excessive throat clearing, there are causes that originate *from above* the throat (e.g., from centrally mediated neurologic reflexes or from secretions dripping down from nasal passages or sinuses); *from below* (e.g., from GERD or from airway inflammation due to asthma/NAEB); *from the environment* (e.g., cigarette smoke); or *from intrinsic disease processes*, either systemic or local, that irritate the laryngopharyngeal mucosa (e.g., mucositis caused by autoimmune diseases) (Fig. 15.1). When chronic cough is associated with a predominant complaint of throat clearing, we suggest that the differential diagnosis remains similar to that of chronic cough except that the likelihood of various possible etiologies is skewed in favor of environmental irritant factors such as cigarette smoke, UACS, and GERD. The implications of this are that, among nonsmokers without environmental irritant exposures, it is probable that the presence of excessive throat clearing, as a predominant complaint, makes UACS and GERD *more* likely the causes of a patient's chronic cough. Conversely, when excessive throat clearing is a predominant complaint it is *less* likely that asthma and NAEB and other pulmonary disorders are the underlying cause of a patient's chronic cough as long as there is not any associated rhinosinus disease and NAEB is not associated with environmental inhalations. Finally, although chronic cough due to somatic or tic disorders is relatively uncommon in adults, and best diagnoses of exclusion, throat clearing and other phonic or vocal sounds are common in tic disorders such as Tourette's syndrome

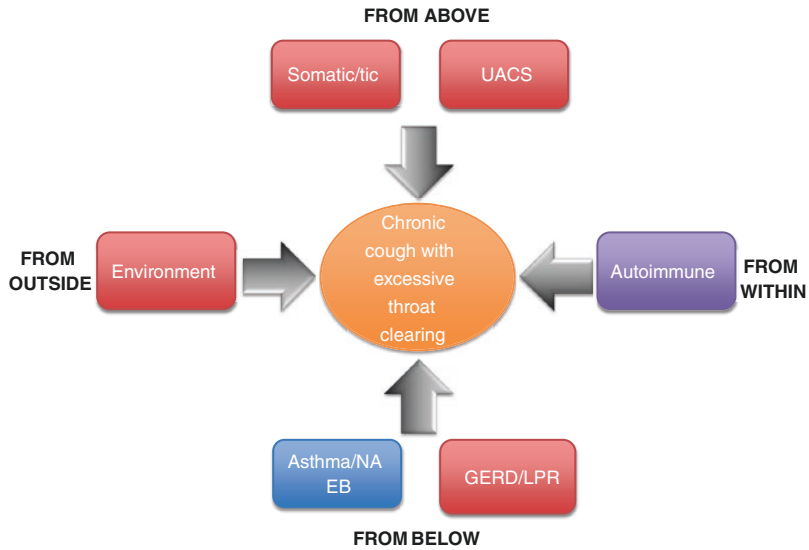

Fig. 15.1 Major etiologies of chronic cough when there is a predominant, associated complaint of excessive throat clearing. For a patient with a normal or near-normal chest radiograph and not smoking or taking an angiotensin-converting enzyme inhibitor or sitagliptin, the possible causes of chronic cough and of throat clearing, as separate symptoms, are broadly similar. Causes can be from above (upper airways or brain), from environmental irritations originating outside the body, from below (GERD/LPR or lower airways), or from intrinsic disease processes irritating the mucosa of the larynx or upper airway. However, compared to chronic cough alone, it is proposed that when chronic cough is associated with a predominant complaint of excessive throat clearing, the underlying etiologies of both symptoms are more likely to be UACS or GERD/LPR or a somatic/tic disorder (*red* shading), and less likely asthma/NAEB (*blue* shading) when asthma is not associated with allergic rhinitis and NAEB is not associated with environmental air pollution. Direct environmental stimuli are more likely the underlying etiology when throat clearing is associated with chronic cough because cigarette smoking is so common and frequently causes both symptoms (*red* shading). Intrinsic diseases, such as organ-specific or systemic autoimmune diseases, that involve the laryngopharyngeal mucosa (*purple* shading) may or may not be similar in frequency when compared to chronic cough alone. Abbreviations: *GERD* gastroesophageal reflux disease, *LPR* laryngopharyngeal reflux, *UACS* upper airway cough syndrome, *NAEB* nonasthmatic eosinophilic bronchitis

[23] and, therefore, it is plausible that the diagnosis of a tic disorder may be more likely when chronic cough is associated with a predominant complaint of excessive throat clearing.

Common Causes of Chronic Cough with Throat Clearing

Gastroesophageal Reflux Disease (GERD)

Cough consensus and evidence-based guidelines recognize GERD as the third most common cause of chronic cough in adults with the following clinical profile: nonsmoking, not on an ACEI or a sitagliptin and with a normal chest radiograph. Guidelines also emphasize that chronic cough can be the sole manifestation of GERD (so-called silent GERD) [8, 11, 12]. Although there are many controversies, chronic cough due to GERD can be diagnosed with the help of 24-h esophageal pH and impedance recordings that correlate instances of reflux before cough events. It is also generally agreed that cough due to GERD usually resolves on specific medications, lifestyle changes, and diet changes that are directed at preventing gastroesophageal reflux (Fig. 15.2) [8]. It has been suggested that GERD causes chronic cough due to the direct mechanical and chemical irritation of the larynx, vocal cords, or airways by acid and nonacid reflux that reaches hypopharyngeal and laryngeal structures and/or by neurally mediated reflex pathways stimulated by a bolus of refluxate into the distal esophagus [24]. The successful suppression of reflux with medications, diet, and lifestyle changes, and, when indicated, surgical intervention, usually results in complete resolution of chronic cough due to GERD, although medical treatment can sometimes take many months to be successful. It is important to stress that treatment

Fig. 15.2 Treatment of chronic cough with excessive throat clearing due to GERD. The general treatment recommendations and common pitfalls in treating GERD are summarized. Abbreviation: *GERD* gastroesophageal reflux disease

limited only to acid suppression will usually fail to control the cough [8, 11].

Subspecialists in ear, nose, and throat (ENT) often evaluate throat clearing and other laryngeal symptoms. When these symptoms are attributable to the retrograde movement of gastric contents into the esophagus, a diagnosis of reflux laryngitis due to laryngopharyngeal reflux (LPR) is often made [25–28]. As with chronic cough caused by GERD, the stimulus causing throat clearing may be direct irritation of the laryngeal and pharyngeal structures by acid and/or pepsin or the indirect effect of neural reflexes triggered by a bolus of refluxate in the esophagus [29]. How LPR is different from GERD is controversial in the ENT and gastrointestinal literature and it is possible that they represent the same general phenomenon [30, 31]. However, some have suggested that LPR is primarily due to failure of the upper esophageal sphincter while GERD is different and due to poor integrity of the lower esophageal sphincter [28, 32]. Supporting a potential difference between LPR and GERD is the observation that patients with LPR less commonly have heartburn or evidence of esophagitis on biopsy and that LPR more commonly occurs in an upright body position during exertion instead of a recumbent position, as is common in GERD [13, 28, 32, 33]. However, the controversy is likely to persist until there is a solid definition of LPR that is based on firm diagnostic criteria.

While some believe that physical findings can help the physician determine whether LPR and GERD are the potential causes of a patient's chronic cough with excessive throat clearing, others disagree. For example, finding edema and erythema of the posterior commissure, cobblestone appearance of the posterior pharyngeal wall, vocal cord ulcers, interarytenoid changes, medial arytenoid wall edema and erythema, vocal cord granulomas, and subglottic stenosis all have been cited as supportive physical findings [34]. However, none of these findings are diagnostic and some are visualized in 64–86% of normal controls [35, 36].

For chronic cough due to GERD, 24-h esophageal pH and impedance and manometry monitoring to correlate reflux events with instances of coughing is an established diagnostic method. However, for the symptom of throat clearing the correlation is not as clear. Although 24-h double-probe pH monitoring may be more specific than the physical examination for establishing a diagnosis of laryngeal reflux, the technique still may not be sufficiently reliable to qualify as a gold standard of LPR. In one study, dual-sensor pH probe testing did not predict the severity of symptoms or signs of reflux pharyngitis and only the symptom of heartburn correlated with recorded instances of reflux [37]. In a systematic review, only a minority of patients diagnosed with reflux laryngitis had pharyngeal reflux events on dual-probe monitoring and, comparing patients with reflux laryngitis to controls, there was no difference in the number of pharyngeal reflux events recorded [25]. These findings certainly challenge the whole concept of LPR causing laryngo pharyngitis. Multiple factors contribute to the difficulties in linking LPR to the commonly made diagnosis of reflux laryngitis, and these include the lack of widely agreed-upon definitions, the lack of consensus on normal pH limits when interpreting recordings, the fact that indirect neural mechanisms may contribute to LPR, and the fact that the number and severity of reflux events needed to establish clinically significant inflammation in the laryngopharynx are not known.

Considering these diagnostic challenges, when GERD-induced chronic cough is associated with prominent and excessive throat clearing, we suggest that the throat clearing is likely due to GERD as well. For a given patient, we suggest that the mechanisms underlying the two symptoms are probably very similar, or closely related, and that both symptoms can be confidently attributed to a diagnosis of GERD when both resolve on specific treatment for GERD. However, to resolve symptoms, GERD treatment frequently needs to be prolonged to be effective. In one study, chronic cough due to GERD only responded to medical treatment after an average of 161–179 days [9, 21].

Medical treatment of GERD is usually effective [8, 11]. The recommended treatment regimen is a high-protein, low-fat (45 g/day), antireflux diet of three daily meals and no foods,

beverages, or medications that lower esophageal sphincter tone or have high acidity. There should be nothing to eat between meals or 2 h prior to reclining and at least 10 cm head of bed elevation. What seems to be most important about the diet is that it targets weight loss [8, 11]. Proton pump inhibitors and prokinetic agents are prescribed to suppress acid and enhance motility, respectively. One randomized, placebo-controlled double-blind study showed that, although omeprazole was no better than placebo in treating reflux laryngitis in general, the specific symptoms of hoarseness and throat clearing were effectively treated by omeprazole [38]. Because GERD is a chronic problem, some form of treatment (e.g., diet) is usually required indefinitely. If, despite adherence to diet and maximal pharmacologic therapy, the chronic cough continues and reflux events are shown to persist on 24-h esophageal pH and impedance and manometry monitoring in spite of therapy, then surgical intervention with antireflux surgery can be considered [8, 11, 39].

Common pitfalls in the management of chronic cough due to GERD include relying only on acid-suppression therapy, a failure to recognize that it may take 2–3 months of medical therapy before cough begins to improve and 5–6 months before cough resolves (Fig. 15.2) [9]. Another error is to assume that cough cannot be due to GERD because cough remains unchanged when gastrointestinal symptoms improve [10]. Finally, other pitfalls include a failure to assess the effectiveness of medical therapy using 24-h monitoring of esophageal pH and impedance when cough fails to resolve on an intensive medical regimen and failure to recognize and treat coexisting diseases that can worsen GERD, such as sleep apnea.

Upper Airway Cough Syndrome (UACS)

In nonsmoking adults not on an ACEI or sitagliptin and having a normal, or near-normal, chest radiograph, UACS is the single most common cause of chronic cough in the United States [7]. The underlying pathophysiology is not established and controversial, but one possibility is that excessive or thick nasopharyngeal secretions containing mucus and inflammatory mediators may drain posteriorly (i.e., postnasal drip) and directly irritate the mucosa and structures of the hypopharynx and larynx to stimulate cough. Alternatively, normal amounts and thickness of secretions may stimulate coughing because the larynx, vocal cords, and hypopharyngeal structures are abnormally sensitive, that is, hypersensitive, to normally innocuous chemical or mechanical stimulation [7, 40]. Because patients can complain of postnasal drip and throat clearing and not be coughing, a hypersensitive cough reflex must be present, in our opinion, for the UACS to become operative.

Throat clearing is commonly associated with rhinosinus disease causing UACS and is an important symptom to elicit in the evaluation of chronic cough [41]. For example, among patients with chronic cough, the symptom of throat clearing is a highly sensitive predictor for the presence of rhinitis (100%) but poorly specific (37%); this is an indication that throat clearing can be caused by other disorders besides rhinosinus diseases [20]. Therefore, when chronic cough is associated with a predominant complaint of excessive throat clearing, rhinosinus disease should be strongly considered in the differential diagnosis, but other common causes, such as GERD, should be considered as well.

The differential diagnosis of UACS due to rhinosinus disease, with or without throat clearing, includes any inflammatory disorder of the nasal or sinus passages and these include allergic rhinitis, perennial nonallergic rhinitis (either vasomotor rhinitis or nonallergic rhinitis with eosinophilia—NARES), postinfectious UACS, bacterial sinusitis, allergic fungal sinusitis, rhinitis associated with anatomic abnormalities (e.g., deviated nasal septum), rhinitis due to physical or chemical irritants, occupational rhinitis, and rhinitis medicamentosa and rhinitis of pregnancy (Fig. 15.3) [1, 7]. Any of these conditions can cause chronic cough due to UACS. The diagnostic approach to UACS is to start with the history and physical examination looking for complaints of a

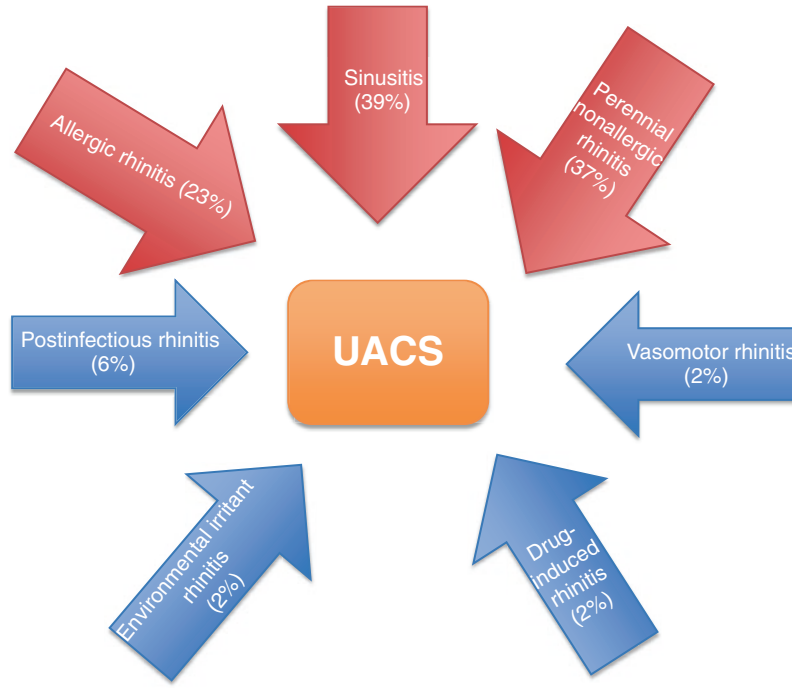

Fig. 15.3 Spectrum and frequency of conditions causing UACS. The most common causes of UACS were sinusitis, allergic rhinitis, and perennial nonallergic rhinitis and these are highlighted in *red* [21]. The percentages do not sum to 100% because some of the patients had more than one condition simultaneously. Abbreviation: *UACS* upper airway cough syndrome

draining or dripping sensation in the back of the throat, a tickle in the throat, hoarseness, throat clearing, nasal congestion, or nasal discharge. Some patients may complain of wheezing. On physical examination, there may be evidence of drainage in the oropharynx, nasal secretions, and a cobblestone appearance or mucus on the mucosa in the posterior pharynx. When bacterial sinusitis is suspected, sinus imaging may be helpful. In a patient with chronic cough and excessive throat clearing, these supportive findings on initial evaluation would lead to a presumptive diagnosis of UACS and the diagnosis would be confirmed with resolution of the symptoms upon treatment for the underlying cause of the rhinosinus disorder causing UACS [7]. The prevalence of throat clearing is as high as 37% among patients with documented respiratory allergies [42], but distinguishing between allergic, nonallergic non-infectious, and infectious causes of rhinosinus disease is important because each is treated differently. However, when the specific etiology of the rhinosinus disease is not identifiable clinically, a trial of empiric therapy is recommended before embarking on an extensive, additional evaluation. When excessive throat clearing is present with UACS, it should be expected that the symptom of throat clearing should resolve along with the chronic cough.

The underlying cause of UACS determines the most appropriate treatment (Fig. 15.4) [5–7]. For allergic rhinitis, skin testing for common allergens and desensitization by immunotherapy may be appropriate if avoidance of allergens, intranasal corticosteroids (e.g., budesonide), newer generation antihistamines (e.g., loratadine), leukotriene receptor antagonists (e.g., montelukast), and saline sinus irrigations, singly or in combination, proves to be ineffective. Patients with chronic cough due to perennial nonallergic rhinitis, postinfectious rhinitis, and environmental irritant rhinitis are treated by avoidance of environmental irritants and administration of intranasal ipratropium bromide and/or corticosteroids, combination older antihistamine-decongestants (e.g., dexbrompheniramine plus D-isoephedrine), or an older antihistamine alone. Cough due to vasomotor rhinitis is treated with intranasal ipratropium bromide. For perennial nonallergic rhinitis, a first-generation antihistamine-decongestant is used for 3–4 weeks and, if there is a favorable response, an intranasal

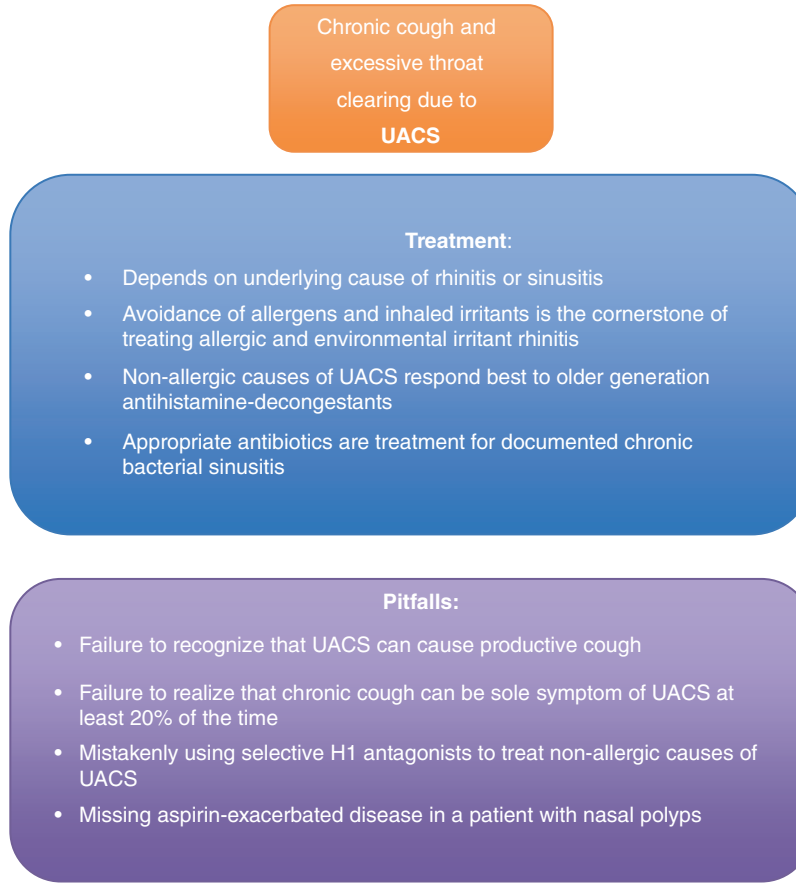

Fig. 15.4 Treatment of chronic cough and excessive throat clearing due to UACS. The general treatment recommendations and common pitfalls in treating UACS are summarized. Abbreviation: *UACS* upper airway cough syndrome

corticosteroid is then substituted for 3 months. Finally, chronic sinusitis due to chronic bacterial infection of the sinuses is another common cause of UACS. Sinus imaging studies should be obtained to confirm the diagnosis rather than prescribing antibiotics empirically. Chronic bacterial sinusitis is treated with antibiotics targeting *Haemophilus influenzae*, *Streptococcus pneumoniae*, and upper respiratory tract anaerobes along with a first-generation antihistamine and decongestant nasal spray.

A common pitfall in the management of UACS is failure to recognize that selective, nonsedating, histamine H-1 antagonists work well only for histamine-mediated conditions such as allergic rhinitis (Fig. 15.4) [5–7]. Rhinitis conditions that are not mediated by histamine respond mainly to nonselective histamine antagonists, instead, probably because these older agents have significant anticholinergic properties.

Direct Exposures

Occupational and environmental exposures, especially cigarette smoke, are causes of chronic cough with excessive throat clearing. Such environmental exposures probably cause cough and throat clearing symptoms through multiple mechanisms that include both direct toxic effects on the laryngopharyngeal and lower airway mucosa and indirect allergic and nonallergic effects that inflame the rhinosinus passages to cause UACS. Also, these irritants may increase the sensitivity of the cough and/or expiration reflex or, over time, promote the development of somatic cough [43]. Both cough and throat clearing are common among cigarette smokers. There is evidence that vocal symptoms, specifically hoarseness and throat clearing, are common among smokers. In one study of 209 cigarette smokers, 54 had chronic cough while 55 had a

main complaint of excessive throat clearing [43]. Other studies suggest that excessive throat clearing may be especially common among women smokers [44]. Because both chronic cough and throat symptoms so frequently occur among smokers, smoking cessation is always required before undertaking an extensive diagnostic evaluation of chronic cough and throat clearing.

Other inhaled irritants in the home, workplace, or outdoor settings include various vapors, gases, dusts, and fumes such as those due to combustion of biomass fuels, air pollution, glues, paints, solvents, cleaning products, and some inhaled medications [45–47]. There is also speculation that, in some cases, chronic exposure to various organic toxins, such as mycotoxins and endotoxins, in the home or workplace can also contribute to chronic respiratory symptoms, commonly including cough and throat symptoms [45, 48]. For example, one study has reported that environmental basidiomycetous fungi can be cultured from the sputa of up to 25% of patients with unexplained chronic cough and another study by the same group found that itraconazole improved cough symptoms in these patients with fungus-associated cough [49, 50]. Therefore, in cases where an environmental exposure is suspected, a home or workplace visit or a consultation with an industrial hygienist often can be very helpful in identifying relevant environmental exposures and a plan for avoidance [45, 51].

Avoidance of occupational and environmental exposures is the cornerstone of managing direct exposures causing chronic cough with throat symptoms. If the symptoms are due solely to the exposure, they should improve or resolve when the exposure is eliminated. For example, when patients stopped cigarette smoking, chronic cough resolved completely in 77% of patients and this resolution occurred within 10 weeks for 74% of them. By 12 months, coughing improved or completely resolved in 96% of patients who quit smoking. When the predominant symptom was throat clearing, smoking cessation led to complete or partial resolution in 73% of the patients and that occurred within 10 weeks for 70% of them and within 12 months for all of them [43].

Asthma and Nonasthmatic Eosinophilic Bronchitis (NAEB)

When the chest radiograph is normal or near normal, the second most common cause of chronic cough in the United States in nonsmoking adults is asthma [5, 6, 52]. However, when throat clearing is a predominant complaint associated with chronic coughing, asthma, unless complicated by allergic rhinitis or chronic rhinosinusitis, is less likely to be placed high among the differential diagnostic possibilities unless other features of the case (e.g., wheezing or variable airway obstruction) strongly suggest asthma. The reason for this is that throat clearing is not widely recognized as a common complaint for asthmatics, at least in adults. It is notable, however, that in children at least one report has suggested that throat clearing, as an isolated symptom, is a potential indicator of asthma [53].

Asthma should be suspected whenever there is episodic shortness of breath and wheezing in association with chronic cough. However, it is important to recognize that for as many as 28% of asthmatics, cough may be the sole presenting symptom [5, 6, 52]. Bronchodilator responsiveness by spirometry or a positive bronchial challenge (e.g., methacholine) is a test result that can further support the diagnosis of asthma as a cause of chronic cough but neither of these tests is highly specific. Bronchial challenge testing is clinically very important because a negative study effectively excludes the possibility of underlying asthma as a cause of chronic cough. As for all causes of chronic cough, a firm diagnosis of asthma requires that the cough resolve completely on specific therapy that includes a controller medication (e.g., inhaled corticosteroids) and a reliever medication (e.g., short-acting beta-adrenergic agonists). Usually, chronic cough due to asthma will start to respond, within 1–3 weeks, to the combined administration of inhaled corticosteroids and bronchodilators, with total resolution taking 6–8 weeks.

Nonasthmatic eosinophilic bronchitis (NAEB) is another cause of chronic cough that is not strongly suggested by associated excessive throat clearing. Like asthma, NAEB is a disorder

characterized by an eosinophilic inflammation of the airways [54, 55]. However, NAEB is distinct from asthma pathologically and patients with NAEB do not have a positive methacholine inhalation challenge test. The cause of NAEB is not known, but NAEB has been associated with both occupational exposures and allergen sensitivity. The frequency of NAEB varies globally but may account for 10–30% of cases of chronic cough outside the United States [54]. Therefore, NAEB should be suspected as a cause of chronic cough when there is sputum eosinophilia but no methacholine responsiveness or evidence of variable airflow obstruction. Most cases of chronic cough due to NAEB respond to inhaled corticosteroids (e.g., budesonide) within 4 weeks [55]. The appropriate duration of therapy is not well established, but is guided by resolution of the chronic cough and a decrease in the sputum eosinophilia [55].

Relevant to the treatment of asthma and NAEB, it is important to note that cough and throat symptoms, including throat clearing, are common complaints for patients who are treated with inhaled corticosteroids and, presumably, this may be a direct local effect of the medication itself, or its formulation, on the laryngopharyngeal mucosa. Hoarseness is the most common throat symptom of these patients with throat clearing being the second most common complaint [56]. In one study of 255 patients using inhaled corticosteroids, 58% complained of vocal or throat symptoms and 35% complained of cough [57]. Throat symptoms were significantly more prevalent among patients using higher doses of inhaled corticosteroids and spacer devices did not appear to be protective.

Refractory Cough and Somatic/Tic Cough

On average 10% of cases, range 0–46%, of chronic cough remain persistently troublesome despite diagnostic evaluations and treatment [22]. It is not clear how much of the variability in successful treatment has been due to investigators not being faithful to published guidelines. When cough remains persistently troublesome, it has been recommended that the clinician first review all aspects of the previous workup to be certain that an appropriate and comprehensive management protocol was followed, for example, the ACCP Cough Guideline Recommendations [12]. Second, the clinician should determine whether all of the pitfalls of managing the different causes of chronic cough have been avoided [22]. When this approach has been followed, the percentage of chronic cough cases that are truly refractory to treatment may only be 0–10% of cases. In only those cases are the coughs truly "unexplained" and the term chronic refractory cough (CRC) or unexplained chronic cough (UCC) appropriate [22, 58].

The causes of CRC, or UCC, are probably multiple but some have proposed conceptualizing the problem under the terms cough hypersensitivity or laryngeal hypersensitivity [59]. Cough hypersensitivity syndrome refers to a hypersensitive cough reflex originating in the larynx or upper airways. Laryngeal hypersensitivity refers to an increase in the sensitivity of the cough reflex originating specifically from the larynx and is associated with cough, dyspnea, dysphonias, or laryngeal spasms [59]. These hypersensitivities may sometimes represent sensitizations of the peripheral, vagal sensory nerves mediating the cough reflex by, for example, inflammatory mediators released during inflammation of the airways or larynx. However, distinct from sensitizations of peripheral fibers, some have proposed that there may be sensitizations where central sensory reflex pathways have increased excitability [59]. These sensitizations of central neural pathways may share many features of neuropathic pain, such as paraesthesias and hyperalgesias, and may underlie many of the common throat symptoms associated with throat clearing.

For unexplained chronic cough, a diagnosis made only after thorough and supervised therapeutic trials have failed, current guidelines recommend a therapeutic trial of multimodality speech pathology therapy [58, 60, 61]. Combined speech pathology treatment and daily pregabalin has been shown to reduce cough symptoms and improve quality of life compared to speech pathology therapy alone [62]. Another approach

to the treatment of unexplained cough that is recommended by current guidelines is a therapeutic trial of gabapentin, but only after careful consideration and reassessment of the risk-benefit ratio [58, 63]. Inhaled corticosteroids and proton pump inhibitors are not recommended for unexplained chronic cough [58].

Diagnoses of psychogenic cough and habit cough were formerly applied in cases of seemingly unexplained cough, but these are now considered outmoded terms [64]. Psychogenic cough is now best referred to as somatic cough and habit cough is best described as tic cough. A diagnosis of somatic cough should be made only after excluding other causes of chronic cough and the patient has had an extensive evaluation to confirm that they meet *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) criteria for a somatic symptom disorder. Similarly, the diagnosis of tic cough should be consistent with the DSM-5 classification of diseases, with an isolated cough tic being classified as a vocal tic disorder. Notably, throat clearing is common in tic disorders. For example, in one study of 239 patients with a chronic tic disorder, cough occurred in 42 patients while 74 patients had throat clearing [65]. Therefore, when chronic refractory cough is associated with prominent throat clearing, a somatic or tic disorder should be considered and further investigated. Treatment of somatic and tic cough is unestablished in adult patients but has included hypnosis or suggestion therapy, combinations of reassurance, counseling, or referrals to a psychologist or psychiatrist, or trials of psychotropic medications [64].

Autoimmune Diseases

Chronic, systemic, or organ-specific inflammatory diseases affecting the laryngopharyngeal and airway mucosa can be a cause of chronic cough with excessive throat clearing. For example, studies of unexplained chronic cough have suggested that autoimmune disease processes may be an underrecognized cause of chronic cough in some patients [66–68]. For example, chronic cough has been associated to celiac disease, hypothyroidism, diabetes type I, pernicious anemia, and other autoimmune diseases [68, 69]. Compared to controls, patients with unexplained chronic cough and self-reported organ-specific autoimmune diseases were more likely to have a significant lymphocytosis on bronchoalveolar lavage [68]. Also, systemic autoimmune diseases such as Sjogren's disease (especially with sicca syndrome), systemic lupus erythematosis, rheumatoid arthritis, scleroderma, and relapsing polychondritis all may cause inflammation (mucositis) or structural distortions of the laryngopharyngeal/airway mucosa, stimulating chronic cough and throat clearing in some patients.

Summary

The diagnosis and management of chronic cough are well established by evidence-based guidelines. Evaluation begins with a careful medical history. When throat clearing is a predominant associated symptom for a patient without environmental exposures (e.g., nonsmoker), the clinician should especially consider GERD and UACS as likely underlying causes. However, cough with throat clearing may also be caused by somatic/tic disorders and by direct irritation of the laryngopharyngeal mucosa. Asthma and NAEB also are possible, but less likely, causes of chronic cough when throat clearing is a predominant complaint unless they are complicated by rhinosinus conditions such as allergic rhinitis and nasal polyposis or provoked by environmental exposures.

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Dysphonia and Laryngopharyngeal Reflux

16

Gregory Postma and Mark A. Fritz

Sally comes to the office today with a lot of nonspecific symptoms including throat clearing and vocal fatigue, and is concerned that her voice has become hoarse and she cannot sing in the choir anymore. She has already seen her primary care provider who attributed the problem to acid reflux. She began her proton pump inhibitor medication 10 weeks ago, and while she has not taken it daily as directed, she feels that there might be a "slight improvement." She then presents to your office with the above question and is obviously still very concerned about not being able to sing in the choir anymore.

The above story is a very typical scenario for an otolaryngologist or a gastroenterologist. Prior to the publication of Koufman's landmark thesis on laryngopharyngeal reflux (LPR) in 1991 [1], the very possibility of extraesophageal reflux was nearly always ignored but the reverse became true over the next 15 years. LPR became the cause of literally any symptom in the head and neck often without any examination of the laryngopharynx. Over the past few years this has been appropriately questioned and we would suggest that a "middle ground" appears reasonable. So for our patient Sally, our answer would be that let us consider other possible causes of your symptoms and get started by examining your larynx and pharynx to appreciate any findings that can guide further evaluation and treatment. As we will discuss, not everything in the throat or a change in voice can be attributed to acid reflux and it is the role of the clinician to tease out the other causes before embarking on long-term therapy with a proton pump inhibitor or surgical treatment of reflux.

LPR has been blamed for a multitude of symptoms over the years, including hoarseness, chronic cough, excessive throat clearing, vocal fatigue, postnasal drip, globus pharyngeus, and dysphagia [2]. Furthermore, it has also been blamed at least in part for the pathogenesis of multiple lesions in the larynx including vocal process granulomas, subglottic stenosis, muscle tension dysphonia, laryngospasm, and even laryngeal carcinoma [3]. Since the early 1990s, there was a move toward attributing much of what we did not know or could not visualize in the larynx as being due to LPR. In many ways, it became the default diagnosis for much of the above problems and symptoms. Proton pump inhibitors provided an easy enough empiric therapy before the patient could see the specialist, but even with visualization of the larynx by some

"My doctor says my reflux is causing my hoarseness. What do you think?"

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otolaryngologists it became the "waste basket" diagnosis when there was nothing else grossly evident on indirect visualization with a mirror or flexible laryngoscopy in the office.

Over the past several years, there has been a push toward better visualization and need to exclude other pathologies such as benign vocal fold lesions that would benefit from surgical excision, muscle tension dysphonia that would be treated with speech therapy, vocal fold paresis that could benefit from a vocal fold injection to assist glottal closure, and so on. Before launching into empiric therapy for LPR, it behooves the clinician to look deeper for the causes of laryngeal symptoms in order to arrive at appropriate therapy.

Clinical Studies

Voice disorders have a lifetime prevalence of around 30% [4]. Reflux has been previously implicated or at least associated with a large number of these voice disorders in the last few decades in multiple clinical studies [5–10]. Koufman et al. described 113 unselected, new patients in an often-cited study from 2000 that presented with a variety of laryngeal and voice disorders [6]. After extensive history and physical examination was performed, all patients with signs and symptoms of LPR (78/113) were sent for ambulatory 24-h double-probe pH monitoring. The authors defined abnormal as a single hypopharyngeal event of pH below 4.0 immediately preceded by a similar drop in the esophageal pH probe, which produced a large number of tests as being abnormal at 57/78 or 50% of the total number that presented. Of these patients, those muscle tension dysphonia had 70% with a concomitant LPR diagnosis compared to neuromuscular conditions with a much lower 19% LPR association.

Ozturk et al. in 2006 attempted to find the prevalence of LPR in those patients with hoarseness and compare it to normal controls [9]. They enrolled 43 patients with hoarseness of greater than 3 months and recruited 20 healthy volunteers. All subjects then received flexible laryngoscopic evaluation as well as 24-h double-probe pH monitoring. 62.8% of the study group had LPR episodes compared to 30% of the healthy population. While there was increased incidence of LPR in the study population, they also showed increased severity of LPR in the study population with significantly increased mean total number of LPR episodes. The most common symptoms of their study population were heartburn and chronic throat clearing and their most common physical finding was a very nonspecific finding of posterior laryngeal pachydermia which was seen in 67% of patients. However, they do not quantitate how many of these patients have LPR on pH testing. They do break down the data to show that 61.8% of those patients with evidence of posterior laryngitis on flexible laryngoscopy had LPR on testing, and 72.7% of those patients with vocal fold lesions (including polyps, nodules, granulomas, leukoplakia, and subglottic stenosis) did as well. Their study is able to show an association between LPR and endoscopic findings but lacks in drawing clear causations and showing data on how many people with these endoscopic findings have LPR.

In a different design, Cohen and Garrett aimed to look at the prevalence of PPI therapy in those patients referred with hoarseness and compare it with their final diagnostic findings [10]. They performed a retrospective review of 299 such patients that were either taking or had taken PPIs in the previous 2 months prior to referral to a tertiary care voice clinic. They found an almost 3:1 female-to-male ratio of patients that met their inclusion criteria, and among those referred, they found that 56.1% had been on or were currently on PPI medications. 29.7% had stopped taking their medication due to continued hoarseness and the other 70.3% had persistent hoarseness despite PPI therapy. They concluded that it was extremely common for patients referred to a tertiary care voice clinic to already have undergone PPI therapy for treatment of their hoarseness but it was of questionable benefit. Of those that quit taking their PPIs, 79.5% of them did not have traditional GERD symptoms of heartburn or regurgitation. The four most common diagnoses after the patient was seen were muscle tension dysphonia, benign vocal fold lesion, GERD, and vocal fold

paralysis. Their study showed how common it is for patients to be started on PPI therapy without evidence of LPR leading to delayed diagnoses and persistent symptoms, and contributing to rising healthcare costs.

Karkos and colleagues attempted to look at a cohort of patients with persistent functional dysphonia and see if there were any pH testing findings that distinguished them from controls [5]. They took 23 patients seen in a voice clinic who had persistent functional dysphonia (defined as lack of any major structural or neurologic abnormality by stroboscopy) for 3 months and compared their 24-h dual-probe pH-metry to 8 healthy controls. They found that most pH-metry parameters did not show any statistical differences between the patients and controls. While they did show this association between certain pH testing findings and functional dysphonia, they could not conclude any causation.

Patel, Carroll, and colleagues attempted to look at the pathology of vocal fold atrophy and determine whether their patients' symptoms of throat clearing and mucus sensation that had been attributed to LPR were really from glottic insufficiency [7]. They retrospectively looked at 26 patients with vocal fold atrophy that had these symptoms and that had been initially attributed to LPR. They found that the majority of their patients improved their reflux symptom index (RSI) scores with a mix of fold augmentation and voice therapy. Specifically though, those patients that had glottic insufficiency that had injection augmentation had improvement in their RSI and voice after treatment. In conclusion, they argued that these symptoms should not only be due to LPR but may also be due to underlying vocal fold atrophy and resulting glottic insufficiency.

Gastroesophageal reflux (GERD) and LPR are not the same disease processes and should not be used interchangeably, but studies have shown a direct correlation between patients' severity of GERD as found by UGI endoscopy and symptom-proven GERD and the prevalence of LPR by use of a questionnaire [11]. Taken a different way, researchers have also described the prevalence of GERD in those patients presenting with only laryngeal complaints [12]. Researchers looked at 30 patients presenting to the otolaryngologist and were then all sent for esophagogastroduodenoscopy (EGD) as part of the study. The patients had a variety of complaints ranging from dysphagia, globus pharyngeus, hoarseness, odynophagia, sore throat, excessive mucus production, throat clearing, laryngospasm, and vocal fatigue. The researchers found a large prevalence of gastroenterological diseases including GERD (43%), hiatal hernia (43%), and *Helicobacter pylori*-positive antrum gastritis (23%). Interestingly, treatment with antireflux medications and eradication of *Helicobacter pylori* infection were able to completely resolve laryngopharyngeal symptoms and findings in 20 of 22 patients (90% success rate) during their 8-month follow-up period. Additionally, they found medical antireflux medication to be effective in the treatment of laryngopharyngeal symptoms.

All of these clinical studies contributed to the association between hoarseness and other laryngeal symptoms with laryngopharyngeal reflux. As the reader can tell, there is a lack of definitions of what constitutes laryngopharyngeal reflux by endoscopic findings as well as even what constitutes an abnormal dual-probe pH testing making drawing clear conclusions difficult for the clinical researcher and even harder for the clinician in the real world.

Basic Science Studies

There have been multiple basic science studies performed in the last 50 years trying to decipher mechanisms of injury from reflux in the larynx. A study in 1968 by Delahunty and Cherry was the first to show in an animal model how gastric acid could cause laryngeal injury. They described a model for vocal fold granuloma development by exposing canine larynges to gastric acid [13]. In their study, they secured gastric acid refluxate from the dogs via nasogastric tube. They then soaked a cotton ball in the refluxate, and placed it on the posterior half of the vocal fold in two dogs every day for 4 weeks. After 4 days, they were able to show mucosal changes, and after 4 weeks, the affected vocal cord of each canine was

markedly inflamed, thickened, and irregular. At day 29 the vocal fold started sloughing, leading to formation of friable granulation tissue that replaced the vocal fold epithelium. Obviously, patients do not have such a high delivery of their own gastric acid to their larynx, but it was the first to show what could happen with chronic acid exposure nonetheless.

In terms of the actual mechanism of injury of LPR on the larynx, an international group of researchers looked at the effect of LPR on laryngeal epithelium to examine the impact of the disease at the cellular level [14]. They looked at carbonic anhydrase, E-cadherin, and MUC gene expression in LPR patients, controls, and an in vitro model. The LPR patients had a decreased carbonic anhydrase level in the vocal fold epithelium but increased levels in the posterior commissure epithelium. Their studies showed a depletion of carbonic anhydrase in reaction to reflux events. In addition, E-cadherin was not even present in 37% of LPR specimens obtained, implying that the larynx does not have a key transmembrane cell surface molecule that can help in epithelial defense making it more susceptible to injury from reflux. Other studies in their group showed that there was indeed injury from reflux at pH above 4 which is classically the pH level under which pepsin becomes activated [15]. In a separate article, pepsin was shown to be co-localized with transferrin in intracellular vesicles, implying that pepsin can be taken up into laryngeal epithelial cells by receptor-mediated endocytosis. This pathway of pepsin into the cells established at least a theoretical mechanism for pepsin damage to the larynx.

Clinical Studies Revisited

More recently, there has been an emphasis from the laryngology community toward eliminating the "waste basket" diagnosis of LPR to the detriment of other causes that then contributes to putting patients on unnecessary medications and delaying the diagnosis and treatment of real underlying pathologies. Patients with a voice complaint will likely present to their primary care physician initially for care. Ruiz et al. surveyed these primary care providers in their treatment of dysphonia, with special attention to LPR [4]. 12.9% of the surveyed physicians responded, yielding 314 completed surveys. The authors found from the survey that most of these physicians preferred to treat patients with hoarseness before referring to an otolaryngologist. Reflux medications (85.8%) and antihistamines (54.2%) were the most commonly used medications for this empirical treatment. 79.2% of these physicians would also treat chronic hoarseness with reflux medication in a patient without evidence or symptoms of gastroesophageal reflux disease. The authors went on to conclude that primary care physicians often attribute dysphonia to reflux. However, they did not look at any patients in particular and just looked at the very high prevalence of PPI therapy without any visualization of the larynx.

As stated above, the tendency to blame reflux first may delay appropriate evaluation and treatment of laryngeal disorders causing hoarseness. Fritz et al. recently looked into a large cohort of patients that were referred to tertiary laryngology practices with the referring diagnosis of LPR [16]. Only 47/132 (35.6%) of patients had LPR confirmed as their final primary diagnosis, whereas 85/132 (64.4%) of patients had a different final diagnosis other than LPR. These other pathologies ranged from the most common of muscle tension dysphonia, vocal fold polyps, and scar to a few instances of leukoplakia and vocal fold paralysis as well as one instance of a laryngeal neoplasm. The authors used stroboscopy to find these alternative pathologies in 76.5% of the cases demonstrating the value of high-resolution imaging and stroboscopy in the evaluation of laryngeal complaints.

Stroboscopy has been shown to be very helpful in the evaluation of voice patients [17, 18]. The combination of increased illumination and magnification as well as the detailed assessment of the glottic closure and mucosal wave make stroboscopy key in the identification of subtle vocal fold pathology. It has been shown to alter the diagnosis of patients that have even had comparable flexible laryngoscopic images performed by the same clinician.

Sulica published a study retrospectively looking at 381 new patients presenting with hoarseness, specifically looking at 26 patients that carried a diagnosis of reflux as the sole cause of their dysphonia [19]. Using stroboscopy he was able to identify another diagnosis other than LPR in every patient including phonotraumatic lesions (42%), neurologic disorders (34%), age-related changes (19%), and infectious causes (4%). He concluded that hoarse patients that fail to improve with empiric antireflux treatment would benefit from further laryngeal investigation and that such empiric therapy may not be appropriate.

In yet another similar study, Rafii et al. prospectively looked at 21 patients that were referred with a sole diagnosis of LPR as the reason for their hoarseness and specifically excluded patients with any other referring pathology [20]. They concluded that none of them had LPR after thorough examination that included flexible laryngoscopy and stroboscopy. They attributed the causes to an array of benign vocal fold lesions (29%), vocal fold paresis (29%), and muscle tension dysphonia (14%), and additionally found two patients with leukoplakia of which one had microinvasive carcinoma. All of these studies strongly suggest that LPR is vastly overdiagnosed and masks other real pathologies that are treated much differently and not with PPI or dietary therapy.

In a private practice setting, Thomas and Zubiaur chronicled the prevalence of LPR in patients referred to their practice, their response to previous PPI treatment, and their eventual final diagnosis [21]. They found 105 patients over a 3-year period that were referred with LPR that was blamed as the cause of hoarseness. 82% of these patients that were on antireflux treatment had no improvement. None of the patients referred with LPR were found by the authors to have LPR as their final diagnosis. Their final diagnoses ranged from behavioral sources of hoarseness to structural causes including malignancy. Their findings additionally show that the overdiagnosis of LPR is not only present in academic tertiary medical centers but also in private practice.

As stated earlier, part of the problem with diagnosing reflux as the cause of laryngological complaints including hoarseness is the fact that there are no agreed-upon physical findings on flexible laryngoscopic examination that are pathognomonic for the diagnosis of LPR. An interesting paper from Hicks et al. looked at pharyngeal signs of LPR in normal controls and showed just how prevalent they were in this population that was screened against any head and neck complaints to begin with [22]. 105 healthy adult volunteers had a flexible laryngoscopic exam and then had two laryngologists exam the videos at two different times. There was presence of at least one LPR finding on video 86% of the time in these healthy individuals and some findings such as an interarytenoid bar were present up to 70% of the time. Other common findings seen more than 10% of the time were arytenoid medial wall erythema, posterior pharyngeal wall cobblestoning, interarytenoid bar erythema, arytenoid medial wall granularity, posterior cricoid wall edema, arytenoid apex erythema, true vocal fold edema, and interarytenoid bar irregularity. This paper serves to caution against trusting the endoscopic exam to diagnose LPR implicitly, because almost all of the healthy individuals in this study had at least one finding that was thought to be related to reflux in the first place. Moreover, there is no agreed-upon criteria for the diagnosis of LPR [23]. Researchers blinded 5 otolaryngologists to clinical information for 122 rigid endoscopic laryngeal examinations and showed very poor agreement between clinicians with regard to severity of LPR and likelihood of an LPR component to their dysphonia symptoms. With such disagreement between physicians that see these patients every day, it even further questions the validity of any criteria for diagnosing LPR as the cause of any laryngeal complaints.

In the gastrointestinal medicine literature, there is also debate as to the need to screen the larynx as part of upper gastrointestinal endoscopy. Researchers looked at 1130 patients who underwent UGI endoscopy who were asymptomatic in the laryngopharyngeal area but who underwent a structured examination of this area before insertion of the UGI scope into the esophagus [24]. They found a rate of 3.89% of pathology suspected by the endoscopist that was then

confirmed by the otolaryngologist colleague, in addition to 0.71% of patients that then were found to have laryngeal pathology on the video examination screened by the otolaryngologist as part of the study. Their most significant findings on their scope were leukoplakia ($n = 4$), posterior laryngitis ($n = 16$), Reinke's edema ($n = 2$), and hyperkeratosis of the arytenoid folds ($n = 2$). They concluded that a screen of the laryngopharyngeal area should thus be performed as part of the UGI endoscopy prior to insertion into the esophagus even in the lack of clear symptoms in the area. While the diagnostic yield of this maneuver is not sufficient to diagnose all pathologies in the larynx, it would be able to catch gross pathologies that would be affecting the larynx and facilitate quicker referral even in those patients without specific laryngeal complaints such as hoarseness.

Treatment

There are many treatment options for LPR and GERD symptoms. One of the first treatments utilized is lifestyle modification with dietary changes. A review paper from the Archives of Internal Medicine looked at the current literature in 2006 found that there was a general lack of evidence that dietary modifications can improve esophageal pH profiles or reflux symptoms [25]. They found that tobacco and alcohol cessation were not associated with any improvement. Additionally, while there was physiologic mechanisms by which tobacco, alcohol, chocolate, and high-fat meals decrease the lower esophageal sphincter tone, there was no published evidence on the efficacy of these measures. They did however find evidence that elevating the head of the bed, lying in the left lateral decubitus position, and losing weight improved pH profiles and therefore symptoms in patients.

The generally recommended medical treatment for patients with LPR is once- or twice-daily dosing of a proton pump inhibitor for 3–6 months. A double-blind placebo-controlled trial evaluating therapy with omeprazole 20 mg twice daily for patients with a reflux finding score >7 and a reflux symptom index >13 was published in 2008 [26]. For their 62 patients, they randomized them to placebo or PPI for 3 months and then repeated the RFS and RSI questionnaires. Both RFS and RSI improved significantly more in the PPI group compared to the placebo group with the most impressive difference between the study groups being the presence of posterior commissure hypertrophy. However, interestingly, another group looked at the response of posterior commissure hypertrophy to long-term acid suppression by PPIs (mean of 32 months) by looking at pre- and posttreatment laryngeal images [27]. They found no significant difference in the posterior commissure hypertrophy from the long-term acid-suppression therapy. While posterior commissure hypertrophy is sometimes a very common finding in LPR, it should not be utilized by itself or to measure the response to therapy.

Another study published by Lee et al. looked at the changes in the quality of life with LPR after medical treatment with PPI therapy [28]. They prospectively took 180 patients that were diagnosed with LPR and treated them with a standard PPI twice-daily dose for 3 months and followed them with the RSI, RFS, Short-Form 36-Item Health Survey version 2.0 (SF-36), and the LPR-health-related quality of life (HRQOL) at 4- and 12-week follow-up visits. They were able to show improvement at the 12-week mark in most categories of the four patient surveys including in the LPR-HRQOL scores for voice.

Medical therapy with PPIs can be difficult for other reasons. There are significant side effects, especially from long-term exposure to PPI therapy. Abramowitz et al. provide an overview of the systematic reviews surrounding adverse events from PPI usage [29]. They found community-acquired pneumonia (CAP), *C. difficile* infection, and bone fractures as being most significantly associated with PPI usage. Patients on PPI had an odds ratio (OR) of 1.38 to have CAP compared to patients not on PPI. However, this correlates with needing 333 number patients to treat (NNT) to make one CAP event. There was an OR of 2.08 for increased risk of *C. difficile* infection, but again the NNT was very large at 1924. Lastly, PPIs were associated with an increased risk of spine, hip, and overall fractures with an OR of 1.26 and a NNT of 644. The authors concluded that while there is an

association with pneumonia, enteric infections, and fractures, these events are relatively uncommon and should only be used to guide the use of the medication in high-risk groups.

Another medical therapy utilized for LPR-related symptoms is a liquid alginate suspension. Authors randomized 24 and 25 patients, respectively, into four times daily alginate therapy after meals and at bedtime or no treatment [30]. They only included those patients with RSI >10 and RFS >5 and evaluated patients 2, 4, and 6 months into their respective therapies. Significant improvements in RFS and RSI were achieved in the liquid alginate therapy group compared to controls.

For those with GERD that is refractory to medical therapy with standard or high-dose PPI medications, laparoscopic Nissen fundoplication (LNF) has been well established in managing patient symptoms. Sataloff and colleagues showed in 2014 that LNF was also useful in professional voice users with LPR symptoms that were insufficiently treated with PPIs [31]. They looked at 25 professional voice users that had been refractory to twice-daily PPIs and showed that LNF was able to allow 60% of them to go off of medications for LPR and 24% took less medications postoperatively. Additionally, 90% of positive symptom indices were negative postoperatively showing it to be a reasonable choice for patients that are refractory to medical management. In addition to open surgical options for reflux, there are also endoscopic therapies that have been shown to reduce esophageal acid exposure by delivering radiofrequency energy below the mucosa at the level of the gastroesophageal junction [32]. These have been shown to reduce the need to treat with proton pump inhibitors from 88.1 to 30% of patients.

Summary

While reflux has been associated in the past with many patients presenting with laryngeal complaints including hoarseness, there is growing evidence that there are many different lesions and etiologies that are visualized with the use of distal chip endoscopes and stroboscopic equipment in the hands of an otolaryngologist that will be initially attributed to reflux. Many of these lesions will not have any relationship to LPR or its treatment and may need other types of therapy. Therefore, while reflux may be a contributor to a patient's hoarseness, often there is another etiology that can be elicited upon careful visualization of the larynx including videostroboscopy. Furthermore, for our high-risk patients, there should at least be consideration of the association of long-term PPI use with the side effects of bone fractures, community-acquired pneumonia, and enteric infections. The use of proton pump inhibitors indiscriminately is therefore not wise with the lack of definite benefit in the dysphonic patient.

In conclusion, our hoarse patient carrying the diagnosis of LPR is more likely to have some other primary cause of their symptom and must be evaluated by laryngovideostroboscopy. Only then can we state that reflux indeed is the cause of their dysphonia.

Future directions in the field will likely include continuing to move away from the empiric treatment with LPR for patients with hoarseness and other more nonspecific laryngeal complaints. Dual-channel 24-h pH probes will continue to be the gold standard for LPR diagnosis. High-resolution manometry additionally may hold information as to the physiologic mechanism of how the reflux occurs. Current and future research will continue to delve into the role not only of acid on the laryngeal mucosa but also of pepsin even in the absence of acid. Musocal biopsies or salivary testing for pepsin might reveal a more sensitive test for LPR than dual-channel 24-h pH probes and be easier for patients to tolerate.

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Aspiration Pneumonia/Bronchitis 17

Masooma Aqeel and Elizabeth R. Jacobs

Patient Question: What Controls Normal Swallowing and What Is "Aspiration"?

Answer to patient: Swallowing is a highly organized bodily function. A healthy adult can swallow up to 2000 times a day. Each act of swallowing involves the fine coordination of 30 separate pairs of nerves and muscles and is under both our voluntary (conscious) and involuntary control (controlled by central nervous system without our awareness). There are four separate stages of swallowing. The first stage allows the sensation of "taste" and involves the breakdown of food into smaller, more digestible, particles with the help of teeth (mechanical grinding) and enzymes that are released from salivary glands in the mouth (chemical digestion). These smaller digested food particles form a "food bolus" that is propelled by a forceful motion of the tongue to the back of the mouth (oropharynx). Up until this point swallowing is under conscious control. Further stages of swallowing are controlled by the central nervous system and are not under voluntary (conscious) control. The next, and most complex stage, involves movement of the epiglottis and voice box (larynx) into a position that prevents the food bolus from entering the lungs and is conducted with a coordination of muscles such that the "windpipe" is temporarily sealed off—preventing entry into the lungs. Once past this stage, food enters the esophagus and progresses to be digested further. As is clear, a miscoordination in any of these steps can lead to ineffective swallowing and "aspiration."

(1–2-min evidence-based reading for clinician): Epidemiology, genetics and pathophysiology, diagnostic test results, treatment options, etc.

Normal healthy adults swallow ~30 times per hour while awake [1] and each act of swallowing lasts approximately 10+ seconds. Swallowing occurs in four phases and requires the fine coordination of more than 30 pairs of nerves and muscles [2, 3].

An initial "*oral phase*" is under voluntary control and is divided into the "*preparatory*" and "*propulsive*" stages. The *preparatory stage* accumulates the food within a closed chamber (oral cavity bound by lips anteriorly, hard palate superiorly, and pharyngeal wall posteriorly) to form a bolus. With the help of dentition and enzyme-rich saliva, food is broken down to smaller particles. It is during this phase that chemoreceptors, located on the tongue and the palate, detect taste and other aesthetics of food—leading to pleasure (or displeasure). During the "*propulsive*" phase the palate moves upwards

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to seal off the nasopharynx (preventing nasal regurgitation) and the tongue moves downwards, hence establishing a wide continuum between the oral and pharyngeal cavities. Then, with a forceful piston-like motion of the tongue, the food bolus is propelled into the oropharynx [2].

The "*pharyngeal phase*" is a reflexive (neural-mediated) and most complex stage of swallowing. With the nasopharynx sealed off, contraction of the superior constrictor muscles propagates the bolus downwards towards the upper esophageal sphincter (UES). The suprahyoid muscles pull the hyoid bone (and the larynx) up and outwards and the epiglottis rapidly flips downwards whereby allowing a temporary closure of the laryngeal vestibule for approximately 0.6–0.7 s during deglutition [2]. The cricopharyngeus muscle (makes up the UES) relaxes allowing the bolus to the next "*esophageal phase*." Esophageal peristalsis then moves the bolus downwards towards the lower esophageal sphincter (LES) which relaxes to allow food into the stomach.

Figure 17.1 depicts the four phases of swallowing.

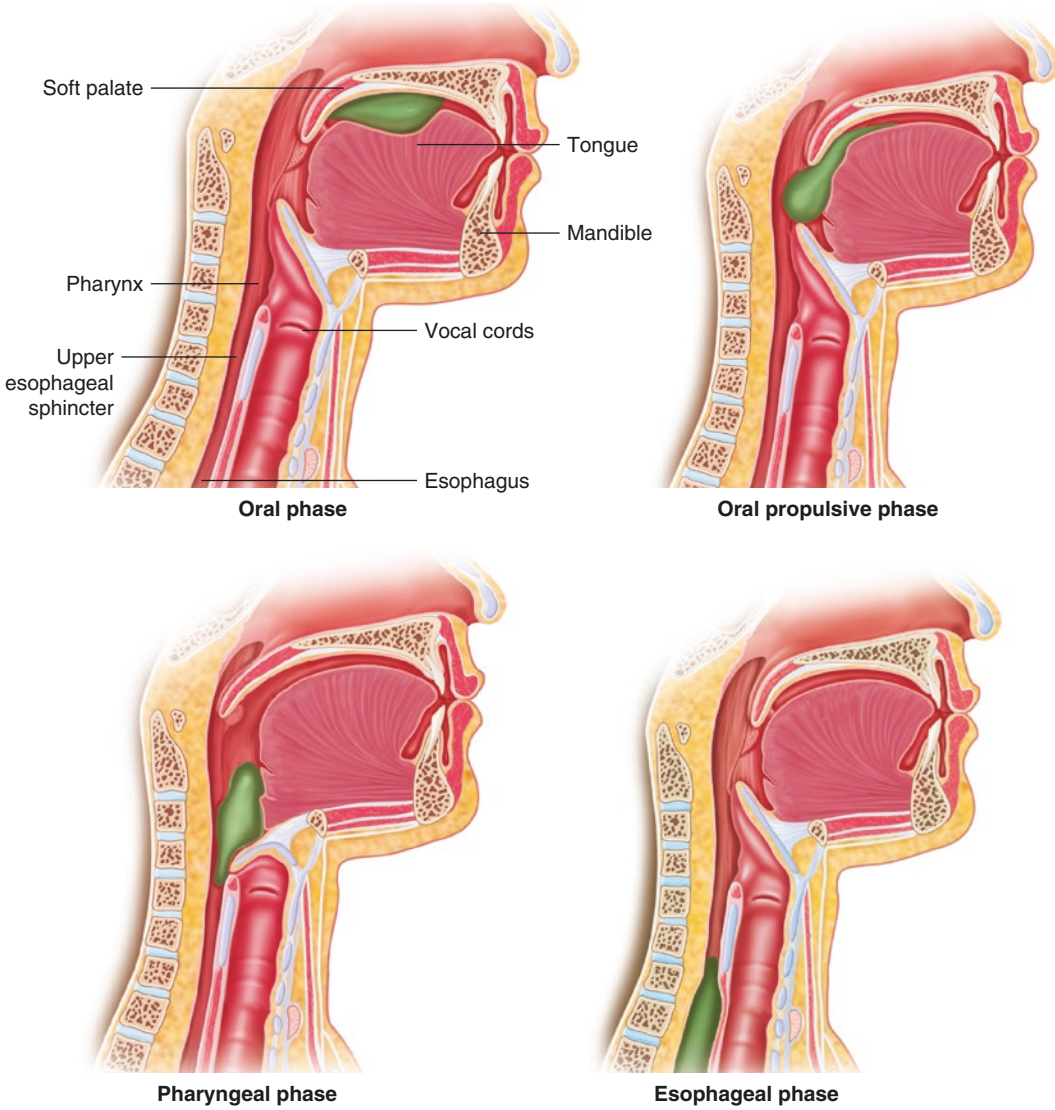

Fig. 17.1 Phases of swallowing

Swallowing is finely coordinated with respiration in order to prevent aspiration, and swallowing is dominant over respiration in health. Physical closure of the laryngeal vestibule, as described above, and a temporary neural-mediated suppression of respiration (for about 0.5–1.5 s) [4] allow this to take place in a safe manner [4, 5] in healthy adults. Problems arise when there are structural and/or functional defects in this highly coordinated act.

"*Aspiration*" refers to the inadvertent inhalation of oropharyngeal secretions or gastric contents below the level of the true vocal cords and into the lower respiratory tract [6, 7]. *Penetration* is the term used to describe entry of food material into the larynx but above the vocal cords [7]. Aspiration is also distinct from regurgitation which implies a "reflux" of gastric contents into the esophagus and oropharynx *without* contamination of the lower respiratory tract.

Patient Question: What Are the Risk Factors That Predispose to Aspiration?

Answer to patient: Almost half of healthy adults routinely aspirate small volumes of oral or stomach contents (see questions 4 and 5 below) during sleep. Several important conditions and risk factors predispose patients to aspiration. Patients at risk can be divided into the young adult population versus *a more elderly and dependent population.*

Firstly, young adults with chronic conditions such as a seizure disorder, or those with gut motility (bowel movement) problems such as scleroderma (a condition that causes slow bowel movement), chronic constipation (such as cystic fibrosis patients), those with feeding tubes or others with drug or alcohol use and overdose problems, are more likely to aspirate.

It is perhaps easier to think of elderly patients in terms of those residing in the community versus *those residing in nursing homes. In general increasing age is an independent risk factor for aspiration. With age, the body becomes frail, loses coordination, and may develop weaknesses such as outpouchings in the upper digestive tract that can "hide" or sequester food and later cause regurgitation (vomiting) of food leading to aspiration. Older patients also have a higher risk for having acid reflux disease (heartburn) that is associated with an increased risk for aspiration.*

In particular, nursing home residents have poorer oral hygiene and have several potentially dangerous bacteria in their mouth that when aspirated lead to pneumonia. They are also more likely to suffer from disorders such as stroke, Parkinson's disease, and dementia (memory loss)—all of which lead to their inability to safely carry out the act of swallowing.

Another important group of patients at risk for aspiration pneumonia are patients on long-term acid-suppressive medications (such as omeprazole, zantac). These medications work to suppress the acidic contents of the stomach in an attempt to prevent injury when acidic stomach contents reflux—however they also allow harmful bacteria to flourish within the stomach environment. Without stomach acid, these bacteria are more readily able to cause pneumonia after aspiration takes place.

(1–2-min evidence-based reading for clinician): Epidemiology, genetics and pathophysiology, diagnostic test results, treatment options, etc.

Some degree of aspiration is inevitable—and even "normal." As described in detail later in this chapter, almost half of healthy normal adults aspirate routinely during the night. However, several structural and functional abnormalities in the aerodigestive tract place certain populations at a higher risk for aspiration.

Amongst these, *the elderly* are an especially high-risk group. They may be further subdivided into those living independently in the community, and those who are institutionalized.

For elderly patients living in the community, a risk for aspiration may stem partly from the physical age-related changes that take place in the human body. Structural abnormalities such as *cervical osteophytes* (bony outgrowths of the vertebra indenting the oropharyngeal tract) [8], *Zenker's diverticula* (pharyngeal outpouching representing weakened muscular spots) [9], and

esophageal strictures and *webs* [10] can lead to misdirection of the food bolus and hence aspiration. Gastroesophageal reflux disease (GERD) is also more common in the elderly and increasing age correlates with the severity of GERD and its complications (erosive esophagitis, Barrett's esophagus) [6, 11].

To demonstrate this increased risk, Kikuchi et al. studied 14 otherwise healthy elderly patients (averaging 77 years) hospitalized with community-acquired pneumonia and compared their aspiration events with age-matched controls without pneumonia. They concluded that elderly patients hospitalized with community-acquired pneumonia were seven times more likely to have aspirated than their age-matched controls (71 vs. 10%) [12]. Other studies too have correlated increasing age (independent of neurological disease) with a higher incidence of impaired oropharyngeal deglutition [13]. Based on these observations, one may argue that age (and associated physiological changes in the body) alone is a risk for aspiration [14].

Institutionalized elderly patients are a different story. They are reported to suffer from poor oral hygiene and care [15, 16] and harbor serious pathogens (Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*) in their oral cavity [6]. In a study on the dental health of patients living in 55 residential homes in the United Kingdom, large numbers of patients were found to have an increased incidence of oral ulcers, glossitis, and coronal and root caries [16]. Consequently, improving oral care is shown to reduce the incidence of pneumonia by almost one and a half times in such groups [17].

The institutionalized elderly are also more likely to suffer from neurological complaints or use of medications that impair swallowing. An interesting study of 1946 patients found that 10% of patients with community-acquired pneumonia and 30% of patients with continuing-care facility (CCF)-associated pneumonia were due to aspiration [18]. Amongst the CCF-pneumonia group, as many as 72.4% of patients had dysphagia secondary to a neurological disease (i.e., stroke, dementia, multiple sclerosis, mental retardation, brain tumors, movement, Parkinson's disease, and Alzheimer's disease) that posed a risk for their aspiration. In addition many of the CCF patients were taking centrally acting medications that could cause sedating or xerogenic (drying) effects reducing salivary flow [18]. Depending on the methods used, up to 78% of patients who have had a stroke exhibit dysphagia and may aspirate at least in the acute phase after a CVA [19].

For adults with community-acquired pneumonia it appears that factors that lead to an altered or a decreased level of consciousness (i.e., alcohol use, 12.9%; drug overdose, 21.3%; or hepatic encephalopathy 7.7%) are the main risk factors leading to aspiration [18, 20].

Other risk factors in the community affecting all ages include the aggressive use of acid-suppressive medications (such as proton pump inhibitors (PPIs) and H2 receptor blockers). Approximately 40–70% of medical inpatients receive acid-suppressive medications and as many as 50% are new prescriptions. PPIs are linked with an almost 1.5–1.89 times higher risk for community-acquired pneumonia [21, 22]. In a large hospital-based epidemiological cohort, use of PPIs was associated with 30% increased odds of hospital-acquired pneumonia (HAP) in non-ventilated patients and this risk was highest within the first few days to a week of PPI use [23]. Acid suppression allows survival of bacterial pathogens (that would normally be killed in acidic contents). Reflux and further aspiration events allow these pathogenic bacteria to find their way into the lungs and cause infection.

This risk from acid suppression has also been demonstrated in critically ill, mechanically ventilated patients. In a randomized controlled trial, patients were assigned to use of sucralfate, antacid, or H2 receptor blocker use. The group with sucralfate use was demonstrated to have significantly lower rates of gastric colonization and late-onset pneumonia (4 days later) when compared to the antacid and H2 blocker groups [24]. These data support the hypothesis that suppression of gastric pH leads to higher rates of gastric bacterial colonization and higher rates of hospital-

acquired pneumonia [25] and current guidelines recommend against use of stress ulcer prophylaxis in patients without a clear indication for their use [26].

Patient Question: How Common Are Aspiration and Aspiration Pneumonia?

Answer to patient: As described earlier, small-volume aspiration takes place routinely in almost half of healthy normal adults. About 15% of patients in the community setting develop pneumonia as a result of aspiration and aspiration pneumonia is associated with worse survival than other community-acquired pneumonias.

Larger volume aspiration pneumonia is also the second most common reason for nursing home patients to require admission to a hospital and is the leading cause of death in this group of patients. Aspiration complicates 1 of every 3000 cases of general anesthesia and continues to be not only a significant financial burden on health care costs but also associated with high rates of death.

(1–2-min evidence-based reading for clinician): Epidemiology, genetics and pathophysiology, diagnostic test results, treatment options, etc.

Aspiration is very common and can occur in both health and disease. The incidence depends on the methods used to detect aspiration, with some sensitive techniques detecting clinically insignificant "microaspirations" while others (e.g., swallow studies) identifying larger boluses of material passing the vocal cords (see question 4 for details). Huxley et al. studied aspiration in 20 normal and 10 patients with depressed consciousness by injecting indium^{131} chloride (radioactive tracer) via a catheter directed into their nasopharynx. Radioactive tracer uptake was seen on post-sleep lung scans (as evidence of nocturnal aspiration) in 45% (9 out of 20) of healthy subjects and 7 out of 10 (70%) patients with depressed consciousness during sleep [20].

In a similar experiment, Gleeson et al. also studied aspiration events in ten healthy adults using radioactive tracer uptake in lungs and sleep patterns using sleep polysomnography over two separate nights [27]. Radioactive tracer solution was instilled in the nasopharynx of all subjects during nocturnal sleep. Although no particular sleep behavior (time spent in bed, sleep efficiency, supine sleep time, etc.) was associated with a higher risk, it was demonstrated that 5 of 10 (50%) healthy subjects *silently aspirate* on at least one of every two nights while asleep.

However, as described earlier, certain populations are much more likely to aspirate and suffer from clinical consequences of this aspiration.

Epidemiological studies indicate that approximately 5–15% of all community-acquired pneumonia is secondary to aspiration [6]. Aspiration pneumonia has a significantly higher 30-day mortality (21%) when compared to community-acquired pneumonia and patients are more likely to be admitted to the intensive care unit (ICU) and require mechanical ventilation [28].

Aspiration pneumonia has been reported to be the second most frequent principal diagnosis amongst Medicare patients [29]. Amongst nursing home residents aspiration pneumonia is the second most common infection (21%) after urinary tract infections, has an annual incidence of new cases between 18 and 48%, and has a higher mortality rate than that of any other nosocomial infection [30].

Aspiration is also well recognized as a complication of general anesthesia occurring in 1 of every 2000–3000 cases in adults [31]. Anesthetic agents can suppress airway protective reflexes and predispose patients to aspiration. Aspiration pneumonia accounts for as many as 10–30% of all deaths associated with anesthesia [6, 32].

It comes as no surprise that "aspiration pneumonia" is considered by some to be an *epidemic*. Admission rates and health care costs for patients with the diagnosis have risen rapidly. Aspiration pneumonia is associated with longer hospital stays (mean increase of 9 days), increased total hospital charges (mean increase of $22,000), higher ICU admission rates (odds ratio 4.0), and a higher in-hospital mortality (OR; 7.6) [30, 33].

Patient Question: What Are the Symptoms of Aspiration and How Is It Diagnosed?

Answer to patient: Some aspiration has no signs or symptoms, and thus is called "silent." When present, symptoms of aspiration can range from subtle, unexplained coughing that persists over several weeks to wheezing similar to that seen in asthma. Choking may be obvious when a patient eating suddenly develops breathing difficulty and distress for no other clear reason. Aspiration may occur in small amounts (microaspiration) and go unwitnessed or be obvious when a patient actively vomits and inhales contents into his/her lungs (macroaspiration).

Bedside swallow evaluations can be performed by trained speech specialists, nurses, and physicians. Concerning signs include drowsy mental state or a cough brought on with swallowing. While very helpful in directing therapy when positive, bedside measures can be falsely reassuring when negative and should be followed with more advanced testing when suspicion for aspiration is high. Advanced tests can be conducted in the presence of a speech therapist and a radiologist and involve recording a video while observing a patient swallow. Direct observation of swallowing allows a much closer look at the problem and can also help with real-time feeding with different consistencies and food types to observe which foods and which swallowing techniques make swallowing safest for the patient.

(1–2-min evidence-based reading for clinician): Epidemiology, genetics and pathophysiology, diagnostic test results, treatment options, etc.

Aspiration may be asymptomatic (silent or unwitnessed) or symptomatic (micro- or macroaspiration). *Microaspiration* refers to aspiration of small amounts of gastric contents or oropharyngeal secretions (usually <1 mL). *Macroaspiration*, on the other hand, refers to the visible aspiration of large amounts of bowel or gastric contents [7]. Signs of acute aspiration include sudden choking, shortness of breath, or chest pain while eating. Most adults, however, are likely to have subtle symptoms—such as a chronic unexplained cough or wheezing.

A diagnosis of aspiration pneumonia requires a high index of suspicion and can be challenging.

Historically bedside evaluation of swallowing has evolved from the care of patients suffering from stroke and resultant dysphagia [19].

A direct observation of swallowing; special attention to certain indicators of altered swallowing such as decreased consciousness, dysarthria, coughing, or choking while eating; and presence of a weak and delayed cough in response to aspiration can alert the physician to a potential problem. However, bedside evaluations are insensitive [6, 34]. In a study by Smithard et al., bedside clinical assessment had a sensitivity of only 47–70% (depending on who performed the assessment) and missed approximately 30–53% aspirators [34]. Such patients are likely to *silently* aspirate (without any overt signs of distress) and evaluation of ineffective swallowing for these patients must be combined with objective instrumental tests.

A *modified barium swallow study (MBSS)* or *video fluoroscopic swallow (VFS)* is a noninvasive test that reviews the oral, pharyngeal, and cervical esophageal stages of swallowing while the patient is upright and swallowing varying consistencies of barium-coated or water-soluble contrast mediums. This test is performed by speech therapists in conjunction with radiologists who acquire a video of swallowing to help elucidate a physiological reason for dysfunctional swallowing. This test has been traditionally considered a gold standard for diagnosing dysphagia.

A *barium swallow* is conducted by the radiologist while the patient is upright or, less commonly, supine. The esophageal phase of swallowing is observed for any structural or motility etiologies as a causation of aspiration.

FEES (or flexible endoscopic evaluation of swallowing) was first described in 1988 by Langmore et al. [35]. This modality can be performed by a trained speech therapist and involves viewing the oropharyngeal and laryngeal phases of swallowing via a nasally inserted laryngoscope. A FEES has several parts to it. First a preliminary assessment of anatomy is conducted and the movement of structures inside the mouth in

response to secretions, etc. is observed. The second part includes observing the patient to swallow meals of varying consistencies and bolus sizes of liquids and solids. This allows the examiner to try several different combinations of consistencies and volumes and different strategies to determine which is handled best by an individual patient. Laryngeal penetration (appearance of contrast in the laryngeal vestibule) and aspiration (food below the vocal cords) can be identified using this technique. The esophageal phase cannot be assessed using this technique. This test is portable and can easily be conducted in the patient's home environment with family/caregiver participation [14].

Lastly, *esophagogastroduodenoscopy (EGD)* is an invasive test that can be performed by a gastroenterologist and can help identify mucosal and other structural abnormalities along the esophageal tract.

Studies evaluating the consistency of results using FEES versus video fluoroscopy (VFS/modified barium swallow (MBSS) suggest a great degree of agreement between the two tests. A study on 21 patients by Langmore et al. [36] evaluating four features (aspiration, penetration, spillage, and residue) concluded that FEES agreed with the results of video fluoroscopy in 90% of cases (sensitivity 0.88, specificity 0.5, positive predictive value 0.69, negative predictive value 0.63). In general both tests complement one another and are considered "therapeutic" in that they allow a greater patient feedback during the test and real-time modification of behavioral strategy and bolus type—in order to achieve the most effective, safest swallowing. FEES may be considered superior for patients with severe dysphagia who have not had any oral intake for several weeks [14].

Patient Question: What Can Happen to Me as a Result of Aspiration?

Answer to patient: Harmful effects of aspiration depend on the amount and nature of the materials aspirated. Aspiration of acidic liquid stomach contents can lead to an inflammation of the smaller airways that presents with wheezing and shortness of breath—very similar to the tell-tale signs of asthma.

Aspiration of solid contents such as solid foreign objects can lead to a blockage of one of the main or central airways leading to asphyxiation or choking. Aspiration of a foreign object is considered a medical emergency as it can lead to death. It requires urgent steps to remove the aspirated materials. Recently aspirated iron tablets or potassium pills have become a focus of attention as these are particularly corrosive (causing chemical burn) and can seriously damage the lining of the airways. If a foreign object is not promptly removed, it can lead to long-term problems of causing stenosis (narrowing) of the bronchial tubes as well as formation of fistulae (abnormal connection between the lungs and other organs) that are extremely difficult to repair and treat.

As explained later in this chapter, the majority of patients who aspirate have no signs or symptoms or develop pneumonia. Some patients have repeated aspiration, and large amounts of bacteria in their oral cavity. Patients whose immune systems are otherwise depressed are more likely to develop pneumonia after aspiration.

(1–2-min evidence-based reading for clinician): Epidemiology, genetics and pathophysiology, diagnostic test results, treatment options, etc.

Aspiration can result in several different clinical syndromes—and pH and volume of aspirated contents are critical determinants of the degree of lung injury [6, 37]. Both micro- and macroaspiration can result in immediate and long-term injury to the lungs.

Some acute consequences of aspiration include aspiration pneumonitis, aspiration pneumonia, and asphyxiation (or choking).

Aspiration or chemical pneumonitis (also known as Mendelson's syndrome) was described in 1946 while observing obstetric patients undergoing general anesthesia. Patients suffered from an acute asthma-like reaction likely from aspiration of liquid contents. By instilling 0.1 N hydrochloric acid into rabbit lungs, Mendelson elicited a pattern of lung injury similar to that seen in

humans and highlighted the importance of *acidic* gastric contents in causing acute lung injury or pneumonitis [38]. Since then several experiments have shown that neutralizing acidic contents of aspirate can mitigate the extent of lung injury [6]. Most authors agree that a volume of more than 20–25 mL and a pH less than 2.5 are critical to causing chemical pneumonitis in adults [6, 37–39]. Studies in rats have demonstrated this to be a biphasic process. There is an initial phase of intense direct chemical burn from acidic contents causing increased capillary permeability and leakage—followed by a quiescent period over the next 2–3 h. At 4 to 6 h an aggressive neutrophilic response peaks and the release of inflammatory mediators leads to lung injury much like the adult respiratory distress syndrome (ARDS) [37].

It is important to differentiate aspiration *pneumonitis* from *pneumonia*—as the latter involves pathogenic bacteria development of a distinct radiographic infiltrate in a patient at risk for aspiration and entails antimicrobial therapy.

Table 17.1 depicts differentiating points between aspiration pneumonia and pneumonitis.

In general a bacterial infection is not thought to play a primary role early in the process of aspiration as acidic contents suppress gastric flora. During silent aspiration adults aspirate volumes in the range of 0.01–0.2 mL [27] and although this may introduce bacteria in sufficient amounts (10^4–10^5 organisms per milliliter) [27, 40] host defenses are usually able to combat disease. Bacterial infection (aspiration pneumonia) develops in situations where host defenses are compromised (impaired glottis closure, cough reflex, acid suppression with medications, impaired ciliary clearance, depressed humoral or cell-mediated immunity) or when a bacterial inoculum is large and deleterious enough to overwhelm defenses [6].

Aspiration of solid components (foreign-body aspiration or FBA) is more common in children and adults with advanced age. In 2014, approximately 4864 people died from choking in the United States and 2751 of them were over the age of 75 [41]. Acute aspiration of a large FB into a central airway can result in asphyxiation and even death—and requires immediate intervention to relieve obstruction. Depending on the size, type, and location of aspirated contents patients can develop serious long-term consequences such as recurrent post-obstructive pneumonias, hemoptysis, and bronchial stenosis from chronic obstruction. Pills (iron and potassium chloride tablets in particular) are being increasingly recognized for causing extensive chemical burn and inflammation in the bronchial epithelium [42, 43].

Patient Question: What Are the Long-Term Consequences of Aspiration?

Answer to patient: Unfortunately, aspiration can harm us in both the short and the long term. The chronic, repetitive damage from inhalation of acidic stomach contents and bacteria can lead to chronic lung conditions such as bronchiectasis. Bronchiectasis refers to an abnormal enlarge-

Table 17.1 Key differential points between aspiration pneumonia and aspiration pneumonitis[a]

	Aspiration pneumonitis	Aspiration pneumonia
Mechanism of injury	Chemical "burn" from aspiration of sterile acidic gastric acid	Bacteria burden from oropharyngeal contents
Bacteria involved	Not initially, may be later	Yes
Clinical symptoms	Asymptomatic to dry cough, wheezing ("bronchospasm"), hypoxemia, respiratory distress	Productive cough, fever, putrid smell
Resolution	Within 12–36 h	Usually within a week
Empiric antimicrobials	Usually not	Yes
Complications	Acute lung injury, ARDS (15–30%)	Empyema, lung abscess

[a]Table adapted from Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med. 2001; 344(9):665–71

ment (dilation) of the smaller airways that leads to a difficulty in clearing mucus and secretions. This in turn can become a nidus for infections.

Patients with untreated or inadequately treated aspiration pneumonia can develop a lung abscess, a known complication of aspiration. Signs and symptoms of a lung abscess can include unexplained fevers, foul-smelling breath, chest pain, etc.

Importantly, aspiration is being linked to the development of lung fibrosis (also known as idiopathic pulmonary fibrosis or IPF) and it is possible that early control and treatment of aspiration can lead to an improved survival in this formidable disease.

(1–2-min evidence-based reading for clinician): Epidemiology, genetics and pathophysiology, diagnostic test results, treatment options, etc.

Aspiration can be injurious in both the short and the long term. While acute effects of macroaspiration are usually self-evident and can be addressed promptly (i.e., choking or acute bronchopneumonia)—the effects of chronic microaspiration may be more occult and a diagnosis may be missed until late into disease progression.

Microaspiration is a repetitive and insidious insult that is shown to cause lung damage in the form of diffuse aspiration bronchiolitis [44], bronchiolitis obliterans in lung transplant recipients [45, 46], refractory asthma [47], bronchiectasis [46, 48], lipoid pneumonia [49], and idiopathic pulmonary fibrosis [50]. Some of these chronic effects are reviewed below.

Exogenous lipoid pneumonia can develop from the inhalation of animal or vegetable oils—such as mineral oil (laxatives), petroleum-based lubricants, and decongestants (Vaseline (Unilever), Vicks VapoRub, or lip gloss). Clinical presentation may include a dry cough, dyspnea, fever, or unexplained weight loss and radiographic findings range from subtle ground-glass opacities to dense consolidation and a "*crazy-paving*" pattern. A CT evidence of fat attenuation (−30 HU (Hounsfield units)) within areas of consolidation is considered to be pathognomonic for this process [49]. Patients may have undergone several rounds of antibiotics without improvement for a non-resolving pneumonia before an accurate diagnosis is made. Therefore a high clinical suspicion, familiarity with clinical situations that predispose patients (i.e., patients with chronic constipation likely to be using mineral oils), and an awareness of key radiographic findings are critical to making an accurate and timely diagnosis. Long-standing inflammation can lead to secondary fibrosis and result in end-stage lung disease, even cor pulmonale.

In a study on 25 patients, Cardasis et al. [46] reviewed histological specimens from patients with chronic occult aspiration and demonstrated that recurrent bronchiolitis (multi-lobar, centrilobular nodules and tree-in-bud appearance), persistent patchy pneumonias with fat attenuation (lipoid), and bronchiolar thickening were some of the most common changes seen with aspiration. Severe and chronic cases developed frank bronchiectasis and fibrosis, and on histology, poorly formed granulomas, exogenous lipoid pneumonia, and foreign body-type multinucleated giant cells with or without foreign material were seen. The authors highlighted that lower lobe distribution *alone* should not be relied upon to "rule in" a diagnosis of aspiration as almost 73% of patients in this study had upper lobe involvement. They also emphasized that occult aspiration should *not only* be considered in the differential of chronic fibrotic interstitial pneumonitis (i.e., idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonitis (NSIP), hypersensitivity pneumonitis (HP)) *but also especially* in the case of an undifferentiated ILD with histological evidence of poorly formed granulomas.

Importantly, there is considerable ongoing debate surrounding the association of microaspiration and idiopathic pulmonary fibrosis (IPF). Although there is no direct evidence that microaspiration causes IPF, studies have identified an association between risk factors for aspiration, such as GERD, and advanced lung disease.

It has been shown that GERD is associated with aspiration [51], chronic cough [52], and aspiration-related lung injury [6, 53, 54]. Newer studies also reveal a high prevalence of GERD (almost 67–88%) amongst patients with IPF [53, 55, 56]. If left untreated, GERD can lead to allograft rejection and bronchiolitis obliterans

syndromes amongst lung transplant recipients [45, 57]—all of which are considered unfortunate rate-limiting steps in the survival of lung transplant recipients. It is hence not surprising that aggressive treatment of reflux alone is shown to achieve clinical stability in the form of reduced oxygen dependence [58], reduced rate of lung function decline [56], and improved survival [59] amongst IPF and lung transplant populations.

Despite these advances—there are many unanswered questions regarding the role of aspiration and lung fibrosis. *Does microaspiration cause IPF or does IPF cause microaspiration? Does microaspiration lead to acute exacerbations of IPF?* Studies on surrogate markers for aspiration such as reflux disease help to extrapolate that chronic microaspiration is perhaps one of the many pathogenic mechanisms for the development and progression of IPF. It is clear, however, that much work still remains to be done.

Patient Question: Do I Need Antibiotics for Aspiration?

Answer to patient: It is important to recognize that not all aspiration events require antimicrobial therapy. In fact, an overuse of antibiotics over the last era has led to significant problems of drug-resistant infections and other antibiotic-associated side effects. Hence both physicians and patients need to be very careful when prescribing or taking antibiotics.

Many initial aspiration events are simply an inhalation of gastric acid and a "chemical burn" of the lung tissue. This can lead to a range of responses spanning the spectrum from a complete lack of symptoms (asymptomatic) to an intense inflammatory reaction that leads to fever, cough, low oxygen measurements, and distress. Most patients recover from this initial episode with the help of oxygen and supportive care. However a smaller group of patients do not improve immediately and may require artificial respirators (mechanical ventilators) to support their breathing until their lung injury resolves. With time and supportive measures most patients completely recover from this injury.

Physicians are trained to recognize which patients are at a higher risk for a bacterial infection after an aspiration event. For example, residents of nursing homes (who may be unable to perform their own oral cares) or elderly patients who suffer from a stroke or younger adults with a history of seizures or alcohol/drug use are also more likely to have harmful bacteria in their mouth that can soil their lungs during an aspiration. It is these patients who should be identified as they may benefit from a timely use of antibiotics in the event of an aspiration.

(1–2-min evidence-based reading for clinician): Epidemiology, genetics and pathophysiology, diagnostic test results, treatment options, etc.

All aspiration does not necessitate antimicrobial therapy, and as elaborated earlier, a bacterial infection is usually not considered a primary event early in the course of an aspiration.

It is simpler perhaps to think of aspiration as potentially leading to one of the three injurious and separate clinical syndromes [60]:

- Chemical pneumonitis (chemical "burn" or injury)
- Primary bacterial pneumonia
- Secondary bacterial pneumonia

Chemical injury can cause no symptoms or precipitate a dramatic clinical deterioration with the onset of fevers, cough, severe hypoxemia, and new radiographic infiltrates (upper or lower lobes depending on the position during which aspiration takes place) [6, 32]. However a large majority of patients (~ 60%) undergo complete resolution of hypoxemia and radiographic infiltrates within 2–4 days of the initial insult [60, 61]. These patients demonstrate an inflammatory reaction to a pure chemical injury [6, 62] and good supportive care (airway clearance therapy, supplemental oxygen, and positive pressure (if needed)) is usually sufficient to resolve their lung injury.

Not everyone is as fortunate. Up to 12% of patients are reported to die shortly after an acute aspiration event [61] and about 15–30% of patients develop an acute respiratory distress syndrome (ARDS) within the first 24–36 h from chemical injury alone [6, 54, 60]. These patients frequently have larger numbers of comorbid conditions and develop a very sudden and severe

inflammatory reaction that causes pulmonary capillary leakage, development of proteinaceous edema, and severe hypoxemia necessitating mechanical ventilation (see Table 17.1). In clinical practice these patients benefit from empiric broad-spectrum antimicrobials up front—as intense chemical injury disrupts the integrity of the pulmonary capillary membranes, weakening host defenses and increasing the risk of nosocomial pneumonia [63].

A smaller subset of patients (~25%) undergo clinical worsening a few days after an initial improvement from chemical pneumonitis [60, 61]. These patients have developed a *secondary bacterial pneumonia* that is associated with a much higher mortality (~60%) [60, 61]. Prompt antimicrobial therapy is necessary and empiric agents should target the organisms that are likely to be acquired in the specific clinical setting. For example patients who suffer from an aspiration event within the health care setting (hospital, nursing homes, dialysis centers, etc.) are more likely to acquire resistant organisms like methicillin-resistant *Staphylococcus aureus* (MRSA) or resistant gram-negative rods such as *Pseudomonas aeruginosa* than patients who aspirate in the community setting [60].

A small proportion of patients develop a true bacterial pneumonia as a primary event during aspiration *(primary bacterial pneumonia)*. To illustrate this, a study by Mier et al. revealed that only 19 out of 52 patients with aspiration pneumonia have bacterial pathogens in substantial counts (>1000 colony-forming units (CFUs/mL)) on respiratory sampling [64]. These patients inhale a bacterial burden sufficient enough to launch disease. In general primary aspiration pneumonia has all the features of any other bacterial pneumonia (fevers, cough, and foul-smelling sputum) but may be more indolent in onset than chemical pneumonitis.

Chemical pneumonitis can be difficult to differentiate from a primary bacterial pneumonia. The decision to initiate antimicrobials early in the course can be guided by knowledge of the actual aspiration event (i.e., a clearly witnessed macroaspiration or a questionable microaspiration) as well as awareness of the high-risk conditions that predispose patients to a large bacterial burden. For example patients suffering from seizure disorders, stroke, chronic alcoholism, esophageal dysmotility, severe constipation, or bowel obstruction [6, 65]; those using tube feedings/gastrostomy tubes [66], histamine H2 antagonists, or proton pump inhibitors; or elderly and nursing home patients who suffer from poor dentition and oral health—all are predisposed to a higher bacterial burden and appear to benefit from early empirical antibiotics after aspiration.

In general, the IDSA guidelines recommend the use of β-lactam/β-lactamase inhibitor combination or clindamycin as first-line agents for aspiration pneumonia (insert IDSA). There are no definite recommendations but in general a 7–10-day course can be employed for uncomplicated pneumonias.

The idea that all aspiration pneumonias involve anaerobic pathogens has been challenged and largely discounted. Data from the 1970s (when transtracheal aspirates were used for respiratory sampling) suggested that anaerobes played a central role in aspiration pneumonia [67]. Moreover, the risks of such "blind" antibiotic therapy have come to light [68] and have prompted a more judicious use of these agents. The medical community now agrees that most cases of aspiration pneumonia do not involve anaerobic pathogens and studies demonstrate good recovery without use of specific anti-anaerobe treatment [67, 69].

Several reviews have looked at risks in specialized populations for specific pathogens. For example elderly patients, in particular nursing home residents (receiving poor oral care) may be colonized with pathogens such as Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* [6]. A study by El Solh et al. demonstrated a preponderance of gram-negative enteric bacilli as the predominant pathogen amongst nursing home patients who aspirated [69]. This study also concluded that, although the risk for anaerobic pathogens is probably overestimated, a poorer functional status correlates with a higher risk for anaerobic pathogens.

Hence according to the IDSA guidelines anaerobic coverage is only clearly indicated in patients with a classic pulmonary aspiration syndrome such as after a seizure event or stroke and alcohol or drug overdose, or in patients with aspiration with known gastroesophageal dysmotility

syndromes or gingival disease (such as the elderly from nursing homes) [70]. In addition anaerobic coverage should be considered in patients with an indolent course, complicated pneumonias, putrid discharge, or necrotizing pneumonias or lung abscess formation [65].

Another important consideration includes aspiration events taking place in the hospital setting. The bacteriology of hospital-acquired pneumonia includes gram-negative flora (47%), *Staphylococcus aureus* (31%), and anaerobic bacteria (35%) [65]. Hence these aspiration events should include antimicrobials targeted against resistant gram negatives as well as an anti-staphylococcal agent [60].

When using anaerobic coverage, several studies have highlighted clindamycin as a superior agent, especially when a lung abscess is suspected [71]. Other agents such as metronidazole have anaerobic coverage but do not penetrate lung tissue as well and should be used in conjunction with a β-lactam/β-lactamase inhibitor.

Figure 17.2 presents an overview of empiric antimicrobial coverage in aspiration pneumonia.

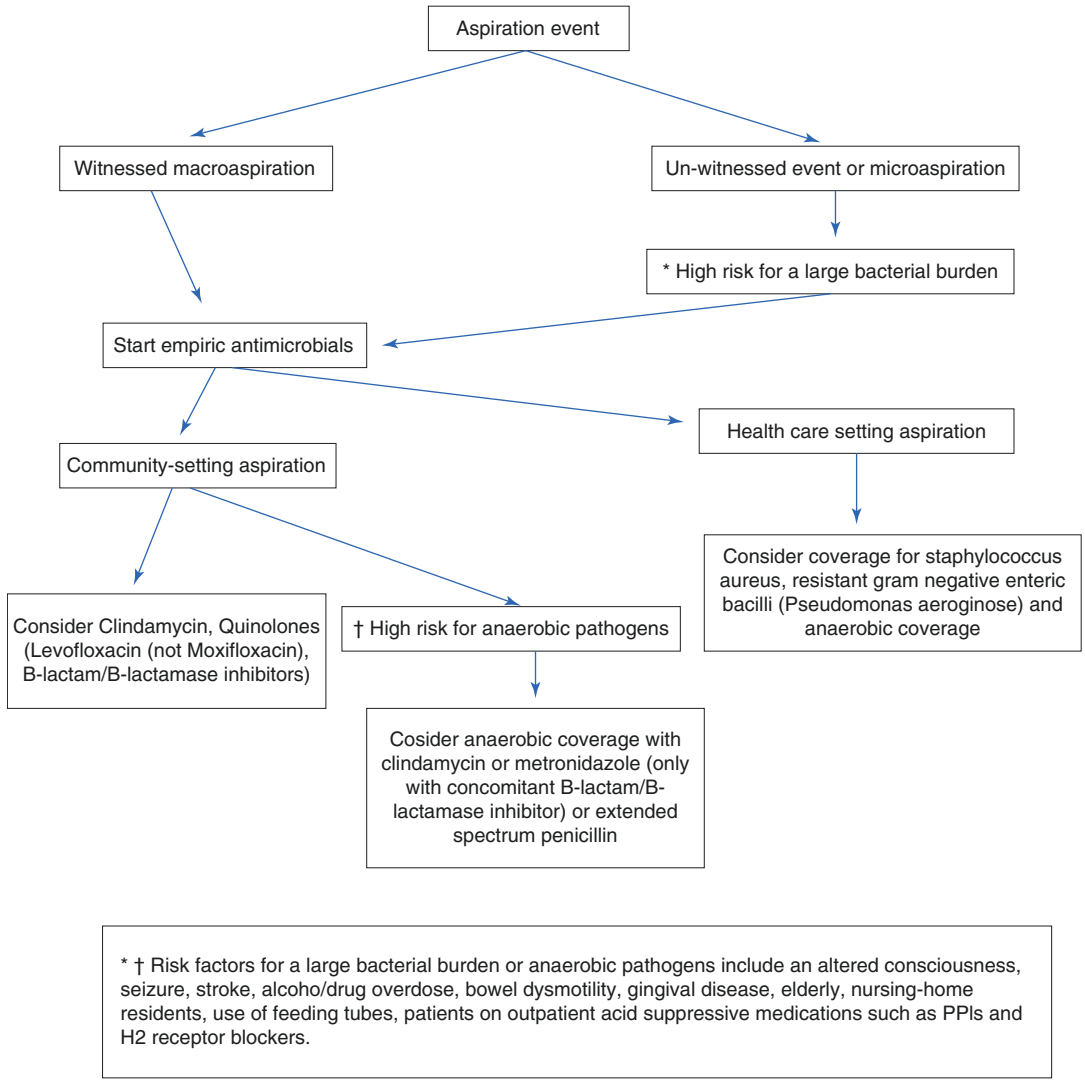

Fig. 17.2 Suggest algorithm for empiric antimicrobial therapy for a suspected aspiration event

Patient Question: What Can Be Done to Prevent Aspiration Pneumonia?

Answer to patient: Several steps can be taken to prevent aspiration in vulnerable patients. A bedside swallow evaluation can be performed by your health nurse or a physician. Advanced techniques (such as video fluoroscopy or FEES) can also help guide an assessment of this risk. Patients can be taught to use a "chin-tuck" or "head-tilt" approach or have thin liquids in a honey or nectar-thickened consistency to reduce aspiration. In addition, family and health care workers can be trained to identify those at a higher risk of aspiration such as patients with stroke, Parkinson's disease, bowel movement disorders, or seizure disorders or the elderly who are unable to function on their own.

In some cases patients with advanced dementia (memory loss) and difficulty with swallowing (dysphagia) may benefit from the placement of a feeding tube (PEG; percutaneous endoscopic gastrostomy tube). PEG tubes help with a better, more consistent delivery of medications in these patients; however it is important to note that they do not reduce the risk of aspiration. Despite all attempts to minimize risks in this patient population, aspiration is frequently the immediate cause of death.

Patients who are on artificial respirators (mechanical ventilators) may have a higher rate of gastric acid reflux and this may increase their risk for aspiration. Several studies have now shown some things that can be implemented to reduce this risk. For instance, frequent oral cares provided by bedside nurses using antiseptics such as chlorhexidine or a 'head-of-bed' elevation while on a respirator can reduce the risk for developing pneumonia while on a respirator.

(1–2-min evidence-based reading for clinician): Epidemiology, genetics and pathophysiology, diagnostic test results, treatment options, etc.

Patients with dysphagia, stroke, abnormalities of the aerodigestive tract, etc. are at a much higher risk for aspiration. Once identified to be at a higher risk, several dietary and behavioral measures can be instituted to reduce the risk for aspiration [14]. Methods such as instituting a honey-thickened or nectar consistency of thin liquids have been shown to reduce the risk of aspiration amongst patients with dementia and Parkinson's disease [72]. Other modifications such as keeping the chin tucked or reducing bite size may be helpful [6, 14].

Patients who continue to aspirate despite these measures may be candidates for placement of a feeding tube. It is important to note that although percutaneous gastrostomy (percutaneous endoscopic gastrostomy or PEG tube) placement is more effective in delivering oral medications and achieving prescribed nutrition in patients with dysphagia—several studies have now established that they do not reduce the risk or incidence of aspiration pneumonia in comparison with nasogastric or post-pyloric tubes [6, 73]. In fact treatment of chronic aspiration in patients particularly with altered mental status outside the acute care setting is difficult. A consequence of aspiration is the most common immediate cause of death in this patient population [74].

Patients who are mechanically ventilated and on enteral nutrition (with nasogastric tubes) are also at a higher risk for aspiration. These patients are consistently demonstrated to have a high incidence of GERD [6, 75] that promotes pneumonia by retrograde oropharyngeal colonization and aspiration into the lower airways. In addition, the presence of a NG tube impairs closure of the lower esophageal sphincter and further increases this risk. A randomized clinical trial on 86 intubated patients on enteral nutrition was interrupted early when it was clear that a semi-recumbent positioning, in comparison with supine positioning, substantially reduced the risk of a nosocomial aspiration pneumonia/ventilator-associated pneumonia (VAP) (3 of 39 [8%] vs. 16 of 47 [34%]; 95% CI for difference 10.0–42.0, $p = 0.003$) [76]. Hence head-of-bed elevation is a standard and relative inexpensive practice to reduce the risk of aspiration-related nosocomial pneumonias in mechanically ventilated patients.

Other factors such as suctioning of subglottic drainage and use of silver-coated endotracheal tubes have not been shown to be associated with

a mortality benefit. Measurement of gastric volume does not correlate with aspiration risk and is associated with poorer caloric feeding due to frequent interruptions and is not routinely recommended [77]. Another trial looked at the role of instituting VAP bundle using five interventions: semi-recumbent position, stress ulcer prophylaxis, deep-vein thrombosis prophylaxis, adjustment of sedation so that the patient can follow command, and daily assessment for extubation—and demonstrated a substantial (71%) reduction in VAP rates amongst mechanically ventilated patients [78].

The risk of aspiration may be highest peri-extubation due to the lingering effects of sedative agents, laryngeal muscle edema, or injury and it is recommended that enteral nutrition be held at least 6 h after extubation in case of need for re-intubation and that diet be slowly progressed starting with pureed soft foods [6].

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Esophageal Manometry

18

Edy Soffer and Anisa Shaker

What Is Esophageal Manometry?

Response to the Patient

Esophageal manometry is a test that measures the motor activity (contractions) of your esophagus, or food pipe. Your esophagus is a muscular tube, about 8 in. long, that lies between the mouth and pharynx above and the stomach below. At both ends the muscle is thickened to form sphincters that are normally closed, but open when you swallow. This structure allows the esophagus to transport swallowed materials from the pharynx to the stomach and to prevent reflux of injurious gastric contents into the esophagus and airways. Esophageal manometry is a technique that provides a graphic image of these functions.

Brief Review of Supporting Evidence

Introduction

The primary functions of the esophagus are to transport swallowed materials from the pharynx to the stomach and to prevent reflux of injurious gastric contents into the esophagus and airways. These tasks are achieved by coordinated actions of the two sphincters at each end of the esophagus, the upper and lower esophageal sphincters, and a series of coordinated contractions within esophageal body [1]. A manometry study measures the pressure events in the esophagus in response to liquid and/or solid test swallows by recording the amplitudes and timing of pressure changes at the two sphincters and in the body of the esophagus. These changes primarily reflect the force and timing of contraction of the circular muscle [2]. These pressure changes are detected by pressure transducers and the signals are then displayed either as line pressure tracings with conventional manometry or as colorful topographic plots with high-resolution manometry (HRM).

Conventional and High-Resolution Manometry

"Conventional manometry" systems consist of catheters incorporating 5–8 water-perfused channels connected to a low-compliance pneumohydraulic pump and pressure transducers, or catheters with built-in pressure transducers, spaced (3–5 cm apart) along the length of the esophageal catheter [3]. Pressure events are displayed as line tracings stacked from proximal to distal esophagus. In this format, motor activity between the sensors cannot be analyzed and reliable pressure recording of asymmetric structures such as the UES and LES is not possible [4].

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An increase in the number of pressure sensors coupled with the use of spatiotemporal plots to display the data led to the advent of high-resolution manometry (HRM) in the 1990s [5]. High-resolution manometry can be performed with water-perfused or solid-state manometric catheters [6]. The close spacing (1 cm) and circumferential distribution of sensors in the solid-state HRM catheter allow for a more representative sampling of esophageal intraluminal pressures along the esophagus and its sphincters. Computerized software programs use best-fit data to fill in points between the pressure recordings and convert the electrical signals into colorful topographic spatiotemporal plots. These smooth color-contour spatiotemporal plots, or "Clouse" plots in honor of their innovator Dr. Ray Clouse, display the direction and force of esophageal pressure that is generated, with time on the *x*-axis, esophageal position on the *y*-axis (from proximal to distal), and pressure depicted as color (Fig. 18.1) [3, 7]. Warmer hues (reds and yellows) represent higher pressures and cooler hues (blues and greens) represent lower pressures.

High-resolution manometry simplifies the manometric procedure and its interpretation, providing "at-a-glance" assessment of the esophagus and both sphincters and precluding the need for technical requirements such as station

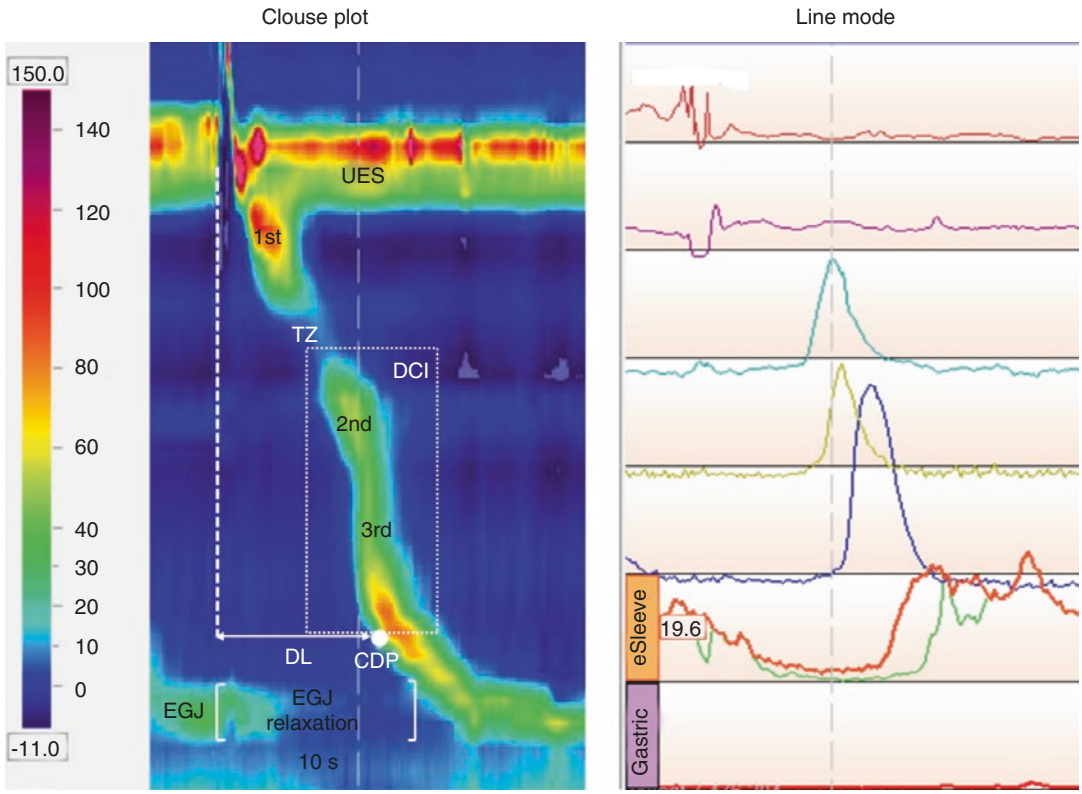

Fig. 18.1 Esophageal pressure topography or Clouse plot (*left image*) and the corresponding line plot (*right image*) from a normal swallow in HRM. The *dotted white line* indicates the start of the swallow at the beginning of UES relaxation. The contraction of the S1 striated muscle segment is followed by contraction of the S2 and S3 smooth muscle segments. The transition from striated to smooth muscle is indicated by the transition zone (TZ). Darker hues represent higher pressures and cooler hues represent lower pressures. The distal contractile integral (DCI) is a measure of esophageal smooth muscle vigor and is calculated from the TZ to the proximal margin of the LES. The contractile deceleration point (CDP) is defined as the inflection point within 3 cm of the proximal margin of the LES. Distal latency (DL) is the interval between UES relaxation and the CDP. IRP is defined as the mean of the 4 s of maximal deglutitive relaxation in the 10-s window, which need not be consecutive, beginning at UES relaxation

pull-through, reducing the time needed for the test [7]. Compared with line tracings, HRM allows for easier identification of anatomic landmarks such as the UES and LES, and pattern recognition of motor patterns such as achalasia, jackhammer esophagus, or absent contractility, and is particularly suited for identification of esophageal outflow obstruction [7]. These aspects support the advantage of HRM over alternative recording techniques. A randomized control trial has demonstrated that compared to conventional manometry, HRM improves the diagnostic yield of esophageal motility disorders in patients with dysphagia [8].

Complete HRM systems consisting of the manometric catheter and recording software are available from several companies (Sandhill Scientific, Sierra Scientific/Given, and MMS). The "Chicago Classification" (Table 18.1) is an evolving analysis paradigm in its third iteration

Table 18.1 The Chicago Classification of esophageal motility V. 3

Achalasia and EGJ outflow obstruction	Criteria
Type I achalasia (classic achalasia)	Elevated median IRP (>15 mmHg[a]), 100% failed peristalsis (DCI <100 mmHg s cm)
	Premature contractions with DCI values less than 450 mmHg s cm *satisfy criteria for failed peristalsis*
Type II achalasia (with esophageal compression)	Elevated median IRP (>15 mmHg[a]), 100% failed peristalsis, pan-esophageal pressurization with ≥20% of swallows
	Contractions may be masked by esophageal pressurization and DCI should not be calculated
Type III achalasia (spastic achalasia)	Elevated median IRP (>15 mmHg[a]), no normal peristalsis, premature (spastic) contractions with DCI >450 mmHg s cm with ≥20% of swallows
	May be mixed with pan-esophageal pressurization
EGJ outflow obstruction	Elevated median IRP (>15 mmHg[a]), sufficient evidence of peristalsis such that criteria for types I–III achalasia are not met[b]
Major disorders of peristalsis	(Not encountered in normal subjects)
Absent contractility	Normal median IRP, 100% failed peristalsis
	Achalasia should be considered when IRP values are borderline and when there is evidence of esophageal pressurization
	Premature contractions with DCI values less than 450 mmHg s cm *meet criteria for failed peristalsis*
Distal esophageal spasm	Normal median IRP, ≥20% premature contractions with DCI >450 mmHg s cm[a]. Some normal peristalsis may be present
Hypercontractile esophagus (jackhammer)	At least two swallows with DCI >8000 mmHg s cm[a,c]
	Hypercontractility may involve, or even be localized to, the LES
Minor disorders of peristalsis	(Characterized by contractile vigor and contraction pattern)
Ineffective esophageal motility (IEM)	≥50% ineffective swallows
	Ineffective swallows can be failed or weak (*DCI*<450 *mmHg s cm*)
	Multiple repetitive swallow assessment may be helpful in determining peristaltic reserve
Fragmented peristalsis	≥50% fragmented contractions with DCI >450 mmHg s cm
Normal esophageal motility	Not fulfilling any of the above classifications

Kahrilas PJ et al. and the International High Resolution Manometry Working G: The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterology and motility 2015, 27:160–74. (With permission)

[a]Cutoff value dependent on the manometric hardware; this is the cutoff for the Sierra device

[b]Potential etiologies: early achalasia, mechanical obstruction, esophageal wall stiffness, or manifestation of hiatal hernia

[c]Hypercontractile esophagus can be a manifestation of outflow obstruction as evident by instances in which it occurs in association with an IRP greater than the upper limit of normal

that takes advantage of the increased detail and accuracy afforded by HRM to classify esophageal motor disorders. It is endorsed by the American Neurogastroenterology and Motility Society and European Society of Neurogastroenterology and Motility and is increasingly used in the interpretation of HRM findings in motility labs [9]. Values that inform the Chicago Classification are derived from water swallows using the Sierra Scientific/Given adult version 36-channel circumferential (sensors 1 cm apart) solid-state HRM catheter (4.2 mm) and software [9]. Normative values have also been established for other systems as well as for solid boluses.

Although software algorithm-based computerized analyses provide an overall interpretation of HRM data according to accepted metrics, each test swallow should be reviewed by the interpreting physician to ensure that anatomic landmarks and measurement parameters are properly identified to avoid misleading diagnoses based on automated analysis. Normal and abnormal esophageal motor patterns, however, can often be recognized quickly without detailed analysis.

Why Do I Need an Esophageal Manometry Study?

Response to the Patient

There are several reasons why your doctor orders an esophageal manometry. The main reason is evaluation of your difficulty in swallowing (dysphagia) for which a definitive diagnosis has not been achieved by endoscopy or radiographic studies. Other indications include evaluation of chest pain once cardiac causes or musculoskeletal pain have been excluded. Manometry is also used to definitively establish the diagnosis of achalasia, an esophageal motility disorder characterized by absent or abnormal esophageal contractions and failure of the lower esophageal sphincter to relax. Other indications include evaluation of esophageal involvement in connective tissue diseases such as scleroderma, identifying the lower esophageal sphincter location for placement of catheters that measure esophageal acid exposure, and evaluating esophageal motor function prior to anti-reflux surgery or evaluation of dysphagia after such operations.

Brief Review of Supporting Evidence

Introduction

Esophageal manometry is used primarily to evaluate esophageal motility and often serves as a complementary study to upper endoscopy and barium esophagram in the assessment of bolus transit. The primary indication for esophageal manometry is evaluation of dysphagia after endoscopy or radiographic studies have not revealed a structural etiology resulting in mechanical obstruction or an inflammatory condition such as eosinophilic esophagitis. It is also used to definitively establish the diagnosis of achalasia after suggestive barium or endoscopic studies. Achalasia subtypes can also be distinguished based on manometric patterns. Symptoms such as regurgitation, heartburn, or chest pain, for which endoscopy and/or barium contrast studies have not provided a structural explanation can also be evaluated with manometry. Other indications include evaluation of esophageal involvement in connective tissue diseases such as scleroderma, identification of the lower esophageal sphincter location for placement of an ambulatory pH and pH-impedance probe, evaluation of esophageal motor function prior to fundoplication, or evaluation of dysphagia and regurgitation following foregut surgery such as fundoplication or bariatric procedures such as laparoscopic band placement [3] (Table 18.2).

Absolute contraindications include esophageal obstruction from an infiltrating process such as a tumor, abnormal nasal passages preventing transnasal catheter insertion, abnormal oropharyngeal anatomy, frank aspiration with water swallows, significantly abnormal coagulation, or altered mental status. Relative contraindications include patients on chronic

Table 18.2 Indications and contraindications for esophageal manometry

Indication	Contraindications
Dysphagia	*Absolute*
Suspicion of achalasia	Frank aspiration
Noncardiac chest pain	Abnormal oral-pharyngeal anatomy
Identification of LES for placement of pH or pH-impedance catheters	Infiltrating tumor or abnormal nasal passages that prevent catheter insertion
Evaluation of esophageal function prior to anti-reflux surgery	Abnormal coagulation
Postsurgical dysphagia	Altered mental status
Evaluation of esophageal involvement in connective tissue disorders, e.g., scleroderma	*Relative*
	Chronic anticoagulation, the inability to swallow on command or the inability to tolerate the catheter

Gyawali CP, Patel A: Esophageal motor function: technical aspects of manometry. Gastrointestinal endoscopy clinics of North America 2014, 24:527–43 (with permission)

anticoagulation, inability to swallow on command, or inability to tolerate the catheter [3] (Table 18.2). In these instances, if the procedure is absolutely necessary, the catheter can sometimes be placed endoscopically. The sedation required for endoscopic placement of the manometric catheter ideally consists of propofol with monitored anesthesia and avoids the use of benzodiazepines and in particular narcotics that may alter esophageal motility [4]. Placement of a manometry catheter in patients with esophageal varices should be approached with caution.

The HRM Manometry Report and the Clinical Implications of HRM

As more and more motility labs are using HRM technology, we will describe the HRM metrics that inform the basis of the Chicago Classification, a hierarchical algorithm for the interpretation of HRM studies and classification of esophageal motility disorders. These include disorders of esophagogastric junction (EGJ) outflow obstruction: achalasia and its variants including EGJ outflow obstruction; major disorders of peristalsis: distal esophageal spasm, jackhammer esophagus, and absent contractility; and minor peristaltic disorders: ineffective motility and fragmented peristalsis [9]. These diagnoses may have clinical implications which are also described below.

HRM Metrics

The resting characteristics of the UES and LES are easily recognized by horizontal bands of higher pressure color in the proximal and distal sensors, respectively. Variations in pressure in the LES induced by respiration can be seen as cyclical changes in color. An electronic tool called the eSleeve is positioned to straddle the LES for 6 cm and calculates the highest pressure at each point in time during a 10-s deglutitive window which begins with relaxation of the UES. LES relaxation is then derived using a 4-s integrated relaxation pressure (IRP) algorithm that calculates the lowest mean of these pressures. IRP is defined as the mean of the 4 s of maximal deglutitive relaxation in the 10-s window, which need not be consecutive, beginning at UES relaxation [9].

HRM allows for better characterization of EGJ morphology compared to conventional manometry as the contractile elements of the EJG (the LES and crural diaphragm) can be readily visualized. Spatial separation of the LES and crural diaphragm disrupts the barrier function of the EGJ and facilitates gastroesophageal reflux [10]. The most recent Chicago Classification, therefore, includes metrics pertinent to EJG morphology and tone. The respiratory inversion point (RIP) normally delineates the location of the crural diaphragm. It is defined as the location along the esophagus at which the negative intrathoracic pressure produced during inspiration converts to the more positive intragastric pressure. During inspiration, the pressures generated by the crural diaphragm become more prominent. In a type 1 EGJ, the LES and crural diaphragm coincide. In a type II EJG, there is a small separation (<2 cm)

between the LES and the crural diaphragm consistent with a small hiatal hernia. Type III is associated with a larger spatial separation between the LES and crural diaphragm, consistent with the presence of a large hiatal hernia, and is further characterized according to the position of the PIP. The locations of the UES and LES, their resting and relaxation pressures, the esophageal length, and, if present, the length of the hiatus hernia are reported in the manometry report.

The esophageal body is characterized by a proximal striated muscle-contracting segment (S1) followed by two distal smooth muscle segments (S2 and S3). There is a pressure trough or transition zone between S1 and S2 that indicates the transition from striated to smooth muscle. Swallowing is characterized by simultaneous relaxation of the UES and LES characterized by color change to cooler hues that reflects lower pressure. This relaxation is followed by a series of segmental contractions of S1, S2, and S3 seen as a diagonal band of color extending from the UES to the LES. Esophageal body metrics measured with software tools are distal contractile integral (DCI), contractile deceleration point (CDP), distal latency (DL), and peristaltic integrity. DCI is a measure of the vigor of esophageal smooth muscle contraction, accounting for contraction amplitude, length, and duration. It is a quantification of the amplitude × duration × length (mmHg s cm) of the distal esophageal contraction that exceeds 20 mmHg from the transition zone to the proximal margin of the LES. It is determined by software program that sums all the pressures >20 mmHg within a box made around swallow-related motor activity in the S2 and S3 esophageal segments. Values greater than 8000 mmHg s cm are not seen in normal individuals. CDP is defined as the inflection point along the 30 mmHg isobaric contour within 3 cm of the proximal margin of the LES when the propagation velocity of peristalsis slows. The CDP reflects the end of esophageal peristalsis and the beginning of emptying of the phrenic ampulla. Distal latency (DL) is a measure of the interval between UES relaxation and onset of slowing of the contraction wavefront in the distal esophagus or the CDP. It reflects post-deglutitive inhibition which requires intact inhibitory neuromuscular function of the smooth muscle esophagus [11]. To assess peristaltic integrity, a 20 mmHg isobaric contour tool is used to draw a contour line around pressures at or higher than 20 mmHg. This minimum pressure has been shown in previous manometric studies performed concurrently with fluoroscopy to be required for normal bolus transit [11]. Intact peristalsis is defined as an intact contour line.

The impact of wet swallows on esophageal motor function including the proportions of peristaltic, premature, and failed swallows is then assessed. An abnormality of the IRP reflects abnormal transit across the EGJ and requires consideration of a disorder with EGJ outflow obstruction such as achalasia variants, EGJ outflow obstruction (thought of as one such variant), or mechanical obstruction [9]. Achalasia subtypes have been identified with the use of HRM and are defined by the absence of peristalsis (type I), presence of pan-esophageal pressurization (type II), or spasm (DL < 4.5 s) (type III) along with elevated IRP. Achalasia subtype identified on HRM helps predict treatment outcome. Type I does better with Heller myotomy than pneumatic dilation, type II has the best treatment outcome and responds well to either treatment modality, and type III has the worst prognosis [12]. Inter- and intraobserver agreement for differentiating achalasia from non-achalasia by clinicians trained in the use of HRM and the Chicago Classification is excellent. There is more variability in inter- and intraobserver agreement when differentiating achalasia subtypes, in particular type I from type II achalasia [13]. In the presence of dysphagia or compatible symptoms, EGJ outflow obstruction requires management aimed at improving transit across the EGJ such as therapy for achalasia or relief of the obstruction. Evidence of EGJ outflow obstruction without characteristic features of one of the achalasia subtypes on HRM should be followed by evaluation for infiltrative disorders at the EGJ or extrinsic compression using endoscopy, and, if needed, imaging studies such as endoscopic ultrasonography or CT scan. When no mechanical obstruction is found, incompletely expressed or early

achalasia should be considered. Watchful waiting in asymptomatic patients or those without evidence of stasis may be appropriate. On the other hand, in those with persistent symptoms such as dysphagia, therapy directed at relief of the EJG obstruction (botox injection, pneumatic dilation, or myotomy) should be considered [14, 15].

The most recent and simplified version of the Chicago Classification has streamlined and simplified the diagnoses of minor disorders of peristalsis into those of ineffective motility (IEM) and fragmented peristalsis. These minor disorders are the most frequently encountered in the motility lab [11]. While the clinical significance of minor disorders of peristalsis continues to be debated, they are characterized by impaired esophageal bolus transit. IEM is defined as ≥50% of swallows with amplitudes <30 mmHg in the distal esophagus or with a DCI <450 mmHg s cm. Fragmented peristalsis is defined as ≥50% of swallows with large breaks (>5 cm) in the 20-mmHg isobaric contour. Finally, findings on alternative swallow positions, alternative test boluses (viscous, solid), and results of provocative testing, if performed, are described in the manometry report, although normative metrics for these maneuvers are not yet included in the Chicago Classification [9].

Clinical Implications

DCI elevation >8000 mmHg s cm in ≥20% of swallows defines jackhammer esophagus while DL < 4.5 s in ≥20% swallows defines the premature contraction seen in distal esophageal spasm (DES). These are both rare diagnoses not seen in normal subjects. They are considered major disorders of peristalsis according to the Chicago Classification. Absent contractility is characterized by 100% of swallows with failed peristalsis and is also considered a major disorder of peristalsis, not seen in normal subjects. Absent contractility should prompt evaluation for systemic disorders including collagen vascular disease such as scleroderma, diabetes, and hypothyroidism. The clinical implication of the achalasia variants was discussed above. Management of these major disorders of peristalsis is primarily dictated by the presenting symptom. Perceptive symptoms such as chest pain may respond to neuromodulators, while transit symptoms may require disruption of smooth muscle contractions, either with systemic smooth muscle relaxants, botulinum toxin injection, pneumatic dilation, or myotomy [16]. Absent or compromised peristalsis in the esophageal body may be associated with abnormal bolus transit and symptoms of dysphagia and abnormal reflux clearance. This information may therefore affect the choice of antireflux surgery; between a full and partial wrap [3]. The minor disorders of peristalsis can be associated with GERD, so in the setting of symptoms of transit or perceptive symptoms, a PPI trial is reasonable.

Of note, the metrics in the Chicago Classification were derived with the Sierra Scientific/Manoview system. There is variability in software metrics between HRM systems. For example, higher IRP thresholds and DCI variations have been reported for MMS and Sandhill systems [17]. Using metrics developed for the Manoview system with these other systems may lead to overdiagnosis of motility disorders. Care must be taken as an overdiagnosis of outflow obstruction based on an elevated IRP has management implications such as decision to pursue LES disruption or myotomy.

How Is Esophageal Manometry Performed?

Response to Patient

Manometry is performed with a thin catheter that has pressure sensors to measure contractions. This catheter is passed through your nose into your esophagus. Once in place, and after you have had a chance to become used to the catheter, you will be asked to focus on your breathing and not swallow for up to 30 s. During this time, measurements are made from the upper and lower sphincters in your esophagus. After this time, you will then be asked to swallow 5 mL of water up to ten times while the pressures in the two sphincters and in your esophageal body are recorded. Esophageal manometry is generally a

very safe procedure. Topical anesthesia is applied to your nasal passage prior to catheter insertion to minimize discomfort. You will have to fast for at least 6 h prior to the procedure to protect you from aspirating. It is usually an outpatient procedure and you will not need a driver.

Brief Review of Supporting Evidence

Introduction

Esophageal manometry is usually performed in the outpatient setting with only topical nasal anesthesia. As such, there is no need for a designated driver. It is generally a safe procedure with few and typically minor complications. The most common are discomfort in the nose or throat and gagging or retching during catheter placement. The use of local anesthetic to the nose ameliorates discomfort. Uncommon risks include epistaxis, chest pain, vasovagal episode, and, in those with oropharyngeal dysphagia or esophageal outflow obstruction, aspiration. Disposable sheaths are available for some HRM catheters.

The Procedure

Equipment and patient preparation have been reviewed in detail elsewhere [3, 4]. Briefly, prior to starting the study, the catheter should be calibrated per manufacturer's instruction. Patients should have nothing to eat or drink for at least 6 h, and in those with suspected achalasia, clear liquids for up to 3 days may be needed to prevent aspiration of esophageal contents. Medications that alter esophageal motility (caffeine-containing medications, prokinetics, nitrates, calcium channel blockers, anticholinergics, opiates, and tricyclic antidepressants) should be avoided if possible. Once the catheter has been adequately positioned, the manometry is typically performed with the patient in the supine position in order to effectively assess the effect of esophageal peristalsis on bolus transit without the effect of gravity.

With water-perfused conventional manometry catheters, the pressure needs to be zeroed to the catheter position in the horizontal position. While the supine position is preferred, a semi-recumbent or seated position may be better tolerated by the patient with regurgitation or aspiration. Normative pressure values for the upright position have also been reported in HRM [18] and can be applied if this position is used. Compared to the supine position, upright peristalsis is less vigorous. Using normative values established for the supine position to analyze swallows in the upright position may lead to an overdiagnosis of hypomotility disorders. Overall, there is good concordance between studies performed in the supine and upright position in the diagnoses of motor abnormalities. Agreement for EGJ outflow obstruction is only moderately good [19]. Some motility labs also perform up to five swallows in the upright position to increase the diagnostic yield of manometry. Under standard conditions, HRM has good reproducibility.

The HRM catheter should extend from the pharynx to the stomach, with at least one pharyngeal and three intragastric sensors. The HRM operator should readily identify the UES, LES, and diaphragmatic crural impression. The inability of the catheter to traverse the LES should be recognized by the HRM operator in real time so that maneuvers can be attempted to traverse the LES including: advancing the catheter with the patient standing up, having the patient raise their arms above the head or take repeated gulps of water, applying a 45° or 90° counterclockwise rotation on the catheter, or finally placing the catheter under endoscopic guidance [3].

Technique

The resting characteristics of the UES and LES are usually recorded in the beginning of the manometry study. This landmark phase is ideally 30 s in duration and it is critical that it occurs without swallow artifacts. Afterward, ten 5-mL room-temperature water swallows are administered in the supine position, at least 20–30 s apart to allow the LES pressure to return to baseline. The Chicago Classification of esophageal motor disorders is based on ten 5-mL water swallows. In addition, dry swallows do not generate the same peristaltic sequence as wet swallows. This duration of time is needed between swallows to avoid swallow-induced suppression of esophageal

motor activity that occurs as a consequence of deglutitive inhibition, a physiologically normal response that allows one to drink large amount of liquids rapidly and without cessation. Additional artifacts secondary to belching, gagging, double swallows, and secondary peristaltic sequences and transient LES relaxations need to be recognized and swallows that occur near these artifacts should be repeated.

Provocative maneuvers such as multiple rapid swallows (five 2-mL water swallows <3 s apart) or free water drinking (200 mL water within 30 s) can also serve as physiologic challenges that can be utilized to assess esophageal peristaltic reserve. These maneuvers rely on the phenomenon of deglutitive inhibition during the swallows, characterized by inhibition of peristalsis and complete LES relaxation, followed by a hypercontractile response following the final swallow. Sphincter dysfunction and structural outflow obstruction may be differentiated with these maneuvers. For example, while the LES will fail to relax in patients with achalasia, there may be partial or complete LES relaxation in cases of structural outflow obstruction as a consequence of intact deglutitive inhibition despite esophageal pressurization [3]. Viscous boluses such as applesauce have also been used to increase the diagnostic yield of outflow obstruction. To use manometry to localize the proximal margin of the LES for insertion of ambulatory pH or pH-impedance catheters, the distance from nares to the proximal LES margin is determined, and the pH or pH-impedance catheter is inserted with the distal tip 5 cm proximal to the upper border of the LES. The pH or pH-impedance catheters should be placed immediately following the manometry procedure.

The operator should also be aware of equipment-related artifacts. Discrepancies up to 7 mmHg can occur in pressures as a consequence of pressure calibration of the catheter at room temperature but pressure acquisition in the body. This discrepancy can be corrected in HRM by obtaining a compensation factor or performing a thermal compensation maneuver with the software algorithm tool. Prolonged studies greater than 20–30 min are at risk for thermal drift and a linear correction may need to be applied. As with all electronic equipment, the HRM catheter is subject to malfunction secondary to catheter leaks or infiltration by body fluids or cleansing solution. Vascular and respiratory artifacts may also affect interpretation of the HRM. Cardiac or vascular impression can be seen in the mid-esophagus and from the left atrium in the distal esophagus. The respiratory cycle can lead to respiratory artifacts. Asking patients to tilt slightly to the left or to sit up allows cardiac structures to fall away from the esophagus and allowing patients to relax to reduce the respiratory rate can mitigate these potential artifacts. Measurements occasionally fail despite correct preparation and following the protocol. The most frequent imperfections are secondary to insufficient number of interpretable swallows and an inability to traverse the LES or diaphragm mostly in the setting of achalasia, hiatal hernia, or previous foregut surgery. Finally, technical problems with sensor or absence of thermal compensation are less frequently encountered causes of an imperfect study [6].

Short Commentary on Future Directions of HRM

Standardization of provocative maneuvers such as multiple rapid swallow, free water drinking, or viscous swallows that provide a physiologic challenges may lead to clinically useful diagnostic criteria for esophageal motor disorders [3]. Future iterations of the Chicago Classification may include normative values for these provocative maneuvers.

The multiple sensors in HRM catheter as well as its rapid response time allow for UES measurements [7]. Elevation of pharyngeal intrabolus pressure readily identified on HRM raises the possibility of a cricopharyngeal bar [11]. Recently high-resolution pharyngeal-esophageal manometry in conjunction with videofluoroscopic swallows has been used to define normative values for several UES metrics [20]. In addition, several publications suggest that HRM UES combined with impedance has a potential

role in the early diagnosis of oral-pharyngeal dysphagia and aspiration risk [9]. The clinical implications of UES manometry and any added value to videofluoroscopy remain an emerging field, however, and therefore normative metrics are not yet included in the Chicago Classification.

HRM-impedance catheters (HRIM) are also available and allow for concurrent assessment of pressure and intraesophgeal impedance measurement [6]. Impedance monitoring has been shown to accurately assess bolus transit in healthy volunteers [4]. HRIM, therefore, has the potential to evaluate effective bolus transit in relation to peristalsis. Its clinical utility in symptomatic patients with motility disorders remains to be established, however, and it currently serves only to complement rather than replace the valuable information regarding anatomic details and bolus transit provided by the barium esophagram. If HRIM catheters are used, the test swallows are conducted with saline rather than tap water in order to generate more intense impedance signal.

Three-dimensional high-resolution manometry is an emerging modality in which eight radially sensing pressure transducers are spaced equidistantly over a 9-cm segment of the catheter. This arrangement is particularly suited for complex and detailed three-dimensional mapping of the asymmetric structures such as the UES and LES. Similar to HRIM, the clinical utility has yet to be established. However, there is data to suggest that 3D HRM provides detailed assessment of LES relaxation and better identifies the contribution of the crural diaphragm to EGJ pressure [4]. Finally, ambulatory HRM would allow symptom association with dysmotility observed on HRM, similar to pH monitors.

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Radiologic Evaluation of Swallowing: The Esophagram

19

Olle Ekberg, Peter Pokieser, and Martina Scharitzer

Three commonly posed patient questions are as follows:

Question 1: Why do I have to go through this radiologic examination for my swallowing problem? I already had endoscopy.

Answer: Swallowing problems may be due to an abnormal transportation of food and drinks from the mouth to the stomach. The endoscopic examination is excellent for visualization of the inner surface, i.e., the mucosa of the gullet. Endoscopy may also detect indentations due to an external mass or tumor. This esophagram monitors transportation of bolus in the gullet. It may also reveal misdirected swallowing and other functional abnormalities.

Question 2: And on top of this I have to swallow a tablet or another solid bolus. Why? It is often so difficult and it sometimes hurts.

Answer: Your clinical history reveals dysphagia for solid bolus. Therefore it is important to test what happens in the gullet during such swallows. You may be asked to swallow a tablet or a bread sphere or something else that simulates solid food.

Question 3: Do I really have to swallow lying down? I am not sure if I can swallow in the recumbent position.

Answer: Transportation through the gullet is due to pushing of the tongue on the bolus and contraction and peristalsis in the musculature of the wall of the gullet, but the gravity helps as well. To separate the effect of gravity and muscle force in the gullet wall, it is important to observe swallowing in a recumbent position.

Dysphagia is a symptom that indicates abnormality in the swallowing mechanism. Disorders may be present in the oral cavity, pharynx, and/or esophagus. Disorders may be either structural or functional in origin. The goal of the radiologic evaluation is to properly localize and classify the specific type of abnormality responsible for the symptom.

Radiology is often claimed to be the gold standard for evaluation of swallowing dysfunction [1–3]. The sensation of difficulty moving food through the mouth, pharynx, and esophagus is often lumped together in the term "dysphagia." Such dysphagia can be either high, meaning due to oral or pharyngeal structural abnormalities, or be due to a motor dysfunction leading either to

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retention of bolus or to misdirected swallowing. Low dysphagia means a sensation in the retrosternal area. The great majority of patients have low dysphagia and the radiologist's role is to detect structural abnormalities, such as rings, achalasia, peptic stricture, and carcinoma (the latter in patients who do not tolerate endoscopy), and, which is much more common, motor dysfunction. This may be due to diffuse esophageal spasm or other motility disorders. Other patients may in fact have an abnormal sensation often referred to as "irritable esophagus," as well as irritable bowel syndrome of not well-understood mechanism [4].

The clinical workup of patients with dysphagia therefore almost always includes a radiologic examination. However, it is important to realize that any symptoms that could indicate the presence of a malignant lesion, i.e., esophageal carcinoma or other malignancies, should undergo endoscopy and not primarily radiology. This presentation will briefly deal with the performance and interpretation of radiologic swallowing evaluation with focus on dysfunction.

Custom-Tail the Radiologic Examination According to Symptoms

The clinical history is the first step in custom-tailoring of the radiologic examination. It is important to have a clear picture of the symptoms so that at the end of the radiologic examination the radiologist or clinician can compare the patient's symptoms with the radiologic finding. Only relevant radiology findings should lead to intervention. The importance of how to take the history in patients with swallowing disorders has recently been evaluated [5] (Table 19.1). The table pinpoints the first step, namely does the patient really have swallowing problems or does the patient have globus. The table also allows us to focus the examination either on the oral cavity, pharynx, or esophagus. Problems and symptoms that are related to gastroesophageal reflux disease are also highlighted. After this analysis of the symptoms, the radiologist will be able to prop-

Table 19.1 Important questions that help the radiologist to decide what type of swallowing problem a patient has

Basic questions I: Dysphagia
Does food get stuck in your throat while you eat?
Where do you feel food sticking throat/thorax/stomach?
Does food come back into your throat/mouth after you swallowed?
Do you have to cut your food into small pieces?
Do you need to take a drink after swallowing solids?
Do you have to vomit occasionally? If so, when?
Do you suffer from too much saliva?
Do you have problems swallowing your saliva?
Do you suffer from hoarseness?
Do you suffer from a gargling voice?
Is there saliva on your pillow when you wake up in the morning?
Do you have hearing impairments?
Do you suffer from any neurological impairment?
Basic questions II: Suspicion of aspiration
Do you have to cough while drinking?
Do you have to cough while eating? Before drink/after swallowing?
Do you have to choke while eating/drinking?
Do you have to cough while choking?
Are you able to cough?
Do or did you suffer from pulmonary complications?
How do you drink? Out of a bottle/from a spoon/by a straw?
Is the symptom connected with respiratory problems?
Basic questions III: Globus sensation
Do you suffer from globus sensation or other related symptoms?
Are your symptoms present while you eat/without eating/both?
Do you suffer from a problem in your throat?
Do you feel a lump in your throat?
Do you feel an urge to clear your throat?
Do you suffer from too much phlegm in your throat?
Basic questions IV: Noncardiac chest pain
Do you feel pain behind the sternum after a swallow?
Do you suffer from noncardiac chest pain or related symptoms?
Do you suffer from heartburning sensations?
Do you suffer from reflux?
Auxiliary questions:
Did you lose weight?
What is your body mass index?
Do you suffer from any mood changes?

(continued)

Table 19.1 (continued)

Did other changes occur, e.g., in speech, walking, writing, cognition, affection?
For how long do the symptoms impair your quality of life?
How much is your quality of life impaired by your symptoms?
Do you go out to eat and drink with other persons?
Can you eat by yourself or need someone's help?
How long does it take for you to finish a meal?
What treatment did you have so far? (medications, previous diagnostic studies, functional swallowing therapy)
What do you eat for breakfast/lunch/dinner?
Do you use compensatory strategies?
Do you suffer from nasal regurgitation?
Do you have a dry mouth?
Do you feel the food going down when you swallow? Do you feel an obstruction for solid food and/or liquids?

This will enable the radiologist to custom-tailor the radiologic examination. If the patient is oriented in time and space and gives a reliable impression he/she is questioned directly. Otherwise an accompanying person is questioned according to the below scheme. Adapted from [5]

erly perform the radiologic examination, thereby being able to evaluate whether specific radiologic findings can explain the patient's symptoms.

Radiologic Equipment

A fluoroscopic unit that includes remote control is mandatory. Spot-film imaging is also important for documentation of anatomy. Videorecording is important for functional evaluation. Modern image intensifiers have a high spatial and contrast resolution. This equipment enables high-quality videorecording which actually makes interpretation easy. Moreover, with a high-quality digital system it is not necessary to use conventional cassette films anymore. Flat-panel detectors (FPD) are solid-state X-ray digital radiography devices similar in principle to the image sensors used in digital photography and video. Amorphous selenium FPDs are X-ray photons converted directly into charge. Flat-panel detectors are sensitive and fast. Their sensitivity allows a lower dose of radiation [6, 7]. They are lighter, smaller in volume, and more accurate. FPD has replaced videofluoroscopy. Therefore the radiologic evaluation should be integrated in the RIS/PACS system of the radiologic department. Recording should be obtained continuously. It is important to monitor all swallows, particularly the first swallow as this often appears to be the worst swallow.

Radiologic Examination Technique: A Practical Approach

The radiologic examination has to include all structures involved in swallowing from the lips to the stomach. But according to the above clinical history the examination is usually focused on one or two specific areas. If there is a high suspicion of misdirected swallowing, the laryngeal vestibule should be included from the beginning in lateral projection. It is very common that the first swallow is the worst swallow, and that only the first swallow will reveal misdirected swallowing. On the other hand, in a patient with suspected misdirected swallowing, it is important that at the end of the examination when the esophagus has been examined and the patient has swallowed several boluses the status in the laryngeal vestibule should be documented, because sometimes the misdirected swallowing is revealed only at the end. In patients with a suspicion of esophageal abnormalities it is important to start the examination with evaluation of the esophagus. That could even mean starting with a solid bolus before the esophagus is extended by air or too much barium is retained.

It is important to distinguish between two types of radiologic examinations. One is custom-tailored for revealing the cause of the patient's symptoms, which means the worst swallow. The other examination is the therapeutic swallowing study which is custom-tailored by either introducing maneuvers or different viscosities or other boluses for compensation of abnormalities [8]. This therefore can be described as how to achieve the best swallow. Different modes of decompensating a compensated swallow are also important [9].

It is always important to observe many swallows because dysfunction may be intermittent.

Radiology of swallowing relies on a systematic approach. One has to look specifically at certain areas of the swallowing apparatus. These can be divided into seven functional units, namely [1] tongue, [2] soft palate, [3] epiglottis, [4] hyoid and larynx, [5] pharyngeal constrictor, [6] pharyngo-esophageal (PE) segment, and [7] esophagus.

Fluoroscopy has to begin before the ingestion of the bolus. Fluoroscopy of the pharynx should also include a few seconds after the passage of the bolus into the esophagus. It is important not to change the position of the central beam during fluoroscopy because otherwise the anatomic details will be unsharp. The bolus should enter and leave the film sequence. The central beam should not follow the bolus. However, in the esophagus in the prone position, the bolus moves slowly at a speed of 1–4 cm/s and should be followed by the central beam from the pharynx to the stomach.

Contrast Medium

(a) Barium

High-density barium (HD) is used for evaluation of the morphology and function of the tongue, soft palate, epiglottis, hyoid and larynx, pharyngoesophageal sphincter, and esophagus. *Low-density barium (LD)* is used for evaluation of the contracting wave in the pharynx and peristaltic wave in the tubular esophagus. The esophagus should be evaluated in the prone right anterior oblique position. It should also be evaluated, if possible, in an erect position.

(b) Water-soluble contrast agents

Low-osmolar iodinated (WL) contrast agents are used if aspiration or a tracheoesophageal fistula is suspected. *Iso-osmolar iodinated (WI)* contrast agents should be used if the patient has restricted pulmonary function and aspiration is suspected. It should also be used in children under 3 years of age. Hyperosmolar iodinated contrast medium should not be used.

(c) Bolus

A *solid bolus (S)* should always be given if a stricture or solid-bolus-induced spasm is suspected. This means that if there are symptoms of solid-bolus dysphagia, the solid bolus should be used. The solid bolus can be in the form of a bread sphere coated with barium. Another option is a tablet with approximately 13 mm diameter, for example an antacidum. The test is positive if the solid bolus stays in the esophagus for longer than 30 s in spite of oral intake of fluid. The obstruction can be due to spasm or hypomotility which can be difficult to reveal. It can also be due to a stricture. In patients with strictures this small solid bolus usually does not give any symptoms while spasm or hypomotility or in fact hypersensitivity usually is symptomatic.

A *semisolid bolus (SS),* i.e., paste or pudding (with barium) or other consistencies, may also be used. Typically patients can safely swallow boluses of a specific consistency whereas aspiration occurs with less viscous consistencies.

Amount of Contrast Medium

The normal bolus in an adult is about 15 ml. However, a much larger bolus can be swallowed. Sometimes a small bolus like 5 ml can be harder to swallow than a bigger bolus. Also the chemical constituency is of importance.

Radiologic Anatomy and Comprehensive Radiologic Physiology

Normal swallowing occurs in a sequential, coordinated, and rapid manner. This can be reliably assessed during the radiologic examination. The act of swallowing can be divided into different steps and follows a certain course of events. The oral stage of swallowing is voluntary and includes (1) ingestion, (2) processing and containment, (3) transfer of the bolus into the back of the tongue, and (4) initiation of transportation. The pharyngeal stage is automatic. It includes (5) retraction

of the tongue base and pharyngeal propulsions, (6) velopharyngeal closure, (7) hyoid bone movements, (8) laryngeal elevation, (9) closure of the airways including the vocal folds, (10) pharyngeal constrictor activity, and (11) pharyngoesophageal segment with tonicity, relaxation, and constricting wave. The esophageal stage is autonomic and includes (12) transportation through the thoracic esophagus, and (13) opening and closure of the lower esophageal sphincter [10].

Swallowing can be conceived as an activity in three muscle pumps: oral cavity, pharynx, and esophagus. The most common abnormality is incoordination between the oral and pharyngeal pumps. This incoordination may lead to that the bolus is propelled into the pharynx before the pharynx is prepared to receive it. In such a situation the bolus may be transported directly into the airways leading to aspiration. The initiation of pharyngeal swallow should not occur later than 0.5 s after the apex of the bolus has passed the faucial isthmus.

According to the above, the boluses pass from the oral cavity through the faucial isthmus into the pharynx by backward sweeping movements of the tongue. The apposition of the soft palate to the posterior wall of the pharynx closes the epipharynx from the mesopharynx. At this moment the vocal folds also are closed.

The hyoid bone is elevated and later moved anteriorly. The vocal cords and supraglottic portion of the laryngeal vestibule are closed. There is an apposition between the thyroid cartilage and the hyoid bone and the epiglottis tilts to a horizontal position. Simultaneously the pharyngeal constrictor musculature starts to contract and the bolus now fills up the pharynx. The epiglottis then tilts down over the arytenoids. Now the subepiglottic space is compressed.

The pharyngoesophageal segment now opens and the bolus flows through into the cervical esophagus. A contracting wave passes through the pharyngeal muscle and then through the cervical esophagus. After the passage of the bolus the larynx and pharynx descend and the epiglottis tilts back into its resting upright position.

Primary peristalsis in the esophagus is elicited simultaneously as the pharyngeal swallowing starts. Peristalsis involves relaxation, propagation of contraction, and then resumption of a resting tonic state.

The Seven Functional Units

All the above physiologic events can be discerned on the esophagram [11, 12]. When interpreting the video films one need to evaluate the seven functional units, first individually and then in the global perspective, namely (1) tongue, (2) soft palate, (3) epiglottis, (4) hyoid and larynx, (5) pharyngeal constrictors, (6) PES, and (7) esophagus. Below are specific comments on these functional units.

Tongue

Ingested material is chewed or blended in the oral cavity. When ready to swallow it is transported on to the back of the tongue and swallowed as a bolus. Before swallow the ingested material is either positioned underneath the tongue, on the floor of the mouth, or held above the tongue against the alveolar ridge and hard palate. It is notoriously difficult to evaluate the oral cavity from a radiological point of view. The reason is the complex 3D anatomy and the fact that oral function is voluntary. It is difficult to know if the patient voluntarily chooses to chew or move the bolus in a certain way, or if this is the result of a dysfunction. This has been particularly cumbersome in patients with psychogenic dysphagia [13]. On the other hand psychogenic dysphagia is extremely rare.

Soft Palate

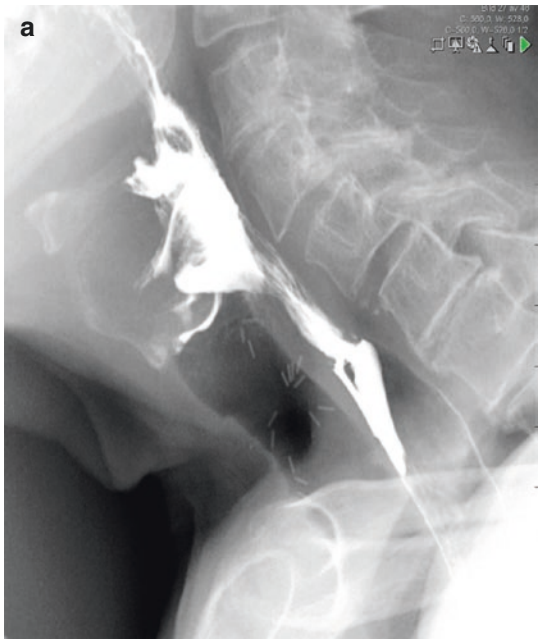
The soft palate and back of the tongue should tighten the oral cavity so that no oral content reaches into the pharynx until the patient is ready to swallow. Incompetence leads to premature leakage of the bolus. This may cause misdirected swallowing. In the same way, the soft palate and superior pharyngeal constrictor tighten against each other so that no bolus during normal conditions reaches up into the nasopharynx.

Epiglottis

Although epiglottis tilting leads to occlusion of the laryngeal introitus, this mechanical obstruction is of very limited value. The value of observing/registering the movement of the epiglottis lies again in the fact that it reflects somehow the global function of the pharynx. During normal conditions the epiglottis tilts from an upright to an inverted position during swallowing.

The Hyoid Bone

The hyoid bone can be compared to a block in a rig in a sailing boat. It is attached by tendons and muscles to surrounding structures. Therefore the position and movement of the hyoid bone as it can be observed in lateral projection are extremely valuable and somehow give the radiologist a global impression about pharyngeal function (Fig. 19.1a). Even in the presence of



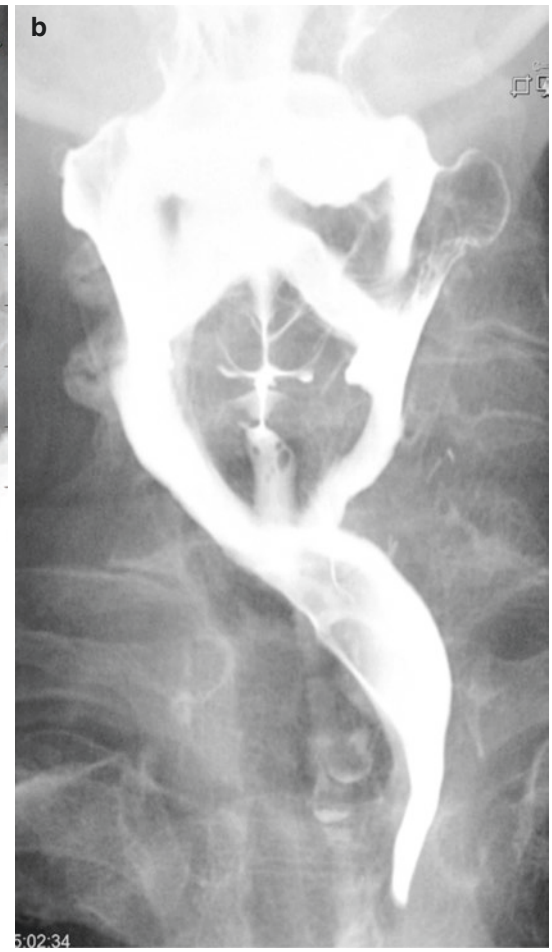


Fig. 19.1 76-year-old male who prior had had a hemithyroidectomy with multiple metal clips in the surgical area. He complains of that food get stuck in the throat when eating. He also had hoarseness and a gargling voice. (**a**) Shows the pharynx and larynx in lateral projection during the pharyngeal stage of swallowing. The hyoid bone (h) is well seen. Contrast material fills the laryngeal vestibule (ve) and has reached below the focal folds (f). (**b**) Shows the pharynx in frontal projection and in the same pharyngeal stage as in (**a**). (**c**) Shows the pharynx after the passage of the bolus. There is retention in the pyriform sinuses (p) and valleculae (va). (**d**) Shows the esophagus and trachea at the end of the examination. Misdirected contrast material has now reached far down in the trachea (tr) without any cough, which indicates chronic aspiration. This is often called "silent aspiration"

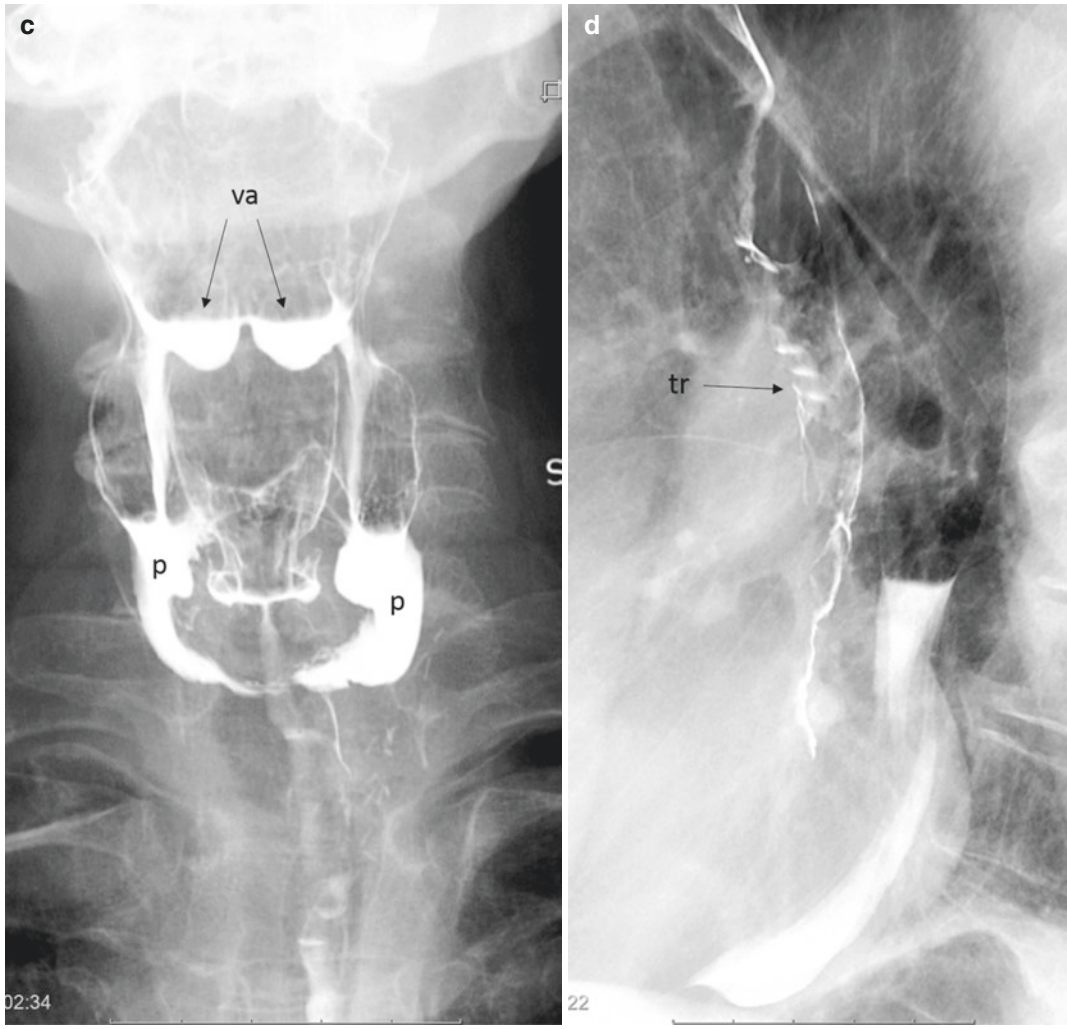


Fig. 19.1 (continued)

bolus retention and misdirected swallowing, if the hyoid bone has an overall normal movement pattern, this indicates a favorable prognosis.

The Larynx

One of the main challenges during swallowing, i.e., the transportation of food and liquids from the oral cavity into the esophagus, is the fact that part of this canal is common for inhalation of air and food. The main mechanism by which this separation is fixed is by a centrally generated apnea. This apnea is of paramount importance. However, the laryngeal vestibule also serves as a mechanical obstruction. To this adds the epiglottis above and the false and true vocal cords inferiorly. Registration of bolus misdirection in terms of either penetration to the laryngeal vestibule or aspiration of material into the trachea is accurately done during the radiologic examination (Fig. 19.1a–d). Misdirected swallowing may lead to symptoms from the airways like asthma (Fig. 19.2).

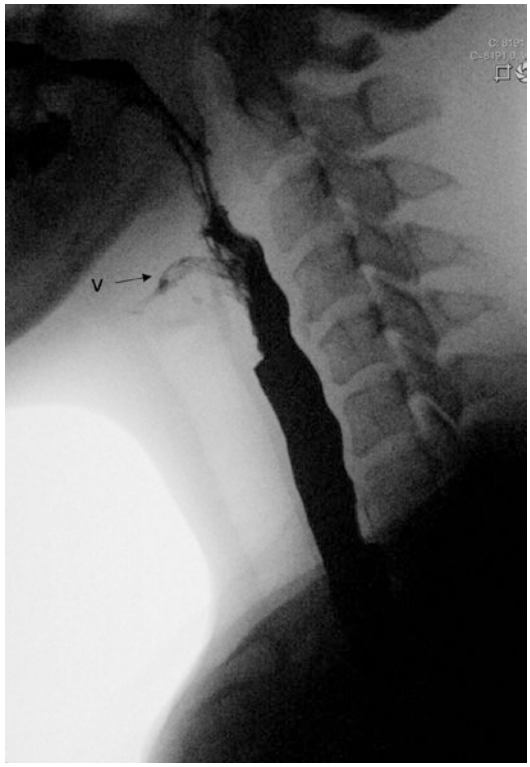


Fig. 19.2 45-year-old female with globus sensation. She also complains of food getting stuck in her throat. She points with her fingers to the right side of the neck. Lateral view of the larynx and pharynx reveals that contrast material reach into the laryngeal vestibule (v). At this time the patient indicates the feeling of something is getting stuck in the neck

The Pharyngeal Constrictor Musculature

The three portions of the pharyngeal constrictor, i.e., superior, middle, and inferior, are of importance for closure of the nasopharynx, stabilizing the pharyngeal tube, and opening and closure of part of the pharyngoesophageal segment.

The pharyngeal constrictors have an important role during the passage of the bolus through the pharynx which in fact is the result of the backward push of the back of the tongue. During this event the pharyngeal walls need to be stiff so that the force of the tongue is propelled in axial direction and perpendicular. After the passage of the bolus the constrictor wave rinses the valleculae and the pyriform sinuses. Failure to do this leads to retention which then may lead to penetration/aspiration (Fig. 19.1c).

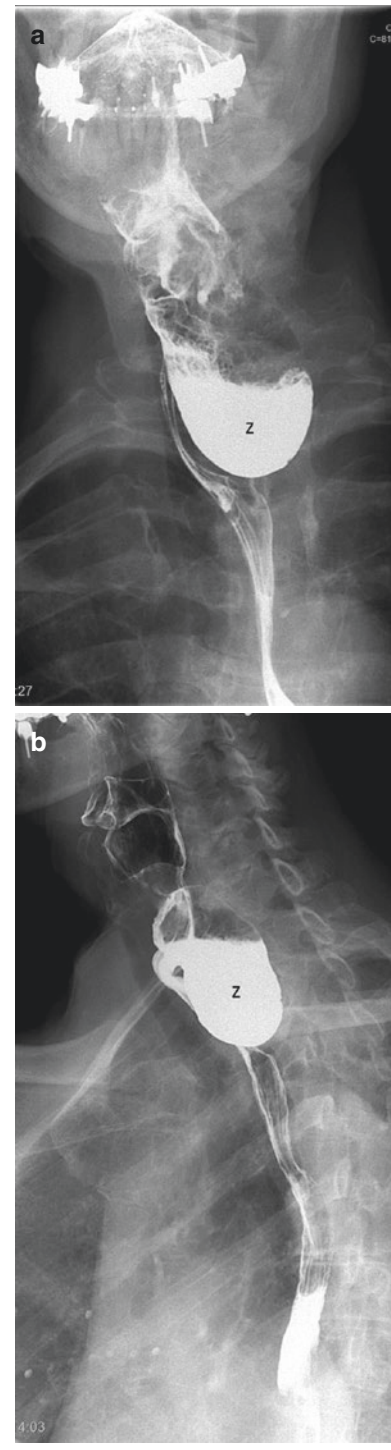


Fig. 19.3 71-year-old female with a globus sensation, i.e., a lump in the throat. She has also experienced periods of difficulty swallowing solids. The examination reveals a 6 cm Zenker's diverticulum (z). (**a**) Frontal projection (**b**) Oblique projection. The diverticulum causes an inbulging and partly obstruction of the cervical esophagus

The Pharyngoesophageal Segment

This segment is the transition between the pharynx and the esophagus. It is composed of three portions, i.e., the inferior portion of the inferior pharyngeal constrictor, the cricopharyngeal muscle, and the upper cervical esophagus with circular and longitudinal musculature. To swallow, the PES should be kept closed so that the person does not inhale air into the esophagus. During passage of the bolus the PES should open. This is the effect of a combination of muscular relaxation and elevation of the PES. Such elevation which also includes the rest of the pharynx and larynx is one of the fundamental mechanisms not only for opening of the PES but also for closure of the vestibule. Defective opening of the PES is often ascribed to an abnormality in the cricopharyngeal muscle while it in fact is due to an impaired elevation of the PES and/or poor intrabolus pressure. A Zenker's diverticulum occurs cranial to the cricopharyngeal muscle (Fig. 19.3). Killian-Jamieson's diverticula occur lateral and inferior to the cricopharyngeal muscle (Fig. 19.4) [14].

Other morphologic abnormalities in the pharyngoesophageal segment easy to overlook are membranes (Figs. 19.5 and 19.6).

Esophagus

Patients with symptoms indicating esophageal malignancies should undergo endoscopy and not primarily esophagram (Fig. 19.7).

During normal conditions the esophageal phase of swallowing is initiated simultaneously with the pharyngeal stage of swallow. The primary peristaltic wave should traverse the esophagus and interrupt it at a speed of 1–4 cm/s. This is best evaluated in the prone position.

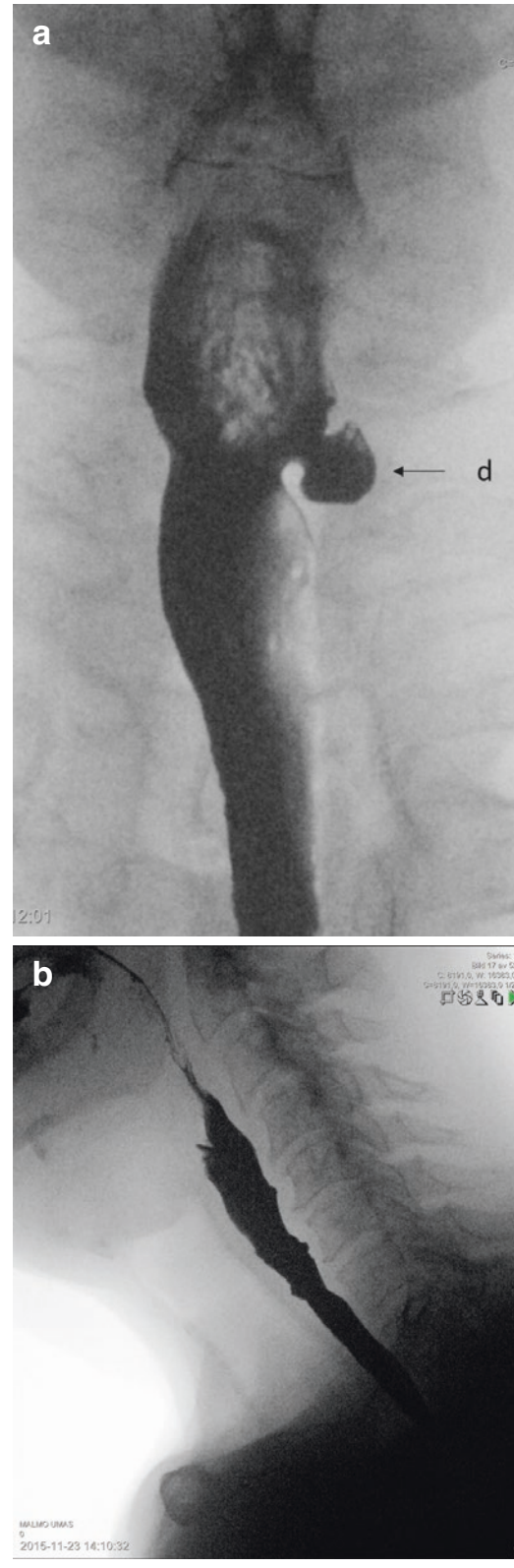


Fig. 19.4 73-year-old male with vague swallowing symptoms. No symptoms of obstruction. (**a**) Frontal and (**b**) lateral projection during barium swallow. There is a 15 mm diverticulum (**d**) on the left side of the pharyngoesophageal segment below the cricopharyngeal muscle. The lateral view proves that it is a Killian-Jamieson diverticulum

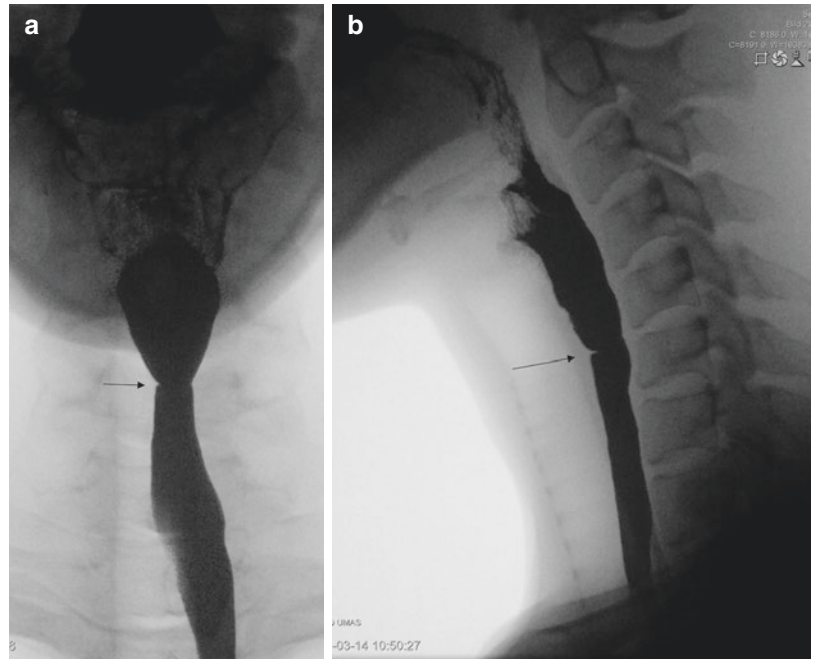


Fig. 19.5 27-year-old female with several episodes of solid food getting stuck in the throat. (**a**) Frontal and (**b**) lateral projection. There is a thin membrane (*arrow*) in the cervical esophagus that leaves only an 8 mm lumen in the pharyngoesophageal segment

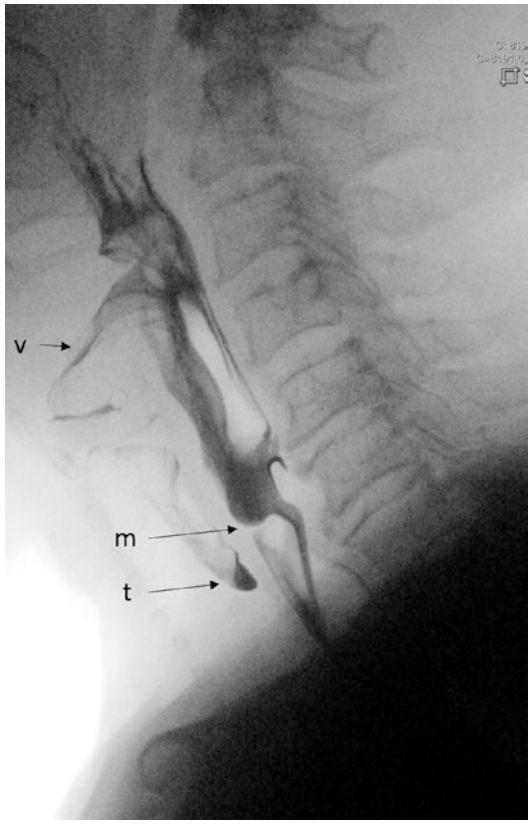


Fig. 19.6 78-year-old male with a prior history of diabetes and hypertension. He had radiotherapy for soft palate carcinoma. He now complains of obstruction for solid food and recurrent pneumonia. Lateral projection of the larynx and pharynx reveals misdirected swallowing to the laryngeal vestibule (v) and trachea (t). There is a membrane-like stricture (m) in the anterior wall of the pharyngoesophageal segment which leaves only 7 mm lumen in the esophagus

Nonpropulsive peristaltic activity is usually called tertiary contractions (Fig. 19.8). Other patients may have an aperistaltic esophagus (Fig. 19.9). This may substantially hinder the transportation of the bolus through the esophagus. Abnormal transportation of the bolus through the esophagus is often not getting proper attention. It is very common that, particularly in the elderly, an abnormal esophageal transportation causes the patient's symptoms. Web-like strictures (rings) are also common in the distal esophagus (Fig. 19.10). Therefore the esophagus should always be included in the examination.

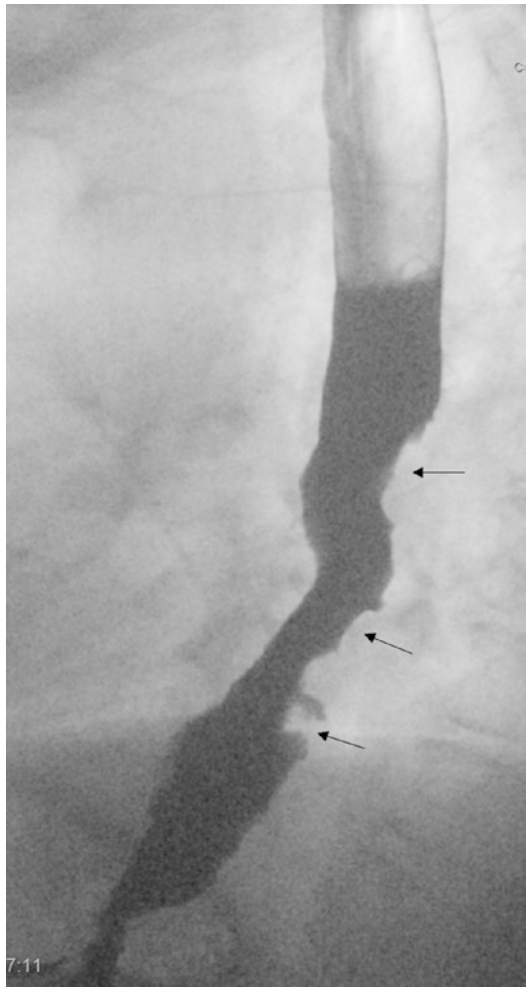


Fig. 19.7 48-year-old male with rapidly progressive solid food dysphagia for 3 months. The esophagram reveals an irregular annular narrowing of the distal esophagus (*arrows*) that was proved to be due to adenocarcinoma

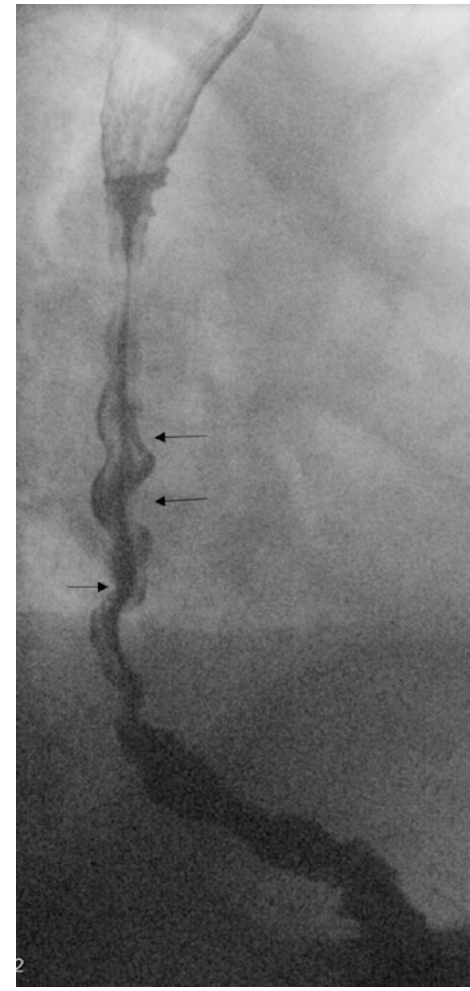


Fig. 19.8 62-year-old male with diabetes and polyneuropathy. He has difficulty swallowing both solids and liquids. The esophagram reveals nonpropulsive tertiary contractions (*arrows*)

The evaluation of the esophagogastric junction's morphology and function poses a challenge, since distal esophagus, hiatus, and stomach are an anatomically complex area that is not connected statically, but moves during bolus passage. Radiology may show signs of increased laxity of the phrenoesophageal ligament leading to incompetence of the esophagogastric junction. These include formation of a hiatal hernia, widening of the esophagogastric junction, change of cardia configuration, and widening of the Angle of His, the insertion angle between the lower esophagus and a tangent to the right side of the gastric fundus.

Summary

The most common functional swallowing abnormality is an incoordination between the oral and pharyngeal stage of swallow. In these patients

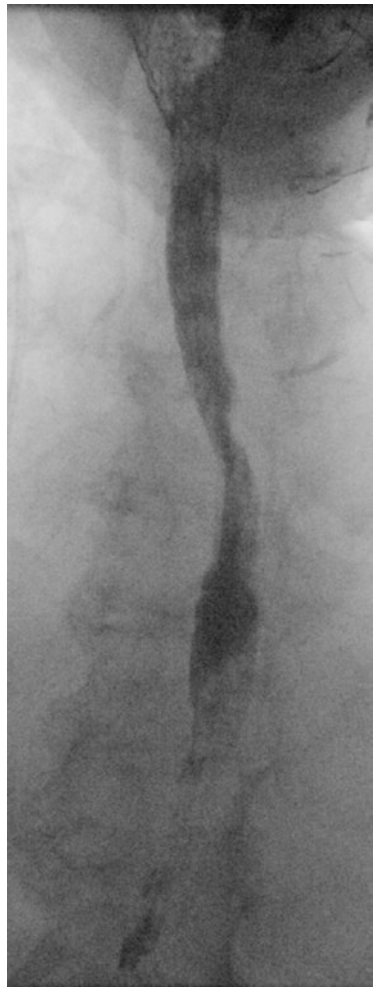


Fig. 19.9 71-year-old male with long-standing dysphagia for liquids and solids. The esophagram shows a noncontracting esophagus

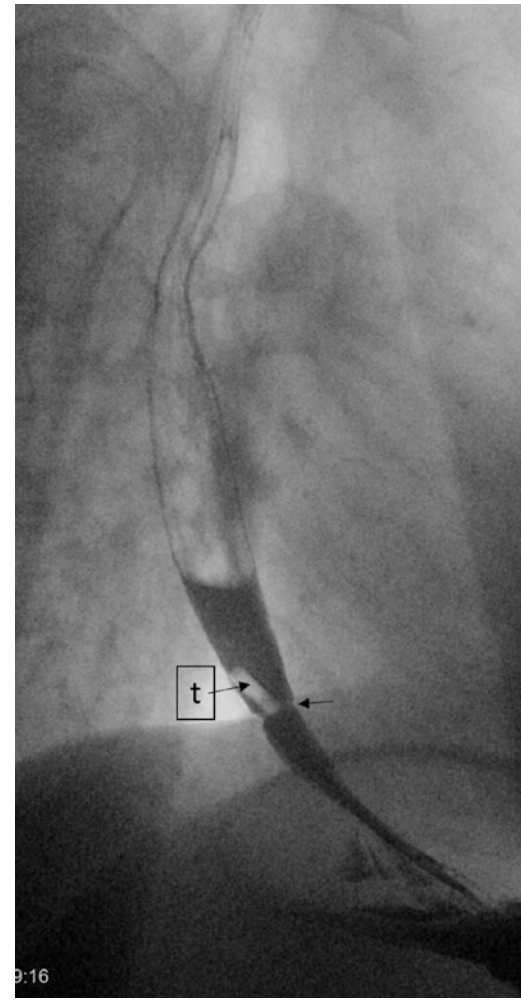


Fig. 19.10 65-year-old male with solid food dysphagia. He sometimes has to vomit obstructing material. The esophagram reveals a ringlike stricture (*arrow*) in the distal esophagus. Above this a tablet (t) got stuck

bolus reaches into the pharynx when the pharynx is not prepared which basically means that the larynx is not closed and thereby swallowed material can reach into the airways. Other abnormalities are retention of bolus in the valleculae and pyriform sinuses. This is then due to paresis of the pharyngeal constrictors. Abnormalities of the pharyngoesophageal segment can be due to delayed or ineffective relaxation, but it is much more common to be due to defective elevation of the PE segment and too low intrabolus pressure. This means that a defective opening of the PE segment is usually due to cranial abnormalities, i.e., within the pharynx, and not due to the functional or morphologic abnormalities in the PE segment itself.

As stated above, it is important to analyze the patient's clinical history and symptoms and then custom-tailor the examination in order to be able to explain the patient's symptoms. But it is as important to analyze if the patient experiences any symptoms during the radiologic examination. This observation should be included in the report so that the referring physician can compare findings with symptoms.

The relation between specific dysfunctions and causes in terms of underlying disease entities

is not always obvious. However, there are some important observations. Lower motor neuron disease causes a global weakness in the pharyngeal musculature with lack of elevation of the pharynx during swallowing. This may cause major aspiration. Upper motor neuron disease affects the oral stage as well as an incoordination with the pharyngeal stage. Instead of a flaccid palsy one may observe spasticity. Such motor neuron disease may be stroke, ALS, MS, etc. Esophageal motor dysfunction is typically seen in diabetes. Severe esophageal motor impairment is seen in achalasia and in scleroderma. Other systemic diseases like dermatomyositis affect the pharynx.

The complex symptomatology that hides behind the term dysphagia together with a plethora of pathogenesis and etiologies favors the establishment of a multidisciplinary swallowing team. The least one can demand is that the clinician and radiologist use a common terminology. This should include the fact that dysphagia is a symptom that may be caused by a dysfunction.

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Painful Swallowing

20

Patrick Sanvanson

It Hurts When I Swallow, Is It My Pill Doing It or an Infection?

Suggested Response to the Patient

There are a number of different reasons for pain with swallowing, and both pill-induced injury and infections are common causes.

There are numerous medications that have been associated with pill-induced injury, including common medications like nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, etc.) and antibiotics and we will go through your medication list to determine if there is a specific medication that is likely to be contributing and if the way you are taking these medications puts you at increased risk for pill-induced injury. If it is your pill that is suspected to be the cause of the pain with swallowing, oftentimes we will have to stop this medication and see if your pain resolves. If your pain does not improve, we will need to perform further evaluation, possibly endoscopic evaluation, to determine if there is another cause of your pain.

There are various infections including bacteria, fungi, and viruses that can cause pain with swallowing. Patients that are immunosuppressed are often affected by these infections, but they may also occur in those without any immunosuppression. Common causes of infection that cause pain with swallowing include *Candida*, herpes simplex virus, and cytomegalovirus. There are treatments for these various infections, but it often requires endoscopy with possible biopsy to make the diagnosis.

Once we identify the cause of your pain with swallowing, we will be able to initiate treatment that should improve your pain.

Brief Review of Literature

Odynophagia indicates pain during any component of the swallowing process. This pain occurs with or shortly after the initiation of a swallow. Pain that occurs during the oropharyngeal phase of swallowing has been attributed to various processes including malignancies, foreign body ingestion, and mucosal inflammation and ulceration. Odynophagia occurring later in the swallowing process is commonly caused by caustic injury or infection and suggests the esophageal phase. However, considerations include tumors and other processes associated with deep mural injury including radiation damage and deep peptic ulceration [1].

In immunocompetent individuals, a common cause of acute esophageal odynophagia is infection with *Candida albicans* or herpes

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simplex virus (HSV). Other bacteria, fungi, and viruses such as cytomegalovirus (CMV) and varicella zoster virus are less commonly associated with odynophagia in the immunocompetent. Topical corticosteroids, diabetes mellitus, and malignancy are known to increase the risk for *Candida* infection of the esophagus. More common offenders for acute esophageal odynophagia in the immunosuppressed are cytomegalovirus and *Candida*. Immunosuppressed populations that are most affected by infectious esophagitis include HIV/AIDS patients, transplant patients, and those receiving chemotherapy [2].

Another frequent cause of odynophagia includes pill-induced caustic injury and has been associated with numerous medications including aspirin, nonsteroidal anti-inflammatory drugs, potassium supplements, tetracycline, ferrous sulfate, and bisphosphonates. Greater than 100 medications have been reported to cause pill-induced esophageal injury. Pill-induced tissue injury to the esophagus can result in deep ulcerations to perforations. In addition, pill-induced tissue injury may evolve into strictures [3]. Injury often occurs at anatomical sites of esophageal narrowing, including near the level of the aortic arch due to extrinsic compression and physiologic reduction in amplitude of the peristaltic wave. In addition to the direct irritant effect of pills causing esophageal injury, certain medications like nonsteroidal anti-inflammatory drugs disrupt the cytoprotective barrier.

In patients with odynophagia, they will frequently describe pain with swallowing from a dull discomfort to a pain of intense severity that interferes with any swallow attempt.

It is important to obtain exposure histories that predispose to mucosal irritation, including prior radiation therapy, corrosive ingestion, foreign body ingestion, and medication history. Medication history should also focus on the timing of pill ingestion (particularly immediately prior to sleep), position when ingesting pills (e.g., recumbent), and amount of water intake with pill ingestion. Tobacco and alcohol use are risk factors for malignancies. Evaluate patient for factors predisposing to opportunistic infections including systemic illnesses (AIDS), immunosuppressive treatment, and antibiotic use.

Pathophysiology

Patients with esophageal odynophagia tend to have disruption of the esophageal mucosa. The theory is that this disruption leads to increased exposure of chemo- and thermo-nociceptors within the mucosa and submucosa. When activated, these nociceptors transmit their impulses through unmyelinated C-fibers or myelinated A delta fibers [4, 5].

Diagnostic Tests

Odynophagia frequently requires examination of the mucosal surface with direct visualization and possible biopsy. Considerations include transnasal endoscopy, laryngoscopy, or esophagoscopy. If a patient has oropharyngeal odynophagia, may consider X-rays of the neck, particularly if a foreign body is suspected. For chronic esophageal odynophagia, this may suggest invasion or extension of mucosa-based processes into deep esophageal layers. In these instances, both radiology (chest X-ray, computed tomography, barium studies) and endoscopy may be needed for diagnosis and to assess extent of esophageal or mediastinal involvement [1].

Endoscopic findings for infectious causes of odynophagia differ depending on the etiology. In *Candida* esophagitis, endoscopy typically reveals numerous small whitish to yellowish plaques. Biopsy will reveal budding yeast forms and pseudohyphae with an inflammatory infiltrate indicative of invasive infection. Cytomegalovirus and herpes simplex virus are often associated with ulceration. Biopsy specimens should be taken from ulcer edges and the center of the ulcer base in cases of suspected HSV and CMV, respectively. In some cases of infectious esophagitis, only general signs of inflammation including erythema and edema may be seen [6].

It is controversial whether endoscopic evaluation should be repeated after treatment completion to evaluate for clearance of disease, but it is generally recommended that endoscopy be repeated if symptoms persist after medical treatment.

Therapeutic Options

Treatment frequently depends on identifying underlying cause of odynophagia.

In *Candida* infection, treatment often requires topical or systemic antifungal medications. When prescribing antifungal medications, the clinician must be conscious of possible drug interactions, particularly in patients requiring immunosuppressive medications. In immunocompetent patients with mild *Candida* infection, a trial of nystatin or clotrimazole topical therapy can be considered. However, fluconazole is commonly prescribed as a first-line treatment particularly in immunosuppressed patients and those with moderate to severe *Candida* infection due to good oral availability and efficacy in treating *Candida*. For severe infections, resistant fungal organisms, or significantly immunocompromised hosts, intravenous amphotericin treatment may be warranted. Management approaches for patients with AIDS with odynophagia include empiric treatment of patients with oral thrush given that *Candida* is common in this population [7].

Antiviral drugs can be used when herpes simplex virus or cytomegalovirus is the cause of the odynophagia. Uncomplicated CMV esophagitis can be treated with oral valganciclovir or famciclovir, but severe or complicated infections require prolonged treatment with intravenous ganciclovir. Although HSV esophagitis in immunocompetent patients may be self-limited, treatment with acyclovir is encouraged in most patients, particularly the immunocompromised [7].

Treatment of pill-induced injury requires avoidance of aggravating pills, if possible. Frequently, acid-suppression therapy particularly in those with gastroesophageal reflux disease is used to prevent acid-related injury compounding esophageal injury caused by other etiologies. Options include proton-pump inhibitors, H2-receptor antagonists, and antacids.

Conclusions

The key factor to management of odynophagia includes identification of the underlying cause so that treatment may be tailored. Clinicians need to be aware of the possibilities of infection and pill-induced injury as contributing to odynophagia so that diagnosis and treatment is not delayed. Risk factors for infectious esophagitis and pill-induced esophageal injury should be minimized, if possible.

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Eosinophilic Esophagitis

21

Calies Menard-Katcher, Dan Atkins, and Glenn T. Furuta

Diagnosis

What Symptoms Are Associated with EoE?

Answer

Based on clinical experiences as well as an increasing body of literature from around the world, symptoms associated with EoE can be nonspecific and commonplace. Children may experience problems typically associated with gastroesophageal reflux such as vomiting, abdominal pain, regurgitation, and heartburn. They often also present with feeding difficulties or food aversions. Adolescents and adults present with stereotypical symptoms of solid food dysphagia or food impaction [1, 2].

Summary of Pertinent Literature and Clinical Pearls

Original clinical descriptions of pediatric patients with EoE recounted histories of children with reflux-like symptoms that did not improve with medical or surgical treatment of GERD, but responded to use of a hypoallergenic, amino acid-based formula [3]. Ten children with reflux-like symptoms were found to have dense esophageal eosinophilia and neither symptoms nor histopathological findings responded to proton pump inhibition or, in some cases, fundoplication. When treated with an elemental formula, all improved clinically and histologically. Clinical experiences and retrospective studies subsequently showed that children with EoE often presented with symptoms of upper abdominal pain, heartburn, or postprandial vomiting that persisted despite treatment with acid inhibition. As experiences grew, clinical reports described feeding difficulties associated with EoE [4, 5]. Symptoms included slow eating, gagging on foods, and lack of interest in trying new foods. More difficult to define were the coping behaviors associated with eating problems. For instance, children developed novel ways to ingest food to maintain nutrition

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that could also be viewed as troublesome, such as excessively long meals, drinking large amounts of fluids to wash foods down, or avoiding eating certain foods because of swallowing problems. These symptoms can create significant stress at family mealtimes and can alter family dynamics.

Solid food dysphagia and food impaction are typical presenting symptoms in adolescents and adults. While clinical experiences suggest that coping mechanisms likely exist, they are not well defined in the literature to date. Dysphagia is the primary presenting symptom of EoE in adults. In addition, EoE is emerging as the most common cause of food impactions presenting to emergency rooms [6]. Original studies found that up to 55% of patients with food impactions presenting to ERs were thought to have EoE as the underlying cause. Subsequent studies continue to support this estimate. Adults with EoE can also have symptoms of heartburn, but this is less common a presenting complaint.

Pearls

1. In children, if reflux-like symptoms persist despite treatment, consider EoE as an underlying cause.
2. If a patient presents with food impaction, EoE must be ruled out unless another obvious cause is present.

How Is the Diagnosis of Eosinophilic Esophagitis Made?

Answer

As of 2016, the diagnosis of EoE requires the presence of symptoms associated with esophageal dysfunction, dense esophageal eosinophilia on mucosal biopsy and ruling out other potential causes of these findings [7–9]. Upper endoscopy is required for diagnosis of EoE in order to obtain mucosal tissue biopsies. Additional supportive evidence for EoE is the finding of otherwise idiopathic esophageal strictures and improvement upon treatment with either dietary exclusion of food allergens, use of an elemental formula, or swallowed topical corticosteroids [10–14]. Significant controversy is developing regarding the role of proton pump inhibition in making the diagnosis of and treating patients with EoE.

Summary of Pertinent Literature and Clinical Pearls

In the early 1990s, two investigators described adults with symptoms of dysphagia and esophageal eosinophilia. Because of the diversity of opinions and lack of a standardized approach, a multidisciplinary group published Consensus Recommendations for the diagnosis of EoE based on the published literature and clinical experiences [8]. This document defined EoE as a clinicopathological disease that required key clinical features and >15 eosinophils per high power field in esophageal mucosal biopsies to make the diagnosis. Other diseases associated with these clinical findings, especially reflux esophagitis, had to be ruled out. Approaches to rule out GERD as a diagnostic possibility included use of pH impedance monitoring of the distal esophagus or a trial of high dose proton pump inhibition.

This document was revised in 2011 to reflect subsequent research findings and clinical advances [9]. Key modifications in the document included a proposed conceptual definition of EoE stating that EoE represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. The acronym was changed from EE to EoE because of confusion with erosive esophagitis and chronic was added to the definition because of increasing knowledge of its natural history. A new term, proton pump inhibitor responsive esophageal eosinophilia or PPI-REE, was also introduced. This term described a group of patients who did not have objective evidence of GERD and whose symptoms and esophageal eosinophilia resolved with the use of PPIs.

In the years since the initial description, basic studies have begun to examine additional molecular mechanisms through which PPIs might reduce eosinophil chemotactic events in the esophageal mucosa. In addition, clinical studies have identified EoE-like patients who

respond to PPI treatment and controversy has arisen over the role of PPIs in the evaluation of patients with esophageal eosinophilia [15, 16]. Some suggest that PPIs may be used to treat patients with EoE and that these medications should not be used to establish the diagnosis of EoE. In contrast, others suggest that PPI treatment is an effective way to rule out GERD and should be used to do so as suggested in the original Consensus Recommendations. Although molecular studies provide support for the former opinion, more studies to determine the role of PPIs in the evaluation and treatment of adults, and perhaps even more so children, are needed [13].

Treatments

What Types of Treatments Are Used for EoE? What Are the Side Effects of EoE Treatments?

Answer

The three Ds, diet, drugs, and dilation, have all been shown to be effective treatments of EoE in children and adults [17, 18]. Diet and drugs reduce both symptoms and esophageal inflammation and early work suggests they may also improve long-term outcomes. Esophageal dilation improves symptoms and increases luminal diameter, but does not impact the inflammatory process.

Summary of Pertinent Literature and Clinical Pearls

Diet: One of the first accounts of EoE demonstrated that esophageal inflammation resolved and symptoms improved with the use of elemental or amino acid-based formula [3]. We now understand EoE is mediated by exposure to certain food allergens in the majority of patients. In fact, dietary therapy for EoE has evolved to include complete elemental diet, empiric food elimination diets, and targeted food elimination diets. Elemental diets in the form of amino acid-based formulas can be highly effective in treating children and adults with EoE but have limited long-term tolerability for patients [19–21].

Targeted approaches to identifying potential offending foods are based on a diet history and results from skin and specific serum IgE (ImmunoCAP) testing. Early studies reported that a targeted approach to developing elimination diets could be effective in reducing eosinophilic density in 53–72% of patients; however a meta-analysis found this approach to be less promising than initial studies [22]. A shortcoming of the targeted approach to diet restriction is that the predictive value of traditional allergy testing is poor in identifying problematic foods in EoE. The potential benefit of the targeted approach is it might reduce the number of excluded foods.

Empiric elimination diets have been based on excluding the six most common food allergens: milk, egg, wheat, soy, peanuts, treenuts, and fish/shellfish. Efficacy at reducing eosinophilic inflammation was 74% in children treated with the six food elimination diet [23]. Studies looking at less restrictive empiric diets including a four food elimination diet (milk, wheat, egg, and legumes), vegan diet, and milk only restriction have demonstrated efficacy in both children and adults [24–26].

In contrast to medications, diet restriction avoids potential steroid side effects. Diet treatment often comes with added cost with respect to groceries and can affect quality of life [27, 28]. Future studies will hopefully help identify an optimal approach to empiric and/or targeted diet restriction in treating EoE.

Drugs: Swallowed topical steroids (STS) and proton pump inhibitors are considered the mainstay of medical treatment for esophageal eosinophilia. Originally EoE was characterized by its lack of response to PPI treatment. However, clinical studies have shown that 25–35% of patients with characteristic esophageal symptoms will have clinical and histologic response to a trial of high dose PPI (PPIREE). Therefore, PPI has been described as a "first line" treatment option for symptomatic patients with esophageal eosinophilia [14]. While controversy exists around the role of PPI in making the diagnosis of EoE, a trial

of high dose PPI is practical to rule out PPI responsive inflammation.

STS in the form of swallowed fluticasone and liquid budesonide have been shown to be effective in treating EoE with response rates between 50 and 90%. Metered dose inhalers (MDIs) have been used to deliver medication to the back of the throat where it is then swallowed, coating the esophagus. Viscous preparations of budesonide were developed primarily to treat children who may have difficulty with coordination in taking the MDI. Sucralose was initially proposed and demonstrated 87% efficacy [29]. Since then several other preparations have been described in both children and adults using foods to prepare a viscous vehicle for the budesonide [30, 31]. Randomized clinical trials with a proprietary viscous budesonide slurry are ongoing in treating patients with EoE.

Complications of STS include *Candida* infections of the mouth or esophagus and adrenal insufficiency (AI) [32–34]. AI has been shown to occur in EoE patients treated with STS ranging from 0 to 45%. The wide range of reported AI associated with STS treatment of EoE exists because of variability in method of testing for AI, lack of control over type and duration of STS, and no control for other forms of steroids used. This later issue may be the most important issue since, in our experience, the use of more than one corticosteroid (e.g., for EoE and asthma) increases susceptibility to developing AI (unpublished data). It is our practice to monitor clinically for signs of AI (decreased height velocity, Cushingoid facies) and screen patients who have been on chronic STS with fasting morning cortisol and if abnormal, refer to an endocrinologist for further evaluation.

Other Drugs: Studies exploring benefits of montelukast to control symptoms and inflammation have been mixed. With the advent of increasing understanding of pathogenetic mechanisms and identification of potential therapeutic targets, antibody-based biologicals have emerged as novel approaches to treatments. Studies examining inhibition of IL-5 and IL-13 demonstrated a positive impact on esophageal eosinophilia but inconsistent findings regarding symptom reduction. Examination of the efficacy, cost benefit, and side effect profile of these approaches will be critical to future care.

Dilation: Dilation should be considered in the setting of severe esophageal narrowing that does not allow passage of a pediatric endoscope or when symptoms of dysphagia persist despite adequate control of inflammation or attempts at medical treatment fail [35–40]. This later circumstance may occur when subepithelial fibrosis has occurred that escapes endoscopic detection. Dilation is effective at improving symptoms by increasing luminal diameter but it does not resolve underlying inflammation that is more appropriately treated with diet restriction or STS. Dilation techniques with wire-guided Savories, bougies, and balloon dilators have all been described in the management of EoE. Although early case series reported high rates of perforations in adult EoE patients treated with dilations, recent studies examining larger numbers of patients as well as children demonstrate the risk of any complications, such as perforation, bleeding requiring transfusion or hospitalization, is low. While risk of serious complications is low, pain is common and has been reported in up to 70% of patients undergoing dilation. Repeat dilation is often needed as a part of long-term management [40]. A careful approach with interval increases in dilator size is often recommended.

Pearls:

1. EoE is a chronic condition. If treatment is discontinued, inflammation eventually returns.
2. In deciding on treatment recommendations, patient and family preferences are important since barriers to implementing a treatment regimen may impact adherence. For instance, some may prefer diet adjustment as opposed to daily medication administration.
3. Proper administration of STS is critical to insure therapeutic success. Since steroids are often administered to patients who use an MDI for asthma, detailed instructions on spraying STS in the mouth and then swallowing without eating or drinking are necessary. See links https://youtu.be/0x7IXhgTsb0 and https://youtu.be/wRKcoMwpXTM.

What Are the Goals of EoE Treatment?

Answer

Since EoE is such a "young" disease, treatment goals may vary depending on whether a patient is participating in a therapeutic trial or is receiving treatment in a clinician's office. For instance, in most industry-sponsored therapeutic trials seeking Food and Drug Administration (FDA) approval, improvement of patient-reported outcomes (PROs) and lowering of eosinophils per high power field (HPF) in a mucosal esophageal biopsy have been used as co-primary endpoints. In contrast, clinicians caring for patients have used a number of different metrics to assess the efficacy of treatment including reduction of primary symptom, decrease in eosinophils/HPF, improvement in endoscopic appearance of the esophageal mucosa, and increase in quality of life. For children, growth and development and balancing risks and benefits of chronic treatment with symptom control and histological improvement remain key considerations.

Summary of Pertinent Literature and Clinical Pearls

Assessment of histopathology: The number of eosinophils per high power field has traditionally been the mainstay of establishing the diagnosis of EoE and defining histologic severity. Initial guidelines support the use of >15 eos/HPF to make the diagnosis of EoE, studies have yet to determine the threshold number of eosinophils that defines effective treatment. Other histologic findings that may help better define this include eosinophil degranulation, eosinophil micro-abscesses, basal layer hyperplasia with rete peg elongation, dilated intracellular spaces, and lamina propria fibrosis [41].

Patient-reported outcomes: Goals of treatment from a patient perspective are to reduce symptom severity and frequency and prevent complications of EoE such as food bolus impaction and esophageal narrowing. STS have been shown to reduce the risk of developing food bolus impaction and while not studied, control of inflammation with dietary restriction is presumed to also prevent or delay onset of fibrosis and complications of disease [42].

Patient symptoms do not always correlate with eosinophil density [43, 44]. This may be a result of either patients developing adaptive coping mechanisms to avoid dysphagia symptoms or because long-standing inflammation leads to a "burned out" fibrostenotic esophagus that is devoid of dense eosinophilia [45]. Assessment of patient-reported symptoms therefore has been a challenge for clinical trials in EoE and requires a detailed history. Ongoing studies have developed patient-reported outcomes that provide validated measures of symptoms in therapeutic studies. While some are more practical in the research setting, others may provide a means of more accurately assessing symptoms in the clinical setting and measuring symptom response [43].

Pearl

1. To identify adaptive coping strategies associated with obstructive symptoms common in EoE, it is recommended to ask a series of questions about feeding preferences. Questions should address eating habits such as: (1) the use of liquids to wash foods down, (2) the use of condiments or other sauces to lubricate foods, (3) slow eating or excessive chewing, and (4) avoidance of highly textured foods such as meats, bread, or rice can be useful in identifying indolent and intermittent solid food dysphagia that is common in EoE.

What Is the Long-Term Outcome of This Disease?

Answer

Adults and adolescents with untreated EoE may develop esophageal fibrosis, esophageal strictures, and food impactions [46]. Children with EoE may present with feeding difficulties that in some circumstance may lead to malnutrition. Esophageal strictures and food impactions can also be seen in children but appear to be a less common finding. Barrett's esophagus and esophageal cancers do not appear to be a long-term com-

plication. Mucosal eosinophilia does not seem to spread to involve other gastrointestinal organs.

Summary of Pertinent Literature and Clinical Pearls

Our understanding the natural history of EoE has been drawn from limited sources of information. First, clinical descriptions of presentations regularly report a long delay between onset of symptoms and establishment of a diagnosis of EoE. In these studies, patients may report up to a 4-year lag from onset of dysphagia, eating problems, or GERD-like symptoms before an endoscopy is performed and the diagnosis of EoE is made. An unknown fraction may go on to develop strictures or food impactions.

Three studies of adults with EoE provide insights into long-term outcomes. In the first retrospective study, investigators measured the incidence of esophageal strictures occurring over time in adults who did not receive treatment. Over the 20-year time span examined, they determined that almost all of the 200 patients followed developed strictures. With the advent of effective treatments, this study will likely not be replicated [47]. In a second study, the same investigators performed a retrospective study to determine if STS reduced the complication of food impaction [42]. In their review of 33 patient records, they determined that the use of STS reduced the incidence of food impactions and if STS were used for longer periods of time, this result was sustained. Finally, statistical modeling was used in a study of 379 adults with EoE to determine the likelihood of developing esophageal fibrosis. Results demonstrated that the longer a patient had EoE, the more likely they were to develop esophageal fibrosis [48].

At present, duration of untreated inflammation appears to be the leading risk factor for developing fibrosis and stricture. Prospective studies however are needed to determine if all patients are at equal risk for this complication and the role of treatment in reducing this risk. Functional testing and molecular analysis may provide key insights into predicting outcomes that will permit a more personalized approach to care [49, 50].

Currently, no cure is available for EoE and the bulk of evidence supports that EoE is a chronic, lifelong disease that can be managed with medication or dietary therapy. Whether some patients outgrow the disease is yet to be determined.

Pearls

1. Endoscopy has been shown to have poor sensitivity in identifying luminal narrowing in EoE. Esophagram is more useful to assess for luminal narrowing in patients who have persistent or recurrent dysphagia.
2. Techniques that measure esophageal lumen stiffness or distensibility such as Endolumenal Functional Lumen Imaging Probe (EndoFLIP) may provide a valuable means of monitoring disease progression in the future.

Commentary on Future Trends and Directions

Since the advent of diagnostic criteria and consensus guidelines almost a decade ago, investigation and clarity into the understanding and management of this distinct chronic esophageal inflammatory disease are urgently needed.

The role of proton pump inhibitors (PPIs) in the care of patients with esophageal eosinophilia continues to undergo examination. PPIs have been used in the past to rule out GERD as an underlying cause of inflammation. However, this practice has been challenged by the observations that (1) adult patients with classical features of EoE without evidence for esophageal reflux have clear clinical and histologic responses to PPI treatment and (2) PPIs may have anti-inflammatory properties related to inhibition of cytokine production by esophageal epithelial cells [51, 52]. These findings support the use of PPIs in older patients in the treatment of symptoms and eosinophilic inflammation [14].

The practical implications of these findings are a paradigm shift from the initial diagnostic approach that requires the use of a PPI to rule out GERD prior to assigning a diagnosis of EoE. In this light, some clinicians proceed directly to endoscopy for evaluation of EoE-like symptoms to more rapidly establish a diagnosis and to document the condition of the underlying naïve mucosa prior to any treatment. In contrast, the

use of PPI pretreatment prior to endoscopic assessment of symptoms remains the approach by others, especially those caring for children. Symptoms associated with pediatric EoE are not as steadfast and lack of pretreatment with the resultant finding of esophageal eosinophilia may lead to more endoscopies. Clarity about the role of PPIs is not only important for the management of patients with esophageal eosinophilia but also to accelerate care and entry into clinical trials.

Monitoring esophageal inflammation still requires endoscopy in order to obtain mucosal biopsies. At present endoscopy remains the only validated means of monitoring esophageal inflammation in EoE. Although counting eosinophils remains a gold standard, this metric is problematic because of variability in size of HPF used, lack of standardization for eosinophil definition histologically, and differences in inflammation along the esophageal mucosa. Ongoing studies investigating novel less-invasive devices to assess mucosal inflammation include confocal microscopy, cytosponge, esophageal string test, and transnasal endoscopy [53–56]. In addition, EndoFLIP may offer a means of assessing functional stiffness of the esophagus [57, 58]. The development and validation of PROs will also provide research studies and clinicians with novel ways to measure patient's symptoms. Going beyond the use of an eosinophil number will be a key advancement in the assessment disease severity.

The long-term outcomes of diet restrictions and STS will also become critical in choices of treatments. Although malnutrition is the primary potential side effect associated with dietary treatment of EoE, other studies suggest that this treatment can increase stress, reduce quality of life, negatively alter family dynamics, and increase meal costs compared to a normal diet. Complications associated with STS for EoE include local viral or fungal infections and adrenal suppression. The exact incidence and severity of these complications is yet to be determined, but for infections range from 0 to 18% and for AI from 0 to 43%.

Addressing the question of, "is the disease or its treatment worse?" is a key consideration for clinical care. In fact, since treatment efficacies can be similar, treatment options may vary with age and other comorbidities; diet may be an effective and tolerable treatment during childhood, whereas STS may be a better choice for adolescents and adults.

Studies evaluating functional assessment of the diseased esophagus, response to treatment and advanced insight into the molecular pathways involved in driving inflammation and differences between subgroups will lead to identifying disease phenotypes. For example, early studies suggest that EoE patients who develop food impaction may have specific functional abnormalities related to esophageal compliance. Another study determined that steroid responsiveness was found in patients with a specific gene associated to FK506 metabolism. The goal of future studies will be to allow for more targeted approaches to treatment and disease management.

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Part II

Gastric Motility Disorders

Chronic Belching and Chronic Hiccups

22

William L. Berger

Chronic Belching

I Seem to be Belching All the Time. What's Going On?

Everyone belches, but when it is frequent and persistent, it becomes a problem. Fortunately it is rarely caused by any serious underlying issue. Let's look at normal belching (or "Eructation").

Generally speaking, there are two kinds of belching: gastric and esophageal. Gastric belching occurs when the stomach becomes overdistended, such as after a very large meal. This causes temporary relaxation of the sphincter between the stomach and the esophagus. Any gas on top of the food in the stomach is then vented into the lower esophagus, which, in turn, vents this through the upper esophageal sphincter in the back of the throat. The belch reflex coordinates this with a protective closing off of the airway the same way it does in vomiting. A characteristic noise can be produced as the gas escapes through the upper esophageal sphincter under pressure.

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With esophageal belching, air is sucked or swallowed into the upper esophagus and then rapidly belched out before ever reaching the stomach. The initiating issue here is excessive air swallowing into the esophagus ("Aerophagia," literally "Air Eating") which is typically a learned behavior. This can be used by patients with a tracheostomy to give "esophageal speech," and many adolescent males will also learn to do this so they can belch at will. It is also a commonly observed habit in developmentally delayed individuals.

Sometimes belching is culturally appropriate. Other times not so much. Unfortunately, the anxiety and any accompanying social embarrassment may actually exacerbate the symptom. Emotions generally accelerate spontaneous swallowing rate even in healthy individuals. Every swallow takes a certain amount of air with it into the esophagus and potentially into the stomach.

This excessive aerophagia in turn causes frequent belching. Pathologic belching can occur up to 20 times per minute. The stomach cannot generate this much gas of its own accord. When aerophagia is particularly severe some air will inevitably pass to the stomach, which can become very distended. That air can pass through the entire GI tract additionally causing bloating and flatulence (passing gas below), which are occasionally severe.

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So, What Causes Someone to Swallow Air?

Aerophagia is commonly a learned behavior, intensified by anxiety. When it is habitual, cognitive behavioral therapy or speech therapy are often effective in controlling the condition.

It may also be that the aerophagia is a result of esophageal stimulation, typically related to gastroesophageal reflux disease (GERD) and hiatal hernia. As such, there may also be associated heartburn, bloating, nausea, early satiety, or abdominal pain, but sometimes belching is the only symptom. If these other, more specific symptoms are present, treating them may also resolve the belching. Excessive belching is typically benign, but belching associated with marked abdominal pain, chest pain, or unintended weight loss should be looked into further, as these may be signs of significant underlying disease.

Other miscellaneous causes include some medications, especially pain medications, laxatives, and drugs that encourage perpetual mouth movement. Also, some activities including drinking through a straw, talking while eating, smoking, sucking on hard candy, and chewing gum can lead to increased aerophagia and belching. CPAP used at night by people with obstructive sleep apnea can pump substantial air into the upper GI tract. Poorly fitting dentures or some ENT surgeries can also stimulate aerophagia.

What, Then, Causes Gastric Belching?

Underlying medical conditions in the upper gastrointestinal tract that can stimulate gastric belching include peptic ulcer disease, gastritis, gallbladder disease, pancreatitis, giardiasis, and Helicobacter infection. Nevertheless, GERD is the most common, even if no heartburn is appreciated. Giardia enjoys a unique characteristic that Peace Corp workers refer to as the "Purple Burps" due to the flavor of the belches. This is often associated with diarrhea and weight loss. Gastric belches are often associated with the flavor or odor of gastric contents.

Is There Any Way to Determine Exactly What Kind of Belching I Have?

Specialized tests, such as esophageal pH, impedance, and manometry can distinguish esophageal from gastric belching as well as from rumination and other esophageal disorders. These techniques, along with 24-hour pH monitoring, are also used to more precisely define GERD severity and mechanism.

If there are any accompanying symptoms to suggest other upper GI issues, these should certainly be evaluated. Often blood tests, upper GI endoscopy (esophagogastroduodenoscopy or EGD), or an imaging study is useful at that point.

So, How Can I Make It Stop?

The first step in therapy is a precise diagnosis. Specifically addressing any underlying cause, most commonly GERD or behavioral, is the most effective way to treat any disorder. You may have noticed that GERD can stimulate either gastric or esophageal belching. Treating for GERD with a proton pump inhibitor, such as Omeprazole, has a very good chance of resolving the symptoms. For esophageal belching unresponsive to GERD therapy, cognitive behavioral therapy or speech therapy has been shown to be effective.

Unfortunately, it is not always possible to define a specific cause. In such cases, empiric treatment should start with the most likely cause. So, if GERD has not yet been specifically treated, a therapeutic trial is certainly worthwhile at this point.

In some cases, Baclofen may be uniquely effective, but Simethicone (Mylacon) does not seem particularly useful, especially for esophageal belching. Biofeedback therapy and hypnosis have been helpful in some reports, but no large-scale trials have confirmed this.

Chronic Hiccups

I Have Been Hiccupping Non-stop for Several Days Now. What's Going On?

Hiccups (also known as "Hiccough" and "Singultus") are a reflex that is hard-wired into our nervous system, just like breathing, swallowing, and vomiting. They can occur in infancy and even in the fetus before birth. The exact purpose is still debated, but the neurologic circuit involved is well defined.

Hiccups are generated in a "Hiccup Center" in the upper spinal cord and an area where the brain connects to the spinal cord called the medulla oblongata. The Hiccup Center coordinates the hiccup through the respiratory center in the brain and through connections to the throat and diaphragm (often only one side of the diaphragm is involved). This "reflex arc" triggers and coordinates an abrupt inspiratory muscle contraction followed within 35 milliseconds by sudden closure of the vocal cords, clamping off the airway. This produces a characteristic "Hic" sound, which virtually all cultures describe with very similar words.

There are many triggers for this reflex. Acute hiccups (an episode of 48 h or less) often have a different set of causes than chronic (persistent or intractable) hiccups, lasting more than 2 days. The most common causes are listed in Table 22.1.

Table 22.1 Causes of hiccups

Causes of acute, benign hiccups	
Esophageal and Gastric distention	Aerophagia, retained food, carbonated drink, rapid gorging
Sudden temperature change	Cold shower, hot/cold food or drink, rapid environmental shift
Intoxication	Alcohol or nicotine
Psychogenic	Emotional stress or sudden psychological shock
Causes of chronic hiccups (persistent and intractable)	
Neurologic	Traumatic, infectious, vascular, multiple sclerosis, Parkinson's, tumor
Toxic/metabolic	Uremia, diabetes, electrolyte abnormalities (esp. Hypocarbia), fever
Drugs/medications	General anesthesia, alpha methyldopa, corticosteroids, benzodiazepines
Irritation, vagal	Pharyngeal, auricular, thoracic, abdominal, or recurrent laryngeal branches (i.e., irritation of almost any internal organ connected to the vagus nerve)
Esophageal	Gastroesophageal reflux disease (GERD), large hiatal hernia, foreign body, tumor
Diaphragmatic	Myocardial infarction, pericarditis, hernia/eventration, abscess, hepatitis
Aerodigestive	Gastric distention, visceral traction, mis-ventilation, glottic stimulation

This Is Really Annoying. How Do I Make It Stop?

By the time someone presents for treatment, they have typically already tried the usual home remedies, Table 22.2. These, however, are often worth reviewing and even trying again in the office. They generally involve little time or risk.

Four randomized controlled trials have demonstrated that acupuncture may be effective, but the best approach, especially for chronic hiccups, is to address any identifiable and treatable underlying condition.

So, How Do We Find This "Underlying Condition"?

It makes sense to start with the most simple, least obnoxious, and least expensive tests, a thorough History and Physical Examination. This will

Table 22.2 Physical (home) remedies for hiccups

Nasopharyngeal stimulation	Vagal stimulation	Respiratory maneuvers
Intra-nasal vinegar or catheter	Cold compress to face	Breath hold (stacked inspiration)
Inhalation of stimulant/irritant	Carotid massage	Re-breathing (hypercapnia)
(e.g., ammonia, "smelling salts")	Induced fright	Valsalva maneuvers
Oropharyngeal stimulation	CPAP-respiration	
(e.g., ice water, granulated sugar)	Induced vomiting	
Strong Traction on the Tongue		

First, clear the esophagus with several gulps of water and encourage belching to decompress the stomach.

Table 22.3 Hiccup workup

History:	Onset, course, timing, aggravating/relieving; PMH, Med/Drugs; ROS/SH/FH
Physical Exam:	Ears, nose, neck, and throat; full chest, abdominal, and neurological
Laboratory:	Basic Chemistry Panel, CBC, CRP, ESR, LFTs; EKG
Imaging:	CT head/chest/abdomen with attn. vagal/phrenic nerve paths
Endoscopy:	Upper GI endoscopy [esophagogastroduodenoscopy (EGD)] with attn. esophagus
Manometry:	Esophageal manometry with 24-h pH and impedance study

guide the ordering of any additional tests. Some of the more common evaluations are listed in Table 22.3.

What Do We Do If We Don't Find a Treatable Cause?

Unfortunately, there is often no clear underlying cause. In that case a good place to start is with an empiric trial of anti-reflux therapy. A proton pump inhibitor (Omeprazole 20 mg twice daily) is easy, safe, and often effective.

Empiric drug treatment for persistent and intractable hiccups usually starts with baclofen and/or gabapentin. If ineffective, chlorpromazine or metoclopramide can be tried. Table 22.4 has a full list of potentially effective pharmaceuticals.

Are Chronic Hiccups Dangerous?

Hiccups by themselves are not usually dangerous. The exception is those patients with endotracheal intubation or a tracheostomy, where airway closure is not possible. Frequent hiccups can then cause hyperventilation.

Given the large number of underlying causes, any real danger is more likely to be related to the cause of the underlying cause than from the hiccups, themselves. As Table 22.1 shows, some causes like aerophagia are important only for their associated hiccups. Other causes, like a brain tumor or multiple sclerosis, are very serious, and hiccups may be the least significant of their symptoms. It is worth noting, however, that it is very rare for one of these more serious underlying causes to present with hiccups as the only symptom. Usually, such diagnoses are well estab-

Table 22.4 Empiric drug therapy for hiccups

Recommended (typical dose/day)	Common and *Serious* side effects
Baclofen (5–20 mg/day)	Sedation, *spasms/fevers with sudden stopping*
Gabapentin (300–600 mg/day)	Sedation, clumsiness/unsteadiness, *liver/kidney problems*
Pregabalin (75–150 mg/day)	Dizziness, blurred vision, sedation, *breathing difficulties*
Second-line	
Metoclopramide (30 mg/day)	Dizziness, diarrhea, neurological (tardive dyskinesia)
Domperidone (30 mg/day)	Neurological, hyperprolactinemia, *long QT syndrome*
Third-line	
Chlorpromazine up to 25–50 mg/day	Dizziness, sedation, neurological, *liver issues*
Other choices	
Carbamazepine, 100–300 mg/day	Blurred vision, neurological, *bad rash, blood/liver issues*
Valproate dose titration to 20 mg/kg/day	Weight gain, neurological, mood*, liver/pregnancy issues*
Phenytoin 100 mg/day	Weight gain, dizziness, neurological, mood
Nifedipine 60–180 mg/day	Dizziness, low blood pressure, headache, mood
Amitriptyline initial 25–100 mg/night	Sedation, constipation, *liver issues, abnormal heartbeat*
Also used: Haloperidol, Marijuana, combination drug treatments (e.g., Omeprazole, Baclofen, Domperidone)	

lished before hiccups appear. Finally, it may be interesting, if not encouraging, to note that no one has ever had hiccups longer than 68 years.

Suggested Readings

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Cyclic Vomiting Syndrome

23

Geoffrey Dang-Vu and Thangam Venkatesan

What Is Cyclic Vomiting Syndrome? Why Did I Get This Disorder? Can I Pass This on to My Children?

Epidemiology and pathophysiology of CVS

Suggested Response to the Patient

Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder where patients experience intense episodes of nausea and vomiting that can last from hours to days. Patients can also have other symptoms such as abdominal pain, sensitivity to light and sound, headaches, drooling, hot and cold flashes, sweating, and diarrhea [1]. There are four phases of CVS: the inter-episodic phase, the prodromal phase, the emetic phase, and the recovery phase [1] (Fig. 23.1).

Patients will typically return to normal health in between episodes. Episodes can occur at any time of the day, but usually start in the middle of the night or early in the morning. Episodes are often triggered by physical and/or psychological stress. This stress can be either positive (holidays or birthdays) or negative such as the death of a loved one or job loss. In women, episodes may occur around the menstrual period and is referred to as catamenial CVS.

The exact cause of CVS is not known but there are several theories that researchers are exploring. CVS is thought to be a functional gastrointestinal disorder (FGID). There are nerves that connect the brain and the gut with the brain functioning like a "supercomputer." Patients with FGIDs have increased sensitivity of the nerves in the gastrointestinal tract (visceral hypersensitivity) where even normal food, fluid, and gas in the gut can provoke pain due to miscommunication between the brain and the gut (malfunction of the brain-gut axis) resulting in symptoms. Recent studies with imaging techniques like functional MRI scans have shown that patients with CVS have alterations in the networks in the brain that are associated with nausea, vomiting, and emotion. There is some evidence that patients with CVS have certain problems with the production of chemicals in the body called endocannabinoids (marijuana-like substances that we all produce in our bodies) that can result in nausea and vomiting.

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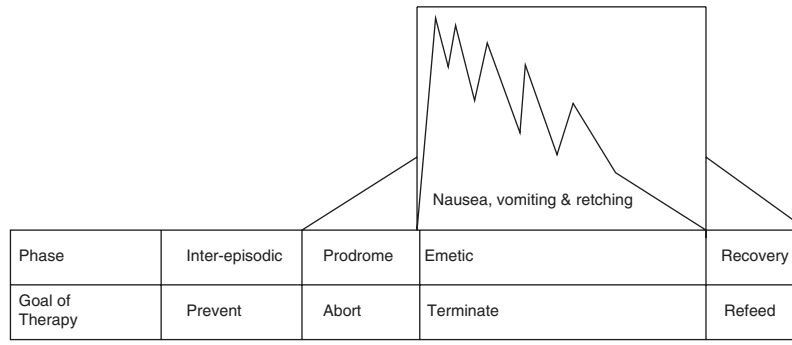

Fig. 23.1 The four phases of CVS with the corresponding goals of treatment are shown. (Reprinted from Fleisher DR, Gornowicz B, Adams K, et al. Cyclic Vomiting Syndrome in 41 adults: the illness, the patients, and problems of management. BMC Med 2005)

Further, dysfunction of genes in the mitochondria (the powerhouses of our cells that help drive energy production) may be associated with CVS in children but this has not been seen in adults [2]. There is no proof that CVS is hereditary though several studies show that various functional disorders like migraine, IBS, and fibromyalgia tend to cluster in families [3–5]. In summary, we do not know what causes CVS but ongoing research has provided us with some clues. Your children may be more predisposed to getting migraines and/or CVS than the general population but there is no definite evidence to prove this.

Brief Review of the Literature

Epidemiology

Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder that was first described in children in 1882 [6]. Initially thought to be a pediatric disorder, it is now being diagnosed increasingly in adults. The prevalence of CVS in children is about 1–2% [7]. The incidence of CVS in Ireland was 3.15 cases 100,000 children per year. The prevalence of CVS in adults has not been systematically studied. CVS affects mostly Caucasians usually in their second and third decade of life and both males and females are affected with some conflicting data on gender preponderance. CVS is also associated with multiple functional disorders such as anxiety, depression, and dysautonomia similar to other FGIDs.

Pathophysiology

The pathophysiology of CVS is unknown; however, mitochondrial DNA polymorphisms and altered endocrine and/or autonomic stress responses have been implicated. CVS has a strong association with migraine headaches with 43% percent of adults having a personal history and 64% a family history of migraine headaches. A strong matrilineal inheritance of both migraines and other functional GI disorders suggests the presence of mitochondrial dysfunction in CVS. This prompted studies that revealed that mitochondrial DNA single nucleotide polymorphisms (mtDNA SNPs) 16,519T and 3010A increased the odds of CVS 17-fold in children with CVS compared to normal healthy subjects [2]. However, the prevalence of these mitochondrial DNA SNPs was not increased in adults with CVS compared to historical controls [4]. These studies did reveal a high degree of matrilineal inheritance of multiple functional disorders in a subset of adults with CVS compared to historical controls. Future studies examining this relationship are warranted.

CVS is thought to be a centrally mediated disorder supported by studies using functional magnetic resonance imaging (fMRI) techniques that showed differences in functional connectivity in areas that are associated with nausea, mood, and

pain processing [8]. There are a number of statistically significant differences in functional connectivity between patients with CVS and healthy controls seen in the right dorsolateral prefrontal cortex, left and right inferior temporal gyrus, and left postcentral gyrus. Nausea network analysis also showed that after emotional stress, there were significant differences observed between patients with CVS and healthy controls in connections between the right premotor area and right middle cingulate cortex and between the right superior temporal gyrus and right perigenual anterior cingulate cortex. These areas are involved in emotion and pain processing and these findings suggest that patients with CVS may have a differential response to stress as opposed to healthy individuals.

Autonomic dysregulation and heightened sympathetic activity have also been implicated in CVS. Sympathetic nervous system dysfunction was seen in 40-90% of patients with CVS with either postural orthostatic dysfunction, sudomotor dysfunction, or both [9]. Rapid gastric emptying, a surrogate marker for autonomic dysfunction, was present in 57% of patients in one study. Rashed et al. and To et al. demonstrated heightened sympathetic cardiovascular tone in patients with CVS. The successful use of dexmedetomidine, an alpha2-adrenergic agonist, to treat CVS corroborates this hypothesis.

Stress is a major trigger for CVS episodes and hypothalamic-pituitary-adrenal (HPA) axis dysfunction has been implicated in CVS. In some patients, increased ACTH and cortisol levels were noted while the patients exhibited hypertension and lethargy. This was first described by Sato and is thought to be a subset of CVS. Tache et al. showed that corticotrophin-releasing factor (CRF) causes gastric stasis and/or emesis in animals [10]. More recently, salivary cortisol and salivary alpha amylase (a surrogate marker for sympathetic nervous system activity) were elevated in patients with CVS who used marijuana during an episode as opposed to nonusers. Approximately 40% of patients with CVS use marijuana to alleviate nausea and anxiety and stimulate appetite. Though the active ingredient in marijuana, Δ^9-tetrahydrocannabinol (THC), has antiemetic properties, chronic marijuana use has been associated with cyclic vomiting [11, 12]. Recently, the Rome Foundation established criteria for cannabinoid hyperemesis syndrome, which has symptoms similar to CVS except for the chronic use of marijuana [13]. Further studies are needed to elucidate the exact relationship between marijuana, the endocannabinoid system and CVS.

What Is Cannabinoid Hyperemesis? I Use Marijuana for My Symptoms, Which Helps with Nausea and Appetite and Reduces My Levels of Stress. Is Marijuana Helpful or Harmful in This Disorder?

The Role of Marijuana and the Endocannabinoid System in CVS

Suggested Response to the Patient

Cannabinoid hyperemesis syndrome (CHS) is a disorder that is thought to be due to chronic marijuana use. This syndrome resembles CVS except for the history of heavy prolonged marijuana use. Patients with this disorder often take very hot showers or baths for relief of symptoms This is referred to as “compulsive hot-water bathing.” It is generally thought that vomiting episodes will get better and resolve with abstinence from marijuana. However, marijuana is stored in the fat cells in the body and with heavy use it can take up to 3 months for this marijuana to be removed completely from the body. Further, patients without marijuana use also report compulsive hot-water bathing making it very difficult to make the diagnosis of CHS.

This is in contrast to studies that show that marijuana helps control nausea and vomiting and stimulates appetite. Many patients also use marijuana to relieve anxiety. One reason for this discrepancy may be that marijuana that is obtained commercially has more than 500 chemicals in it and the concentration of THC in marijuana is very high which could result in it having the opposite effect. So, until further studies are done, it is best that patients with CVS avoid marijuana and discuss alternative options to manage anxiety, nausea, and vomiting.

Brief Review of the Literature

Chronic Marijuana Use and the Role of the Endocannabinoid System in CVS

Cannabinoid hyperemesis syndrome (CHS) is a chronic disorder that .is characterized by recurrent episodes of nausea and vomiting that are indistinguishable from CVS. Experts coined this term based on studies showing an association between cyclic vomiting and chronic marijuana use (for several years). Compulsive hot-water bathing was observed in 72% of patients with chronic pathognomonic of marijuana use. However, this pattren of bathing is not pathognomonic and is reported in 42% of non-marijuana users with CVS. Recently, the Rome Foundation established clinical criteria for making the diagnosis of CHS (Table 23.1) [13].

The cause for the compulsive hot-water bathing pattern is not known but it is proposed that this could be due to the effects of marijuana on the limbic system and thermoregulatory systems in the brain. Chronic marijuana use is seen mostly in young males; a retrospective study of 82 patients with CVS showed that 37% of patients with CVS used marijuana in comparison to 11% in functional vomiting and 13% in irritable bowel syndrome. A recent Internet survey showed that about 80% of patients with CVS used marijuana and reported relief of nausea, vomiting, and anxiety. These patients also stated that it improved appetite and overall well-being [14]. In contrast to these data, which were by patient report, multiple case series report the association of chronic heavy marijuana use with cyclic vomiting. Allen et al. described ten patients who had a pattern of cyclic vomiting and a compulsive hot-water bathing pattern associated with chronic marijuana use [11]. The largest series of cyclic vomiting associated with chronic marijuana use included 98 patients. Follow-up was available only in ten patients of which three (30%) did not abstain from cannabis use and continued to have symptoms. Symptoms resolved in six patients (60%) who stopped using marijuana but the longest duration of follow-up was only 1–3 months [15]. Lack of long-term follow-up is a major limitation of these studies and there is still no clear data that prove causation.

Table 23.1 Rome IV criteria for cannabinoid hyperemesis syndrome

Must include all of the following:
• Stereotypical episodic vomiting resembling cyclic vomiting syndrome (CVS) in terms of onset, duration, and frequency
• Presentation after prolonged excessive cannabis use
• Relief of vomiting episodes by sustained cessation of cannabis use
Supportive remarks
May be associated with pathologic bathing behavior (prolonged hot baths or showers)

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

The diagnosis of CHS can be challenging, as it is often difficult to convince patients to abstain from marijuana especially given its legalization in many states in the USA and purported health benefits. Further, many patients who abstain from marijuana use continue to have CVS episodes. Of historical interest, even Charles Darwin appears to have had CVS and was prescribed hydrotherapy though there is no indication that he used marijuana [16].

The major psychoactive ingredient in marijuana is Δ^9-tetrahydrocannabinol (THC). However, the cannabis plant contains almost 500 different chemicals aside from THC including cannabidiol, cannabichromene, cannabidivarin, and terpenoids. Marijuana that is obtained illegally in the USA, UK, and other countries has almost exclusively THC and seldom other phytocannabinoids. THC binds to two G-protein coupled receptors called cannabinoid receptors 1 and 2 (CB1 and CB2), which are densely distributed in the central and

peripheral nervous system. These receptors are activated endogenously by two ligands called endocannabinoids [*N*-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), which modulate the stress response and play an important role in nausea and vomiting. These ligands, their corresponding receptors, and degrading enzymes are collectively referred to as the endocannabinoid signaling system (ECS). The ECS plays an important role in the modulation of stress, nausea, and vomiting [18]. CB1 agonists inhibit vomiting and CB1-receptor antagonists can cause vomiting. This is in contrast to data that suggests that THC causes cyclic vomiting. One possible explanation could be that chronic THC exposure downregulates and desensitizes CB1 receptors.

A recent study in patients with CVS showed a significant increase in endocannabinoid-related lipids during an episode of CVS, which correlated with poor sleep quality and nausea. The same study also showed a significantly higher salivary cortisol (surrogate for HPA axis activity) and salivary alpha amylase concentration (marker for sympathetic nervous system activity) during an episode of CVS in marijuana users compared to nonusers [18]. These results could be due to a heightened response of the HPA axis and the sympathetic nervous system with chronic marijuana use but it is also possible that marijuana use attenuated the stress response in CVS. Future studies should help clarify the effects of chronic marijuana use and the role of the endocannabinoid system in CVS. This should present us with unique opportunities to develop targeted therapies for CVS.

Do I Need Further Testing, Such as Lab Tests, Imaging or Endoscopic Procedures? Pitfalls in Diagnosis: How to Avoid Unnecessary Testing and Making the Correct Diagnosis

Suggested Response to the Patient

CVS is a clinical diagnosis, meaning that the key to diagnosis is based upon a careful review of the patient's presenting symptoms and clinical history. There are no blood tests or imaging studies that will definitively diagnose CVS. This level of diagnostic uncertainty can understandably be frustrating. Instead, physicians must rule out life-threatening causes of recurring nausea and vomiting such as blockages in the gastrointestinal tract, twisting or rotation of the intestines, masses in the brain, along with disorders of the pancreas that can mimic CVS.

In order to rule out these disorders, basic laboratory tests to assess liver and kidney function, upper endoscopy (EGD) and routine imaging of the abdomen are usually performed. If they return normal and symptoms are consistent with CVS, further diagnostic testing is generally not required and treatment for CVS should be initiated.

Further genetic testing or in-depth testing for hormonal disorders or disorders of metabolism need not be performed unless there is a high index of clinical suspicion, or if there is no response to therapy. Typically these types of metabolic disorders affect children at a younger age. Clues to such metabolic disorders are episodes, which are always precipitated by fasting, intercurrent illness, or a high-protein meal [19]. If these symptoms are present, appropriate workup with blood and urine tests and referral to a metabolic specialist may be indicated. Imaging of the brain is usually not necessary unless neurologic symptoms or abnormal physical exam findings are present or if there is a history of trauma to the head.

Brief Review of the Literature

As with other functional GI disorders, there are no biochemical markers to make a diagnosis of CVS. The diagnosis of CVS is based on the Rome IV criteria for CVS and is included in Table 23.2 [13].

The Rome IV criteria differ from Rome III in that a provision was made to include patients with a coalescent pattern of symptoms. Patients usually return to normal health in between episodes but in some instances can coalesce with nausea and dyspepsia in between episodes. It is important to recognize this phenomenon and

Table 23.2 Rome IV criteria for cyclic vomiting syndrome

• Stereotypical episodes of vomiting regarding onset (*acute*) and duration (*less than 1 week*)
– Abrupt in onset
– Occurring at least 1 week apart
• 3 or more discrete episodes in the prior year
– Two episodes in the past 6 months
– Absence of nausea and vomiting between episodes
– But other milder symptoms can be present between episodes
• No metabolic, gastrointestinal, central nervous system, structural, or biochemical disorders

obtaining a careful history is vital in making an accurate diagnosis.

The differential diagnosis for CVS is quite broad ranging from structural, metabolic, and endocrinologic diseases. Such considerations include anatomic obstruction (malrotation with intermittent volvulus), intermittent small bowel obstruction, peptic ulcer disease, pancreatitis, intestinal pseudo-obstruction, intracranial mass, hyperemesis gravidarum, cannabinoid hyperemesis, disorders of fatty acid oxidation, urea cycle defects, acute intermittent porphyria, diabetes with ketoacidosis, and Addison's disease. The majority of these conditions in adults are quite rare, and assaying for each and every one of them should be avoided except when clinical suspicion is high. Indications for a more extensive workup include an abnormal neurological exam, attacks precipitated solely by fasting, intercurrent illness and a high-protein diet suggesting metabolic disorders, a family history of metabolic disorders, or nonresponse to adequate therapy for 3–6 months.

There is a lack of data on the most effective approach in diagnosing CVS. One study in children based on a decision analysis showed that an Upper GI small bowel follow through plus empiric therapy was the most cost-effective initial strategy to treat CVS [20]. Exhaustive evaluations are generally unlikely to yield an alternative diagnosis and should be avoided.

It is the practice of the author, based on available evidence and expert consensus, to obtain basic laboratory tests: complete blood count, electrolytes, blood urea nitrogen, creatinine, hepatic panel, and a pregnancy test. An EGD and either a CT scan or UGI series with a small bowel follow through are also obtained to ensure patency of the gastrointestinal tract. Many patients with CVS have rapid gastric emptying rather than delayed gastric emptying. A common pitfall leading to an erroneous diagnosis of gastroparesis instead of CVS occurs when a gastric emptying study is obtained during an episode of CVS. If gastric emptying studies are performed, they should be done at baseline and in accordance with guidelines established by the American Neurogastroenterology and Motility Society (ANMS) [21]. In summary, a thorough clinical history along with basic tests such as an EGD and an abdominal CT scan/ultrasound should be sufficient to make a diagnosis of CVS. Empiric therapy should be initiated and further testing is indicated when patients either fail to respond to treatment or have clinical signs or symptoms that indicate an alternate diagnosis.

How Do You Treat This Condition? Are There Any Prescription or Over-the-Counter Medications That Will Help Me? Management of CVS Using a Biopsychosocial Model

Suggested Response to the Patient

CVS is best treated with what we refer to as a biopsychosocial approach. This means that in addition to medications, both physicians and patients should work together to address any psychosocial barriers to health. Treatment of CVS must be tailored depending on how frequent or severe episodes are. The primary goal is to prevent symptoms from occurring in the first place. If symptoms are manageable and rarely noticeable except for rare times of extreme distress, only "abortive therapy" may be needed. Abortive medications are used to stop an episode of nausea and vomiting. These medications are most effective when administered as early as possible in the prodromal phase of the illness. Prophylactic

therapy or medications to prevent episodes from occurring are started if patients have frequent and/or severe episodes that interfere with activities of daily living. Preventative medications are recommended to reduce the frequency and severity of episodes and restore the patient's ability to return to normal function. Lifestyle changes and treatment for any other concurrent problems such as anxiety and depression that are often associated with CVS is key to improving overall quality of life.

Because of its close relationship to migraine headaches, CVS is treated with medications that are used for migraine headaches. The most effective medication in CVS thus far is amitriptyline, which is a tricyclic antidepressant. Even though it is in an "antidepressant," the effect on CVS is thought to be independent of its antidepressant effects. The dose of amitriptyline that is used in CVS is also much lower than that used to treat depression. Amitriptyline has been shown to reduce the frequency and severity of CVS episodes in different studies. Anti-seizure medications (Topiramate) and less frequently beta-blockers (propranolol) are also used to prevent episodes.

There is some evidence to suggest that CVS is due to mitochondrial disorders, and over-the-counter supplements like Coenzyme Q 10 and L-Carnitine are thought to improve mitochondrial function. Mitochondria are the "power houses" in the cells in the body and it is thought that CVS may be the result of an energy crisis because of mitochondrial dysfunction. However there are insufficient data to prove this and researchers are actively working to see how this is involved in CVS. A few small studies have shown that mitochondrial supplements reduce the frequency and severity of CVS and improve the level of energy in patients.

Abortive therapy is used to prevent episodes when patients feel an episode coming on and before patients vomit. Commonly used abortive medications are ondansetron, compazine, aprepitant, diphenhydramine, and sumatriptan. These medications are used to treat nausea and vomiting. Sedatives can help patients sleep during an episode and terminate the episode. These medications are usually given in combination and can completely stop symptoms and prevent progression to a full-blown episode. Sometimes, these measures may not work and patients will need to be seen in an emergency department/infusion clinic or admitted directly to the hospital for further management.

Lastly, lifestyle modifications cannot be overemphasized. Identification and avoidance of triggers is paramount to reduce the frequency of episodes. Certain triggers include excitement, low-energy states (fasting, illness, etc.), sleep deprivation, and foods (chocolate, cheese). In general, it is also helpful to maintain good sleep hygiene, perform regular exercise, keep regular meal schedules, and abstain from marijuana use. Stress management is also very important and seeing a psychologist and incorporating various relaxation therapies such as yoga and meditation can help control symptoms.

Brief Review of the Literature

The treatment of CVS as with other functional GI disorders should be managed using a biopsychosocial approach. Therapy consists of pharmacotherapy to manage episodes of nausea and vomiting, treatment of comorbid conditions such as anxiety and depression, and addressing psychosocial factors that may be contributing to poor quality of life that is often seen in CVS patients. Prophylactic therapy should be considered if patients have: (1) frequent and severe episodes, (2) multiple emergency department visits and hospitalizations, or (3) symptoms that interfere with activities of daily living. Tricyclic antidepressants are considered first-line treatment for prophylaxis of CVS. This is based on mostly retrospective studies, open label trials, and expert consensus and there are no randomized control trials supporting its use. An open label trial with 41 patients showed an 80% improvement in clinical status by subjective global assessment. There was also a significant reduction in both frequency and duration of episodes and a reduction in ED visits over a two-year period. Side effects were seen in 34% of patients and included dryness of mouth, somnolence, fatigue, constipation, and

mild hallucinations but patients were able to continue the treatment at the same dose or with dose reduction [22]. A retrospective study of 101 patients found that 86% had either a partial or complete response to treatment with use of tricyclic antidepressants, topiramate, and/or mitochondrial supplements [23]. Almost 25% of patients had side effects and needed to stop TCAs. Nonresponse to treatment was associated with chronic marijuana use, chronic opiate use, coexistent psychological disorders, and noncompliance.

Anticonvulsants such as topirmate are also used as prophylactic therapy, despite the lack of controlled clinical trials in CVS. The justification for its use has been its efficacy in migraine headaches. Topiramate was effective either alone or in conjunction with TCAs in a retrospective study involving 101 patients. Another study with 20 patients showed that 75% of patients responded to zonisamide (median dose of 400 mg/day) or levetiracetam (median dose of 1000 mg/day); 20% of these patients achieved complete clinical remission [24]. Mitochondrial supplements such as coenzyme Q 10, L-carnitine, and vitamin B2 are also used in CVS based on retrospective studies demonstrating efficacy [25]. These supplements have not been associated with any significant side effects and can anecdotally improve energy and overall well-being in patients. Medications commonly used as prophylactic treatment for CVS are shown in Table 23.3.

Abortive therapy is most effective when administered during the prodromal phase of a CVS episode, akin to migraine headaches. Sumatriptan, a 5-HT1 antagonist, resulted in resolution of symptoms in 56.8% of patients. Other medications that are recommended include antiemetics such as phenothiazines, 5-HT 3 antagonists like ondansetron and benzodiazepines for sedation. Used in combination, these can avert an episode and allow the patient to return to normal health. More recently, aprepitant, an NK1-receptor antagonist, was effective as a prophylactic agent in 76–81% of children who were placed on weekly therapy. Aprepitant is used for prevention of nausea and vomiting in chemotherapy-induced nausea and vomiting (CINV). While aprepitant is available for oral use, its intravenous form, fosaprepitant has also been approved for use in CINV but not in CVS. Medications used to abort CVS episodes are shown in Table 23.4.

In instances when prophylactic and abortive therapy fail and patients have an acute episode of CVS, management is largely symptomatic. A quick history and examination should be sufficient to ensure that symptoms are not due to any other intercurrent medical emergency. In general, intravenous fluids containing dextrose, antiemetics, and sedatives are administered. Often, opiates such as hydromorphone may be necessary to control the severe pain that can be present but should be carefully monitored given the risk of dependence and addiction with frequent use. In addition, allowing the patient to rest in a quiet, dark room and minimizing interruptions by staff is recommended. Unnecessary and repeated investigations such as CT scans, abdominal X-rays, and EGDs should be avoided as they are mostly noncontributory and are ineffectual in management.

In summary, reassurance of patients and families of the benign nature of the condition, prompt diagnosis and treatment, and education of patients, families, and referring physicians about CVS should be instrumental in improving overall patient outcomes.

Resources for Patients and Families

1. Cyclic Vomiting Syndrome Association (CVSA)

   PO Box 270341
   Milwaukee, WI 53227
   Phone 414 342–7880
   Email: cvsa@cvsaonline.org
   Website: cvsaonline.org

2. Links for patients

   NIH Cyclic Vomiting Syndrome
   E Medicine CVS

Table 23.3 Prophylactic medications used in CVS

Tricyclic antidepressants			
Medication	Dosage[a]	Side effects	Other comments
Amitriptyline	Start at 25 mg at night Titrate by 10 mg every 5 days to a target dose of 75–100 mg.	Weight gain (less with nortriptyline) Sedation (improves after 8–12 weeks) Constipation	QT_C prolongation (monitor with EKG) Obtain baseline EKG and repeat during dose titration and after target dose is reached.
Nortripyline, desipramine and imipramine may also be used		Xerostomia Urinary retention Blurred vision Bad dreams Mood changes Serotonin syndrome (rare)	Use cautiously in cardiac disease (myocardial infarction or conduction abnormalities) Avoid with concurrent use of Monoamine Oxidase Inhibitors within 14 days **Black box warning:** Suicidal ideation if patient has severe depression, usually within 2 weeks of initiation (*not reported in CVS*)
Antiepileptics			
Topiramate	Start at 25 mg at night Increase by 25 mg every week with target dose of 100 mg. May increase further if no response. May check levels to guide therapy	Cognitive dysfunction, difficulty with memory, speech, language Sedation Renal stones Paresthesias Diarrhea Acidosis	Contraindicated in patients with nephrolithiasis Cautious use in patients with glaucoma can cause acute myopia, discontinue with decrease in visual acuity or ocular pain Caution in patients with hepatic disease Check bicarbonate levels every 6 months
Zonisamide	Start with 100 mg daily Median effective dose (400 mg/day in divided doses)	Mental confusion	Aggressive behavior may improve with dose reduction Increased suicidal ideation may occur with use
Levetiracetam	1000 mg/day in divided doses		May increase risk of kidney stones
NK1 receptor antagonists			
Aprepitant kit			
(contains a 125 mg pill and two 80 mg pills)	One kit weekly 125 mg on day 1 and 80 mg on day 2 and day 3 of each week	Fatigue Alopecia Constipation Headache Hypersensitivity reactions including anaphylaxis have been reported (<0.5%)	Side effects are uncommon Very expensive; insurance may not cover for off-label use in CVS

(continued)

Table 23.3 (continued)

Tricyclic antidepressants			
Medication	Dosage[a]	Side effects	Other comments
Mitochondrial supplements			
Coenzyme Q 10	200 mg twice daily	Abdominal discomfort Headache	Caution in patients with soy allergy
L-Carnitine	330 mg three times daily (Max 1 g TID)	Fishy Odor Diarrhea Abdominal discomfort	Caution in patients with seizure disorder

[a]Denotes usual dose used in adults

Table 23.4 Medications used as abortive therapy in CVS

5-HT1 agonist			
Medication	Dosage[a]	Side effects	Other comments
Sumatriptan			
(Intranasal or IM)	Single dose 20 mg intranasal (can be repeated after 2 h), not to exceed 40 mg daily	Dizziness Paresthesia Unpleasant taste Chest discomfort or pressure	Contraindicated in ischemic heart disease, stroke, peripheral vascular disease, uncontrolled hypertension Do not use within 14 days of discontinuing MAO inhibitor Alternative medications such as zolmitriptan, frovatriptan and rizatriptan may be used
NK1-receptor antagonists			
Aprepitant (PO)	125 mg day 1, 80 mg day 2 and 3	Fatigue Alopecia Constipation Headache Hypersensitivity reactions including anaphylaxis have been reported (<0.5%)	Very expensive, insurance may not cover as it is for off-label use in CVS
5-HT3 receptor antagonists			
Ondanstetron (PO, ODT, or IV)	8 mg every 8–12 h	QT_C prolongation Headache Malaise Drowsiness Serotonin syndrome when combined with SSRI, SNRI, MAOi,	Obtain baseline EKG and careful dosing if $QT_C > 440$ in males or >460 in females
H1-Receptor antagonists			
Diphenhydramine (PO or IV)	25 every 6–8 h	CNS depression (sedation, confusion) Anticholinergic side effects: constipation, xerostomia, urinary retention, blurred vision	Use with caution in patients with glaucoma and BPH, as well as the elderly Use with caution in patients with ischemic heart disease and hypertension

(continued)

Table 23.4 (continued)

Benzodiazepines			
Lorazepam (PO or IV)	0.5–2 mg every 4–6 h as needed	CNS Depression Anterograde amnesia Respiratory depression Hypotension Paradoxical aggression in elderly	Use cautiously as they can result in dependence Chronic use can lead to acute withdrawal symptoms upon discontinuation
Dopamine, Alpha-adrenergic and H1 receptor antagonist			
Promethazine (PO or IV)	12.5-25 mg every 4–6 h as needed	CNS Depression Bradycardia Extrapyramidal symptoms Anticholinergic symptoms Rare cause of Neuroleptic Malignant syndrome QTC prolongation	IV administration can cause severe tissue injury including burning, gangrene or thrombophlebitis Use cautiously in patients with glaucoma and benign prostate hypertrophy
Dopamine antagonist			
Prochlorperazine (PO, IV or suppository)	5–10 mg PO or IV every 6–8 h not to exceed 40 mg/day. 25 mg Suppository every 12 h	CNS Depression Anticholinergic symptoms (constipation, xerostomia, blurred vision, urinary retention) Leukopenia, agranulocytosis, neutropenia Extrapyramidal symptoms Rare cause of Neuroleptic Malignant syndrome	Caution in patients with history of drug-induced leukopenia or neutropenia Cautious use in patients with hypertrophy

[a]Denotes usual dose used in adults

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Gastroparesis, Postprandial Distress

24

Henry P. Parkman

Common Patient Asked Questions

My Recent Gastric Emptying Test Was Normal, Though It Was Delayed in the Past and I Was Told I Had Gastroparesis. What Do I Have?

Gastric emptying testing is needed to diagnose gastroparesis. The standard gastric emptying test is gastric emptying scintigraphy, which uses a radiolabeled isotope bound to solid food to image the meal emptying. However, there is variable methodology used at different centers. Standardization of gastric emptying among different centers has been suggested using a 4 h imaging protocol with scans taken 0, 1, 2, 4 h after ingestion of a radioactive Tc-99m-labeled low-fat egg white with jam and two pieces of toast. The shorter duration tests lasting 60–90 min using different meals are not as helpful. Relatively high variability in gastric emptying constitutes another limitation of gastric motor testing. Unfortunately, gastric emptying rates measured by gastric motor testing do not correlate well with symptoms of gastroparesis. Patients can have severe nausea and vomiting with normal gastric emptying. These patients also represent a significant medical problem and are, for the most part, indistinguishable from those with gastroparesis. These findings suggest that factors in addition to slow gastric emptying contribute to symptoms.

My Abdominal Pain Is Still Present and Getting Worse. My Prior Gastroenterologist Gave Me Percocet for the Abdominal Pain. What Will You Do?

Abdominal pain in gastroparesis is a difficult symptom and a difficult symptom to treat. The classic teaching is to look for other causes of abdominal pain in patients with gastroparesis who have abdominal pain. This can entail evaluation for gallbladder or pancreatic causes of abdominal pain. Other causes may include functional dyspepsia, irritable bowel syndrome, and visceral hyperalgesia. Nevertheless, some studies show that moderate to severe abdominal pain is prevalent in gastroparesis (66% of patients), impairs quality of life, and is associated with idiopathic etiology. The abdominal pain does not correlate with the delayed gastric emptying. Pain has largely been ignored in gastroparesis; its cause is unknown. The presence of abdominal

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pain unfortunately is a poor predictor of a good improvement in overall gastroparesis symptoms. Abdominal pain can be difficult to treat. Narcotic analgesics can delay gastric emptying as well as also provoke symptoms of nausea and vomiting. They are best to be avoided. Symptom modulators, such as low dose tricyclic antidepressants, are often tried.

Can My Gastroparesis Be Cured?

Symptoms of gastroparesis may be constant or they may fluctuate with worsening periods. The medications used for gastroparesis are designed to bring the symptoms under better control. Controlling glucose in diabetic gastroparesis may also help improve symptoms. In all patients, dietary management is important and nutritional consultation may be helpful. It has been suggested that idiopathic gastroparesis of acute onset with infectious prodrome could constitute postviral or viral injury to the neural innervation of the stomach or the interstitial cells of Cajal in the stomach. In some series, patients with postviral gastroparesis improve over time, generally several years.

I Have Joined an Online Chat Room for Gastroparesis. Many of the Patient Have Received Botox for Their Gastroparesis with Good Results. Is This Something That Will Help Me?

Several studies have tested the effects of pyloric injection of botulinum toxin in patients with diabetic and idiopathic gastroparesis. Endoscopic treatment entails injection of botulinum toxin (Botox; Allergan, Inc) into the pyloric sphincter. Initial studies were unblinded in small numbers of patients from single centers and observed mild improvements in gastric emptying and modest reductions in symptoms for several months. Two double-blind studies have been reported; these show an improvement in gastric emptying, but no effect on symptoms compared to placebo. Thus, botulinum toxin injections do not result in sustained improvement in symptoms of gastroparesis. Some patients though do seem to improve. Identifying who these patients are is the subject of current research. If botox injection helps symptoms, it generally lasts 3–6 months. Other treatments such as pyloromyotomy may be longer lasting.

My Doctor Told Me Not to Take Metoclopramide Due to Its Side Effects and Referred Me to You for Treatment. What Will You Do?

Metoclopramide (Reglan) is a dopamine type 2 receptor antagonist both in the CNS and in the stomach. Metoclopramide exhibits both prokinetic and antiemetic actions. It has been the mainstay of treatment of gastroparesis. The prokinetic properties of metoclopramide are limited primarily to the stomach. Reglan can cause both acute and chronic CNS side effects in some patients. These side effects should be discussed with the patient prior to treatment and documented in the patient's medical record. In the United States, metoclopramide is approved for diabetic gastroparesis for up to 12 weeks duration. Patients with gastroparesis have chronic nausea and often need longer periods of treatment. If used, the dose is usually limited to 10 mg four times a day, for several months. Domperidone has similar effects to metoclopramide and has less central side effects than Reglan. Domperidone may well help symptoms of gastroparesis. It does have some cardiac side effects. Since it is not fully approved, patients need to pay themselves for this medication.

Introduction

Gastroparesis is a chronic symptomatic disorder of the stomach manifested by delayed emptying without evidence of mechanical obstruction [15]. This classic motility disorder of the stomach can lead to marked dysfunction in patients with poor

quality of life. Although in many patients symptoms can be controlled with medical therapy, some patients remain markedly symptomatic with progressive weight loss. This chapter provides an overview of gastroparesis and updates the present status of our understanding of this disorder and the treatments available.

Epidemiology

Gastroparesis occurs more often in women than men. Interestingly, this is true for each of the three main forms of gastroparesis: idiopathic, diabetic, and even postsurgical. The epidemiology of gastroparesis, however, has not been well systematically studied. This stems from the fact that for proper diagnosis, a gastric emptying test is needed, one that is difficult in population studies. Data from the Rochester Epidemiology Project, a database of linked medical records of residents of Olmsted County, Minnesota, show that the age-adjusted incidence of definite gastroparesis per 100,000 person-years for the years 1996–2006 was 9.8 for women and 2.4 for men [16]. Definite gastroparesis was defined as diagnosis of delayed gastric emptying by standard scintigraphy and symptoms of nausea and/or vomiting, postprandial fullness, early satiety, bloating, or epigastric pain for more than 3 months. The age-adjusted prevalence of definite gastroparesis per 100,000 persons was 37.8 for women and 9.6 for men. More recent estimates have suggested that these prevalence of gastroparesis were an underestimation and the prevalence is greater, being approximately 1.8% of the general population [17].

The prevalence of gastroparesis might be increasing. Data from the US Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS), a nationally representative sample of 5–8 million hospitalizations per year, show that, from 1995 to 2004, hospitalizations with gastroparesis as the primary diagnosis increased by 158% and those with gastroparesis as the secondary diagnosis increased by 136% compared with a 13% increase in all hospitalizations [18]. The increase in hospitalization rate for gastroparesis has occurred since the year 2000, and could reflect increasing prevalence and/or the effects of heightened awareness about and better identification of gastroparesis [18]. This increase in gastroparesis hospitalizations may also be due, in part, to the increasing rate of diabetes leading to more cases of diabetic gastroparesis, withdrawal of some gastroparesis treatments from the market (cisapride, tegaserod) with hospitalizations for symptoms not adequately being treated, and hospitalizations needed for insertion of the gastric electric stimulator.

Symptoms

Common symptoms of gastroparesis include nausea (>90% of patients), vomiting (84% of patients), and early satiety (60% of patients) [19]. Other symptoms include postprandial fullness and abdominal pain [20, 21]. Symptoms can be persistent or can manifest as episodic flares. Weight loss, malnutrition, and dehydration may be prominent in severe cases. Although weight loss is classically described in gastroparesis, some patients can be overweight, especially patients with T2DM. In diabetics, gastroparesis may adversely affect glycemic control with both hypoglycemia and hyperglycemia.

Symptom profile can be established and symptom severity assessed with the Gastroparesis Cardinal Symptom Index (GCSI), a subset of the Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM) [22]. The GCSI comprises three subscales (nausea and vomiting, postprandial fullness and early satiety, and bloating) that the patient scores with reference to the preceding 2 weeks [22]. A variant on the GCSI, the GCSI daily diary (GCSI-DD) can be used to record symptoms on a daily basis and may be more accurate in recording symptoms [23]. The daily diary assesses severity of nausea, early satiety, postprandial fullness, and upper abdominal pain as well as records the number of episodes of vomiting. A composite score can be calculated for overall severity of gastroparesis. This GCSI can be used to assess individual symptoms which may then be individually targeted for treatment.

Single symptom approaches to treatment may be more feasible than attempts at global symptom improvement for gastroparesis.

Although it has been a common assumption that the gastrointestinal symptoms can be attributed to delay in gastric emptying, most investigations have observed only weak correlations between symptom severity and the degree of gastric stasis. In general, the symptoms that appear to be best correlated with a delay in gastric emptying include nausea, vomiting, early satiety, and postprandial fullness [24, 25]. Some symptoms that have been present in patients with gastroparesis such as bloating and upper abdominal pain are not correlated with delayed gastric emptying and might be related to sensory alterations that might also be present in patients with gastroparesis. Accelerating gastric emptying by itself may not lead to successful treatment of all gastroparesis symptoms.

Etiology

Major etiologies of gastroparesis are diabetic, postsurgical, and idiopathic [15, 26, 27]. Less common causes of gastroparesis include connective tissue disease, neurologic disease such as Parkinson's disease, eating disorders, metabolic or endocrine conditions (hypothyroidism), critical illness, and medications such as opiates and anticholinergics [26]. In addition, GP-1 analogs, such as exenatide, used for treatment of type 2 diabetes mellitus can delay gastric empting [15].

Gastroparesis is a relatively common complication of diabetes: delayed gastric emptying has been found to occur in approximately 40% of patients with long-standing type 1 diabetes and approximately 20% of patients with type 2 diabetes [26, 27]. These estimates though are from academic medical centers and true estimates appear to be lower in the general population in patients seeing primary care physicians. In the Rochester Epidemiology project, cumulative incidence of developing gastroparesis was found to be 5.1% in type 1 diabetes mellitus (T1DM) and 1.0% in type 2 diabetes mellitus (T2DM) patients [28].

In diabetic patients in the NIH Gastroparesis Consortium Registry, baseline symptoms were similar in T1DM and T2DM patients, even though T1DM patients had worse gastric emptying delays and higher HbA1c [29]. Diabetic gastroparesis is often attributed to chronic hyperglycemia-induced damage to the vagus nerve, and is frequently observed in association with other diabetic complications such as neuropathy, retinopathy, and nephropathy. Enteric pathology may also exist in diabetic gastroparesis including loss of interstitial cells of Cajal (the pacemaker cells), loss of nitric oxide-containing nerves, and presence of an inflammatory infiltrate. Glucose can modify gastric emptying tests and symptoms: hyperglycemia can delay gastric emptying and worsen symptoms of gastroparesis, whereas hypoglycemia may accelerate gastric emptying.

Postsurgical gastroparesis can occur with many types of operations but is most often observed after upper abdominal procedures because of injury or sectioning to the vagus nerve [15]. In the past, surgery for peptic ulcer disease such as antrectomy with vagotomy was associated with the development of gastroparesis. However, this type of surgery is less often being performed due to the use of proton pump inhibitor treatments of ulcers and treatment for helicobacter pylori. Presently, Nisson fundoplication is probably the more common surgical procedure associated with gastroparesis [30]. Bariatric surgeries and pancreatic surgery have also been associated with gastroparesis.

Idiopathic gastroparesis, with no obvious cause for the gastroparesis, is a common classification for gastroparesis. Characteristics of 243 patients with idiopathic gastroparesis enrolled in the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium Registry were recently characterized based on medical histories, symptoms questionnaires, and gastric emptying scintigraphy [31]. Patients' mean age was 41 years, and the majority (88%) were female. Half (50%) had acute onset of symptoms. The most common presenting symptoms were nausea (34%), vomiting (19%), and abdominal pain (23%). Severe

delay in gastric emptying (>35% retention at 4 h) was present in 28% of patients. Severe delay in gastric emptying was associated with more severe symptoms of nausea and vomiting and loss of appetite compared with patients with mild or moderate delay. 86% of these patients with idiopathic gastroparesis met criteria for functional dyspepsia, predominately postprandial distress syndrome. Thus, idiopathic gastroparesis is a heterogeneous syndrome that primarily affects young women and often affects overweight or obese individuals.

A minority of patients with idiopathic gastroparesis (19% in the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium Registry study above (17)) report an initial infectious prodrome such as gastroenteritis or respiratory infection. It has been suggested that idiopathic gastroparesis of acute onset with infectious prodrome could constitute postviral or viral injury to the neural innervation of the stomach or the interstitial cells of Cajal in the stomach. In some series, patients with postviral gastroparesis improve over time, generally several years.

Pathophysiology

Gastric emptying is mediated by the vagus nerve, which helps regulate fundic accommodation, antral contraction, and pyloric relaxation [15]. These regional gastric motility changes with food ingestion are then mediated through smooth muscle cells, which control stomach contractions; interstitial cells of Cajal, which regulate gastric pacemaker activity; and enteric neurons, which initiate smooth muscle cell activity [15]. The pathophysiology of gastroparesis has not been fully elucidated but appears to involve abnormalities in functioning of several elements including autonomic nervous system, smooth muscle cells, enteric neurons, and interstitial cells of Cajal. Histologic studies demonstrate defects in the morphology of enteric neurons, smooth muscle cells, and interstitial cells of Cajal and increased concentrations of inflammatory cells in gastric tissue [15, 26, 31].

Diagnosis

Differential diagnosis of gastroparesis entails excluding other possible causes including peptic ulcer disease, gastric outlet obstruction, neoplasm, and small bowel obstruction [26]. For evaluation of these, an upper endoscopy is performed.

For evaluating gastric emptying, the standard test is gastric emptying scintigraphy, which uses a labeled isotope bound to solid food to image gastric emptying [26, 32]. There is variable methodology used at different centers. Standardization of gastric emptying among different centers has been suggested using a 4 h imaging protocol with scans taken 0, 1, 2, 4 h after ingestion of a radioactive Tc-99m-labeled low-fat egg white with jam and two pieces of toast [33].

Use of the wireless motility capsule to quantify luminal pH and pressure is an alternative to gastric emptying scintigraphy [26]. Gastric emptying is manifested by a sharp increase in pH representing the capsule passing from the acidic stomach to the alkaline small intestine [34]. Using a 5 h cutoff for gastric emptying, the capsule discriminated between normal or delayed gastric emptying with a sensitivity of 0.87 and a specificity of 0.92. This test also measures whole-gut transit—that is, gastric emptying, small bowel transit, and colonic transit. Colonic transit abnormalities has been reported in 18% of patients with gastroparesis, possibly suggesting a more diffuse GI motility disorder and it could be contributing to symptom presentation [35].

Breath tests for gastric emptying, another alternative to gastric emptying scintigraphy, measure labeled nonradioactive 13-CO_2 in exhaled breath samples after ingestion of a 13-CO_2-labeled meal. Breath samples are obtained periodically over several hours. The exhaled 13-CO_2 represents the gastric emptying, duodenal absorption, hepatic metabolism, and pulmonary excretion where gastric emptying is the rate limiting step [32]. Findings generally correlate well with results of gastric emptying scintigraphy. This test has been used clinically in Europe for years, whereas in the United States, a breath test for gastroparesis

had been generally used for research studies, but is now available for clinical practice [36].

Gastric emptying testing is useful in diagnosing gastroparesis. There are several drawbacks. First, gastric emptying rates measured by gastric motor testing generally correlate poorly with symptoms and quality-of-life impact of gastroparesis [37, 38]. Patients can have severe nausea and vomiting with normal gastric emptying [38]. These patients also represent a significant medical problem and are, for the most part, indistinguishable from those with gastroparesis. Chronic nausea from any gastrointestinal cause is a large unmet need regardless of the cause. These findings suggest that factors in addition to slow gastric emptying contribute to symptoms. Relatively high interindividual and intraindividual variability in gastric emptying rates measured with gastric motor testing constitutes another limitation of gastric motor testing [26]. The relative contributions to these variabilities of gastric motor testing methodology and biologic inconsistency in gastric emptying are not currently known.

Management

Management of gastroparesis is guided by the goals of correcting fluid, electrolyte, and nutritional deficiencies; identifying and treating the cause of delayed gastric emptying (e.g., diabetes); and suppressing or eliminating symptoms [15]. Care of patients generally relies on dietary modification, medications that stimulate gastric motor activity, and antiemetic drug therapy.

The outcome of patients with gastroparesis has not been well characterized. It is often felt by clinicians to be a difficult disorder to treat, reflecting the paucity of medications that are available for this condition. The outcome of gastroparesis patients were assessed in the NIH Gastroparesis Consortium in patients with either diabetic or idiopathic gastroparesis [39]. Surprisingly, only 28% of 262 patients symptomatically improved at 48 weeks as determined by a decrease GCSI $\geq$1. This illustrates the chronic nature of gastroparesis and that the disease burden remains high. Predictors for improvement included more severe gastroparesis symptoms, more severe delay in gastric emptying, and an initial infectious prodrome. Predictors for a poor improvement included moderate/severe abdominal pain and being overweight.

Dietary Treatment

Dietary measures entail adjustment to meal composition and frequency [15, 26]. Eating small meals is recommended as patients often have early satiety, that is feeling full when eating a normal size meal; in addition, larger meals may alter gastric emptying times. Consuming mainly liquids such as soups can be useful as gastric emptying of liquids is often preserved in patients with gastroparesis [15]. Avoidance of fats and indigestible fibers is recommended because they delay gastric emptying [15, 26]. When small meals are used in the gastroparesis diet, more frequent meals, 3 meals per day plus 2 snack-type meals, are often needed to maintain caloric intake. These dietary recommendations have often been made empirically as to effects on gastric emptying [40, 41]. Recently, these have been looked at in respect to symptom generation. A high-fat solid meal significantly increased overall symptoms among individuals with gastroparesis, whereas a low-fat liquid meal had the least effect [42]. With respect to nausea, low-fat meals were better tolerated than high-fat meals, and liquid meals were better tolerated than solid meals. These data provide support for recommendations that low-fat and increased liquid content meals are best tolerated in patients with symptomatic gastroparesis. Another study assessed patient tolerances to foods [43]. Foods provoking symptoms were generally fatty, acidic, spicy, and roughage-based. Foods worsening symptoms included: orange juice, fried chicken, cabbage, oranges, sausage, pizza, peppers, onions, tomato juice, lettuce, coffee, salsa, broccoli, bacon, and roast beef. The foods that were generally tolerable were generally bland, sweet, salty, and starchy. Saltine crackers, jello, and graham crackers

moderately improved symptoms. Twelve additional foods were tolerated by patients (not provoking symptoms): ginger ale, gluten-free foods, tea, sweet potatoes, pretzels, white fish, clear soup, salmon, potatoes, white rice, popsicles, and applesauce.

Many patients with gastroparesis have diets deficient in calories, vitamins, and minerals. Unfortunately, nutritional consultation is obtained infrequently but this is suggested for dietary therapy and to address nutritional deficiencies [44].

Glucose Control in Diabetic Patients

Diabetic patients with gastroparesis frequently exhibit labile blood glucose concentrations with prolonged periods of significant hyperglycemia. Hyperglycemia itself can delay gastric emptying. Hyperglycemia can counteract the accelerating effects of prokinetic agents on gastric emptying. Improvement of glucose control increases antral contractility, corrects gastric dysrhythmias, and accelerates emptying. To date, there have been no long-term studies confirming the beneficial effects of maintenance of near euglycemia on gastroparetic symptoms. Nevertheless, the consistent findings of physiologic studies in healthy volunteers and diabetic patients provide a compelling argument to strive for near-normal blood glucose levels in affected diabetic patients. Generally, patients give their meal time insulin after ingesting the meal, to ensure that the entire anticipated meal is actually consumed and without vomiting.

In a recently reported multicenter pilot study (GLUMIT), continuous subcutaneous insulin infusion with insulin pump therapy with continuous glucose monitoring reduces hypoglycemia in diabetes with gastroparesis [45]. There were also associated improvements in gastroparesis symptoms and nutrient tolerance benefits which were maintained for the 24 week phase of intensive monitoring and therapy. This pilot study shows the feasibility and potential for dual benefits improving both diabetes control and lowering gastroparesis symptom burdens.

Prokinetic Agents

Medications with gastric prokinetic properties, which are the mainstay of treatment for gastroparesis, include metoclopramide, erythromycin, and domperidone [46]. Intravenous agents currently available to treat hospitalized patients include metoclopramide and erythromycin. Several prokinetic agents are being studied for patients with gastroparesis; these include newer 5-HT4 receptor agonists with less cardiac side effects, newer motilin receptor agonists with less tachyphylaxis phenomenon and without antibiotic properties, and newer ghrelin receptor agonists.

Metoclopramide

Metoclopramide, a substituted benzamide structurally related to procainamide, exhibits both prokinetic and antiemetic actions. The drug is a dopamine type 2 receptor antagonist both in the CNS and in the stomach. Metoclopramide also has 5HT-3 receptor antagonist activity that might also provide an antiemetic effect. In addition, it has some 5HT-4 agonist activity releasing acetylcholine from intrinsic myenteric cholinergic neurons that might help enhance gastric emptying. The prokinetic properties of metoclopramide are limited primarily to the stomach. Reglan can cause both acute and chronic CNS side effects in some patients. These side effects should be discussed with the patient prior to treatment and documented in the patient's medical record. In the United States, metoclopramide is approved for diabetic gastroparesis for up to 12 weeks duration. Patients with gastroparesis have chronic nausea and often need longer periods of treatment. Recently, in Europe, it has been suggested that metoclopramide be used for only several days duration for acute treatment of chemotherapy-induced vomiting.

Erythromycin

The macrolide antibiotic erythromycin exerts prokinetic effects via action on gastroduodenal receptors for motilin, an endogenous peptide responsible for initiation of the migrating motor complex (MMC) in the upper gut. When administered

exogenously, motilin stimulates antral contractility and elicits premature antroduodenal phase III activity. Erythromycin produces effects on gastroduodenal motility similar to motilin.

Clinically, erythromycin has been shown to stimulate gastric emptying in diabetic gastroparesis, idiopathic gastroparesis, and postvagotomy gastroparesis. Erythromycin may be most potent when used intravenously; it is often used to clear the stomach from blood prior to an upper endoscopy for a patient with upper gastrointestinal bleeding. Limited data exist concerning the clinical efficacy of erythromycin in reducing symptoms of gastroparesis. In a systematic review of studies on oral erythromycin with symptom assessment as a clinical end point, improvement was noted in 43% of patients. One study comparing erythromycin and metoclopramide in an open-label, crossover fashion in diabetic gastroparesis found similar efficacy.

Oral administration of erythromycin should be initiated at low doses (e.g., 100–125 mg three times daily before meals). Liquid suspension erythromycin may be preferred because it is rapidly and more reliably absorbed. Intravenous erythromycin (100 mg every 8 h) is used for inpatients hospitalized for severe refractory gastroparesis. Side effects of erythromycin at higher doses (500 mg) include nausea, vomiting, and abdominal pain. Because these symptoms may mimic those of gastroparesis, erythromycin may have a narrow therapeutic window in some patients. There is report that erythromycin chronically may be associated with higher mortality from cardiac disease, especially when combined with agents that inhibit cytochrome p-450, such as calcium channel blockers.

Domperidone

The effects of domperidone on the upper gut are similar to those of metoclopramide, including stimulation of antral contractions and promotion of antroduodenal coordination. In addition to prokinetic actions in the stomach, domperidone exhibits antiemetic properties via action on the area postrema, a brainstem region with a porous blood–brain barrier. Domperidone does not readily cross the blood–brain barrier; therefore, it is much less likely to cause extrapyramidal side effects than metoclopramide. Side effects to domperidone include breast lactation, headaches, and palpitations. Domperidone has been associated with prolongation of the cardiac QTc interval.

The FDA has developed a program for physicians who would like to prescribe domperidone for their patients with severe upper GI motility disorders that are refractory to standard therapy to open an Investigational New Drug Application (IND). An IND is a request for FDA authorization to administer an investigational drug to humans. Such authorization would allow the importation, interstate shipment, and administration of the drug even though it is not approved for sale in the USA. Use of this IND mechanism for use of domperidone also will require IRB approval. An EKG and blood work to check potassium and magnesium, are obtained prior to starting domperidone; these are repeated after 4–8 weeks of treatment. The patient will need to pay for their domperidone medication since insurance companies do not for this nonapproved treatment.

The benefits and side effects of domperidone to treat symptoms of gastroparesis were recently reported from a large single-center cohort [47]. In this large single-center study of 125 patients treated with domperidone, side effects necessitating discontinuing treatment occurred in 12%. The most common side effects were headache, tachycardia/palpitations, and diarrhea. The majority of patients (60%) experienced an improvement in symptoms of gastroparesis, particularly postprandial fullness, nausea, vomiting, and stomach fullness.

Antiemetic Medications

Antiemetic agents are given acutely for symptomatic nausea and vomiting. The principal classes of drugs that have been used for symptomatic treatment of nausea and vomiting are phenothiazines, antihistamines, anticholinergics, dopamine receptor antagonists, and more recently serotonin

receptor antagonists. The antiemetic action of phenothiazine compounds appear to be mediated primarily through a central antidopaminergic mechanism in the area postrema of the brain. Commonly used agents include prochlorperazine (Compazine), trimethobenzamide (Tigan), and promethazine (Phenergan).

Serotonin (5-HT-3) receptor antagonists, such as ondansetron (Zofran) and granisetron (Kytril), have been shown to be helpful in treating or preventing chemotherapy-induced nausea and vomiting. The primary site of action of these compounds is probably the chemoreceptor trigger zone, since there is a high density of 5-HT-3 receptors in the area postrema. Zofran is now frequently used for nausea and vomiting of a variety of other etiologies. It is best given on a prn basis due to their expense. Granisetron transdermal system (GTS) is an appealing delivery system for patients with gastroparesis. In an open-label study, GTS was moderately effective in reducing nausea and/or vomiting in 76% of gastroparesis patients [48]. Side effects can occur such as constipation, skin rash from the patch, and headaches.

Neurokinin receptor antagonists are being used for chemotherapy-induced nausea and vomiting. Aprepitant (Emend) is a recently approved substance P/neurokinin 1 receptor antagonist for chemotherapy-induced nausea and vomiting. In a recent abstract presentation [49], the effects of the neurokinin-1 receptor antagonist aprepitant, on symptoms in patients with gastroparesis (Gp) and related syndromes associated with chronic nausea and vomiting patients. Aprepitant resulted in a greater decline in mean 4-week daily hours of nausea and mean 4-week GCSI score. These data suggest that aprepitant has potential for safe improvement of a variety of symptoms in gastroparesis and related disorders.

Refractory Patients with Gastroparesis

Patients with refractory gastroparesis need treatment at a variety of levels directed at nutritional care, prokinetic medications, antiemetic therapies, pain control, glycemic control, and often psychological measures. Surgical and endoscopic approaches are considered in patients in whom drug therapy is ineffective and who cannot meet their nutritional requirements [15]. Surgical treatments include placement of jejunostomy tubes, gastric electrical stimulation, and pyloromyotomy [15]. These options are typically considered only in patients with severe, refractory gastroparesis.

Combination Therapy

In moderately to severely symptomatic patients, often therapy with both a prokinetic agent and antiemetic agent is needed. One needs to be careful about added side effects with combination therapy. Prokinetic agents can act via different mechanisms to enhance gastric emptying. Theoretically, addition of a second prokinetic agent may augment the response of the first drug if the two agents act on different receptor subtypes. Dual prokinetic therapy with domperidone and cisapride had been reported to accelerate emptying and reduce symptoms in some patients with refractory gastroparesis. Combinations of available prokinetic agents in the United States, such as metoclopramide and erythromycin or domperidone and erythromycin, have not been specifically studied. Usually, these are not combined due to the possibility of increasing cardiac side effects. Since metoclopramide and domperidone are both D2 receptor antagonists, these should not be used together.

Pyloric Botulinum Toxin Injection

Gastric emptying is a highly regulated process reflecting the integration of the propulsive forces of proximal fundic tone and distal antral contractions with the functional resistance provided by the pylorus. Manometric studies of patients with diabetic gastroparesis have shown in some patients prolonged periods of increased pyloric tone and phasic contractions, a phenomenon termed pylorospasm. Botulinum toxin is a potent inhibitor of acetylcholine neuromuscular transmission and has been used to treat spastic somatic muscle disorders as well as achalasia.

Several studies have tested the effects of endoscopic injection of the pyloric sphincter with botulinum toxin in patients with diabetic and idiopathic gastroparesis [15]. Initial studies were unblinded in small numbers of patients from single centers and have observed mild improvements in gastric emptying and modest reductions in symptoms for several months. Two double-blind studies have been reported; these show an improvement in gastric emptying, but no effect on symptoms compared to placebo. Thus, botulinum toxin injections do not result in sustained improvement in symptoms of gastroparesis.

Psychotropic Medications as Symptom Modulators

Tricyclic antidepressants may have significant benefits in suppressing symptoms in some patients with nausea and vomiting as well as patients with abdominal pain. Doses of tricyclic antidepressants used are lower than used to treat depression. A reasonable starting dose for a tricyclic drug is 10–25 mg at bedtime. If benefit is not observed in several weeks, doses are increased by 10- to 25-mg increments up to 50–100 mg. Side effects are common with use of tricyclic antidepressants and can interfere with management and lead to a change in medication in 25% of patients. The secondary amines, nortriptyline and desipramine, may have fewer side effects. The recent NIH gastroparesis consortium study with nortriptyline in idiopathic gastroparesis did not show an effect on overall symptoms of gastroparesis [49]. However, there was a suggestion that low nortriptyline doses (10–25 mg) might decrease nausea, whereas higher doses (50–75 mg) might decrease fullness. There are limited data on the use of selective serotonin reuptake inhibitors in gastroparesis or functional dyspepsia.

Gastric Electric Stimulation

Gastric electric stimulation is a treatment for refractory gastroparesis. It involves an implantable neurostimulator that delivers a high-frequency (12 cpm), low-energy signal with short pulses. With this device, stimulating wires are sutured into the gastric muscle along the greater curvature during laparoscopy or laparotomy. These leads are attached to the electric stimulator, which is positioned in a subcutaneous abdominal pouch. Based on the initial studies that have shown symptom benefit especially in patients with diabetic gastroparesis, the gastric electric neurostimulator was granted humanitarian approval from the FDA for the treatment of chronic, refractory nausea and vomiting secondary to idiopathic or diabetic gastroparesis. The main complication of the implantable neurostimulator has been infection, which has necessitated device removal in approximately 5% of cases. More recently, a small minority of patients can at times have a shocking sensation. Symptoms of nausea and vomiting can improve with stimulation; however abdominal pain often does not. The symptomatic benefit occurs more often in diabetic gastroparesis than in idiopathic gastroparesis. Further investigation would be helpful to definitively show the effectiveness of gastric stimulation in long-term blinded fashion, which patients are likely to respond, the optimal electrode position, and the optimal stimulation parameters, none of which have been rigorously evaluated to date. Future improvements may include devices that sequentially stimulate the stomach in a peristaltic sequence to promote gastric emptying as well as endoscopically placed gastric electric stimulators.

In a recently reported cohort of 151 patients with refractory gastroparesis treated at a single center, GES improved symptoms in 75% of patients with 43% being at least moderately improved [51]. Response in diabetics was better than in nondiabetic patients. Nausea, loss of appetite, and early satiety responded the best.

Other Surgical Treatments for Persistently Refractory Gastroparesis Patients

Other treatments include feeding jejunostomy for nutritional support with a jejunostomy tube that bypasses the affected stomach for feedings. Venting gastrostomy tubes have been tried with

success in some patients. Recently, pyloromyotomy has reemerged as a treatment for patients with gastroparesis. This can be performed surgically or more recently endoscopically. Open-label studies report good responses. Gastrojejunostomy has been performed in the past with limited success. Gastric bypass with gastrojejunostomy has been used by several centers to treat gastroparesis. Partial gastrectomy should be used rarely, and only in carefully selected patients. In postsurgical gastroparesis, occasionally completion gastrectomy is performed for persistent gastroparetic symptoms.

Likely Future Trends and Directions

In the last several years, emerging technologies have been introduced for evaluation of gastroparesis. The gastric emptying scintigraphy test has been enhanced by measuring emptying out to 4 h and protocols to standardize this among centers. In addition to gastric emptying scintigraphy, two other office based tests for gastric emptying have been approved: wireless motility capsule and breath testing. In addition, others assessments for gastric pathophysiology are being developed including assessment of gastric accommodation using scintigraphy and/or nutrient drink tests. Hopefully, tests for gastric hypersensitivity will be developed. Less invasive gastric barostat would allow improved evaluation of gastric pathophysiology.

New treatments for gastroparesis are being tested for gastroparesis, and newer treatments are being developed. In 2015, a draft guidance document was issued by the FDA for treatment trials in gastroparesis [52]. This has enhanced interest in treatments with gastroparesis. Studies are ongoing with ghrelin receptor agonists, motilin receptor agonists, 5HT-4 receptor agonists, dopamine D2/D3 receptor antagonists, and novel metoclopramide delivery systems. Agents for specific symptoms, especially for nausea and vomiting, are also being tested including the use of 5HT-3 receptor antagonists and NK1 receptor antagonists. In addition, surgical procedures such as gastric bypass, endoscopic pyloromyotomy, and combining gastric electric stimulation with pyloromyotomy are being explored.

Conclusions

Gastroparesis is identified through the recognition of the clinical symptoms and documentation of delayed gastric emptying. Management of gastroparesis includes assessment and correction of nutritional state, relief of symptoms, improvement of gastric emptying, and, in diabetics, glycemic control. Patient nutritional state should be managed by oral dietary modifications. Medical treatment entails use of prokinetic and antiemetic therapies. Unfortunately, current approved treatment options do not adequately address clinical need. Attention should be given to the development of new effective therapies for symptomatic control.

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Gastric Pacing

25

Pratik S. Naik and Richard W. McCallum

How Does Current Understanding of Pathophysiology of GP Explain the Theory Behind Gastric Electric Stimulation (GES)?

One must understand the myoelectric activity of stomach to comprehend the mechanisms of GES. Gastric motility is controlled by various regions in stomach. The proximal part of stomach, mainly the fundus, relaxes to accommodate and store the food bolus. Subsequently, these contents are slowly delivered into the distal stomach by contractions synchronized with electrical slow wave activity. The gastric electrical signal is generated by the interstitial cells of Cajal (ICC) located in the gastric muscularis propria. These "slow" waves begin in the region of the junction of fundus and body (pacemaker zone) at the rate of 2.5–3.5 cycles per minute (cpm) and are conducted circumferentially and distally towards the pylorus. Contractions only occur when there is electro-mechanical coupling and over time those contractions triturate the solid food eventually resulting in gastric emptying of nutrient particles <4–5 mm in size through the pylorus [1]. Loss of ICC is linked to the absence of coordinated slow waves and damage of these cells in pathologic conditions, such as diabetic and idiopathic GP, will interrupt the propagation of slow waves resulting in dysrhythmias [2, 3]. The vagus nerve also plays a vital role in gastric emptying both of digestive and non-digestive solids as well as during the fasting state. Accidental vagal nerve damage occurring during procedures such as fundoplication, Wallerian degeneration accompanying diabetes mellitus, and demyelination associated with disorders such as multiple sclerosis can affect vagal nerve nuclei contributing to impaired motility [1].

What Is Gastric Electric Stimulation?

The concepts of GES apply the general principles of cardiac pacing with the goal of overcoming abnormal rhythm and regulating slow waves of the stomach. It is estimated that up to 30% of the patients with GP will fail to respond to pharmacotherapy and dietary treatments. GES may be offered to alleviate symptoms of refractory GP namely nausea, vomiting, postprandial fullness, and satiety. Two main types of GES are available: (1) low-frequency/high-energy GES (gastric pacing); and (2) high-frequency/low-energy GES (neurostimulation).

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Low-Frequency/High-Energy GES (Gastric Pacing)

It is also referred to as "long-pulse stimulation" and applies pulses with durations of 10–600 ms, at a frequency of approx. 3 cpm, similar to the physiologic rate in the stomach. This low-frequency/high-energy waveform was shown in a dog model to "pace" the stomach by entraining gastric slow waves [4] resulting in enhanced gastric emptying and improvement in vomiting.

Kelly et al. performed the first experiments in an animal model (dogs) which demonstrated that gastric pacing could entrain slow waves at 0.8–1.6 times the intrinsic frequency and could reverse spontaneous slow wave dysrhythmias [5]. Subsequent studies also in a dog model showed gastric pacing improved gastric emptying and reversed dysrhythmias [6]. The foundations for "gastric pacing" were built on these studies. In applying those principles in the clinical setting, the following studies have been published. Gastric stimulation in the post-gastric surgical setting did not show improvement in gastric emptying [7]. Subsequently, nine patients (five with diabetic, three with idiopathic, and one postsurgical etiology) with severe GP who had failed standard medical therapy underwent "gastric pacing" to assess the effects on gastric emptying and gastrointestinal symptoms [8]. The common symptoms of these patients included nausea, vomiting, bloating, abdominal pain, weight loss, and anorexia. Four pairs of temporary pacing wires were placed surgically 4 cm apart, and the most distal pair was located 2–4 cm proximal to the pylorus. The proximal pair was used for electrical stimulation while the three distal pairs recorded the effects. The gastric slow wave was completely entrained in all patients using a frequency 10% higher than the intrinsic slow wave frequency. In the distal antrum the amplitude of the gastric slows wave was higher during electrical stimulation compared to the sham. Gastric emptying studies performed after 4 weeks of gastric pacing showed a significant improvement in gastric retention observed at 90 min compared to pretreatment (68.6% ± 7.1% vs. 86.1% ± 3.1%; $P < 0.05$, paired t test) and at 2 h (56.6% ± 8.6% vs. 77.0% ± 3.3%; $P < 0.04$, paired t test). Patients also reported an overall 50% decrease in their symptoms and 90% of patients were able to discontinue jejunal feedings [8]. A recent study in rats was confirmatory of this work showing that long-pulse stimulation improved gastric emptying and one hypothesis advanced was that long-term stimulation promoted regeneration of ICCs via insulin-like growth factor-1 (IGF-1) [9] hence a more regular basal rhythm would result.

The major limitation of long duration pulses is that it requires high energy through external leads. The battery life required is a challenge for a single electrodes implanted in a patient for long-term treatment [1]. This concern was addressed by a study in a dog model showing low energy consumption and improved gastric emptying with a two-channel gastric pacing system compared to single channel [10]. Subsequently in a clinical study utilizing two-channel gastric pacing in 19 patients with severe GP refractory to standard medical therapies, four pairs of temporary pacing wires were inserted on the serosa of the stomach at the time of laparotomy to place the Enterra System (Fig. 25.1). Two of the pairs were for electrical stimulation and the other two for recording. Five days after surgery the optimal pacing parameters for the entrainment of gastric slow waves in each patient were identified by serosal recordings. Two-channel gastric pacing

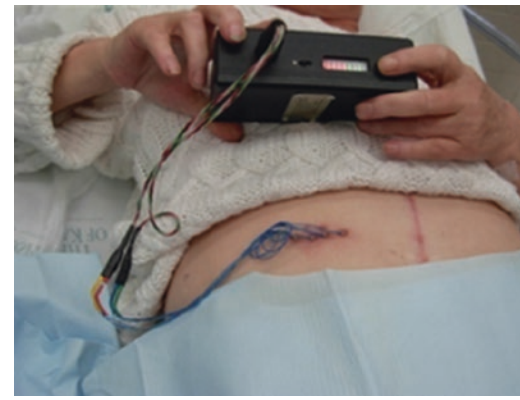

Fig. 25.1 Two-channel gastric pacing prototype device pulse generator (*black box*) is attached to external wires in a patient with refractory GP. These external wires stimulate electrodes that were surgically attached to the serosa of the stomach when the device is activated after meals

was then initiated for 6 weeks using an external multichannel pulse generator. Electrogastrogram (EGG), total symptoms score (TSS), and a 4-h gastric emptying test were assessed at baseline and after 6 weeks of active gastric pacing. Enterra device was turned OFF during the duration of this study. Two-channel gastric pacing at 1.1 times the intrinsic frequency entrained gastric slow waves and normalized gastric dysrhythmia. The gastric pacing also showed significant reduction in GP symptoms (nausea, vomiting, early satiety, bloating, postprandial fullness, epigastric pain, and epigastric burning) and mean 4-h gastric retention also improved after 6 weeks ($P < 0.05$) [11]. The two-channel system has also shown improvement in emetic responses induced by vasopressin in a dog model which was not seen in single channel system in previous studies [4, 10]. In future, development of an implantable gastric pacing system is encouraged to effectively treat refractory GP.

High-Frequency/Low-Energy GES (Neurostimulation)

This approach is also referred to as "short-pulse stimulation" and applies pulses with duration of 300 ms, at a frequency of approx. 12 cpm which is four times the physiologic rate of stomach [12]. This higher frequency does not entrain the slow wave of stomach and has no effect on gastric dysrhythmias. The main purpose of neurostimulation is to treat intractable nausea and vomiting. Gastroparetic patients who are the best candidates for gastric neurostimulation have daily nausea and vomiting refractory to aggressive antiemetic and prokinetic drug therapy for at least 1 year in duration.

Different programming parameters were studied in humans and animal models to evaluate response of symptoms and gastric emptying. Studies done by Familoni et al. with low-energy/high-frequency device initially reported increased gastric contractility in canines and improvement in symptoms and liquid gastric in a diabetic patient with severe GP [13, 14]. The first implantable device named Enterra Therapy System (Medtronic, Inc. Minneapolis, MN) was developed to incorporate those high-frequency low-energy parameters and was approved by the Food and Drug Administration (FDA) under a Humanitarian Use Device status based on the result of a multicenter double-blinded crossover study called WAVESS (World Anti-Vomiting Electrical Stimulation Study). Thirty-three patients with chronic gastroparesis (17 diabetic and 16 idiopathic) underwent implantation of this GES device which provided continuous high-frequency/low-energy gastric electrical stimulation parameters after surgery. They were randomized in a double-blind crossover design to stimulation ON or OFF for 1-month periods. The second phase was unblinded where all patients were programmed to stimulation ON and followed a further 6 and 12 months. The weekly vomiting frequency (WVF) was a primary objective. In the double-blinded phase, there was a significant reduction in self-reported vomiting frequency in the ON vs. OFF period ($P < 0.05$). In the unblinded portion of the study, vomiting frequency decreased significantly ($P < 0.05$) at 6 and 12 months. Scores for symptom severity and quality of life significantly improved ($P < 0.05$) at 6 and 12 months; however, gastric emptying was only modestly accelerated [12]. Overall 80% of the patients reported more than 50% improvement in symptoms after the total of 12 months of follow-up.

Subsequently, Enterra therapy has been studied in multiple open labeled clinical trials which have shown sustained and significant improvement in symptoms such as nausea and vomiting in patients who have failed aggressive medical therapies. When a controlled study was performed again in 2010, 55 patients with refectory diabetic GP patients were implanted with the Enterra system. All patients had the system turned ON for 6 weeks after surgery. Patients were then randomly assigned to groups that had consecutive 3-month crossover periods with the device either ON or OFF. The devices then were turned ON in all patients and they were followed for up to 12 months. There was a significant reduction in nausea and vomiting in the initial 6 weeks but there was no significant differences

shown between the ON and OFF treatments during the 3 months crossover period. However, there was a significant decline in WVF from baseline values (median reduction, 68%; $P < 0.001$) by 12 months when all patients had devices tuned ON. The study participants also had improvements in total symptom score, gastric emptying, quality of life, and median days in the hospital [15].

Previous studies have shown higher treatment failure of GES in patient with idiopathic compared to diabetic GP. In multicenter randomized crossover study evaluated the efficacy of GES in 33 idiopathic GP patients, the stimulator was turned ON for 6 weeks after the surgery followed by double-blind randomization to consecutive 3 month crossover periods with the device either ON or OFF followed by an unblinded treatment period of 4.5 months. A total of 25 patients completed the crossover period and 21 patients continued 12 months follow-up with device ON. During the unblinded first 6 weeks ON period, there was a significant reduction in WVF from baseline (61.2%, $P < 0.001$). During the subsequent crossover period the median reduction of WVF approx. 17% ($P > 0.10$) between ON and OFF phase of the study was not significantly different. At 1 year, the mean WVF remained decreased by 87% ($P < 0.001$), and it was accompanied by improvements in GP symptoms, gastric emptying, and days of hospitalization ($P < 0.05$) [16].

Both studies [15, 16] did not show significant improvement in WVF during the cross over periods. This observation may be related to the presence of other variables that contributed to the symptom reporting. During the first 6 weeks following implantation, all patients had the device activated. One plausible theory is that initial activation of the system may lead to a "memory" or "imprinting" effect on the CNS pathway which was activated and which may have led to a sustained response during the crossover period even when the device was turned off. Differences in symptoms may potentially be confounded by effects of the initial surgery related to the use of pain medications, alterations in glucose control, and the placebo effect of the surgery itself [15]. However, placebo effects tend to last for not more than few weeks, hence the sustained response observed for more than 1 year would seem to be related to the effects of the GES therapy.

Long-term observations have also been published. Brody and colleagues reported sustained symptoms response and pain reduction during their follow-up period of 8 years [17]. In a prospective non-randomized study 79 patients had GES implanted for refractory GP between 2003 and 2013 and were analyzed for pre- and postoperative pain and function scores over time at a single institution. Symptom scores were available for 60 participants at baseline, 52 participants at 1 year, 14 participants during years 2–3, and 18 participants for 4–8 years. Overall, symptom reductions were maintained for 8 years for both functional and pain symptoms. At 1 year follow-up, 44 and 31% of the participants experienced at least a 25% reduction in symptom distress for functional and pain symptoms, respectively. At 4–8 year follow-up, 67 and 33% of the participants experienced at least a 25% reduction in symptom distress for functional and pain symptoms, respectively [17]. This study has limitations as it was a non-randomized and also data was available for less than 40% of the patients beyond 1 year follow-up. However, the finding of patients reporting substantial improvement beyond 12 months would be further evidence against a "placebo" effect. These patients had hospitalizations in the time preceding the GES surgery and had been clinically unstable. These aspects were now changed.

The largest study on long-term safety and efficacy of GES therapy was reported in a case series study where 221 patients with refractory GP ($n = 142$ diabetic, $n = 48$ idiopathic, and $n = 31$ postsurgical) who were treated with the Enterra device were followed for up to 10 years. At 1 year, 188 (85%) of the initial 221 subjects enrolled were available for follow-up. Total symptom score was reported to have decreased by 53% ± 32% ($P < 0.001$). Participants with diabetic GP had greater symptom reduction than those with postsurgical and idiopathic GP (55% vs. 48% vs. 47%, respectively). Of 119 subjects with gastric emptying data, 26% normalized their

results after GES therapy ($P < 0.05$). In addition, 89% of patients were able to stop jejunostomy tube feeding within 12 months and had a significant improvement in their weight. There was a reduction of hospitalization days by 87% ($P < 0.001$) in the last year of follow-up for all patients with diabetic GP. Overall, the use of GP medications in all subject groups was reduced after 1 year of GES (74% at baseline vs. 56% for prokinetics, $P = 0.05$; and 65% at baseline vs. 58% for antiemetics, $P = 0.025$) [18]. Patients with idiopathic GP had less response compared to diabetic GP subjects. Idiopathic GP patients represent a heterogeneous mixture of patients etiologically compared to other groups and they report more abdominal pain which is the symptom least likely to respond to neurostimulation [18].

Meta-analysis of 10 studies (n = 601) by Chu et al. showed significant improvement of total symptom severity score ($P < 0.00001$) and gastric retention at 2 h ($P = 0.003$) and 4 h ($P < 0.0001$) in patients with diabetic GP with GES. However, gastric retention at 2 h ($P = 0.18$) in idiopathic GP patients and gastric retention at 4 h ($P = 0.23$) in postsurgical GP patients receiving GES were not significant [19].

Predictors of Response

There are some factors that have been identified which could predict a suboptimal outcome to GES. Patients with concomitant chronic opioid use will do worse due to inhibition of gastric emptying by opioid use as well as induction of nausea and vomiting by central mechanisms. GES improves nausea and vomiting which may lead to less abdominal pain; however, when chronic abdominal pain is the predominant preoperative symptom, use of GES should be carefully considered as pain control is not a primary goal of the therapy. Idiopathic GP patient tend to have higher abdominal pain levels than diabetic GP which could also explain the higher treatment failure of GES in idiopathic GP patients.

Patients with different disease processes such as rumination syndrome, dumping syndrome, cyclic vomiting syndrome, and eating disorders can have nausea and vomiting, which will not improve with GES. Hence, making a right diagnosis is crucial. 50% of patients with GP are lacking the normal ICC populations in their antral smooth muscle based on full-thickness biopsies done during surgery, and overall this ICC deficiency has been found to have higher association with a suboptimal treatment outcome with GES [20, 21].

How Is Surgery Accomplished of the Enterra System?

The Enterra gastric stimulation system consists of three main elements: a pair of leads, a pulse generator, and a programming system (Fig. 25.2). Two electrodes are implanted surgically, by either laparotomy or laparoscopy, depending on the expertise and training of the surgeon, in the muscular layer of the body of the stomach, along the greater curvature, approx. 1 cm apart 9 and 10 cm from the pylorus generally on the greater curvature. Leads from the electrodes are connected to a pulse generator which is placed in a subcutaneous pocket in the abdominal wall (Fig. 25.3) in the left or right upper quadrant. The pulse generator was adapted from existing devices in clinical use, which could sustain long-term requirements of a low energy type of stimulation. It is programmed by an external interrogator which both monitors and determines parameters, e.g., 5 mA as a standard current, 14 Hz micro-second, cycle on and cycle off 0.1 and 5 s, respectively. There are no controlled trials regarding the best programming parameters. The usual initial setting is the "default" setting where current and voltage are based on the resistance in ohms between the two gastric electrodes. Further adjustments may or may not be warranted. Clinicians can increase current and voltage in increments of 20–30% during follow-up if a patient reports poorly controlled symptoms in the hope that energy may be helpful in reducing symptoms [18, 22]. However this is very subjective. Battery life of the pulse generator is estimated to be at least 5–10 years, depending on the pulse parameters used [23]. When the

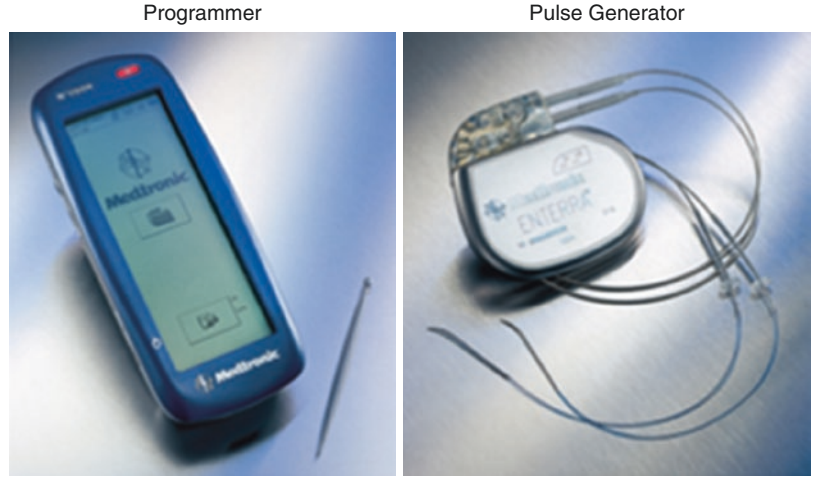

Fig. 25.2 Enterra system components (From Reddymasu SC: Severe Gastroparesis: Medical Therapy or Gastric Electrical Stimulation, Clin Gastroenterol Hepatol. 2010; 8(2):117–24) (Reprint permission obtained from *Elsevier* publication)

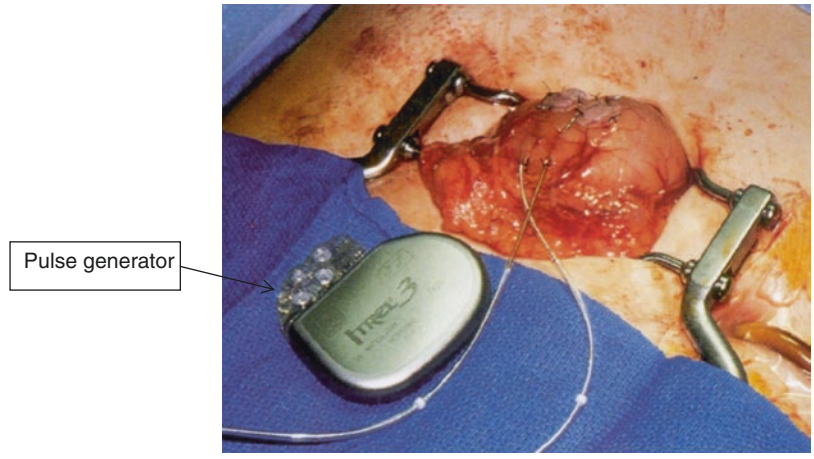

Fig. 25.3 Example of the Enterra Device: An open laparotomy surgical implantation of electrodes in gastric smooth muscle 9 and 10 cm proximal to the pylorus with leads attached to pulse generator which then will be positioned in abdominal wall pocket

battery is depleted, the pulse generator is replaced by local intervention. Hospital stay is short, approximately 2–3 days, following laparoscopic insertion, and is shorter when compared to placement via laparotomy (6.4 days) [24].

What Are the Mechanisms of Action of Enterra System?

Neurostimulation can induce a sustained response in improving nausea and vomiting with variable effect on gastric emptying which is usually not improved. GES also does not convert dysrhythmias to normal rhythm. There are three proposed mechanism which can explain the substantial improvement in nausea and vomiting (Fig. 25.4) [25].

1. Effect on autonomic function: The effect of GES on autonomic function leads to increase in vagal activity as manifested by decrease in sympathovagal balance which is determined by assessing low- (sympathetic) and high-frequency (vagal) aspects of the power spectral analysis of heart rate variability [25].
2. Effect on gastric tone and accommodation: The response of GES on increased gastric tone and accommodation was evaluated using a Barostat methodology which shows better fundic relaxation and ability to eat and store more food due to decrease in gastric sensitivity to distention which is mediated by increased vagal response [25].
3. Changes in cerebral activity: Cerebral activity analysis using positron emission tomography (PET) scan shows increase in thalamic and

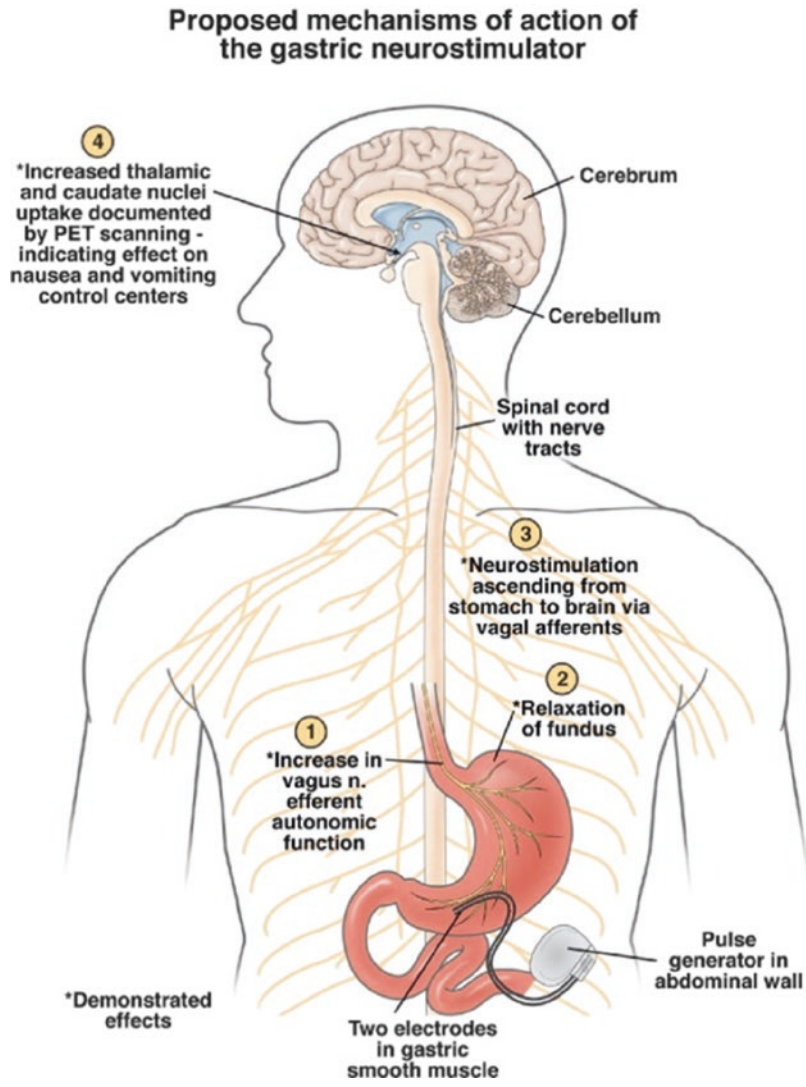

Fig. 25.4 Proposed mechanisms of action of the GES (Enterra device) (From Reddymasu SC: Severe Gastroparesis: Medical Therapy or Gastric Electrical Stimulation, Clin Gastroenterol Hepatol. 2010; 8(2):117–24) (Reprint permission obtained from *Elsevier* publication)

caudate nuclei activity with chronic stimulation by Enterra therapy. Neurostimulation has inhibitory effects on nausea and vomiting through this central control mechanism via stimulation of vagal afferent pathway transmitting impulses to the solitary tract nucleus in the dorsal medulla and to the thalami via the reticular formation [25].

What Are the Adverse Events?

There are a number of adverse events reported which are directly or indirectly related to the GES device implantation. Infection is the most common complication associated with the device in the subcutaneous pocket, occurring in up to 6% of all subjects over time [18, 26, 27] mainly due to uncontrolled diabetes with associated infections (skin or urinary) or due to trauma or falls. Meta-analysis of nine studies by Chu et al. reported the most common complications as infection (3.9%), lead or device migration (2.7%), and pain at the implantation site (0.7%) [19]. Infrequent complications include erosion of the abdominal wall by the device, penetration of the leads through the gastric wall into the gastric lumen, tangling of wires in the generator pocket, unexplained "pocket pain," formation of adhesions which can lead to a small bowel obstruction

requiring surgery for management. Enterra system may need to be removed entirely if there is infection of the pocket; however, it can be reinserted, usually within 3–6 months after the infection is fully controlled [27].

There is no increase in mortality with GES implantation. However, GES does not change the other complications of diabetes so that overall mortality rate may not be affected. GES, by stopping vomiting, permits diabetic patients to become surgical candidates for transplants, e.g., renal and pancreatic as they now can tolerate and absorb their rejection medications. In general, patients with diabetes have a poorer survival rate compared to idiopathic GP which is related to the complications of their underlying disease process and not related to GES itself [27].

What Is a Role of Pyloroplasty Is the Setting of GES?

The suboptimal results from Enterra device were that only a modest 50% symptom improvement occurred and gastric emptying was not significantly improved. Therefore the role of the pylorus became a focus and whether pyloric dysfunction was present in GP patients. A recent study suggests ICC loss and fibrosis in the pyloric smooth muscle is more common than in the antrum of refractory GP patients [28]. These findings provide one explanation for pyloric dysfunction as a contributing factor to the pathophysiology of GP. Improperly timed phasic pyloric contractions of abnormal intensity (> 10 mm Hg) and duration (> 3 min) can produce "pylorospasm" which has been observed in some patients with diabetes [29] and after vagotomy. The concept that in GP there is a combined antral and pyloric dysfunction inducing delayed gastric emptying can be viewed in similar way to achalasia where the lower esophagus sphincter fails to relax adequately in response to a food bolus while at the same time there is loss of peristaltic function in the esophagus. Currently, pyloric compliance or opening is being assessed by the endo-flip method. There are a number of approaches being used to treat impaired pyloric relaxation such as Botox injection, pyloric stenting, pyloroplasty (PP), and endoscopic pyloromyotomy. Surgical PP is the only permanent treatment available and can be accomplished laparoscopically.

Since GES dose improve nausea and vomiting but it has little or no effect on gastric emptying, PP can overcome this therapeutic deficiency in GES by accelerating gastric emptying significantly in patients with GP. In a recent study by Sarosiek et al. [30], 49 patients with GP refractory to prokinetics and antiemetics underwent GES implantations. Etiologically patients could be separated into diabetic GP (17 patients), idiopathic GP (9 patients), and postsurgical GP (23 patients) groups. Out of 49 patients 26 additionally received PP. The mean follow-up was 7 months. Total Symptoms Score were significantly improved in both groups compared to their baseline scores, Enterra and PP or GES alone ($P < 0.001$). Gastric emptying improved by 64% at 4 h ($P < 0.001$) in patients with Enterra and PP, compared to only 7% observed after GES therapy alone. The postsurgical patients group had most improvement in their gastric emptying. There were no adverse events with this dual therapy approach. These results were similar in a recent study which was presented at Digestive Disease Week 2016. The mean retention of isotope during gastric emptying was decreased with combined GES and PP and 62% of patients actually normalized their gastric emptying. In addition follow-up, hospitalizations were significantly reduced from 78 to 10 days per patient/year. This study also reported no adverse events related to adding PP to the GES surgery. Patients can have some response in nausea and vomiting with GES ranging from 20 to 60%. By adding PP which improves or normalizes gastric emptying nausea and vomiting is reduced by 70–80% overall. Hence this "dual" practice is now the treatment of choice in patients with refectory GP.

Laparoscopic Heineke-Mikulicz pyloroplasty is safe and effective procedure with minimal risk or postsurgical complications and a robotic platform has been developed with excellent safety profile (Fig. 25.5) [31]. Gastric peroral endoscopic myotomy (G-POEM) is emerging as a less

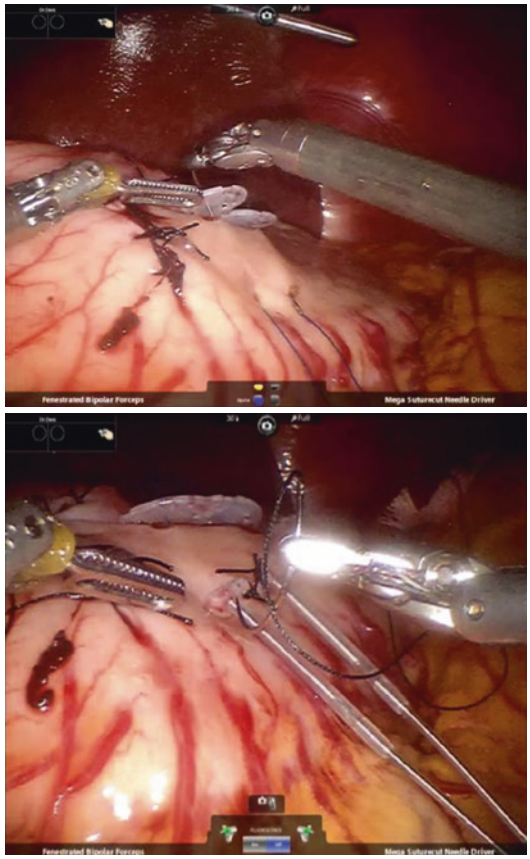

Fig. 25.5 Robotic laparoscopic surgery demonstrating attachment of electrodes to gastric smooth muscle and performance of a pyloroplasty

invasive surgical procedure which is similar in principle to the submucosal dissection and myotomy performed for the treatment of achalasia. The first multicenter study of G-POEM involving 30 patients shows promising result in improvement of gastric emptying [32]. However, this was a small not randomized study and half of the patients had prior therapies included Botox injection in 12, transpyloric stenting in 3. Also, repeat gastric emptying data was available in only 17 out of 30 patients. Future randomized prospective studies are needed to evaluate efficacy and safety profile of G-POEM compared to laparoscopic PP.

Conclusions

Gastroparesis can lead to refractory symptoms of nausea and vomiting. Enterra therapy is the only FDA approved implantable GES which can be considered after aggressive therapies with prokinetics and antiemetic have failed to improve nausea and vomiting. Low-frequency/high-energy waveform can actually "pace" the stomach by entraining gastric slow waves resulting in enhanced gastric emptying and improvement in vomiting but is not available commercially. There are evolving identifying factors which can predict a suboptimal response to GES; namely opioid use, severe abdominal pain, the wrong etiology to explain vomiting, and deficient ICC are negative predictors. High resolution gastric mapping is an emerging concept which can help us understand how GES controls nausea and vomiting as well as it effects on dysrhythmias. The combination treatment of neurostimulation and gastric pacing in one device would be a significant achievement. This would allow high energy/low frequency to regulate gastric emptying in the postprandial setting while chronic nausea and vomiting could be addressed by neurostimulation between meals. A novel concept of prolonged endoscopic placement of a wirelessly powered miniature gastrostimulator has been tried in an animal model which can set the stage for the possibility for a less invasive approach in future.

Pyloric dysfunction is an evolving concept in understanding the pathophysiology of GP. Pyloroplasty is the emerging treatment option to improve gastric emptying. GES improves nausea and vomiting by CNS mechanisms and adding PP normalizes gastric emptying thus maximizing symptom improvement and essentially is a "cure." A new emerging approach is non-surgical endoscopic pyloromyotomy but much more follow-up in necessary.

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Rapid Gastric Emptying/Pyloric Dysfunction

26

Alexander Pontikos and Thomas L. Abell

Why Did This Happen to Me? (Overview)

Rapid gastric emptying is the constellation of symptoms including abdominal symptoms (diarrhea, nausea, bloating, early satiety, and epigastric pain) as well as systemic symptoms (tachycardia, palpitations, hypotension, headache, and flushing) usually presenting within 30 min following a meal. The cause of rapid gastric emptying, commonly referred to as dumping syndrome (DS), is typically multifactorial, or caused by several different factors. Gastric surgeries, such as vagotomy and pyloroplasty (V&P), bariatric surgeries, and pylorectomy/pyloroplasty have been well-known as causes of dumping syndrome since the early 1900s. More recently, diabetes mellitus, including type II, as well as viral illnesses, have been associated with DS. This syndrome usually develops in adults, but can affect children who have had surgeries for gastroesophageal reflux disease. Around 20–50% of individuals who have undergone gastric surgery have some clinical features of DS, but only 1–5% of individuals have severe symptoms [1]. The incidence related to diabetes and viral illnesses is unknown due to the similarity of symptoms to other gastrointestinal disorders such as gastroparesis; current research efforts are helping to differentiate these entities.

What Are the Typical Symptoms of Dumping Syndrome? (Presentation)

Dumping syndrome can be divided into early and late forms, depending on the timing and type of symptoms associated with a meal. A majority of individuals have early dumping, approximately 25% of people have late dumping, and few have features of both [2]. Clinical appearances of dumping syndrome include two broad categories, gastrointestinal (abdominal) and vasomotor (systemic) symptoms. Gastrointestinal symptoms include early satiety, nausea, cramps, bloating, diarrhea, and vomiting. Vasomotor symptoms include sweating, flushing, tachycardia, palpitations, hypotension, headache, and syncope. Early dumping syndrome is defined as symptoms that occur within 10–30 min of consuming a meal and is related to bowel distention, gastrointestinal hormone hypersecretion, and autonomic dysregulation [3]. Most people have both gastrointestinal

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and vasomotor symptoms with early dumping syndrome. On the other hand, late dumping syndrome is defined as symptoms that occur 1–3 h postprandial and is related to reactive hypoglycemia that occurs during this time period. The symptoms of late dumping syndrome are predominantly vasomotor in origin. If the symptoms are severe enough, individuals can develop protein-wasting malnutrition [4], and late dumping syndrome may be associated with food aversion.

How Is Dumping Syndrome Diagnosed? (Diagnosis)

The diagnosis of dumping syndrome is largely related to clinical presentation, as well as several other measurable parameters in an individual who has risk factors for the disease (e.g., previous gastric surgeries, diabetes mellitus, or recent viral illness). Sigstad developed a diagnostic scoring system in 1970 that is based on the symptoms of dumping syndrome [5]. The scoring system is easy to use, the more points that an individual has, the higher the likelihood of the disease. A score of greater than 7 on this scale is suggestive of dumping syndrome, while a score of less than 4 suggests another disease. This system is very helpful in evaluating the effectiveness of a treatment when a baseline value is obtained prior to the initiation of treatment and reassessed at specific intervals. The disadvantage of the Sigstad score is separating the similar symptoms seen postprandial from those of dumping syndrome. The Sigstad scoring system can be used in conjunction with other diagnostic criteria.

The oral glucose challenge is a useful test for the diagnosis of dumping syndrome and helps to evoke the symptoms associated with it. The test includes a 10 h fast prior to the administration of an oral 50 gram glucose bolus. Blood pressure and pulse rate are monitored before, during, and after ingestion. An increase in heart rate by ten beats per minute in the first hour after glucose ingestion is considered a positive result [6]. Hematocrit and blood glucose levels are monitored during the test to provide additional information. A hematocrit increase of 3% in the first 30 min suggests early dumping syndrome and hypoglycemia 2–3 h after ingestion suggests late dumping syndrome [7]. The oral glucose test is reported to have a sensitivity and specificity of 100 and 94%, respectively [6].

Radionuclide scintigraphy, also known as gastric scintigraphy, is a useful tool for diagnosing the functional ability of the stomach to empty a meal (whether delayed or rapid) and other symptoms related to dumping syndrome. The presence of rapid gastric emptying is the hallmark of dumping syndrome, and must be present in order to be diagnosed with this disorder. The ingestion of a Technetium (TC)-99m sulfur colloid radiolabeled meal consisting of scrambled egg substitute, two slices of whole wheat bread, and 120 mL of water is the standard of practice. Imaging (both anteriorly and posteriorly) of the stomach is taken at 0, 1, 2, 3, and 4 h after ingestion [8]. Rapid gastric emptying is defined as <30% isotope retention at 1 h, and recent studies have shown gastric emptying percentages of 25.2, 10.2, and 3.5% at 1, 2, and 4, respectively [9]. Delayed gastric emptying is defined as >90% retention at 1 h, >60% at 2 h, and >10% at 4 h. Gastric scintigraphy is most specific at the 4-h mark necessitating the need for studies to be continued for the whole duration rather than relying on the 2 h scan.

Additional tests, such as colonoscopy, endoscopy, stool studies, and other lab tests (complete blood count, comprehensive metabolic panel, tissue transglutaminase IgA, and breath tests), are also performed on a routine basis to help diagnose other diseases that may present with similar symptoms. These include gastroparesis, irritable bowel disease (IBS), idiopathic diarrhea, pancreatic insufficiency, lactose intolerance, and celiac disease, to name a few.

Why Doesn't Dumping Syndrome Affect Everyone? (Pathophysiology)

The mechanisms involved in dumping syndrome are beginning to be understood, but are likely multifactorial in nature, from ideas related to

chyme characteristics, fluid shifts, and hormone mediated factors. The hallmark of dumping syndrome is the rapid introduction of chyme (partially digested food) into the small intestine. This decreased transit time of food from the stomach to the small intestine causes a cascade of events leading to the symptoms of dumping syndrome. Chyme is both hyperosmolar and voluminous [10], and the consumption of liquids is more likely to cause the symptoms of dumping syndrome than solids alone. The enteric nervous system, or network of nerves that control aspects of the gastrointestinal tract, such as gastric motility and distensibility, are tightly linked to the symptomatology of dumping syndrome. The adaptation of the enteric nervous system also plays a key role in dumping syndrome, allowing some individuals to have resolution of symptoms, and others to have persistence of symptoms. When the chyme enters the small intestine at a faster rate than normal, this causes distention. The small bowel reflexively contracts via the muscular layer (muscularis muscosa) and relaying this to the enteric nervous system causes the postprandial abdominal pain observed in dumping syndrome. The rapid infusion of glucose into the small bowel has demonstrated these symptoms, even in healthy individuals [11, 12].

Early dumping syndrome is defined as symptoms that occur within 10–30 min postprandially. Hormone secretion, such as VIP, serotonin, and GLP-1, and parasympathetic responses cause a fluid shift from the intravascular space to the intestinal lumen and intestinal blood supply [13]. This physiological response is also known as splanchnic blood pooling [14]. In an unaffected individual, the sympathetic activity, which consists of an increase in heart rate, vasoconstriction, and plasma norepinephrine levels, helps to keep the blood pressure from fluctuating during this time [15–17]. The fluid shift seen in dumping syndrome overwhelms the sympathetic activity and results in symptoms such as fatigue, weakness, dizziness, and hypotension. Reflex sympathetic activation then causes diaphoresis and palpitations.

Several hormone abnormalities have been implicated in dumping syndrome [18], during the period in which nutrient-rich chyme reaches the small intestine and causes bowel distention. The influence of vasoactive intestinal peptide (VIP) and serotonin have been studied widely in dumping syndrome. Vasoactive intestinal peptide is a potent vasodilator, regulating smooth muscle activity, epithelial cell secretion, and blood flow in the gastrointestinal tract [19]. Serotonin also may play a role in dilating intestinal blood supply. These physiological factors lead to the rapid fluid shift seen in dumping syndrome and the subsequent systemic sequelae. Higher plasma levels of adrenaline and noradrenaline were also found in early dumping syndrome, which correlates to the increased sympathetic drive [20].

Late dumping syndrome is defined as symptoms that occur 1–3 h postprandially. Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide (GLP-1) are released as a result of the hyperosmolar chyme that enters the small intestine. These two hormones stimulate insulin secretion from the pancreas due to the high glucose load in the intestine. This rise in insulin causes a reactive hypoglycemia [21] and symptoms of low blood sugar such as diaphoresis and fainting episodes. GLP-1 levels as well as GIP are found to peak around 1 h following ingestion of a meal [22] and correlate with these episodes. In addition to the increased insulin release, GLP-1 also inhibits glucagon, the hormone responsible for increasing the serum glucose levels by mobilizing the stored glucose, compounding the hypoglycemia seen in dumping syndrome.

What Caused Me to Develop This Disease? (Causes)

Dumping syndrome has both surgical and non-surgical causes. Diabetes mellitus has been linked to dumping syndrome, but many other idiopathic cases have been reported. As opposed to gastroparesis, which is characteristically associated with chronic diabetes mellitus, dumping syndrome is often seen in individuals with new onset diabetes mellitus, specifically type II diabetes mellitus, but is not exclusive [23]. Multiple

mechanisms for the role of diabetes mellitus have been proposed, including Wallerian degeneration (early vagal nerve damage) and increased contractility or motor activity in the gastric fundus [24]. The resulting motor abnormality of the stomach is one of the leading hypotheses related to diabetes induced dumping syndrome.

An emerging correlation between dumping syndrome and cyclic vomiting syndrome (CVS) has also begun to be established. In one study, nearly three-quarters of individuals with CVS met the criteria for dumping syndrome [25]. A link to autonomic dysfunction can be seen as a result of dumping syndrome occurring during the vomiting-free period of CVS [26].

Dumping syndrome has also been seen as a complication of fundoplication for gastroesophageal reflux disease (GERD), resulting in accidental vagal nerve injury. Both delayed and rapid gastric emptying have been reported following this procedure [27]. Reduced pyloric relaxation, resulting in decreased gastric accommodation as well as impaired feedback inhibition to slow gastric emptying, can be seen after vagotomy. Functional dyspepsia, or chronic pain of the upper abdomen, has also been correlated with dumping syndrome. Nearly one-third of individuals with the diagnosis also exhibited rapid gastric emptying on gastric scintigraphy [28]. In addition, a small subset of patients who initially presented with symptomatology of abdominal pain and cramping and were diagnosed with irritable bowel syndrome, have a component of dumping syndrome [29].

The surgical treatment of peptic ulcer disease was the primary cause of this syndrome prior to the treatment of *H. pylori*. The anatomic alterations related to resection or bypass of the pylorus and vagotomy (whether intentional or accidental) altered the innervations of the stomach, resulting in the symptoms of dumping syndrome. It is reported that 15–20% of patients after partial gastrectomy [2] and 6–14% of patients after truncal vagotomy [30] experienced some form of dumping syndrome, but only 10% of these individuals had symptoms severe enough to be diagnosed with dumping syndrome [31]. The most common surgical cause of dumping syndrome in adults today is gastric bypass, with an incidence as high as 75% of patients [32]. In children, Nissen fundoplication for GERD is the leading surgical cause of dumping syndrome [33]. The surgical modifications change the anatomy of the gastrointestinal tract, resulting in rapid transit of chyme from the stomach to the small intestine. The pylorus and antrum function to inhibit gastric emptying. After gastric surgeries such as antrectomies and pyloroplasties, both the gastric remnant and pylorus are disrupted, resulting in the rapid transit of chyme seen in dumping syndrome. In regard to bariatric surgery, Roux-en-Y is the most common cause of surgically induced dumping syndrome [34], but with the newer technique of sleeve gastrectomy, the incidence of dumping syndrome has decreased with regard to this modality [35].

Now That I'm Diagnosed with Dumping Syndrome, What's Next? (Treatment)

The first-line recommendations for the treatment of DS are related to dietary modifications. Food intake should be divided into smaller and more frequent meals (around six per day), with particular attention in reducing the amount of carbohydrates. Complex carbohydrates (e.g., oatmeal, brown rice, potatoes, pasta, and beans) are preferred and better tolerated over simple sugars (e.g., soda, candies, cookies, and other sweets). Fluid intake during meals should be limited and ideally occur 1 h after ingestions of solids, since liquids tend to accelerate gastric transit. Milk and other dairy products usually exacerbate symptoms and generally should be avoided by individuals with DS. Increasing the overall consumption of proteins, as well as fats, has been shown to decrease symptoms and help make the meal nutritionally complete, despite the limit in carbohydrates. Increasing dietary fiber has also helped treat the reactive hypoglycemia by slowing gastric emptying [36]. Pectins and guar gum have been shown to be an effective dietary additive, especially in children, delaying glucose absorption and prolonging chyme transit time by

forming a gel with the carbohydrates [37]. For individuals who have low blood pressure and feel light headed after eating, lying down for 30 min may help, delaying gastric emptying and increasing venous return. If cases of severe DS, malnutrition may occur and dietary intake must be closely monitored and supplemented where needed. Some may need the expertise of a registered dietician to find a dietary plan that suits their specific symptoms. Many individuals improve with these dietary modifications, but other therapies exist in cases of persistent symptoms.

Despite dietary modifications, roughly 3–5% of individuals will continue to have symptoms of severe dumping. This can be frustrating for both the patient and clinician, but several other pharmacological interventions have been found to be of benefit in controlling symptoms, as noted below. As a perceived failure with dietary changes, patients can develop a fear of eating with progressive weight loss. It is important to control these symptoms so as to not persist in a state of malnutrition. Several over-the-counter medications can help with symptoms such as diarrhea (e.g., loperamide), nausea (e.g., promethazine, meclizine), or anti-gas (e.g., simethicone). Tincture of opium has been shown to be helpful in treating diarrhea associated with dumping syndrome [38]. Simple ingestion of a hard candy can relieve the hypoglycemia of late dumping syndrome. The gas and bloating associated with the rapid emptying of chyme into the intestines may be controlled with probiotics. These medications target only the symptoms of dumping syndrome and not the underlying causes.

Acarbose, a competitive inhibitor of α—glycoside hydrolase, has been shown to be useful in the treatment of late dumping syndrome [39]. The mechanism of acarbose is to reversibly inhibit the conversion of complex carbohydrates to monosaccharides. By doing so, it effectively dampens the postprandial rise of glucose and insulin, which ultimately helps to control the reactive hypoglycemia that occurs after a meal [40]. Conflicting data has been published in regard to the effectiveness of short- and long-term use of acarbose. Relief of palpitations and dizziness was reported after 4 weeks of therapy with acarbose in patients with dumping syndrome and non-insulin dependent diabetes mellitus [41]. On the other hand, studies have not shown a statistically significant improvement in symptoms despite lowering hyperglycemia and postprandial insulin levels in individuals [42]. The side effect profile of acarbose (e.g., diarrhea and flatulence) may limit the use to specific individuals, but the severity of these symptoms usually resolves over time.

The anticholinergic group of medications is another pharmacological option for the treatment of dumping-related symptoms. The underlying mechanism of this class is to slow the gastric emptying by inhibiting the action of acetylcholine near parasympathetic sites in smooth muscle, including the stomach and small intestines. Medications such as dicyclomine and propantheline also serve as antispasmodics, which may help with the abdominal pain and cramping that some individuals experience.

Diazoxide is also an alternative for controlling reactive hypoglycemia not controlled with dietary modifications or acarbose [43]. The activation of potassium channels in the beta cells of the pancreas by this medication help to ultimately impede the release of insulin from the pancreas, thus decreasing the abrupt rise in postprandial insulin and subsequent hypoglycemia associated with dumping syndrome.

Somatostatin, also known as octreotide (synthetic analog), has been shown to be effective in patients with dumping syndrome intractable to therapies described previously [44]. Short-term use of octreotide has proven to be efficacious in treating dumping syndrome, while the long-term effects, though limited by research, are promising [45]. Octreotide has several mechanisms of action, mainly as an inhibitor of hormones such as VIP, serotonin, and insulin. This helps to delay accelerated gastric emptying and small intestine transit time, inhibit enteral hormone secretion (VIP), inhibit insulin release and postprandial vasodilation/splanchnic vasoconstriction, and increase the intestinal absorption of water and sodium [46]. All of these effects help to improve

the symptoms of both early and late dumping syndrome. Octreotide is administered as a subcutaneous injection 5 min before each meal (starting dose of 50mcg but titrated between 25 and 100 mcg for effect). Several small-randomized clinical trials in the 1990s showed the effectiveness of both short- and long-term therapy with octreotide, with resolution of symptoms ranging from 55 to 100% of patients [46, 47]. Long-acting release octreotide is a newer formulation and is administered as an intramuscular injection once per month. Since injection site redness and pain are side effects of the daily octreotide regimen, long-acting release octreotide is an alternative option for an individual who has responded well to the daily injections. The usual dose is either 20 or 40 mg intramuscularly, once per month. If symptoms return towards the end of the month, supplementation with daily octreotide injections until the next month's dose may be required, due to the variable half-life in certain individuals. The use of octreotide is limited by side effects such as diarrhea, steatorrhea, weight gain, injection site redness, and the formation of gallstones. Octreotide can be an expensive medication and is not used as the first-line treatment for dumping syndrome [46]. It should only be used after all other options have failed to provide relief of symptoms. Research into an oral or nasal formulation may help to expand the use of octreotide for the treatment of dumping syndrome.

Gastric electrical stimulation (GES) may be a newer treatment modality for individuals who have failed both diet modifications and pharmacological therapy. The role of GES in patients with gastroparesis is known to improve symptom and nutritional scores as well as decrease mortality compared to medically managed patients [48]. GES in patients with dumping syndrome was relatively unknown but research has shown promising results. Individuals with rapid gastric emptying who underwent GES had increased gastric retention at 1, 2, and 4 h as well as improvement in nausea, vomiting, and total symptom scores [9]. GES implantation would not be a first-line treatment modality for dumping syndrome, but may serve a role for individuals who have failed various other treatments.

Brief Literature Review

Dumping syndrome has been a condition recognized since 1913 as a result of gastric surgeries. The evolution of the etiology of dumping syndrome has transformed from surgeries related to the management of peptic ulcer disease to bariatric surgeries, and more recently "idiopathic" causes. These relatively unknown causes are starting to become revealed with new research and imaging modalities. The presentation of DS is well understood, which is divided into early and late stages. The pathophysiology is also well agreed upon, resulting from a gastrointestinal response to a large hyperosmolar chyme that is rapidly transitioned from the stomach to the small intestine, with subsequent gastrointestinal and vasomotor symptoms.

More recently, research has shown newer causes of dumping syndrome in individuals who do not have a history of gastric surgeries who presented with unexplained nausea, bloating, and fullness [49]. Dumping syndrome has also been reported in patients with functional dyspepsia [50]. In addition, patients with early type II diabetes may display signs and symptoms of rapid gastric emptying [51]. The nausea and pain seen with rapid gastric emptying can be similar and very hard to distinguish clinically from gastroparesis. Gastric emptying scintigraphy (GES) is used to evaluate patients with symptoms related to altered gastric emptying [52]. GES is now recognized as the standard for assessing gastric motility due to its physiologic, noninvasive, and quantitative measurement of gastric emptying [53]. Dumping syndrome has also been linked to adults with cyclic vomiting syndrome [54, 55]. The prevalence of rapid gastric emptying in autonomic dysfunction was more common than delayed gastric emptying [56]. The development of the EndoFLIP technology which uses impedance planimetry to characterize the hollow structures which it is deployed across may help to better characterize dumping syndrome in the future. This technology has been shown to be helpful in determining pyloric pressures and distensibility [57]. The use of gastric electrical stimulation, as described above, is a promising alternative for refractory

dumping syndrome and is currently being studied more in-depth. Additional research on the pathophysiology of dumping syndrome in diabetes and other "idiopathic" conditions is gaining focus, as well as the treatment of dumping syndrome in these patients.

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Helicobacter pylori and Other Gastritides

27

Nimish Vakil

Patient Questions Related to Gastritis

What Is Gastritis?

Gastritis refers to inflammation if the lining of the stomach.

What Are the Causes of Gastritis?

The most common cause of gastritis worldwide is infection with a germ called *H. pylori*. The other principal cause of gastritis is inflammation caused by medications such as aspirin and pain medications of the anti-inflammatory category such as ibuprofen. Chemical irritants such as alcohol can also cause gastritis.

What Are the Complications of Gastritis?

Chronic gastritis can alter the normal mechanisms of acid secretion and interfere with factors that protect the stomach resulting in ulcers in the stomach or duodenum. When gastritis is present for a long time it causes loss of stomach glands, a condition called atrophy, which can be a precancerous condition.

How Is Gastritis Treated?

Gastritis related to *H. pylori* infection is treated with antibiotics. Abstaining from the use of alcohol and nonsteroidal anti-inflammatory drugs can cure the gastritis caused by these agents.

History of *H. pylori* Gastritis

The microbiome of the stomach is an important component of the gut microbiome and has a role in acid secretion, appetite control, absorption, and obesity. Although bacteria were described in the stomach in the early 1900s, the importance of these findings was not realized until 1983 when Warren and Marshall described *H. pylori* and its association with ulcer disease [1]. Since then, there has been a growing understanding of *H. pylori* infection and its relationship to both chronic gastritis and peptic ulcer disease and also its relationship to chronic atrophic gastritis and gastric cancer.

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Definition of Gastritis

Gastritis is defined as any inflammation of the mucosa of the stomach diagnosed pathologically [2]. The term is also used variably in endoscopy to describe redness, erosions, and submucosal hemorrhages in the stomach but these changes do not uniformly correlate with pathological gastritis. Based on clinical history a distinction between acute and chronic gastritis is made. From a pathological standpoint, acute gastritis is self-limited and resolves spontaneously, while chronic gastritis does not. Gastritis may be further subclassified pathologically as atrophic or non-atrophic. Atrophic gastritis is defined by the loss of gastric glands from the mucosa and has important implications because it is a step on the pathway to gastric cancer.

Diagnosis and Classification Systems of Gastritis

Gastritis is diagnosed by endoscopic biopsy of the stomach (Figs. 27.1, 27.2 and 27.3). The use of structured systems that describe the degree of inflammation and atrophy have lead to a more standardized and reproducible approach to describing gastric inflammation. The Sydney system grades inflammation and atrophy based on anatomical regions of the stomach and therefore multiple gastric biopsies are required for assessment from the antrum, corpus, and angularis of the stomach [3]. The Sydney system is a structured descriptive system for pathologists. In countries where gastric cancer is prevalent, biopsies are also used to assess the risk for gastric cancer and two additional classification systems have been described that provide a more direct assessment of gastric cancer risk. Both systems grade biopsies on a 4 point scale with Stage 4 having the highest cancer risk. Details of the operative link on gastric cancer assessment (OLGA) and the operative link for gastric intestinal metaplasia (OLGIM) may be found elsewhere [4]. Pathologically, acute gastritis is characterized by a neutrophilic infiltrate whereas a mononuclear infiltrate is characteristic of chronic gastritis.

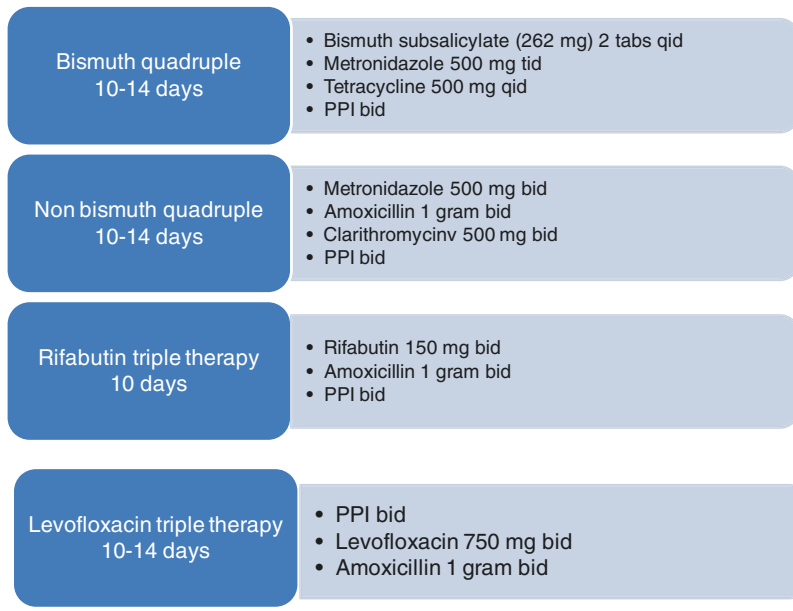

Fig. 27.1 Chronic *H. pylori* gastritis. The *arrow points* to the chronic inflammatory exudate. Courtesy of Timothy Wallace, MD

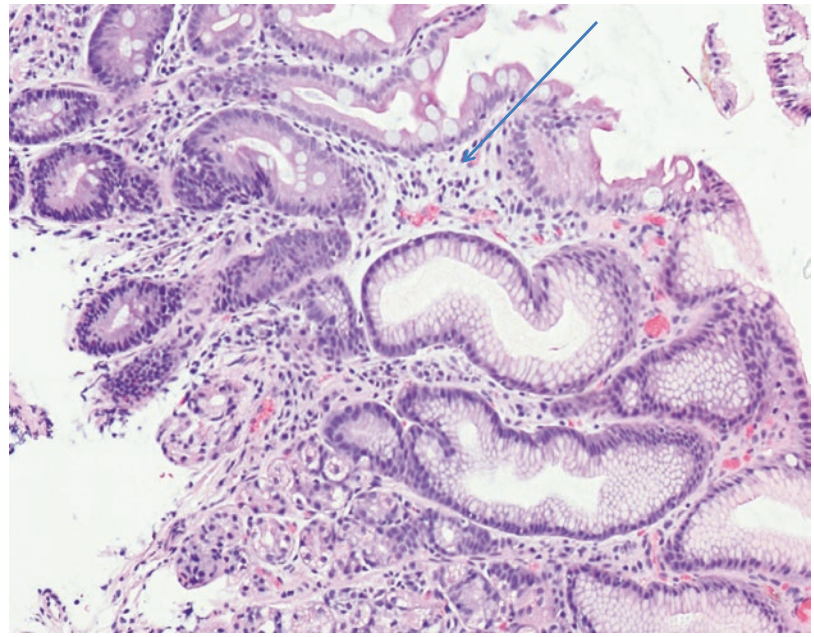

Fig. 27.2 *H. pylori* gastritis: immunological stain for *H. pylori*. The *arrow points* to *H. pylori* organisms. Courtesy of Timothy Wallace, MD

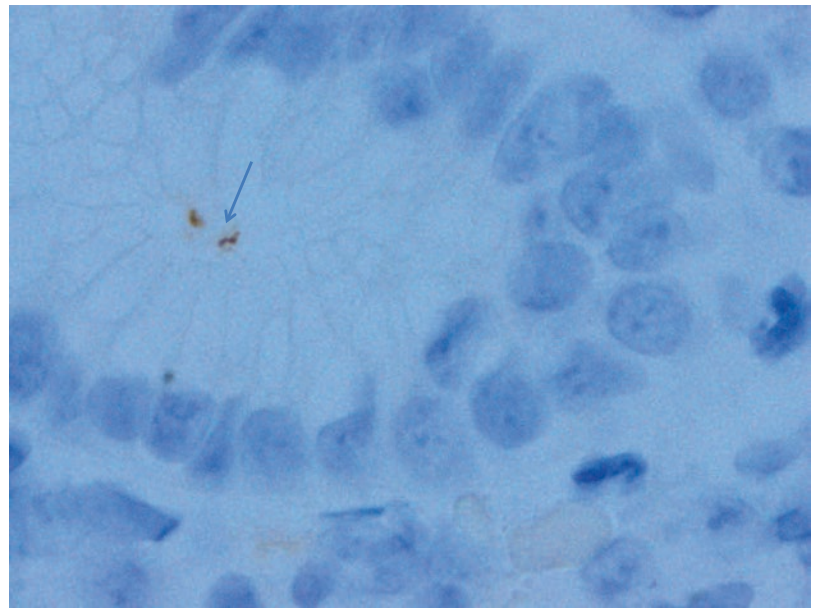

Fig. 27.3 Chronic *H. pylori* gastritis with intestinal metaplasia. *Arrow points* to metaplastic cells. Courtesy of Timothy Wallace, MD

Pathogenesis of *H. pylori* Gastritis

H. pylori is an organism that is uniquely equipped to deal with the harsh environment of the stomach. *H. pylori* has very strong urease activity, which allows it to adjust the acidity of its microenvironment.

The fecal-oral route of transmission is the most well documented method of transmission but there are reports of gastric-oral and oral-oral infection [5]. Children have been shown to transmit the infection by emesis in day care settings and *H. pylori* has been shown to exist in dental plaque. The risk of acquiring *H. pylori* is

increased by the presence of infected parents and siblings [6]. Crowded living conditions, poor sanitation, and poor hygiene are risk factors for transmission.

Evolution of Gastritis and Pathogenesis

Infection with *H. pylori* causes a transient acute gastritis after which the infection may resolve or may go on to become chronic. Acute gastritis is associated with a neutrophilic infiltrate and a transient hypochlorhydria [2]. If the organism colonizes the stomach successfully, an antrum-predominant gastritis develops (Figs. 27.1, 27.2). This form of gastritis is associated with reduced somatostatin production, enhanced gastrin production, and increased gastric acid secretion. The increased acid is delivered into the proximal duodenum and can cause ulcers in some cases. As the infection proceeds progressive inflammation causes a loss of gastrin producing cells and acid production falls. This is accompanied by changes of atrophy on biopsy and intestinal metaplasia develops in some cases. As the environment becomes more alkaline, the infection moves into the corpus of the stomach where continuing inflammation causes a loss of gastric glands and further decreases in acid secretion. Gastric cancer is associated with extensive corpus gastritis, atrophy, and extensive intestinal metaplasia [2] (Fig. 27.4).

Symptoms of Gastritis

Gastritis may be asymptomatic or may be associated with mild dyspeptic symptoms. In other patients, symptoms resembling peptic ulcer disease may be present, including epigastric burning pain and postprandial distress. None of these symptoms is diagnostic of the pathological condition of gastritis but clinicians often use the term gastritis to describe this constellation of symptoms although this use of the term has no specific pathological correlation.

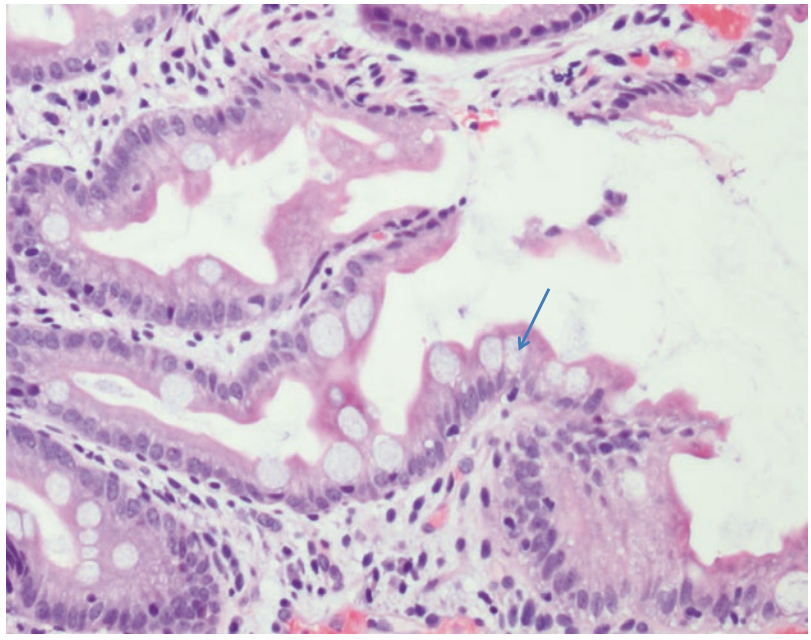

Fig. 27.4 Treatmentregimens for *H. pylori*

Diagnostic Testing

Several tests are available to check for *H. pylori* infection, including noninvasive and invasive approaches. Endoscopy with biopsy is the only way to demonstrate gastritis but the presence of infection can be determined by noninvasive tests.

Serology

Serologic tests for *H. pylori* are an indirect test of *H. pylori* infection [7]. Serologic tests are no longer useful for clinical testing in most countries because of the high rate of false positives.

Stool Antigen Test

The fecal antigen test is an accurate test for use both before and after treatment of *H. pylori* infection [8]. The sensitivity and specificity of the monoclonal stool antigen test is better than 90% and it is comparable in efficacy to the urea breath test. As with the urea breath test the accuracy of the stool antigen test can be impaired by the recent or current use of PPIs or antibiotics [9]. PPIs should be discontinued for approximately 2 weeks before the fecal antigen test, to allow time for the organism to repopulate the stomach.

Urea Breath Test

Another noninvasive, accurate testing option for *H. pylori* is the urea breath test, which is approved for use before and after treatment [10]. The normal human stomach lacks urease activity. *H. pylori* has strong urease activity and therefore evidence of urease activity is diagnostic of *H. pylori* infection. Radiolabeled urea is administered orally. If the stomach is infected, the urea is broken down. The urea breath test is affected by proton pump inhibitors much as the stool antigen test [11].

Treatment of Gastritis Caused by *H. pylori*

Anti-microbial therapy is required to eradicate *H. pylori* and this results in a gradual improvement in gastritis. Eradication of *H. pylori* reduces recurrences of peptic ulcer disease and can be curative of early MALT lymphoma and prevent recurrent gastric cancers in patients who have a resection of an early gastric cancer. The recently published guidelines of the Maastricht IV consensus suggest that standard triple therapy may be used in parts of the world where clarithromycin resistance is less than 15% [12]. Doses and durations are listed in Fig. 27.2. In patients with amoxicillin resistance, metronidazole may be substituted. Bismuth-based quadruple therapy is recommended in areas with high clarithromycin resistance. Second-line therapy recommended by the Maastricht group is levofloxacin-based triple therapy [12]. If second-line therapy fails, culture and sensitivity testing are recommended if available. High dose PPI therapy with amoxicillin and rifabutin triple therapy are alternatives when culture and sensitivity testing is not available.

Disease Associations with *H. pylori* Gastritis

Peptic Ulcer Disease

In developing countries 90% of duodenal ulcers and 80% of gastric ulcers are caused by *H. pylori* infection and eradication prevents relapse [13–15]. In developed countries, *H. pylori* infection causes fewer duodenal and gastric ulcers because nonsteroidal anti-inflammatory drugs are a more frequent cause of ulceration than in developing countries.

Gastric MALToma

Eradicating *H. pylori* in patients with gastric MALToma leads to tumor regression in 60–90% of successfully treated patients and prevents relapse [16, 17].

NSAIDs

H. pylori and NSAIDs are both independent risk factors for peptic ulcer disease [9]. *H. pylori* infection may act in synergy with NSAIDs to increase the risk of ulcer disease [18, 19].

Gastric Cancer

H. pylori has been classified as a carcinogen by the World Health Organization. It is now well established that *H. pylori* eradication decreases the risk of a metachronous gastric cancer developing after resection of an early gastric cancer [20]. It may be possible to prevent gastric cancer by eradicating *H. pylori* infection early in life before atrophy and intestinal metaplasia develop but progression to cancer after eradication therapy may still occur if these changes are present [21–23].

Auto-Immune Gastritis

Autoimmune gastritis is an inherited disorder associated with an immune reaction against parietal cells and intrinsic factor [24]. It occurs in all races and is more common in women. The individuals have varying degrees of chronic inflammation, atrophy, and metaplasia of the gastric epithelium. The patients have elevated levels of antibodies to intrinsic factor and to parietal cells. Patients typically present with pernicious anemia but they may also present with iron deficiency anemia caused by hypochlorhydria.

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Gastric Emptying Studies

28

Henry P. Parkman

Introduction

Gastric emptying testing is useful in the evaluation of patients with dyspeptic symptoms in whom an upper endoscopy does not reveal a cause [1]. Gastric emptying studies are important to help diagnose patients with gastroparesis as well as detecting rapid gastric emptying which might suggest dumping syndrome. There are three types of gastric emptying studies approved for clinical use: gastric emptying scintigraphy, breath testing using stable C-13 isotopes, and wireless motility capsule. Physicians and health care providers ordering these tests and managing patients who have had these tests for their evaluation need to know some aspects on how to perform the tests, how to interpret the tests, and how to use a gastric emptying test in patient management.

Gastric Emptying Testing

There are several clinical reasons for obtaining a gastric emptying study [2]. The most common reason is the evaluation of a patient with dyspeptic symptoms such as nausea, vomiting, abdominal pain, early satiety, and postprandial fullness. A gastric emptying test is obtained after excluding ulcer, obstruction with an upper endoscopy. Another reason is the evaluation of patients with severe reflux symptoms not responding to proton pump inhibitors (PPIs). These patients might have delayed gastric emptying partly responsible for their lack of improvement. Gastric emptying test may be performed in patients with constipation to help identify a pan-GI motility disorder. Patients with delayed gastric emptying and colonic inertia respond less favorable to total colectomy. At our center, we often obtain a whole gut transit scintigraphy study that assesses gastric emptying, small bowel transit, and colonic transit. Other centers use the wireless motility capsule which provides similar information. Diabetic patients with poor glycemic control may have delayed or erratic gastric emptying. Clinically, when a diabetic patient starts having hard to control glucoses, one should suspect that they now have gastroparesis. Occasionally, a gastric emptying test is obtained to evaluate a patient's response to a prokinetic agent.

Results of a gastric emptying test can be normal, delayed, or rapid. Delayed gastric emptying often suggests gastroparesis. Some patient with functional dyspepsia may have delayed gastric emptying. Delayed gastric emptying was detected in 33.5% of 343 patients with functional dyspepsia seen in referral center [3]. Independent factors

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predicting delayed gastric emptying include female gender, postprandial fullness (moderate to severe), and vomiting (severe). In addition, delayed gastric emptying can be seen in patients with anorexia, often with severe weight loss. Rapid gastric emptying suggests the dumping syndrome. Although this is more commonly seen after gastric surgery, it can also be seen in patients with functional dyspepsia [4]. Rapid gastric emptying can also be seen in patients with cyclic vomiting syndrome during the asymptomatic phase [5]. Rapid gastric emptying can also be seen postfundoplication—the wrap prevents fundic accommodation and leads to rapid movement of the ingested meal from the proximal stomach to the distal stomach.

There are several areas to appreciate with gastric emptying testing. First, gastric emptying rates measured by gastric motor testing generally correlate poorly with symptoms of gastroparesis. Patients can have severe nausea and vomiting with normal gastric emptying [6]. These patients also represent a significant medical problem and are, for the most part, indistinguishable from those with gastroparesis. At our institution, 1499 patients underwent gastric emptying scintigraphy from September 2007 to January 2010 [7]. GES was performed with ingestion of a liquid egg white meal with imaging at 0, 0.5, 1, 2, 3, and 4 h. Patients completed the Patient Assessment of Gastrointestinal Symptoms (PAGI-SYM). 629 of 1499 patients (42%) had increased retention at 4 h (>10%) consistent with gastroparesis. The symptoms correlating with gastric retention at 4 h included early satiety ($r = 0.170$; $p < 0.01$), vomiting ($r = 0.143$; $p < 0.01$), postprandial fullness ($r = 0.123$; $p < 0.01$), and loss of appetite ($r = 0.122$; $p < 0.01$). The r correlation coefficients are low suggesting poor correlation. Thus other factors in addition to gastric emptying appear to impact on patient's symptoms. Second, there are relatively high interindividual and intraindividual variability in gastric emptying rates measured with gastric motor testing, which constitutes another limitation of gastric motor testing [8]. The relative contributions to these variabilities of gastric motor testing methodology and biologic inconsistency in gastric emptying are not currently known. Finally, and importantly, the usefulness of emptying tests in directing therapy and predicting response is debated [9, 10]. Some other causes of nausea/vomiting can be associated with delayed GE. These include functional dyspepsia, GERD, cyclic vomiting syndrome, rumination syndrome, eating disorders (bulimia, anorexia nervosa), and superior mesenteric artery (SMA) syndrome.

Radionuclide Gastric Emptying Scintigraphy

For evaluating gastric emptying, the standard test is gastric emptying scintigraphy, which uses a radiolabeled isotope bound to solid food to image gastric emptying of a solid meal [2]. Gastric emptying scintigraphy remains the best current test for measuring gastric emptying because it is sensitive, quantitative, and physiological. It is used to confirm the presence of gastric stasis after excluding structural or mucosal disorders.

There is variable methodology used at different centers. Most centers use a ^{99m}Tc sulfur colloid-labeled egg sandwich as a test meal [2]. A consensus statement from the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine recommends a standardized method for measuring gastric emptying by scintigraphy [11]. A low-fat egg white meal (Eggbeaters egg whites (ConAgra Foods, Inc.; Downers, IL) with imaging at 0, 1, 2, 4 h after meal ingestion, as described by a published multicenter protocol [12], provides standardized information about normal, delayed, and rapid gastric emptying and is currently the best way to conduct a scintigraphic gastric emptying test. Adoption of this standardized protocol will help resolve the lack of uniformity of testing, add reliability and credibility to the results, and improve the clinical utility of the gastric emptying test [11]. This test meal has a low fat content and theoretically might produce different results than conventional meals.

The radiolabel needs to be cooked into the egg white so that the radioisotope binds to the solid phase, thus preventing elution of the radiotracer

into the liquid phase with an erroneous measurement of the faster liquid phase of gastric emptying [8].

Imaging is performed in the anterior and posterior projections at least at four time points (0, 1, 2, and 4 h) [11, 12]. The 1 h image is used to help detect rapid gastric emptying. Our center also obtains a 30 min image to assess for rapid gastric emptying. The 2 and 4 h images are used to evaluate for delayed gastric emptying. Imaging for gastric emptying up to 4 h increases the detection of delayed gastric emptying and is now recommended as the standard in all tests to obtain reliable results for the detection of gastroparesis [13, 14]. When gastric scintigraphy is performed for shorter durations, the test is less reliable because of large variations in normal gastric emptying.

Patients should discontinue medications that may affect gastric emptying for an adequate period before this test based on drug half-life. Generally, this is for 3 days prior to the test. The drugs to be primarily concerned about include narcotic opioid analgesics and anticholingergic agents that can delay gastric emptying and prokinetic agents that can accelerate gastric emptying. Other agents may also impact on gastric emptying including those used to treat diabetes, including pramlintide (an amylin-like compound), and exenatide (a GPL1 receptor agonist). Serotonin receptor antagonists such as ondansetron, which have little effect on gastric emptying, may be given for severe symptoms before performance of gastric scintigraphy.

Diabetic patients should try to be in relatively good control for this test. Hyperglycemia (glucose level > 270 mg/dL) delays gastric emptying in diabetic patients. It is not unreasonable to defer gastric emptying testing until relative euglycemia is achieved to obtain a reliable determination of emptying parameters in the absence of acute metabolic derangement.

Premenopausal women have slower gastric emptying than men, so some advocate using separate reference values for premenopausal women [3].

Emptying of solids typically exhibits a lag phase followed by a prolonged linear emptying phase. The lag phase for solids represents the time required for trituration of solid food into 1- to 2-mm particles that can then empty through the pylorus [15]. A variety of parameters can be calculated from the emptying profile of a radiolabeled meal. The simplest approach for interpreting a gastric emptying study is to report the percent retention at defined times after meal ingestion (usually 2 and 4 h). Curve-fitting techniques can calculate the half-emptying time, the time for half of the stomach contents to have emptied from the stomach. Extrapolation of the emptying curve to predict the half-emptying time may be unreliable if the emptying has not reached 50% during the actual imaging [16].

Measurement of gastric emptying of solids is more sensitive than measurement of gastric emptying of liquids for detection of symptomatic gastroparesis because emptying of liquids is often preserved until the disorder is advanced. Determination of emptying rates of liquid meals is less sensitive [17] and generally reserved for the evaluation of dumping syndrome and postgastric surgical disorders. In patients who have undergone gastric surgery, a dual solid and liquid emptying test may be indicated because symptoms may result from slow solid emptying or rapid liquid emptying.

Advances in scintigraphy may provide information on fundic and antral abnormalities. Regional gastric emptying can assess intragastric meal distribution and transit from the proximal to distal portions of the stomach and may provide greater information regarding fundal and antral function. Visual inspection of fundal and antral gastric emptying and quantification of regional emptying with fundic and antral regions of interest can be helpful for defining abnormal physiology and explaining dyspeptic symptoms, especially when global gastric emptying values are normal [11]. Studies have shown an association between symptoms of nausea, early satiety, abdominal distention, and acid reflux with proximal gastric retention, whereas vomiting is associated more with delayed distal GE [18]. Dynamic antral scintigraphy with frequent 1-s imaging can evaluate antral wall contractility and has been used in clinical research studies [19].

Wireless Motility Capsule to Assess Gastric Emptying

The wireless motility capsule (SmartPill) is an ingestible capsule that measures pH, pressure, and temperature using miniaturized wireless sensor technology. The wireless motility capsule is swallowed by the patient; pH and pressures are recorded as the capsule traverses the gastrointestinal tract. From these measurements, gastric emptying and total gastrointestinal tract transit time can be obtained. In addition, the wireless motility capsule will characterize pressure patterns and provide motility indices for the stomach, small intestine, and colon. The gastric residence time of the wireless motility capsule has a high correlation (85%) with the T-90% of gastric emptying scintigraphy, suggesting that the gastric residence time of the wireless motility capsule represents a time near the end of the emptying of a solid meal [20]. It appears to empty with the phase III migrating motor complex signifying completion of the postprandial phase and return to the fasting condition [21]. The gastric residence time of the wireless motility capsule is able to differentiate normal gastric emptying from delayed gastric emptying similar to scintigraphy [20].

One advantage of the wireless motility capsule is the ability to not only measure gastric emptying, but also assess small bowel transit and colonic transit [22]. In addition, pressure profiles provide motility indices for the stomach, small intestine, and colon.

There have been several reports of capsule endoscopy used to measure gastric emptying; this technique is able to visualize the capsule emptying from the stomach and thus measure gastric emptying of the capsule from the stomach. These studies have been limited by the need to perform this technique in the fasting stomach. How this relates to a physiological meal has not been determined.

Stable Isotope Breath Tests for Gastric Emptying

Stable isotope breath tests for gastric emptying represent a way to evaluate gastric emptying noninvasively and without radiation exposure. Breath tests using the nonradioactive isotope ^{13}C bound to a digestible substance have been validated for measuring gastric emptying. Most commonly, ^{13}C-labeled octanoate, a medium-chain triglyceride, is bound into a solid meal such as a muffin [23–25]. Other studies have bound ^{13}C to acetate or proteinaceous algae (*Spirulina platensis*) [26]. This is the test that has been approved for clinical practice. After ingestion and stomach emptying, ^{13}C-octanoate is absorbed in the small intestine and metabolized to $^{13}CO_2$, which is then expelled from the lungs during respiration. The rate-limiting step is the rate of solid gastric emptying. Thus, C-13 breath testing provides a measure of solid-phase emptying. The ^{13}C breath test provides reproducible results that correlate with findings on gastric emptying scintigraphy [26]. As these tests do not involve radiation exposure, they can be used in the clinic or at the bedside. Breath samples can be preserved and shipped to a laboratory for analysis. Stable isotope breath testing has been used mainly in a research setting. Promising validation studies have been performed with a shelf-stable product consisting of a freeze-dried egg mix labeled with ^{13}C platensis, saltine crackers, and meal [26]. This meal was simultaneously evaluated with scintigraphy in 38 normal subjects and 129 patients with gastroparetic symptoms. Individual breath samples were collected at 45, 150, and 180 min after meal ingestion with 89% sensitivity for identifying delayed gastric emptying and 93% sensitivity to identify accelerated gastric emptying.

The ^{13}C-breath test has been used in clinical research and pharmaceutical studies. It is now approved for clinical practice in the evaluation of patients. It is considered an office-based test, one that a gastroenterology practice can perform. Validation of this test in patients with emphysema, cirrhosis, celiac sprue, and pancreatic insufficiency is needed, because it is not clear whether substrate metabolism in these disorders may also be a rate-limiting step for $^{13}CO_2$ excretion.

Ultrasonography

Transabdominal ultrasonography can measure several parameters of gastric motility. Serial

changes in antral cross-sectional area are measured as an index of gastric emptying; emptying is considered complete when the antral area returns to the fasting baseline [27]. Duplex sonography may be used to evaluate transpyloric flow of liquid gastric contents. Ultrasonography has also been employed to measure accommodation in the proximal and distal stomach [8]. Unfortunately, ultrasonography for gastric emptying is operator dependent and generally measures liquid emptying only. The test is suboptimal in obese people. Ultrasonography is most commonly used only in research settings.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging can measure gastric emptying and gastric volume, and index of gastric accommodation. In this test, transaxial abdominal scans are generally obtained in the supine position every 15 min before and after a predominately liquid meal applying a spin-echo technique with T1 weighted images [8]. Magnetic resonance imaging can differentiate between gastric meal volume and total gastric volume, allowing determination of gastric secretory rates. This noninvasive test is appealing as MRI can be used to measure gastric emptying, volume, and wall motion without radiation exposure. In addition, MRI has the ability to separately assess the emptying of fat and water from the stomach. Recent studies suggest that postprandial gastric expansion is accompanied by increased air. Further studies need to understand the contribution of gastric relaxation and swallowed air to postprandial volume changes. The specialized equipment, time needed for interpretation, and expense have limited MRI's role in assessing gastric motility to use in clinical research. The supine position of the patient for imaging is also a potential limitation as this is not the normal position postprandially. Studies suggest that body position does not affect gastric relaxation and initial postprandial gastric volumes; however, meal emptying is slower supine than sitting.

Likely Future Trends and Directions

In the last several years, emerging technologies have been introduced for evaluation of gastroparesis. The gastric emptying scintigraphy test has been enhanced by measuring emptying out to 4 h and protocols to standardize this among centers. In addition to gastric emptying scintigraphy, two other office-based tests for gastric emptying have been approved: wireless motility capsule and breath testing. In addition, others assessments for gastric pathophysiology are being developed, including assessment of gastric accommodation using scintigraphy and/or nutrient drink tests. Hopefully, tests for gastric hypersensitivity will be developed. A less invasive gastric barostat would allow improved evaluation of gastric pathophysiology.

Conclusions

Gastric emptying testing is useful in patients with dyspeptic symptoms. It is extremely helpful to diagnose a patient with gastroparesis. A gastric emptying test is also used to help diagnose dumping syndrome. Three types of gastric emptying studies are now approved for clinical use: gastric emptying scintigraphy, breath testing, and wireless motility capsule, allowing physicians access to a number of technologies to assess gastric emptying and hopefully to help direct patient care.

Appendix

Common Patient Asked Question

1. My recent gastric emptying test was normal, though it was delayed in the past and I was told I had gastroparesis. What do I have?

Gastric emptying testing is needed to diagnose gastroparesis. The standard gastric emptying test is gastric emptying scintigraphy, which uses a radiolabeled isotope bound to solid food to image the meal emptying. However, there is variable methodology used at different centers. Standardization of gastric emptying among different centers has been suggested using a 4 h imaging

protocol with scans taken 0, 1, 2, 4 h after ingestion of a radioactive Tc-99m labeled low-fat egg white with jam and 2 pieces of toast. The shorter duration tests lasting 60–90 min using different meals are not as helpful. Relatively high variability in gastric emptying constitutes another limitation of gastric motor testing. Unfortunately, gastric emptying rates measured by gastric motor testing do not correlate well with symptoms of gastroparesis. Patients can have severe nausea and vomiting with normal gastric emptying. These patients also represent a significant medical problem and are, for the most part, indistinguishable from those with gastroparesis. These findings suggest that factors in addition to slow gastric emptying contribute to symptoms.

Suggested Reading

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Pathikonda M, Sachdeva P, Malhotra N, Fisher RS, Maurer AH, Parkman HP. Gastric emptying scintigraphy: is four hours necessary? J Clin Gastroenterol. 2012 Mar; 46(3):209-15.

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Gastric Functional Tests: Upper Gatrointestinal Barium Studies

29

Marc S. Levine

Introduction

Gastric motility plays an important role in the digestive process by promoting mechanical breakdown of ingested solids in the stomach in combination with peptic acid and other enzymes to facilitate digestion and absorption of nutrients. A nuclear medicine gastric emptying scan is often performed as an indirect measure of gastric motility by quantifying emptying of solids from the stomach; patients are presumed to have gastroparesis (i.e., decreased or absent gastric peristalsis) when these scans show delayed emptying of solids from the stomach in the absence of gastric outlet obstruction on endoscopy or barium studies [1]. However, gastroparesis can also be diagnosed on barium studies by direct observation of decreased or absent gastric peristalsis on real-time fluoroscopy. Other radiographic signs of this condition include gastric dilation, retained food or fluid in the stomach, and delayed gastric emptying of barium. While some patients with nausea and vomiting have underlying gastroparesis as the cause of their symptoms, others paradoxically have increased peristalsis with intense gastric contractions, a condition that has been described on barium studies as a "hyperirritable" stomach [2]. The purpose of this chapter is to present the findings on barium studies in patients with gastric motility disorders and to discuss the clinical features of these conditions.

Question #1: Apart from showing morphologic findings of gastric outlet obstruction, do upper gastrointestinal (GI) barium studies have a role in evaluating functional causes of nausea and vomiting?

It is important to recognize that upper GI barium studies are valuable not only for detecting morphologic abnormalities in the upper GI tract but also for assessing gastric motility and, more specifically, for determining whether gastric peristalsis is normal, decreased, or absent. While morphologic abnormalities are found by careful review of a series of spot images obtained during the barium study, gastric motility is assessed by direct observation of gastric peristalsis on real-time fluoroscopy as the procedure is being performed. In patients with recurrent nausea and vomiting, the upper series therefore can be used to detect not only morphologic findings of gastric outlet obstruction, but also a decrease in the frequency, strength, or velocity of peristaltic waves in the stomach at fluoroscopy. When significantly decreased or absent gastric peristalsis is observed in the

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absence of findings of gastric outlet obstruction, a diagnosis of gastroparesis can be made as the cause of the patient's symptoms. The following sections discuss in greater detail the predisposing factors as well as the clinical and radiographic findings in patients with this condition.

Normal Gastric Motility on Barium Studies

Gastric peristalsis is typically characterized on single- or double-contrast upper gastrointestinal (GI) barium studies by a progressive stripping wave that transiently narrows successive portions of the stomach as it passes from the proximal body to the distal antrum on real-time fluoroscopy. Because there is no peristalsis in the gastric fundus, patients who undergo bariatric surgery or partial gastrectomy with surgical bypass or resection of the gastric body and antrum are at increased risk for developing gastric bezoars (see later section, *Gastric Bezoars*).

Gastric peristalsis may be manifested at fluoroscopy by smooth, tapered, or conical indentations on both the lesser and greater curvatures of the stomach that progressively narrow the lumen as the peristaltic wave passes caudally from the upper body to the distal antrum and pylorus, often culminating in expulsion of a bolus of barium from the stomach into the proximal duodenum. In many patients, however, fluoroscopy reveals incomplete peristaltic waves traversing only a portion of the gastric body or antrum or asymmetric waves indenting only one wall of the stomach (the lesser or greater curvature) rather than both. The rate at which these peristaltic waves traverse the stomach and the interval between peristaltic waves also is variable. In some patients, gastric peristalsis may be transiently inhibited when the stomach is initially distended with barium, erroneously suggesting gastroparesis. In such cases, however, gastric peristalsis usually reverts to normal within several minutes. Decreased or absent peristalsis that occurs as a transient finding early in the fluoroscopic study therefore should not be interpreted as gastroparesis if normal peristalsis is subsequently observed, especially in patients who are asymptomatic.

When a double-contrast examination of the upper GI tract is performed at our institution, we often administer 1 mg of glucagon intravenously to induce gastric hypotonia and optimize detection of mucosal abnormalities in the stomach [3]. If a patient presents with nausea and vomiting, however, administration of glucagon or other pharmacologic agents that inhibit gastric persistalsis is contraindicated, as such agents preclude fluoroscopic evaluation of gastric motility. We therefore do not administer glucagon to patients with nausea and vomiting, so the radiologist performing the barium study can assess not only for gastric outlet obstruction but also for gastroparesis as a possible cause of symptoms.

Gastroparesis

Predisposing Conditions

The two most common predisposing factors responsible for gastroparesis are diabetes and narcotics [1, 4]. Other causes include vagotomy, hypothyroidism, collagen vascular disease, chronic renal failure, cystic fibrosis, and medications such as calcium channel blockers, beta antagonists, and anticholinergics [1, 5]. In the absence of any known causes of decreased gastric motility, a diagnosis of idiopathic gastroparesis should also be considered. This condition occurs primarily in young women and accounts for 36–54% of all patients with gastroparesis [6–8].

Clinical Findings

Gastroparesis is a common GI motility disorder that causes a variety of clinical findings. Intractable nausea and vomiting are the two most common symptoms; nausea has been reported in 92–93% and vomiting in 68–84% of patients with gastroparesis [7, 8]. Other findings include bloating, early satiety, postprandial fullness, and,

rarely, upper GI bleeding [7–9]. These patients may also present with abdominal pain, but it is unusual to experience pain in the absence of other symptoms [8, 9]. Patients with gastroparesis are also at risk for developing serious complications, including reflux esophagitis, gastric bezoars, and Mallory-Weiss tears [1, 10, 11]. In patients with severe disease, intractable vomiting may cause dehydration, electrolyte imbalances, and malnutrition [12], so gastroparesis can be a potentially life-threatening condition.

Despite its seriousness, gastroparesis is thought to be a treatable disease, as symptoms often can be alleviated by pharmacologic agents and/or correction of the underlying factors responsible for this condition. In one meta-analysis of pharmacologic management of gastroparesis (usually prokinetic agents to increase gastric peristalsis), symptom scores improved by 50–75% after treatment with metoclopramide, cisapride, erythromycin, and domperidone [13]. In patients with diabetic or idiopathic gastroparesis, two multicenter trials also reported a 76–80% reduction in symptoms over a 15-month period by the use of gastric electrical stimulators [14, 15].

More than 75% of patients with gastroparesis are women [7, 9]. This high female predominance is most likely related to slower rates of gastric emptying in women than in men (particularly during the luteal phase of the menstrual cycle), as cyclic secretion of progesterone decreases contraction of gastric muscle [16, 17]. Some of the underlying causes of gastroparesis, such as hypothyroidism and collagen vascular disease, are also more common in women.

Radiographic Findings

Since its introduction by Griffith et al. in 1968 [18], a nuclear medicine solid gastric emptying scan has become widely accepted as the definitive test for the diagnosis of gastroparesis in patients with recurrent nausea and vomiting [19]. This test is thought to be positive when it shows delayed emptying of solids from the stomach in combination with endoscopy or barium studies showing no evidence of gastric outlet obstruction [1]. This approach is based on the assumption that gastroparesis is equated with delayed gastric emptying of solids. Nevertheless, the value of this test has been questioned by some investigators because of poor correlation between patient symptoms and gastric emptying rates [20–25]. Other studies have shown that nuclear medicine solid gastric emptying scans can be normal in patients with gastroparesis [26, 27], and, conversely, that nuclear medicine solid gastric emptying scans can be abnormal in patients who have no symptoms of gastroparesis [28, 29]. Quantification of delayed gastric emptying also is not standardized and varies widely among institutions [30]. These findings raise questions about the fundamental assumption that delayed gastric emptying of solids on a nuclear medicine scan is a prerequisite for the diagnosis of gastroparesis.

In a position paper by the American Gastroenterological Association (AGA) in 2004, barium studies were not mentioned as a possible diagnostic tool for gastroparesis [1]. An accompanying technical review from the AGA even recommended that barium studies not be used to assess for delayed emptying of barium from the stomach [2]. The barium study traditionally has been considered to be a suboptimal test for evaluation of gastric emptying because fluoroscopic assessment of the rate of emptying of barium from the stomach may be subjective and therefore is prone to interobserver variation [31, 32].

In a study by Levin et al. in 2008 [33], however, 50 patients with nausea, vomiting, or related symptoms had a diagnosis of gastroparesis on upper GI barium studies if the strength, velocity, and/or frequency of gastric peristaltic waves was substantially decreased or absent at real-time fluoroscopy (Fig. 29.1). Ancillary findings of gastroparesis included delayed gastric emptying of barium (Fig. 29.2), gastric dilation (Fig. 29.3), and/or residual fluid (Fig. 29.4) or debris (Fig. 29.5) in the stomach in the absence of morphologic findings of gastric outlet obstruction. Using these criteria, 46 (92%) of 50 patients were thought to have gastroparesis on the basis of the barium studies.

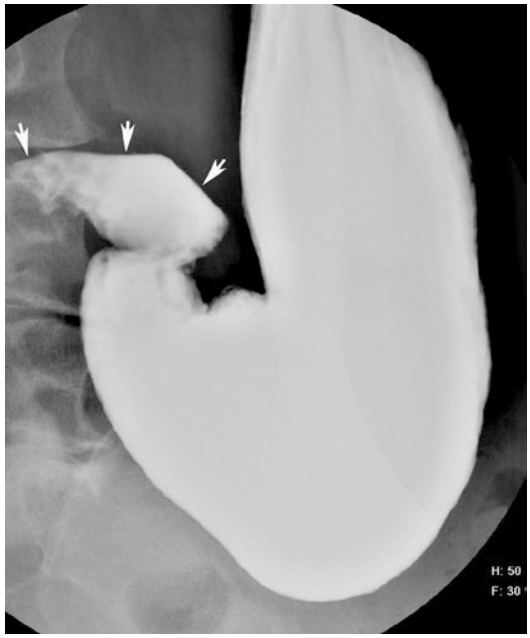

Fig. 29.1 Gastroparesis in a patient with diabetes. Left posterior oblique view of the stomach from a single-contrast upper GI examination shows a flaccid, mildly dilated stomach. There was no gastric peristalsis at fluoroscopy. Nevertheless, barium is seen to empty from the stomach into the duodenal bulb (*arrows*) without evidence of gastric outlet obstruction

Forty-two (84%) of these 50 patients were treated for gastroparesis, and 35 (83%) of the 42 had symptoms that decreased or resolved after treatment, corroborating the radiographic findings [33]. The upper GI barium study therefore has been shown to be a useful test to evaluate for gastroparesis in patients with recurrent nausea and vomiting.

Surprisingly, in the study by Levin et al., seven (35%) of 20 patients with gastroparesis who underwent nuclear medicine solid gastric emptying scans had normal emptying of solids from the stomach [33]. Four of these patients were treated for gastroparesis and three (75%) had symptomatic improvement, suggesting that they had gastroparesis despite normal emptying of solids on the nuclear scans. These findings support the observations of other investigators that delayed

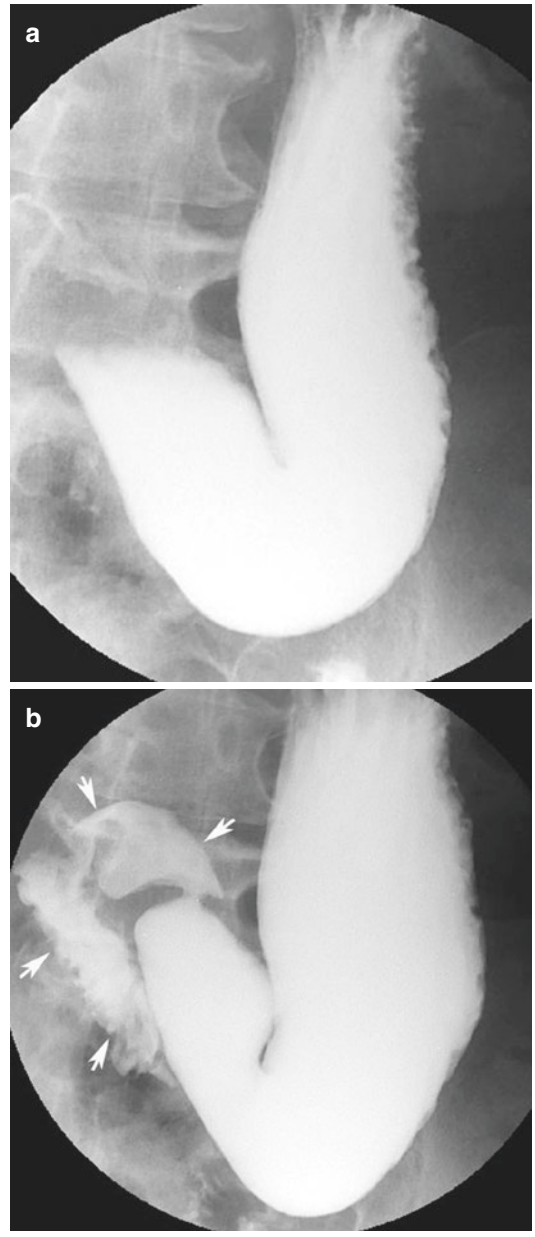

Fig. 29.2 Gastroparesis in a patient on narcotic medication for chronic low back pain. Supine view from a single-contrast upper GI examination shows a flaccid stomach with delayed emptying of barium into the duodenum. There was no gastric peristalsis at fluoroscopy. Repeat view later in the study shows emptying of barium into the duodenal bulb and descending duodenum (*arrows*) without evidence of gastric outlet obstruction

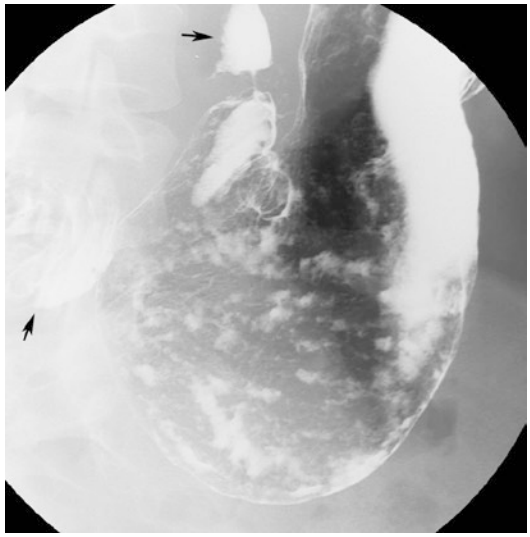

Fig. 29.3 Gastroparesis in a patient with hypothyroidism. Left posterior oblique view from a double-contrast upper GI examination shows a considerably dilated stomach with retained intraluminal fluid causing flocculation of ingested barium. There was markedly decreased gastric peristalsis at fluoroscopy. Despite these findings, note barium in the duodenal bulb and descending duodenum (*arrows*) without evidence of gastric outlet obstruction

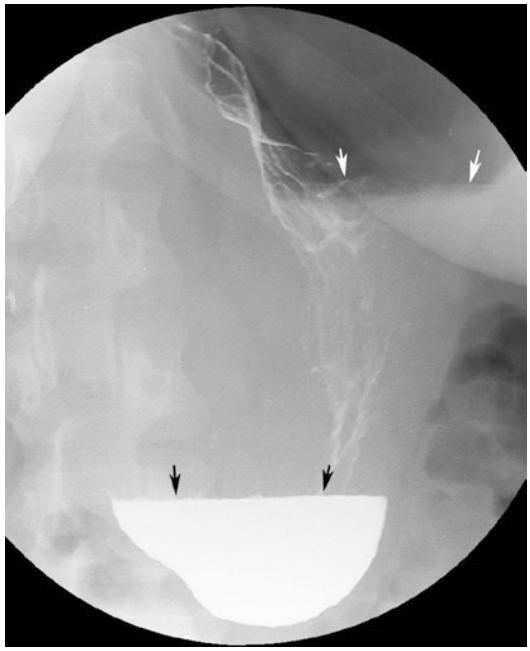

Fig. 29.4 Idiopathic gastroparesis in a young woman. An upright frontal view from a single-contrast upper GI examination shows a barium level (*black arrows*) in the gastric antrum and a fluid level (*white arrows*) in the upper gastric body due to gastroparesis with markedly delayed emptying of fluid and secretions from the stomach. Also note the absence of any barium in the duodenum on this early image from the study

gastric emptying of solids on a nuclear medicine scan is not a prerequisite for the diagnosis of gastroparesis [26, 27]. These discrepancies can be explained by the fact that delayed emptying of solids from the stomach is one marker for gastroparesis and that decreased or absent gastric peristalsis is another marker for an overlapping group of patients with this condition.

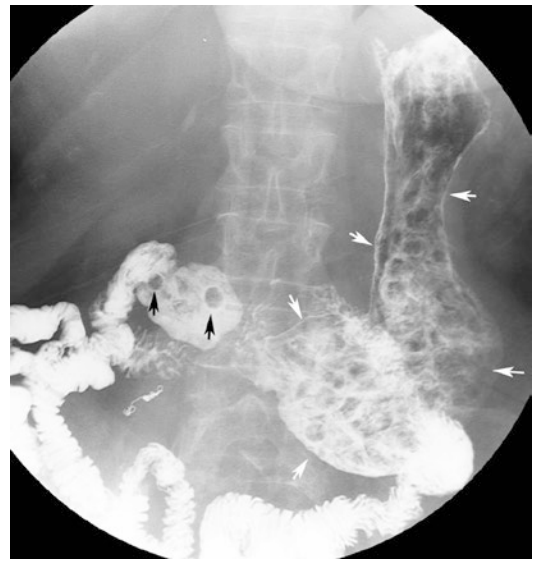

Fig. 29.5 Gastroparesis in a patient with diabetes. There is a large amount of retained food/debris (*white arrows*) in the stomach secondary to marked gastroparesis. Also note several food particles (*black arrows*) in the duodenal bulb. Despite retention of undigested food in the stomach, there is normal emptying of barium into nondilated duodenum and proximal small bowel without evidence of gastric outlet obstruction

Gastric Bezoars

Predisposing Conditions

Gastric bezoars, defined as conglomerate masses of food or foreign matter in the stomach, have a reported incidence of less than 1% in the general population [11]. Bezoars classically have been attributed to ingestion of fruit or vegetable matter (especially persimmons) that form conglomerate masses, also known as *phytobezoars*, or to ingestion of hair that forms matted hair balls, also known as *trichobezoars*, in the stomach [34–36]. However, most gastric bezoars are now believed to be caused either by gastroparesis [37–41] or by partial gastrectomy [42–44] or bariatric surgery [41, 45–47]. Whatever the underlying cause, decreased or absent gastric peristalsis results in poor mechanical breakdown of ingested solids that go on to form conglomerate masses of undissolved food matter in the stomach. In one study, 58% of patients with gastric bezoars had known risk factors for gastroparesis, and barium studies revealed markedly decreased or absent peristalsis in the stomach in 62% of patients who had not undergone partial gastric resection or bariatric surgery [41].

It is well recognized that gastric bezoars may develop as a complication of partial gastrectomy for gastric ulcers or other abnormalities [42–44]. Such bezoars are thought to develop as a result of gastric resection and vagotomy, with loss of gastric peristalsis and the normal mixing function of the distal part of the stomach [42, 43]. Such bezoars have been shown to occur after partial gastrectomy even in the absence of anastomotic strictures (Fig. 29.6), so these bezoars presumably develop because of surgical absence of the gastric antrum and body—the portion of the stomach normally responsible for breaking down ingested solids by active peristalsis. Thus, even in the absence of anastomotic strictures, these patients have the functional equivalent of severe gastroparesis as the cause of bezoar formation.

Similarly, patients who undergo bariatric procedures such as Roux-en-Y gastric bypass or laparoscopic gastric banding may develop bezoars within the gastric pouch even in the absence of strictures or obstruction of the pouch (Fig. 29.7), presumably because of surgical

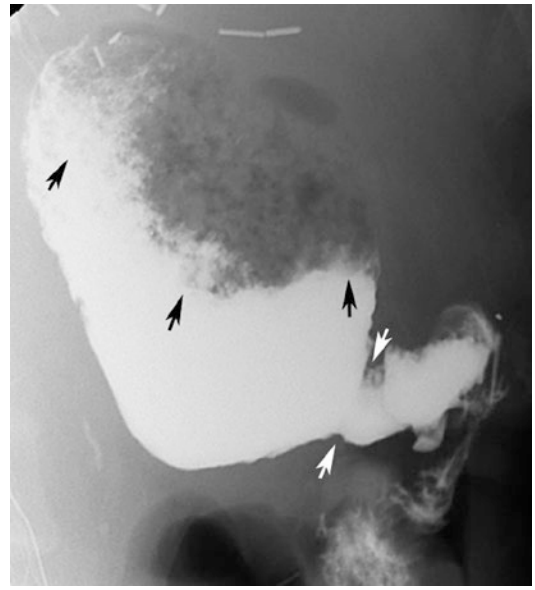

Fig. 29.6 Gastric bezoar after partial gastrectomy and gastrojejunostomy for ulcer disease. The bezoar is seen as a large conglomerate mass of undigested food (*black arrows*) in the gastric remnant. Despite the bezoar, this patient has a patent gastrojejunal anastomosis (*white arrows*) without evidence of anastomotic obstruction

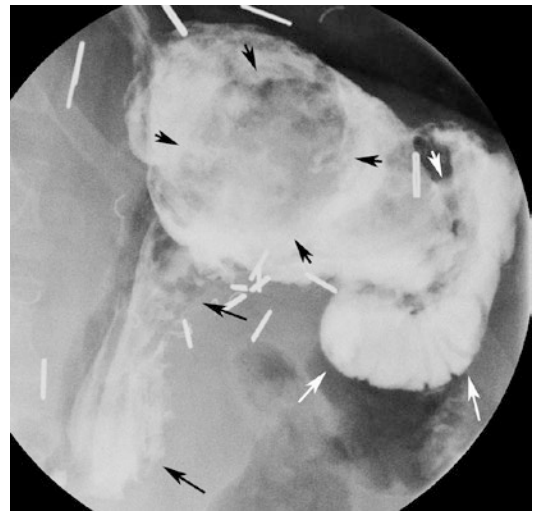

Fig. 29.7 Gastric bezoar after Roux-en-Y gastric bypass. A large radiolucent bezoar (*short black arrows*) is present within the gastric pouch. Note emptying of barium from the pouch into the jejunum (*long white arrows*) via a patent gastrojejunal anastomosis (*short white arrow*). Also note barium entering the excluded gastric body/antrum (*long black arrows*) secondary to breakdown of the gastric staple line

bypass of the gastric antrum and body or laparoscopic banding of the proximal stomach that delays emptying of ingested food into the antrum and body (where gastric peristalsis normally occurs), so these patients also have the functional equivalent of severe gastroparesis [41, 45–47]. With the rising popularity of bariatric surgery for treatment of morbid obesity, gastric bezoars are likely to be encountered with greater frequency as a complication of this surgery in the future.

Clinical Findings

Patients with gastric bezoars may present with a variety of symptoms, including epigastric pain, bloating, nausea, vomiting, early satiety, upper GI bleeding, or even intermittent dysphagia caused by mobile bezoars that periodically obstruct the gastric cardia [37, 41, 48]. The development of intractable symptoms occasionally necessitates treatment by dissolution or suction of the bezoar at endoscopy.

While bezoars might be expected to develop slowly over a long period of time, it has been shown that some patients have symptoms for less than 1 week and that bezoars can resolve quickly on dietary restrictions and pharmacologic agents without need for endoscopy [41]. Thus, some patients with gastric bezoars have an acute clinical presentation, and some bezoars can heal rapidly on conservative management.

Radiographic Findings

Gastric bezoars classically appear on barium studies as mobile masses in the stomach that float in the barium pool and typically have a mottled appearance secondary to trapping of barium in the interstices of the mass (Fig. 29.8) [41]. However, some gastric bezoars have a more homogeneous appearance (Fig. 29.9) or can be immobile at fluoroscopy if they are adherent to the gastric wall [41]. Rarely, bezoars can become so large that they occupy virtually the entire stomach (Fig. 29.10) [41]. Even when freely mobile, bezoars may sink to the most dependent portion of the barium pool (rather than floating in the barium pool) because of their high density [41]. As a result, gastric bezoars can be manifested by a spectrum of findings on barium studies, depending on their

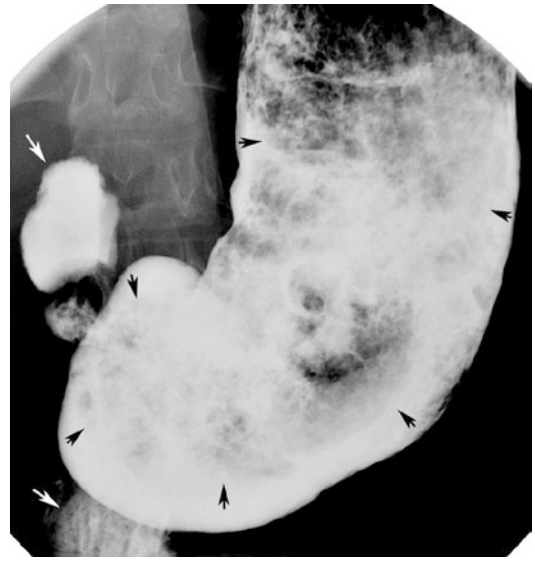

Fig. 29.8 Giant gastric bezoar in patient with underlying gastroparesis. The bezoar is seen as a large conglomerate mass of undigested food (*black arrows*) in a dilated stomach. Note the mottled appearance of the bezoar secondary to trapping of barium in the interstices of the mass. Also note barium in the duodenum and proximal jejunum (*white arrows*) without evidence of gastric outlet obstruction

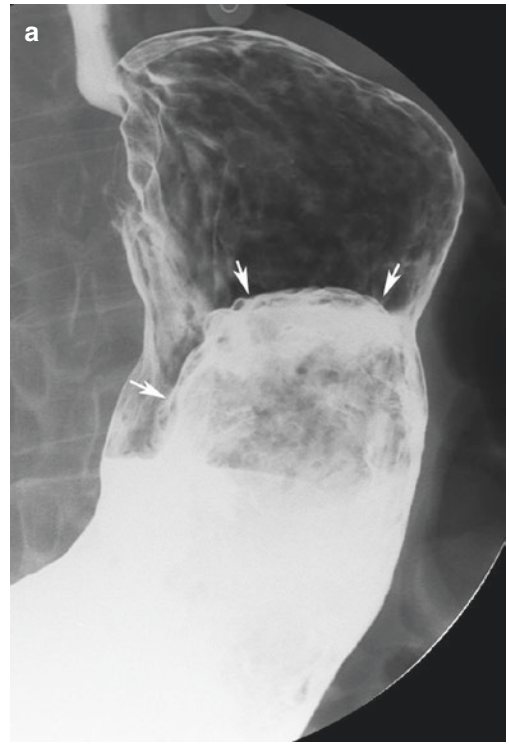

Fig. 29.9 Two examples (**a** and **b**) of gastric bezoars that have a more homogeneous appearance (*arrows*) than the bezoars shown in Figs. 29.6 and 29.8. Also note how the bezoar in Fig. 29.9a is floating in the barium pool

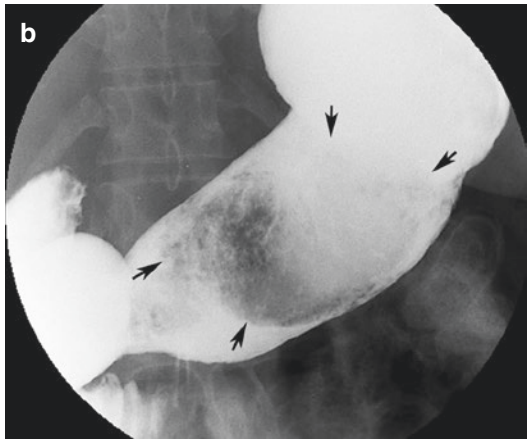

Fig. 29.9 (continued)

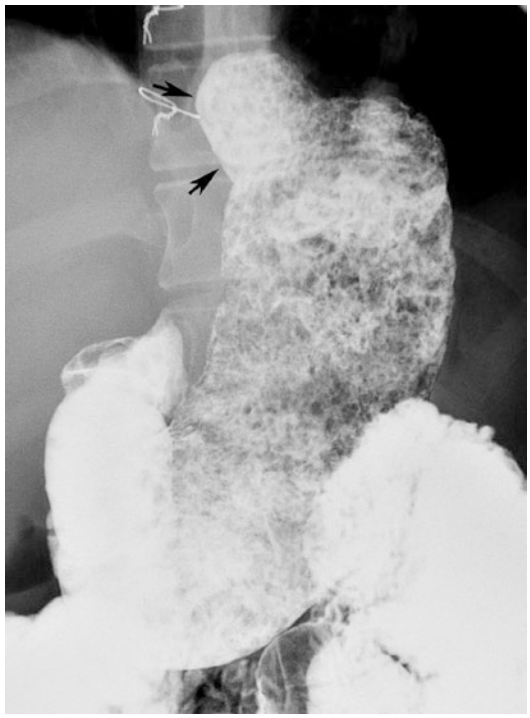

Fig. 29.10 Gastric bezoar filling virtually the entire stomach as a giant conglomerate mass of undigested food. Also note food within the lumen of a small hiatal hernia (*arrows*)

cohesiveness and density. It therefore is important to recognize the value of barium studies with real-time fluoroscopy for assessing the appearance and mobility of a bezoar and its relationship to the gastric lumen.

Competitive Speed Eating

Competitive speed eating has emerged over the past decade as an increasingly popular competitive sport with a growing legion of worldwide fans. These contests raise a fascinating question about how speed eaters are able to consume such enormous quantities of food in such short periods of time. In a study by Levine et al. from 2007 [49], this issue was addressed in a speed eating simulation with fluoroscopic observation of a professional speed eater ranked as one of the top competitors in the world by the International Federation of Competitive Speed Eating (IFOCE). The speed eater was found to have markedly altered gastric motility at fluoroscopy, as his stomach rapidly accommodated an enormous quantity of ingested food by progressively expanding until it became a giant, flaccid sac occupying a major portion of his abdomen (Fig. 29.11). Put differently, his stomach acted as a compliant, expansile receptacle, dilating to a degree that it could accept an almost unlimited volume of food. Conversely, gastric peristalsis was virtually absent at fluoroscopy, and little or no ingested food emptied into the duodenum. Though the simulation involved only a single speed eater, the fluoroscopic findings were so spectacular that the investigators postulated that the profound gastroparesis observed in their subject could be extrapolated to speed eaters in general as the basis for their speed eating skills [49].

On subsequent questioning, the speed eater indicated that he developed his speed-eating skills by extensive training, forcing himself to consume ever-increasing amounts of food despite a sensation of satiety [49]. In effect, he was able to overcome the usual checks and balances associated with eating by exercising extreme self-discipline to consume larger and larger quantities of food than "normal" eaters could ever ingest. Only as a result of this prolonged and intensive training was the speed eater able to adapt his stomach until it could withstand the rigors of competitive speed eating. In that sense, a world-class speed eater requires a level of commitment and will power comparable to those of professional athletes honing their skills for other sports.

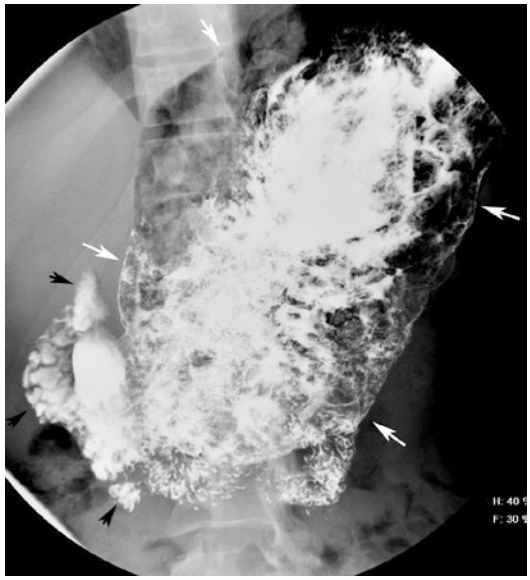

Fig. 29.11 Competitive speed eater's stomach after consuming 36 hot dogs in a speed-eating simulation. The stomach is filled with undigested hot dog pieces and has expanded to form a giant, flaccid sac (*white arrows*) occupying a major portion of his upper and midabdomen. Nevertheless, a small amount of barium is seen to enter the proximal duodenum (*black arrows*) without evidence of gastric outlet obstruction

Nevertheless, the investigators who performed the simulation expressed concern that a chronically dilated, flaccid stomach with profound self-induced gastroparesis could eventually decompensate, becoming an enormous sac incapable of shrinking to its normal size and incapable of peristalsing and emptying solid food [49]. If so, long-term competitive speed eaters could develop intractable nausea and vomiting, potentially necessitating a partial or total gastrectomy to relieve their symptoms and restore their ability to eat normally [49]. In this context, competitive speed eating could be viewed as a self-destructive form of behavior, so competitive speed eaters need to be aware of the potential long-term risks of this sport.

Question #2: When patients with nausea and vomiting experience immediate retching and emesis of ingested barium on upper GI barium studies, should the examination be aborted or does it still have a potential role in determining the cause of nausea and vomiting in these patients?

When patients with recurrent nausea and vomiting have immediate retching and emesis of ingested barium on an upper GI barium study, some radiologists erroneously assume that there will not be an adequate volume of barium in the stomach to obtain a diagnostic examination. It turns out, however, that even a small amount of residual barium in the stomach often enables differentiation of gastric outlet obstruction or gastroparesis from extraintestinal causes of recurrent nausea and vomiting, such as narcotics, chemotherapy, acute infectious conditions, seizures, increased intracranial pressure, and vestibular disorders. Patients with gastric outlet obstruction or gastroparesis typically have a dilated stomach with intraluminal fluid and/or food that dilutes ingested barium and delays emptying of barium into the duodenum and proximal small bowel. In contrast, patients with extraintestinal causes of nausea and vomiting typically have a collapsed or partially collapsed stomach with rapid emptying of residual barium into collapsed or partially collapsed duodenum and proximal small bowel. In such patients, the combination of rapid emesis of ingested barium and a collapsed stomach with rapid emptying of residual barium from the stomach have led to the designation of a so-called "hyperirritable" stomach [2]. These findings therefore should prompt a careful search for extraintestinal causes of nausea and vomiting in affected individuals. The following section discusses in greater detail the predisposing factors as well as the clinical and radiographic findings in patients with a hyperirritable stomach.

Hyperirritable Stomach

Patients with recurrent nausea and vomiting may undergo barium studies to determine if their symptoms are caused by a mechanical blockage (i.e., gastric outlet obstruction or small bowel obstruction) or by a functional disorder (i.e., gastroparesis or small bowel ileus). In some patients, however, rapid emesis of ingested barium paradoxically prevents adequate visualization of the upper GI tract, causing the radiologist to abort

the examination. In such cases, the study typically is reported to be unsuccessful, as the volume of residual barium in the stomach is not thought to be sufficient for diagnostic purposes. Ironically, it is the symptoms for which the patient is being evaluated (i.e., recurrent nausea and vomiting) that undermine the examination.

In a study from 2008 [2], Naeger et al. reported a subset of patients with nausea and vomiting in which barium studies reveal a constellation of findings characteristic of a so-called hyperirritable stomach. This condition is manifested by rapid emesis of ingested barium (usually in less than 30 seconds), with varying amounts of residual barium in a collapsed or partially collapsed stomach and variable emptying of barium into a collapsed or partially collapsed duodenum and proximal small bowel (Fig. 29.12) [2]. When this set of findings is encountered on barium studies, gastric outlet obstruction and gastroparesis are both extremely unlikely, as these conditions are associated with a dilated rather than a collapsed stomach, often with retained fluid or debris and delayed gastric emptying of barium. Small bowel obstruction and adynamic ileus are equally unlikely, as these conditions are associated with barium filling dilated jejunal loops rather than collapsed or partially collapsed loops of proximal small bowel [2]. When typical findings of a hyperirritable stomach are detected on barium studies, extraintestinal causes of vomiting have been found as the explanation for this phenomenon in more than 90% of cases [2].

Major extraintestinal causes of emesis include pharmacologic agents such as narcotics, chemotherapy, and anticonvulsants [2, 50–52]; nausea and vomiting occur in 40–70% of patients on narcotics for pain control and in 20% of patients on chemotherapy (especially cisplatinum) [50, 52]. Infectious causes include acute infectious conditions such as *Candida* fungemia, psoas abscess, *C. diffficile* colitis, *E. coli* cystitis, and soft-tissue cellulitis, whereas noninfectious causes include renal calculi, acute renal failure, progressive liver metastases, acute intermittent porphyria, Ménétrier's disease, labyrinthine disorders, increased intracranial pressure, seizures, motion sickness, pregnancy, and psychogenic vomiting [51–57]. In the previously mentioned study of the hyperirritable stomach, almost all patients had marked improvement or resolution of their nausea and vomiting after successful treatment of the underlying cause or withholding of the responsible pharmacologic agents combined with antiemetic medication [2]. Thus, recurrent nausea and vomiting in patients

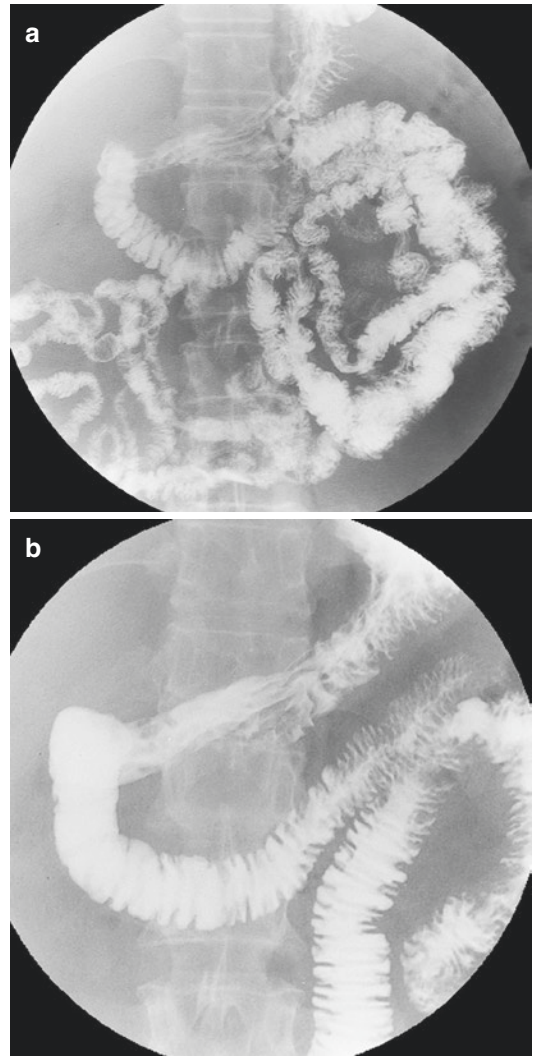

Fig. 29.12 Two patients with a hyperirritable stomach secondary to chemotherapy in one (**a**) and narcotic medication (**b**) in the other. Both patients experienced rapid emesis of barium from the stomach with residual barium in a partially collapsed gastric lumen and free emptying of barium into a partially collapsed duodenum and jejunum. These findings are characteristic of a hyperirritable stomach and should suggest an extraintestinal cause for recurrent nausea and vomiting

with a hyperirritable stomach on barium studies almost always results from extraintestinal causes, and successful treatment of the underlying cause almost always leads to improvement or resolution of symptoms in these patients.

It is believed that extraintestinal causes of nausea and vomiting affect the central nervous system by stimulation of peripheral afferent pathways to the brain or release of neurotransmitters such as serotonin [51, 52]. Affected individuals are thought to develop nausea and vomiting as a result of various neurologic pathways leading to the area postrema, a chemoreceptor trigger zone (CTZ) in the brain [58]. Because the CTZ is located in the medulla adjacent to the floor of the fourth ventricle, it is exposed to emetic toxins in the blood and cerebrospinal fluid. As a result, certain neurotransmitters and neuromodulators in these toxins could stimulate the CTZ, which in turn triggers the emetic center in the brain, causing the patient to experience recurrent nausea and vomiting [51, 58]. Whatever the actual pathogenesis, rapid emesis of barium on upper GI examinations in the absence of gastric outlet obstruction, gastroparesis, or small bowel obstruction or ileus should be considered a positive finding that elicits a search for extraintestinal causes of recurrent nausea and vomiting.

Conclusion

Barium studies can be a useful test for evaluating gastric motility disorders in patients with recurrent nausea and vomiting in the absence of gastric outlet obstruction. Decreased gastric motility (i.e., gastroparesis) may be manifested at fluoroscopy by a diminished strength, velocity, or frequency of gastric peristalsis, often associated with delayed emptying of barium from a variably dilated stomach containing undigested food. Once the diagnosis is made, symptoms of gastroparesis can often be ameliorated by treatment of the underlying cause (e.g., diabetes) and prokinetic agents (e.g., metoclopramide) to increase gastric peristalsis without need for further testing. Radiographic detection of superimposed gastric bezoars may necessitate endoscopic intervention for mechanical dissolution of bezoars. Conversely, extraintestinal causes of nausea and vomiting such as increased intracranial pressure, vestibular disorders, and pharmacologic agents (e.g., narcotics and chemotherapy) may be manifested on barium studies by a hyperirritable stomach characterized by immediate emesis of ingested barium in the absence of findings of gastric outlet obstruction or gastroparesis. The presence of a hyperirritable stomach at fluoroscopy therefore should prompt a careful search for extraintestinal causes of nausea and vomiting.

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Part III

Small Intestinal and Colorectal Motor Disorders

Small Intestinal Bacterial Overgrowth

30

Mark Pimentel and Ali Rezaie

Introduction

Small intestinal bacterial overgrowth (SIBO) is a condition described a number of decades ago as a cause of bloating and diarrhea. However, the last decade has seen a resurgence of research on this topic, in parallel to the interest in the human microbiome. Much of our knowledge of SIBO prior to this last decade was experiential and, now that science is brought to bear on this topic, there is a new and growing understanding of the importance of small bowel microbes in human disease. In this chapter, we will be describing the techniques and strategies for diagnosing SIBO, disease associations, and treatment options available for clinicians treating these disorders.

It is most important to understand that SIBO is not a disease. The condition known as SIBO is nearly always an epiphenomenon caused by another underlying condition. For example, and as will be discussed in this chapter, SIBO can occur in a patient with partial small bowel obstruction. In this case, the mechanical stasis of the bowel leads to SIBO. Thus looking for, or identifying, SIBO is always in the context of understanding the underlying cause. In some cases, there is a patient with Crohn's disease with strictures who has bloating but no active inflammation. The ongoing symptoms of bloating and change in bowel pattern could be due to SIBO caused by the stricture. A workup for SIBO in such Crohn's patients may be important clinically. The corollary is likewise true. If there is a patient with diagnosed SIBO, it may be important to understand why this patient has SIBO.

Definition

As evidenced by the terminology "small intestinal bacterial overgrowth," SIBO represents an increase in the abundance of bacteria colonizing the small bowel [1]. However, how this is defined has been a matter of discussion [2–5]. Initial descriptions of SIBO from the 1960s focused on patients who had been identified as having SIBO in the setting of blind loop syndrome, antrectomy, Billroth II, etc. [6, 7]. In those patients, the clinical setting is iatrogenic diarrhea, bloating, and malabsorption. Furthermore, the levels of small bowel bacteria seen in these cases (as determined by culture of small bowel aspirates) often reached levels of $>10^5$ cfu/mL [8]. Unfortunately, this level of bacteria remained the gold standard definition for SIBO for almost four decades.

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Recent evidence-based reviews of the literature suggest that this range is not accurate [2, 3, 9, 10]. In fact, the level of $>10^5$ cfu/mL in the small bowel is more reflective of blind loop syndrome and not just simple SIBO. Since normal humans should be the basis for definition of normal levels, a recent consensus determined that SIBO is now defined as small bowel (especially duodenal) colony counts of $>10^3$ cfu/mL [11]. This now represents the standard for clinical and research diagnosis using culture-based techniques.

Diagnosing SIBO

There are various techniques for identifying SIBO. While culture has traditionally been the gold standard, unfortunately there are limitations to this technique. The use of culture has to occur through a special understanding with a microbiology lab to receive samples in an expedited fashion with consideration of aerobic and anaerobic conditions. Samples need to be acquired with great care during endoscopy using specialized protected catheters to avoid oral contaminants [4]. In addition, the best location for sampling remains a question. The small bowel is 15 feet in length and the nature and degree of colonization along this length remains unknown. These challenges still point to indirect techniques for the evaluation of SIBO.

The prime indirect technique for diagnosing SIBO is the breath test. The premise for breath testing to diagnose SIBO is that there are gases produced during fermentation that are uniquely related to bacterial fermentation [12]. In the case of gut fermentation, the four main gases produced are carbon dioxide (CO_2), hydrogen (H_2), methane (CH_4), and hydrogen sulfide (H_2S). Since CO_2 is produced by humans as a byproduct of cellular respiration, the other three gases are candidate gases to reflect bacterial fermentation exclusively. The challenge with H_2S is that it experiences a large first pass effect in the liver. This leaves two gases as candidates for evaluating the gut bacteria.

The principal of breath testing is to measure the main surrogates of bacterial fermentation, H_2 and CH_4, during a period of time after the ingestion of a priming carbohydrate. After a baseline human breath sample is obtained, patients are administered a substrate. Repeat breath samples are then obtained at intervals for up to 3 h. A rise of >20 ppm in hydrogen [13, 14] or any methane >10 ppm [14, 15] during this time is considered positive based on the recent consensus paper [11].

Based on this technique, various substrates have been used. There is a rationale for each substrate chosen based on their characteristics (Table 30.1). However, the two most commonly used substrates for breath testing to diagnose SIBO are glucose and lactulose [7, 16, 17]. While the most widely used of the two, lactulose has its pitfalls [18]. Lactulose is a non-digestible substrate [19, 20]. As such, it will not be absorbed and thus it will traverse the full length of the small intestine and ultimately enter the colon. Upon reaching the highly microbial colon, the lactulose will ferment generating H_2 and CH_4. The challenge with lactulose is that a patient with rapid intestinal transit may have a false positive breath test [18]. In the case of glucose, this substrate is almost entirely absorbed by humans within the first 3 feet of small bowel. Thus, only excessive bacteria in the most proximal small bowel will be discovered. Thus, the glucose breath test is very specific but not sensitive as there is a high false negative rate [4, 7].

Breath testing has become the mainstay of diagnosing SIBO for its simplicity compared to direct culture and has been useful in assessing the outcome of treatment as well. In studies of SIBO and treatment with antibiotics, the breath test has also been

Table 30.1 Comparison of glucose and lactulose breath testing

Factor	Glucose breath test	Lactulose breath test
Test dynamics	More specific but less sensitive	More sensitive by less specific
Absorption characteristics	Readily absorbed by small bowel	Not absorbed
What positive means	High likelihood of SIBO	Could be SIBO but cannot rule out rapid transit
Pitfalls	Could miss distal SIBO	Higher false positive rate
Ease of use	Easy	Easy

important in predicting outcomes. For example, in a trial of antibiotics for rifaximin, a reduction in breath hydrogen was associated with a greater improvement in symptoms among patients with IBS [21].

Methane as a Special Case

During breath testing, the focus over the last four decades had been the hydrogen level. Now recent data suggest a greater importance of methane as a marker of disease. Methane appears to be a marker of constipation. In a series of studies, it is now clear that methane is associated with clinical constipation as well as a more constipated Bristol Stool Score [22]. Physiologic data suggest that methane gas itself slows intestinal transit [23]. Methane on the breath test also has a proportional relationship with constipation [22, 24–26]. The greater the methane, the more severe the constipation clinically [24].

In the era of the microbiome, methane is interesting in that this gas is produced not by bacteria but by a group of older organisms, the Archaea. Discoveries surrounding methane and the microbiome have allowed the identification of the organism primarily responsible for gastrointestinal methane production. This organism is *Methanobrevibacter smithii*. Like its byproduct methane, *M. smithii* levels in the colon appear to be proportional to the degree of constipation [27].

The understanding of this relationship between methane and constipation continues to grow. While older studies suggested that the methanogenic Archaea were relegated to the colon (in particular the left colon), more recent evidence suggests they have a presence in the small intestine as well [28, 29].

Symptoms of SIBO

Logically, having a greater abundance of microbes in the gut would lead to a greater capacity for gas production. Consistent with this, bloating is one of the most common features of SIBO. This can lead to cramping and abdominal distress or discomfort. Flatulence or belching is also common. Traditionally, changes in bowel function have often been attributed to SIBO. Depending on the cause, these could range from diarrhea to steatorrhea, such as in the case of the blind loop syndrome [6].

More recently, with the growing understanding of the microbiome, methane and the presence of *M. smithii* are associated with a particular constellation of symptoms. These include bloating, constipation, and even greater body weight [22, 27, 30–35].

It is because of this wide variety of symptoms that bacterial overgrowth may need to be considered in a large number of patients with gastrointestinal complaints.

Conditions Associated with SIBO

As mentioned earlier in this chapter, it is important to look at SIBO as an epiphenomenon. There should be a reason for SIBO. Most commonly this is due to a motility problem such as irritable bowel syndrome (IBS) but there are many others (Table 30.2).

Table 30.2 Potential conditions associated with SIBO

Category	Specific conditions
Motility disorders	IBS
	Pseudo-obstruction
	Colonic inertia
	Gastroparesis
Mechanical	Bowel obstruction
	Intussusception
	Stricture (e.g., Crohn's disease)
	Adhesions
	Lumen occluding lesions (polyps, tumors)
Metabolic	Diabetes
	Achlorhydria (primary and secondary)
Immune	IgA deficiency
	HIV
	Scleroderma
	Lupus
	Combined variable immunodeficiency
Other	Pancreatitis
	Cirrhosis
	Ehlers Danlos syndrome
Medications	Opiate agonists
	Antidiarrheals
	Acid-reducing medications

The most common disease now associated with SIBO is IBS. This development was initially controversial due to the nature of IBS research at the time. Now there is strong evidence that much of IBS is due to alterations in the intestinal microbiome and SIBO. This thinking formed the basis for a recent approval of rifaximin by the FDA as a treatment of IBS [36]. The mechanism behind the development of SIBO in IBS is still being explored. However, data suggest that the SIBO could be linked to an initial exposure to acute gastroenteritis [37]. In a validated animal model, infection with *Campylobacter jejuni*, one of the most common causes of acute gastroenteritis [38, 39], precipitates the development of IBS-like symptoms which correlate with the development of SIBO [40, 41]. Newer data demonstrate that this is through the development of autoimmunity to the cytoskeletal protein vinculin which could impair enteric neuromuscular function and anatomy leading to stasis [42]. These anti-CdtB and anti-vinculin antibodies are now being used in a diagnostic test for post-infectious IBS [43]. If these data continue to hold, a subset of IBS is essentially an autoimmune condition resulting from gastroenteritis and subsequent gut neuropathy leading to SIBO.

In addition, new revelations in the study of IBS identified a link between methane and constipation-predominant IBS [22, 24–26]. It is now known that nearly all patients with methane on breath test ("methane overgrowth") have constipation as a phenotype.

Although there is a great deal of excitement around these developments in IBS, traditional associations between SIBO and motility disorders still hold. For example, patients with pseudo-obstruction can have SIBO due to the ileus pattern. Recall that SIBO can be caused by any reduction in bowel flow. The same is true for gastroparesis. While in gastroparesis the emphasis is poor flow through the stomach, the motor disturbances are not defined by a line of normalcy past the pylorus. The dysfunction often extends into the small bowel leading to SIBO.

As already discussed briefly, mechanical impairments to the flow of small bowel contents will lead to SIBO. The most common of these are intestinal adhesions secondary to previous surgery [1, 3, 44]. While tradition describes blind loops and antrectomy as a common cause of SIBO, these are now rare. Few people have antrectomy for refractory peptic ulcers these days and blind loop syndrome is more uncommon. While bariatric surgery such as Roux-en-Y gastric bypass alters anatomy, the intestinal flow rate is often higher than normal leading to less SIBO compared to older techniques [1].

Metabolic causes of SIBO are also common. Diabetes has a dual effect on the development of SIBO. It is theoretically possible that hyperglycemia is a risk, yet acute hyperglycemia itself (not necessarily chronic) can have profound inhibiting effects on intestinal motility [45–48]. As diabetes is very common, this may be a common cause of chronic intestinal symptoms in diabetic subjects.

More obvious is the association between achlorhydria and bacterial overgrowth [2, 3, 49]. In this case, the lack of gastric acid leads to easier colonization of the upper intestinal tract by bacteria. Often in this case, the colonization is due to oral flora (less gram negative bacteria). This is also true for the iatrogenic causes of low acid such as use of proton pump inhibitors [3, 50]. However, this may be more complicated as reduced acid reduces the protons needed to fuel methane production. In one study, the use of proton pump inhibitors was associated with a lower prevalence of methane on breath testing [51].

A number of disorders of immune function are also associated with SIBO. Conditions that reduce immunity of the gut such as IgA deficiency and combined variable immunodeficiency can reduce the response to gut microbes leading to SIBO [6, 52, 53]. Advance HIV and its effect on immune function has also been an important cause of SIBO in the past. Better treatments of HIV have made this less common now.

In addition to diseases of reduced immune function, autoimmune disease has been associated with SIBO as well although the mechanisms by which this occurs are less clear. In the case of scleroderma, the changes in gut motor function (neuropathy) are an obvious cause of SIBO [6, 54]. However, lupus and fibromyalgia [55] are less well understood.

Finally, medications can have an impact on the development of SIBO. Acid-reducing drugs have already been discussed. Yet, the greatest impact may be opiate agonists. In studies from the 1990s it was demonstrated that even a short course of opiate agonists could lead to SIBO even in healthy volunteers [56]. With growing reports of opiate prescription and overuse, this could be an important cause of SIBO.

Treatment and Management of SIBO

Management of SIBO comprises three goals: (i) controlling disease flares (induction of remission); (ii) decreasing the chance of recurrence after induction of remission (maintenance of remission); and (iii) identifying and addressing the modifiable underlying cause(s) [1].

Induction of Remission

Antibiotics

Antibiotics remain the mainstay of treatment for SIBO. Systematic review of the literature has shown that at least 23 trials have assessed the efficacy of antibiotics in management of SIBO [7]. Several antibiotics have been shown to be effective in treatment of SIBO, including clindamycin, metronidazole, neomycin, rifaximin, tetracycline, ampicillin, amoxicillin, chloramphenicol, ciprofloxacin, erythromycin, and trimethoprim/sulfamethoxazole. It is not possible to pool the results of all of these studies as the antibiotic type, dose, duration, and definition of response were variable among these studies. As compared to placebo, antibiotics are more efficacious in eradication of bacterial overgrowth (51% vs. 10%), yielding a number to treat of 2 [57].

Rifaximin remains the most extensively studied drug in treatment of SIBO. In a small study of 21 subjects Di Stefano et al. observed a higher rate of SIBO eradication with rifaximin (70%) as compared to tetracycline (27%) [58]. Similarly, Lauritano et al. assessed the efficacy of rifaximin 400 mg thrice daily as compared to metronidazole 250 mg thrice daily in 142 SIBO patients. After 1 month, glucose breath test normalized in 63% of patients in the rifaximin group versus 44% in the metronidazole group ($P < 0.05$) [59]. The number of dropouts was significantly greater in the metronidazole group. One other advantage of rifaximin is its long-term safety profile even with repeated courses of therapy. The TARGET 3 trial, which assessed 2579 patients with diarrhea-predominant IBS, showed that adverse events are statistically similar between patients who repeated courses of rifaximin compared to placebo [60].

While the exact dosing and duration of rifaximin in treatment of SIBO remains to be determined, we recommend a course of 550 mg thrice daily for a total of 10–14 days for induction of remission in hydrogen-predominant SIBO.

In contrast, treatment of SIBO patients with excessive methane production with rifaximin alone may not be sufficient. This is likely due to resistance of methanogenic archaea to numerous antibiotics including rifaximin [1]. There has been only one randomized controlled trial which systematically evaluated the effect of antibiotics in patients with methane-predominant bacterial overgrowth. Pimentel et al. [61] randomized 31 patients with constipation and excessive methane production to neomycin (500 mg twice daily) plus placebo or neomycin plus rifaximin (550 mg thrice daily) for 2 weeks and followed by a 4-week observation period. Patients treated with rifaximin plus neomycin showed a statistically significant improvement in constipation severity, bloating, and straining compared to the neomycin-alone group. Similar to this study, we recommend combination antibiotic therapy for methane-predominant bacterial overgrowth for a total of 14 days. Anecdotally, neomycin alone, metronidazole (500 mg thrice daily), or amoxicillin-clavulanic acid may also be considered in these patients. Further studies are required to systematically address the efficacy of such regimens in methane-predominant SIBO.

As a practical pearl, we prefer systemic antibiotic therapy rather than nonabsorbable antibiotics (e.g., neomycin and rifaximin) in treatment of SIBO in patients with a blind loop or surgical

Roux limb. Nonabsorbable antibiotics may not fully reach the microbial content of blind loops.

Elemental Diet

Options to treat SIBO patients refractory to or intolerant of antibiotics are scarce. Elemental diet is a safe alternative for eradication of bacterial overgrowth. Originally developed for patients with short bowel syndrome, elemental diet is absorbed in the proximal small bowel and provides no nutrients to mid and distal small bowel bacteria [62]. A 2-week course of elemental diet has been shown to be effective in 80% of patients with methane- or hydrogen-predominant SIBO. If the breath test does not normalize by week 2, continuation of therapy for another week can increase the success rate to 85% [63]. The main limiting factors in use of elemental diet are cost, palatability, and weight loss. Elemental diet provides an intriguing alternative option for SIBO patients with concomitant inflammatory bowel disease, eosinophilic esophagitis, or eosinophilic gastroenteritis [64, 65].

Statins

Statins inhibit HMG-CoA reductase (3-Hydroxy-3-methylglutaryl coenzyme A reductase) which is an integral enzyme in the biosynthesis of archaeol and caldarchaeol, two of the main cell membrane components in archaea [66], and is also central to the biosynthesis of cholesterol in humans [67], hence the widespread use of statins to lower cholesterol. In addition to their role in inhibiting cell membrane biosynthesis, the lactone forms of statins have recently been shown to also inhibit methanogenesis directly, by inhibiting a key methanogenesis enzyme F420-dependent methylenetetrahydromethanopterin dehydrogenase (*mtd*) [68]. Consistent with this, a recent phase II, randomized controlled trial on patients with methane-predominant bacterial overgrowth (NCT02495623) has shown promising results by decreasing methane levels and improving clinical symptoms [69]. Ongoing larger-scale trials and research studies will further clarify the efficacy and safety of statins in management of SIBO.

Maintenance of Remission

Promotility Drugs

Intact peristalsis is integral to keeping the gut microbiome in balance. Hence, one primary strategy to treat SIBO and decrease the number of flares is the use of promotility drugs. This is mainly directed towards facilitation of phase III migrating motor complexes (MMC) or *housekeeper waves* which occur every 90–120 minutes and sweep through the whole length of the small bowel [70]. These waves clear the small bowel of residual food, secretions, and microorganisms. Several diseases that are associated with SIBO are known to have impaired MMCs, including IBS, opioid-induced dysmotility, diabetes, and bowel obstruction [71]. Several receptors can be targeted to accentuate MMCs including motilin, 5HT4, ghrelin, and acetyl-choline receptors [72, 73].

In a small randomized trial of 34 cirrhotic patients [74], cisapride (a 5-HT_4 agonist) was shown to be superior to placebo and non-inferior to antibiotics in normalization of the breath test. In a retrospective study, SIBO patients who underwent maintenance of remission with tegaserod (another 5-HT_4 agonist) had less recurrence as compared to patients with no maintenance therapy, while treatment with erythromycin had a towards trend benefit [75]. Larger prospective studies are required to elaborate the exact dosing, timing, and duration of promotility drugs in maintaining the remission among SIBO patients.

Laxatives and Secretogogues

Similar to promotility drugs, it appears intuitive that dilution of small bowel contents and improving the flow of gut content would help to decrease the bacterial population in the small bowel. However, very limited data exist to support this hypothesis. A recent prospective uncontrolled study has shown that 2 weeks of therapy with lubiprostone was effective in normalization of breath tests in 7 out of 17 patients with SIBO [76]. Future studies are needed to systematically define the role of these classes of medications in the management of SIBO.

Diet

Intolerance to fructose and lactose are common findings among patients with SIBO, and avoiding these food ingredients can lead to improvement of associated symptoms [77]. While a low FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet has shown to have a significant effect on gut microbiota, the efficacy of low fermentation diets in eradication of SIBO has not been systematically addressed [78]. Nevertheless, in theory, foods which contain fermentable ingredients provide a more favorable environment for the overgrowth of bacteria in the small bowel and avoiding these food should decrease the risk of bacterial overgrowth.

Treating the Underlying Cause

When possible, it is critical to address the underlying cause of SIBO, otherwise the chance of maintenance of remission will remain low.

Patients with narcotic-induced dysmotility may benefit from partial μ-receptor antagonists (e.g., methylnaltroxone [79] and naloxegol [80]), prucalopride [81], or lubiprostone [82]. Intraabdominal adhesions can significantly impair peristalsis, and lysis of adhesions can be considered in such patients. Recent advanced techniques such as the use of bioabsorbable membranes have shown promising results in decreasing the risk of recurrence of adhesions [83]. Stricturing diseases of the small bowel such as Crohn's disease, tuberculosis, anastomotic stricture, and NSAID enteropathy should be addressed appropriately with medications, radiation enteritis, endoscopic intervention, or surgery. Underlying inflammatory small bowel diseases such as Crohn's disease and celiac disease should be treated accordingly. Avoiding diabetic drugs known to slow gut motility (e.g., glucagon-like peptide-1 agonists) [84] and strict glycemic control are two strategies which can be adopted in patients with diabetic enteropathy and SIBO. Patients with connective tissue diseases and joint-hypermobility syndromes may benefit from promotility drugs.

Summary

There is a growing interest in the importance of SIBO in the cause of human health and disease. It is again important to recognize SIBO as a consequence of other factors. While treating SIBO with antibiotics, diet or other therapies maybe effective, keeping SIBO and the associated symptoms under control may depend on the use of interventions designed to treat the underlying cause.

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Short Bowel Syndrome

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Harold J. Boutte Jr. and Deborah C. Rubin

What Is Short Bowel Syndrome (SBS)?

For the Patient

Short bowel syndrome occurs when patients have surgical removal of intestine due to a variety of illnesses, and the **remaining small intestine is less than 200 centimeters in length.** Short bowel syndrome may also be found even when a normal bowel length is present if there is **reduced, poor function** of the small intestine such as seen in intestinal motility disorders (disorders of intestinal movement). Multiple surgeries or radiation can injure the intestine and cause problems with motility. Autoimmune disorders such as scleroderma may result in poor movement of the intestine with functional short bowel syndrome.

For the Practitioner

It is estimated that in the United States, approximately 10,000–20,000 suffer from short bowel syndrome (SBS) [1]. The normal length of small bowel varies from 300–850 cm, and previous definitions of short bowel syndrome have included those patients with less than 200 cm of small bowel remaining after surgery. Most consensus articles define short bowel syndrome when 70–75% of the small intestine has been resected [2]. This does not always translate clinically, however, as patients can have symptoms of functional short bowel syndrome with greater than 200 cm of residual small intestine. Intestinal failure is therefore better defined by the degree of fecal energy loss due to decreased absorptive capacity, increased rapid transit through the gut, and decreased oral intake rather than residual bowel length [3]. More recently, efforts have focused on defining a subset of patients with intestinal failure, who have a worse prognosis and who require intensive intestinal rehabilitation [4]. Patients with SBS and intestinal failure and TPN dependence generally have either < 100 cm of small bowel ending in a jejunostomy, <35 cm of jejunum with a jejunoileal anastomosis, or <50 cm with a jejuno-colonic anastomosis [5].

Why Did This Happen to Me and What Causes It?

For the Patient

Short bowel syndrome results from extensive removal of the intestine during surgery due to

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illnesses like Crohn's disease, where the diseased intestine causes blockage, pain, or other complications that don't respond to medication changes, and must be removed. There are many other diseases that can result in the need to remove large amounts of small intestine, including *ischemic bowel*, in which disease and sometimes death of the intestine is caused by lack of normal blood flow. Other causes include *volvulus* or *internal herniation* of the bowel, in which there is twisting or trapping of the intestine that causes bowel death due to strangulation. *Trauma*, such as in car accidents, can result in severe damage to the intestine and its blood supply that portions of the bowel must be removed.

For the Practitioner

Short bowel syndrome can be subdivided into two categories: primary and secondary. Primary short bowel syndrome describes patients with a congenital process, generally confined to the pediatric population (i.e., jejunal or ileal atresia). Secondary short bowel syndrome typically is the result of surgical resection due to an acquired illness (i.e., obstruction due to volvulus or internal herniation, ischemia, multiple resections due to Crohn's disease, malignancy). The etiology of the disorder which leads to SBS is therefore also relevant as the underlying disease status plays an important role in the patient's prognosis and management [6–10].

How Common Is It?

For the Patient

Short bowel syndrome in adults is uncommon, and is estimated to affect between 10,000 and 20,000 people in the United States. Short bowel syndrome in adults is the result of surgical removal of the intestines for various reasons as mentioned above.

For the Practitioner

It is estimated that in the United States, approximately 10,000–20,000 suffer from short bowel syndrome (SBS) [1]. Due to the variety of etiologies that lead to SBS (i.e., Crohn disease, trauma, malignancy, radiation, mesenteric ischemia), the numbers above are derived from parenteral nutrition registries. A more accurate estimation is difficult to ascertain given the lack of ICD-10 codes and a comprehensive disease registry for short bowel syndrome. It has been reported that the United States has a similar prevalence of SBS compared to European cohorts.

What Are the Symptoms of Short Bowel Syndrome?

For the Patient

The most common symptoms of SBS are weight loss and diarrhea. Many patients have abdominal pain and cramping, flatulence (gassiness), and symptoms of dehydration (fatigue and loss of energy). Because patients have reduced absorption of nutrients, vitamins, and minerals, patients may have symptoms related to these dietary deficiencies. These include tingling or numbness of the feet and hands, easy bruising, low blood counts with fatigue due to anemia or very low vitamin D levels. Many patients experience other less common symptoms of nutrient deficiency such as skin rashes or hair loss.

For the Practitioner

As previously mentioned the pathophysiologic changes that occur following small bowel resection include a loss of intestinal absorptive capacity and increased, more rapid transit time through the gut. This typically results in malnutrition, diarrhea, dehydration, vitamin deficiencies, and electrolyte imbalances. The portion of small bowel removed plays a large role in how much the absorptive capacity of the small intestine is affected. The duodenum typically measures 25–30 cm, extending

from the duodenal bulb to the ligament of Treitz. The duodenum is responsible for absorption of micronutrients such as calcium, magnesium, iron, and folic acid. Also, the duodenum plays a key role in activating pancreatic enzyme secretion, thus resection may lead to impaired digestion. Resections of the duodenum may also contribute to causing dumping syndrome.

From the ligament of Treitz to the ileocecal valve, the proximal two-fifths are defined as the jejunum. The jejunum is responsible for absorbing complex proteins, carbohydrates, fats, vitamins, and minerals. Those with less than 100 cm of jejunum remaining following surgery typically have a net secretory response to food [11]. Though jejunal resections can lead to diarrhea, steatorrhea, and vitamin deficiencies, those with an intact ileocecal valve and colon left in continuity can typically better accommodate with regard to absorption of water and sodium. Calorie salvage via absorption of short-chain fatty acids to reduce energy loss also occurs in patients with even part of the residual colon in continuity.

The lack of inhibitory enterohormones produced by the jejunum such as gastric inhibitory peptide and vasoactive peptide results in gastric acid hypersecretion, which lowers intestinal pH and can inactivate pancreatic enzymes. This process typically leads to fat malabsorption, diarrhea, and steatorrhea [12].

The ileum comprises the latter three-fifths of the small intestine. Similar to the jejunum, it is responsible for the absorption of fats, fat-soluble vitamins, water, and electrolytes, but the ileum is specifically required for the absorption of nutrients such as vitamin B12 and for the salvaging/absorption of bile salts as part of the enterohepatic circulation. Loss of the ileum results in bile salt wasting into the colon which precipitates a secretory diarrhea. This process occurs when colonic bacteria deconjugate bile salts entering the colon into free bile acids, which stimulate colonic motility and secretion thus leading to diarrhea. The ileocecal valve serves as a transition point between the small bowel and the colon and allows for slowing of transit of gastric and small bowel contents into the colon. The ileocecal valve is also responsible for the prevention of reflux of colonic bacteria into the small intestine, thus resection can also predispose patients to developing small bowel bacterial overgrowth, which can also adversely affect nutrient digestion and absorption [13]. The presence of a colon in continuity with the remaining small bowel is also important as it can slow intestinal transit, increases absorptive capacity, and reduces the loss of water and nutrients which improves the chances of recovery to a point of nutritional autonomy where patients are no longer dependent upon parenteral support [14].

In addition to diarrhea, dehydration, and weight loss, patients with SBS who are not fed with parenteral nutrition and intravenous vitamin and micronutrient supplementation are at risk to develop symptoms associated with deficiencies. For example, patients may develop neurologic symptoms such as peripheral neuropathy or myopathy (due to B12, vitamin E, copper, or thiamine deficiencies), rashes (zinc, niacin, and vitamin A deficiency (rare)), and fatigue due to anemia from B12, folate, or iron deficiency. Fat soluble vitamin deficiency is common, so in addition to vitamin E deficiency, patients may develop fatigue due to vitamin D deficiency (associated with very low vitamin D levels), or easy bruising due to vitamin K deficiency. Vitamin A deficiency may result in reduced vision, bitot spots, and dermatitis (phrynoderma).

How Is Short Bowel Syndrome Diagnosed and What Tests Should Be Done?

For the Patient

Short bowel syndrome in adults is typically the result of surgical removal of the gut due to a variety of underlying illnesses as mentioned previously. When the remaining length of small intestine is less than 200 centimeters in length, patients are considered to have short bowel syndrome (SBS). This may occur however in those that have more than 200 centimeters of bowel remaining if there is reduced or poor function of the small intestine. The length of the remaining

small bowel is typically measured by the surgeon during the resection. Another way to determine small bowel length following surgery is by radiologic imaging. There are no blood tests to diagnose short bowel syndrome; however, blood is typically tested to check vitamin, nutrient, and electrolyte levels which can be deficient in short bowel syndrome.

For the Practitioner

As previously mentioned, the normal length of small bowel varies from 300 to 850 cm, and previous definitions of short bowel syndrome have included those patients with less than 200 cm of small bowel remaining after surgery. This, however, does not always translate clinically as patient's can have symptoms of functional short bowel syndrome with greater than 200 cm of residual small intestine. The residual length of the small intestine remaining following surgical resection is thus only one determinant of intestinal function and prognosis. Length of the remaining small bowel still remains a vital aspect in terms of need for long-term TPN or intravenous fluids. It is often difficult to ascertain an accurate estimate of residual small bowel length. The details of the operative report following surgical resection is typically the most useful source, however this sometimes may not be included in the final report. It is typical practice to report how much bowel was removed, however not all surgeons report how much small bowel remains following resection. It is also important to note whether or not the patient's small bowel is in continuity with the colon as this plays an important role in the adaptation process and affects long-term prognosis. If intraoperative estimate of small bowel remnant length is unavailable, radiologic evaluation may provide valuable information. Magnetic resonance (MR), computed tomography (CT), and barium contrast radiography can all be used to estimate small bowel length. Radiologic studies are also useful as they may also help determine structural features that may be relevant to prognosis, such as the presence of inflammation, stricture, or small bowel dilatation.

How Is Short Bowel Syndrome Treated? When Will I Need TPN and When (If at Any Time) Can I Stop TPN?

For the Patient

The treatment of short bowel syndrome is focused on nutritional management, electrolyte replacement, and medications to reduce diarrhea and improve nutrient absorption. We absorb vitamins, nutrients, proteins, water, and electrolytes through our gut from our diet. Each portion of the gut plays a special role in absorption. When portions of the gut are removed, the ability of the gut to absorb adequate nutrition is impaired. Fluid and electrolytes can also be lost in diarrheal stools, which result from this reduced absorptive capacity. Part of the treatment for short bowel syndrome includes reducing diarrhea by using medications that slow down the time that food passes through the intestinal tract, to allow more time to absorb nutrients. There is a newer medication that can be injected under the skin that helps the intestinal absorptive surface grow and thus improve nutrient absorption. We prescribe vitamin, micronutrient, and electrolyte replacements (both by mouth and by injection) and special diets that help reduce diarrhea and improve nutrient absorption. We also prescribe "oral rehydration solutions" that are specially formulated to improve fluid and electrolyte absorption from the shortened intestine.

As the gut adapts to its shortened length in short bowel syndrome, people often require additional nutritional support to help maintain a healthy weight. The most common form of nutritional support that can be used in addition to an oral diet is parenteral nutrition (PN). PN is a combination of vitamins, nutrients, and electrolytes that can be infused into the blood stream through an intravenous (IV) line to ensure that they get absorbed. The major complications associated with PN are infections of the IV line used to provide PN, blood clots in the IV line, liver test abnormalities, and even loss of bone strength, mineralization, and density, which we work hard to prevent by monitoring closely and

by providing patients with extra vitamin D. The amount of gut remaining after surgery plays a large role in whether or not someone will require TPN, and how long they will require it.

For the Practitioner

Some of the key factors involved in the treatment of SBS are nutritional management, electrolyte repletion, and diarrhea control. The nutritional management of SBS can be subdivided into three phases based on intestinal accommodation following small bowel resection: the acute phase, the adaptation phase, and the maintenance phase. The acute phase is the period immediately following small bowel resection and can last from 1 to 3 months. This phase is characterized by malabsorption of fats, proteins, carbohydrates, vitamins, electrolytes, and water. Fluid loss from the gastrointestinal tract tends to be greatest during the first few days to weeks postoperatively and can result in life-threatening dehydration, hypotension, and electrolyte imbalances. Eventually, the remaining small bowel will increase in length to a very limited extent, but will also increase in diameter and villus height resulting in a variable increase absorptive capacity and improve its ability to adequately absorb nutrients. This process however can take up to 1–2 years following surgery. Thus, the initial inability of the small bowel to adequately absorb nutrients during the acute phase is what typically necessitates the need for total parenteral nutrition (TPN) [15, 16].

An estimated 41% of short bowel syndrome (SBS) patients in the USA are dependent on TPN and another 12% are dependent upon intravenous fluids and electrolytes alone (data on file; NPS Pharmaceuticals, Salt Lake City, UT; 2002). Approximately 50–70% of the short bowel patients who initially require TPN can be weaned off TPN successfully in optimal settings [17]. Whether or not your patient will require PN or TPN following their small bowel resection is influenced by the length of the remaining small bowel, and the presence or absence of the ileum, the ileocecal valve, and all or part of a functional colon. Patients with intestinal failure who will likely need permanent total or partial PN infusion support generally have either < 100 cm of small bowel ending in a jejunostomy, <35 cm of jejunum with a jejunoileal anastomosis, or <50 cm with a jejuno-colonic anastomosis [5].

To qualify for Medicare reimbursement, home TPN must be required for at least 3 months, fat malabsorption must be documented, and oral feeding must have failed.

TPN is typically initiated in the first postoperative week after the patient has proven hemodynamic stability. Other issues such as potential infections and cardiovascular or pulmonary complications should also be addressed prior to initiating TPN as well. The average caloric goal recommendation for TPN formulation is between 25 and 35 kcal/kg/day. Of that formulation, roughly 20–30% of total calories should be given as intravenous fat to prevent essential fatty acid deficiency. There should also be a goal of providing on average 1–1.5 g/kg of protein per day. The remaining calories can come from carbohydrates [18]. Blood glucose should be monitored closely, at least on a daily basis in the average patient and up to 4 times per day in diabetics. Vitamins and minerals should also be included in the TPN formulation to compensate for intestinal losses and normalize blood concentrations [19].

The treatment of short bowel syndrome patients with TPN requires a team approach, including a dietitian, home care pharmacist, and home care nursing/infusion team as well as a physician. If long-term TPN is required after bowel resection, permanent central access is established for administration of TPN at home. These include tunneled catheters such as a Hickman or Broviac, implantable ports, or percutaneously inserted central catheter (PICC) lines. PICC lines are generally not recommended for long-term PN management. Home health and infusion services are required in order to provide patients and their families teaching with regard to care and maintenance of these central lines. TPN is typically started as a continuous infusion in the inpatient setting; however efforts should be made to reduce this to nighttime infusions over a 10–12 h period as they transition to an outpatient or home TPN setting. The infusion time depends on the

cardiopulmonary and renal health status of the patient. These feeds can then be reduced (fewer calories per day or reduction in the days per week in which infusions are performed) as oral feeding increases based on tolerability over time. Some patients will require additional fluid and electrolyte repletion to supplement the fluids provided in the PN formulation. Thus, during the acute phase after TPN is initiated, patients need close monitoring of electrolytes and hemodynamics.

If possible, patients should also initiate oral or enteral nutrition to avoid TPN induced intestinal atrophy that leads to decreased intestinal surface area and function. Early initiation of oral nutrition is important once intestinal fluid losses have become more manageable and patients can tolerate an oral diet [13, 17].

Reducing intestinal fluid losses thus plays a large role in correcting nutritional deficiencies. Gastric hypersecretion as a result of increased production of gastrin occurs for several months up to 1 year following resection. This occurs to a greater extent after jejunal resections compared to ileal resections. The increased gastric secretions and acidity inactivate pancreatic enzymes, reducing the efficiency of protein and lipid digestion, and stimulate peristalsis. For this reason, proton pump inhibitors and histamine type 2 receptor antagonists as second line agents along with pancreatic enzyme replacement play a role in decreasing diarrhea and aid in digestion of complex nutrients in SBS [15]. Clonidine is an alpha-2 adrenergic receptor agonist which helps to decrease gastric acid hypersecretion, slow intestinal motility, and enhance sodium and fluid absorption [18, 20, 21].

Diarrhea is typically worse in the acute phase after small bowel resection. In addition to TPN and fluid and electrolyte replacement, antidiarrheal agents can be used as a first-line therapy to prevent complications such as hypotension and electrolyte imbalances from insensible gastrointestinal loses. Medications such as loperamide, diphenoxylate/atropine, and tincture of opium slow intestinal transit via their actions on opiate receptors. These drugs can be used both in the early and in the maintenance phase after small bowel resection as antidiarrheal agents. Another agent that has also been used in the treatment of SBS associated diarrhea is octreotide. This long-acting somatostatin-analog decreases gastric acid and small bowel secretion and may enhance absorption of water and salts. Octreotide can also be useful in the setting of high-output jejunostomy or ileostomy and secretory diarrhea; however, there is no significant effect in patients requiring permanent parenteral nutrition. Furthermore, octreotide is expensive, reduces gallbladder motility thus promoting the risk of cholelithiasis, already increased in TPN dependent patients, and reduces pancreatic secretions, thus potentially exacerbating fat malabsorption. Because of the risk of tachyphylaxis with prolonged use, octreotide is likely most useful in the acute phase. Growth hormone (somatropin) has been FDA- approved for SBS and has been shown to reduce TPN calorie requirements. However, growth hormone is generally not used by SBS patients and physicians due to systemic side effects which are common and include glucose intolerance/type 2 diabetes mellitus, edema and musculoskeletal discomfort, and the need for continuous treatment to maintain efficacy. More recently, teduglutide has been released for use in SBS, which helps reduce TPN and IV fluid requirements; this is a glucagon-like peptide 2 analog that enhances crypt cell proliferation, villus and crypt growth, and increases fluid, electrolyte, and nutrient absorption, and will be discussed further below.

The second phase is known as the adaptation phase. Adaptation is typically characterized microscopically by increased mucosal surface area with enterocyte hyperplasia, villus hyperplasia, and increased crypt depth. The colon is also able to adapt by increasing its absorptive surface capacity; importantly, colonic bacteria convert unabsorbed carbohydrates into absorbable short-chain fatty acids through fermentation. As much as 500 kcal per day can be absorbed through the colon [22]. The adaptation phase typically lasts up to 2 years post resection, but may extend even further as supported by case reports of late weaning from PN [23, 24]. During this phase it is possible to begin transitioning from TPN to oral nutrition. This transition is in

large part based on stability of body weight, hydration, and electrolyte balances. Total parenteral nutrition should be gradually reduced, as oral nutrition is gradually increased in order to optimize intestinal adaptation [25]. Total intestinal adaptation is achieved when patients are able to wean completely off of TPN. The lower limit of small bowel length necessary to wean from TPN ranges from 50 cm of small bowel remnant in the setting of an intact colon, or 100 cm if the resection includes a colectomy [26–28].

The process of weaning off TPN should be gradual process dictated by the clinician who is responsible for managing the patient. This is often accomplished as a multidisciplinary effort between the primary care provider, relevant subspecialists, nutritionists, TPN coordinators, pharmacists, and home health providers. When the patient's overall nutritional requirement is less than 75% dependent upon parenteral support, they should have vitamin (A, D, E, and B12) and trace element (zinc, copper, selenium) levels checked at least twice annually. At each visit, their access site should be assessed for signs of infection including erythema, warmth, or purulence. Weaning should be conducted in a stepwise fashion, for example, going from daily to every-other-day administration without altering formula or duration of infusion simultaneously. The process of weaning should occur over weeks to months with close monitoring of electrolytes, vitamins, and particularly symptoms including weight loss and diarrhea as these may be signs of intolerance to weaning.

What Will Happen in the Long Run?

For the Patient

The long-term goal for patients with short bowel syndrome is to reach a point where they are nutritionally stable. This means that they are maintaining a healthy weight, and both their vitamins and electrolyte levels are within the normal range. Ideally this would be achieved by taking the appropriate antidiarrheal medications, consuming multiple small, nutritionally appropriate meals per day, drinking plenty of oral rehydration solution, and taking vitamin supplements if necessary. Long-term management includes regular follow-up with your doctor to help monitor your weight, check appropriate labs, and provide screening for preventable complications such as bone mineral loss. Some patients have so little small bowel remaining that they will need long-term TPN and/or long-term intravenous fluid supplementation to reach this point.

For the Practitioner

The maintenance phase is defined as the period when the absorptive capacity of the small intestine is at a maximum. Although some patients still require parenteral nutrition, others do well on oral dietary supplementation with multiple small meals per day and vitamin supplementation. All require ongoing antidiarrheal therapies mentioned above. Typically, if the small bowel remnant is greater than 100 cm, there is a good chance that TPN will not be required long-term. The 3-year survival rate for patients receiving home TPN in the setting of a non-neoplastic etiology is roughly 70% and is dependent upon the underlying diagnosis [17, 29]. Typical long-term complications of TPN support include septicemia from central line infections, hepatic dysfunction, progressive renal insufficiency, and bone demineralization [18]. Those that still require parenteral nutritional support or intravenous electrolyte repletion during this phase should be considered for pharmacologic enhancement of intestinal adaptation.

One newer form of pharmacologic therapy to increase intestinal adaptation in those with short bowel syndrome who are incapable of weaning off parenteral support is the glucagon-like peptide 2 (GLP-2) analog, teduglutide. GLP-2 is produced by enteroendocrine L-cells and systemic administration results in increased villus height, crypt depth, and increased blood flow to the small intestine. Studies have shown that teduglutide can increase villus height and crypt depth by up to 50% in SBS patients, which in turn increases the fluid, electrolyte, and nutrient absorptive capacity

of the remaining small bowel [30–33]. Also, SBS patients were found to have a reduced need for TPN by 1–2 days per week, with complete independence from TPN occurring in a smaller subset of patients [34]. The initial starting dose of the medication is 0.05 mg/kg subcutaneous daily. Side effects include nausea, headache, and abdominal pain, and animal models showed an increased risk of adenoma production, thus a screening colonoscopy prior to initiation and follow-up colonoscopies while on treatment are required [35]. In a study of patients who have been treated with teduglutide for weeks, adverse effects that were thought to be treatment-related occurred in 10% of patients and included gastrointestinal stoma complications, abdominal pain, intestinal obstruction, cholecystitis, portal hypertension, Crohn's exacerbation, and injection site hematoma. One patient had metastatic adenocarcinoma but had a history of Hodgkin's disease with chemotherapy and radiation two decades prior to initiation of treatment [36].

Do I Need Special Follow-Up?

For the Patient

Patients with short bowel syndrome need regular follow-up at first following surgery; however once they have reached a point of nutritional stability can be spaced out to annual or semi-annual visits. These visits should be focused on weight management, checking vitamins and electrolytes, and monitoring bone density. Follow-up with other specialists is only required if there is a chronic condition associated with your short bowel syndrome, such as Crohn's disease or Cancer. Those patients, who are treated with special medications such as teduglutide, require more regular colonoscopies given the increased risk of polyp formation.

For the Practitioner

Due to the high degree of variability in the presentation and therefore management of adult patients with short bowel syndrome, there are currently no published guidelines for management by either the American College of Gastroenterologists (ACG) or the American Gastroenterological Association (AGA). The AGA last released a technical review of the current literature in short bowel syndrome management in 2002 and then a follow-up medical position statement in 2003 [2, 37]. Follow-up of these patients is thus based on their individual needs with regard to nutritional and fluid management. Close follow-up is typically recommended in the acute phase where the majority of patients are still requiring TPN and the rate of intestinal fluid losses is higher. Adjustment of their anti-gastric secretion and anti-motility agents is a large part of the clinical treatment of these patients, aside from adjusting their TPN and IV fluids to ensure that they are meeting their daily requirements and gaining weight back appropriately. Close follow-up is still recommended in the adaptation phase as most patients begin transitioning from TPN to oral nutrition. This effort typically requires a multidisciplinary approach with primary care physicians, gastroenterologists, nutritionists, and home care/home infusion services. During the maintenance phase, once patients have reached some degree of nutritional autonomy and are transitioned off TPN, follow-up can increased to an annual or semi-annual basis. Follow-up during those visits primarily consists of assessing vitamin and micronutrient sufficiency, bone health screenings with DEXA scans, and age-related cancer screenings. As mentioned above, those that have been placed on teduglutide will require a screening colonoscopy prior to initiation and at 1 year; subsequent colonoscopy timing depends on the patient's individual risk profile and whether or not polyps are found, but should occur no later than in 5 years.

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Hydrogen Breath Tests

32

Tamar Thurm and Yishai Ron

Commonly asked questions by patients:

Question 1: Doctor, I recently started having a sensation of bloating and distention after drinking milk or having an ice cream. I think I get the same feeling even after having my morning cereals of which I enrich with healthy fruits like blackberries, cherry, fig, kiwi, and apple. Why do I feel bloated after ingesting these products?

You may be suffering from carbohydrates intolerance, of which the most common is lactose intolerance. Fructose (a monosaccharide found mainly in fruits) intolerance is second in prevalence to lactose intolerance and presents clinically in the same manner as lactose intolerance.

Lactose, also known as milk sugar, is a disaccharide consisting of two monosaccharides, galactose bound to glucose. Small bowel absorption of lactose requires hydrolysis (chemical decomposition) to free glucose and galactose, a reaction catalyzed by lactase (an enzyme on the mucosal brush border of the small bowel). Low lactase activity allows undigested lactose to reach the colon where bacterial fermentation yields multiple products and gases such as hydrogen (H_2), carbon dioxide (CO_2), and methane (CH_4) as well as short chain fatty acids. Unfermented lactose may cause abdominal pain, bloating, flatulence, and diarrhea.

As majority of world's population are lactase deficient (meaning that the lactase activity in the small bowel is much less of that of a normal infant), majority of adults have lactose malabsorption (meaning that a large fraction of ingested lactose reaches the colonic bacteria and is fermented). However, symptomatic malabsorption is seen in only a fraction of the population and is called lactose intolerance.

Question 2: Doctor, in addition to that, I have an occasional abdominal discomfort and diarrhea after certain foods of which I′m not certain. My wife says it's all in my head, that I work too hard and that I have IBS (irritable bowel syndrome). Is she right? Do I have IBS?

The symptoms of IBS may be identical to those of carbohydrates intolerance. In fact, many people who embark on elimination diets still have symptoms even after completely avoiding milk and dairy products or withdrawing fruits, soft drinks, and artificial sweeteners from their diet. The same applies for small intestinal bacterial overgrowth (SIBO).

Unabsorbed carbohydrates that reach the colon undergo bacterial fermentation. The short chain fatty acid products of this fermentation may cause diarrhea. The proposed mechanism is by stimulating secretion of 5 hydroxytryptamine

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(serotonin) from the enterochromaffin cells of the brush border of the mucosa, which initiate high-amplitude propagated contractions in the colon, thereby propelling colonic content rapidly and cause diarrhea. In addition, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are poorly absorbed in the small intestine and may induce symptoms of IBS.

Question 3: How to test for lactose malabsorption?

The techniques commonly used to assess lactose absorption in the clinical setting involve measurements of *blood glucose level or breath hydrogen concentrations* after lactose ingestion. A blood glucose increase of <20 mg/100 mL after ingestion of 50–100 g of lactose has been used as evidence of lactase deficiency. Hydrogen breath test has ousted the blood glucose measurement as the preferred diagnostic test for lactose intolerance.

Question 4: What is a hydrogen breath test?

A hydrogen breath test is a diagnostic tool for carbohydrate malabsorption (such as lactose, fructose, and sorbitol) and SIBO. These tests are simple, noninvasive, and require 8–12 h of fasting. However, some patients do not produce hydrogen and produce methane, so some physicians test for hydrogen, methane, or their combination.

The bases for the tests is failure of the patient to absorb the given sugar, subsequently, the gut bacteria metabolize the sugar and produce hydrogen or methane. The more gas is produced, the less of the sugar was absorbed by the patient.

Question 5: How is the test preformed?

Lactose malabsorption test requires recording the patients' baseline reading of hydrogen in their breath. Then the patient is given 50 g of pure lactose to drink. The hydrogen level in the patients' breath is measured every 15 min for 3 h. If the reading exceeds 20 parts per million (ppm) for hydrogen, 12 ppm for methane, or 15 ppm for their combination, within the testing time, the test is positive for lactose malabsorption.

Question 6: Can bloating be explained by malabsorption of other carbohydrates?

Bloating, distention, flatulence, abdominal pain, or otherwise unexplained diarrhea could be the symptoms of carbohydrate malabsorption, IBS, and SIBO. As with lactose intolerance, the patient may complain of diarrhea or bloating following fruit consumption, others may state an excessive use of artificial sweeteners such as sorbitol and might notice improvement of symptoms with the reduction of these products.

Patients suffering from SIBO might complain of the same symptoms, however, many will have risk factors raising the suspicion for SIBO: motility disorders of the gut (scleroderma, celiac disease, postsurgical blind loop formation, or small bowel diverticula causing stasis and bacterial overgrowth), immunologic conditions (IgA deficiency, hypogammaglobulinemia, common variable immunodeficiency, immunosuppression, and chronic pancreatitis), and conditions that expose the small bowel to bacteria-rich environment as colon (after ileocecectomy surgery in Crohn's disease patients), or stomach (post bariatric surgery) and the use of proton pump inhibitors.

Some functional conditions were linked to SIBO, such as IBS, fibromyalgia, and rosacea, showing that treatment of SIBO induced improvement of the symptoms attributed to these conditions.

Question 7: How are the tests for SIBO and other carbohydrate malabsorption preformed?

Fructose malabsorption—As with lactose, the patients' base reading of hydrogen in their breath is recorded. Then the patient is given 25 or 50 g of pure fructose to drink. The hydrogen level is tested in patients' breath every 15 min for 3 h and if the hydrogen reading rises above 20 ppm, the methane level rises above 12 ppm, or their combination rises above 15 ppm, the test is positive for fructose malabsorption.

Sorbitol malabsorption—Sorbitol is a sugar alcohol widespread in plants and especially found in fruits. It is also found in sweets, chewing-gum, dietetic food, and drugs and is in use as a sugar substitute. Sorbitol is poorly absorbed from the small intestine and low doses as 5g could give a positive response in H_2 breath test. The patient is given 5 or 10 g of pure sorbitol

to drink. The hydrogen level is tested in patients' breath every 15 min for 3 h and if the hydrogen reading rises above 20 ppm, the methane level rises above 12 ppm, or their combination rises above 15 ppm, the test is positive for sorbitol malabsorption.

Glucose and lactulose malabsorption (testing for SIBO)—A baseline hydrogen reading in patients' breath is collected. Then the patient is given a challenge dose of glucose (100 g) or lactulose (10 g) and hydrogen/methane readings are collected every 15 min for 3–5 h. A peak in the first 2 h (above 20 ppm for hydrogen and 12 ppm for methane) suggests SIBO in proximal small intestine, another peak reading is seen when the lactulose reaches the colon.

Question 8: What do the results mean?
Positive breath test for lactose, fructose, or sorbitol can be interpreted as malabsorption for the specific sugar tested. However, malabsorption for carbohydrates tested combined with positive test for SIBO should raise a question of a false positive result and should be challenged before the patient is granted with a diagnosis and life style changing dietary requirements.

Question 9: How to treat carbohydrate malabsorption?
Lactose malabsorption should be managed by either completely stopping or gradually reducing the amount of lactose in the daily diet. Yellow cheese has the lowest amount of lactose followed by solid cheese and soft cheese. Drinking over 12 g of milk (a glass of 250 mL) could cause symptoms. A substitute to the lacking enzyme is found in different pills. The usual recommendation is two tablets with a glass of milk and a single tablet with a dairy product.

As for Fructose and Sorbitol malabsorption—Total elimination is not recommended as they are found in different concentration in fruits and vegetables. A dietitian consultation about the relative amount of fructose/ sorbitol in each ingredient and the optional tradeoffs is necessary.

IBS could be the perpetuating factor in about 2/3 of patient non-responding to these measures.

SIBO is an infectious process and should be treated by antibiotics. Locally active antibiotics such as rifaximin are preferable to systemic antibiotics. In patients allergic/unresponsive to antibiotic therapy, an elemental diet is an option (a liquid diet containing essential amino acids, fats, sugars, vitamins, and minerals). Low FODMAP diet significantly affects the gut microbiota; however, so far, no study has specifically addressed its effects on SIBO.

The role of probiotics/prebiotics/synbiotics in the management of SIBO remains to be clarified.

Prokinetic (pro-motility) drugs can aid in prevention of recurrence of SIBO.

Literature Review

Carbohydrate Malabsorption and Small Intestinal Bacterial Overgrowth (SIBO)

Among the most common complaints at the gastroenterologists' office are bloating, flatulence, abdominal pain, and diarrhea. Many of these patients are diagnosed as having IBS. Yet, high rates of the general population suffer from carbohydrate malabsorption that can explain their complaints and might respond to dietary change and specific treatments. Moreover, prevalence of patients with carbohydrate malabsorption is higher within patients diagnosed with IBS [1]. Identification of these patients and adequate treatment might improve the personal and socioeconomic burden of the disease, by improving patient quality of life and reducing healthcare costs [2].

Approximately 75% of the human population has a reduced ability to digest lactose after infancy. Lactose intolerance in adulthood is most prevalent in people of East Asian descent, affecting more than 90% of adults in some communities; it is also very common in people of West African, Arab, Jewish, Greek, and Italian descent. However, in north European population lactase deficiency is rare, affecting less than 5% of the population. Lactase deficiency means that the lactase activity in the small bowel is much less of that of a normal infant, yet lactose malabsorption,

meaning a large fraction of ingested lactose reaches the colonic bacteria and is fermented, does not affect all. Lactose intolerance may result rarely from congenial disorder in infancy but its incidence is unknown. This condition is most common in Finland, where it affects an estimated 1 in 60,000 newborns [3].

Symptomatic malabsorption is seen in only a fraction of the population and is called lactose intolerance. Unfortunately, no specific complaint predicts lactose malabsorption, with sensitivities ranging from 0 to 90% and specificities ranging from 18 to 96% for symptoms such as bloating, diarrhea, flatulence, and abdominal pain [4]. Self-reported milk intolerance is also of little value, showing sensitivities ranging from 30 to 71% and specificities from 25 to 87% [4].

Lactase deficiency (hypolactasia) can be a primary autosomal recessive condition resulting from the physiological decline of LPH enzyme activity in the intestinal cells, occurring in a large proportion of individuals, or secondary as in celiac disease, gastroenteritis, and Crohn's disease, leading to transient lactase deficiency and appearance of abdominal symptoms like those of primary lactose malabsorption [5].

The ability of the human small intestine to absorb fructose is physiologically limited, thus healthy populations exhibit a high prevalence of fructose malabsorption ranging from 38 to 81%, based on a dose of 50 g of fructose [6]. High prevalence of carbohydrate malabsorption is seen in patients with IBS-like symptoms [7]. Of the patients with IBS-like symptoms, approximately 64 and 35%, respectively, are symptomatic fructose and lactose malabsorbers [7]. Considering similar prevalence of healthy controls and indirect mechanism of symptom generation, fructose malabsorption might act as a triggering factor in subjects with underlying pathophysiology: visceral hypersensitivity, SIBO, or abnormal colonic microbiota. Therefore, symptom development during a breath test is more frequently observed in patients with IBS than in control subjects [8].

The inability to properly utilize fructose can be a genetic variation called hereditary fructose intolerance, resulting from a deficiency of the hepatic enzyme aldolase B, or fructose malabsorption, not known to be a genetic condition, in which the capacity of the gut to transport fructose across the intestinal epithelium is exceeded [9].

Patients with SIBO may be clinically asymptomatic or have symptoms that fit the diagnostic criteria of IBS [10].

Pathophysiology of Carbohydrate Malabsorption

Lactose

Lactase synthesis is a function of LCT gene located on the long arm of chromosome two [11]. Congenital lactase deficiency, an autosomal recessive condition, is a rare condition. It is the consequence of two defective alleles on that gene. The expression of the LCT gene is a function of a promoter located 14Kb upstream from this site [12]. Variations in the promoter are related to ethnic variability in the persistence or non-persistence of lactase activity. The wild-type promoter is associated in the age-related reduction in lactase synthesis observed in majority of humans. Lactase activity declines to 5–10% of early childhood levels in most of the world's populations. People with lactase persistence have a point mutation cytosine—thymine. This mutation, which usually appears in people of northern European origin, eliminates the programmed reduction in activity of the promoter with age. Most lactase-deficient people are non-whites. Especially Asians, Africans, Latino, and native Americans are lactase non-persistent. Even whites residing in southern Europe and Mediterranean basin are lactase non-persistent [13, 14]. In fact, 75% of world population become lactase deficient after weaning. Lactose content of milk and different dairy products is given in Table 32.1.

Lactase deficiency may also be secondary to diseases that diffusely involve the small intestine such as celiac disease, infectious enteritis, or extensive Crohn's disease. The loss of lactase activity usually resolves after healing of the injured mucosa. Secondary lactase deficiency is more common in developing countries.

Table 32.1 Lactose content of milk and dairy products (percentage)

Whey	39–78
Milk powder	36–52
Coffee creamer	35–55
Milk, condensed	10–16
Milk: low fat, whole fat (cow, goat, sheep)	4–5
Cream: light, half and half, sour	4
Yogurt, whole milk	4
Ice cream	3–8
Buttermilk	3–5
Cream, whipping	3
Yogurt, low fat	2–7
Cheese, ricotta	1–5
Cheese: cottage or cream, mozzarella	1–3
Sherbet	1–2
Butter	0.5–1
Cheese, feta	0.5
Cheese: brie, camembert, Parmesan, gruyere	0.1–1
Cheese, emmentaler ("Swiss")	0–3
Sheep cheese	0.1

Fructose

Fructose is a monosaccharide commonly found in fruits and as a sweetener. Fructose is found either as a monosaccharide or as a part of the disaccharide sucrose molecule. The average daily consumption in diet is 11–54g [6]. The normal human fructose absorption capacity is limited—up to 25g. It's usually dependent on other absorbed nutrients and other yet unknown factors [15, 16]. Fructose absorption along the small bowel is in a passive diffusion, facilitated by glucose transport protein 5 (GLUT5, Slc2a5) which is the main apical fructose transporter, while GLUT2 (Slc2a2) plays a facilitative and inducible role. The gene encoding for GLUT5 has been isolated on the short arm of chromosome 1 [17]. In contrast to lactose, malabsorption of fructose decreases with age. In human adults, small intestinal tissue GLUT5 expression is greater than in fetal tissue [18]. Glucose stimulates fructose uptake in a dose-dependent manner. The greatest effect was seen when equivalent amounts of fructose and glucose were used. The absorption capacity of fructose was much higher when given as sucrose [19].

GLUT5 is responsible for the majority of luminal fructose uptake, with GLUT2 becoming relevant only when high doses of fructose are ingested [20, 21]. GLUT2 expression may be susceptible to stress as well as to corticosteroids, a factor that is relevant in IBS patients. In fact, most people consume less than 8gr of fructose as fruits or soft drinks. Only few types of chocolates, caramel, and pralines contain up to 40 g per 100 g of food. So, the 25–50 g fructose test, which is supra-physiologic dose, may not reflect a true intolerance. As most people complaining of fructose intolerance do not have defect of the gene that encodes the luminal fructose transporter *(GLUT5)*, other mechanisms such as the coexistence of IBS or abnormal colonic bacterial activity should be considered [22, 23]. Fructose and glucose content of different foods is given in Table 32.2.

Sorbitol

Sorbitol is a sugar alcohol that is found in fruits and is also used as an artificial sweetener. Sorbitol is not completely absorbed in the small bowel. Positive breath test can be reached in dose as low as 5gr, mild symptoms in 10gr, and severe symptoms in 20gr (abdominal pain and diarrhea). Fructose absorption may be impeded when given together with sorbitol. Worsening of IBS symptoms after giving a combination of fructose-sorbitol is still controversial [8, 24].

Pathophysiology of SIBO

The normal human gut microflora is a very complex ecosystem, comprising at least 400 different species. As the small intestine is the major organ for digesting and absorbing food, it should be devoid of bacteria, potentially competing on these nutrients and potentially penetrating the permeable small bowel mucosa. The definition of SIBO depends on the concentration of bacteria in certain anatomical locations along the small bowel. The most accepted definition is $>10^5$ colony forming units (CFU) in the jejunum; however, other

Table 32.2 Fructose and glucose content in gram/100 g product

	Fructose	Glucose
Blackberries and cranberries—fresh	3	3
Blackberries and cranberries—jam	20	22
Strawberry—fresh	2	2
Strawberry—jam	19	22
Artichoke	2	2
Tomato—juice	2	1
Tomato—fresh/carrot/lemon/lemon juice/broccoli/eggplant/ green beans/leek/fennel/cucumber/zucchini	1	1
Bread, rye, whole meal	1	1
Potato	0.2	0.2
Salad	0.2	0.4
Mushrooms	0.1	0.1

reports are in favor of concentrations >10^3 CFU [25]. Mucosal injury induced by bacteria or their toxins could bring a brush border enzyme loss, injury to epithelium leading to increase mucosal permeability and inflammatory response leading to cytokine secretion. Intraluminal bacteria may compete over nutrients and potentially cause malnutrition and vitamin deficiencies. Bacterial metabolism could cause liver injury, creation of toxic metabolites, and symptoms compatible with functional gastrointestinal disorders (such as bloating, distension, flatulence, and diarrhea).

The most important defensive factors against the development of SIBO are gastric acid and intestinal motor activity**.** Gastric acid destroys most of the bacteria entering the stomach, thus preventing the development of SIBO. Small intestinal motor activity, especially phase III of the inter-digestive migrating motor complex (MMC III, "house keeper"), limit the colonizing ability of bacteria [26]. Other protective factors are the integrity of the intestinal mucosa, including its protective mucus layer and intrinsic antibacterial mechanisms (e.g., defensins, immunoglobulins); the enzymatic activities and bacteriostatic properties of intestinal, pancreatic, and biliary secretions; the protective effects of the commensal flora; and the mechanical and physiologic properties of the ileocecal valve [27].

Motility disorders are especially common in patients with type 1 diabetes (diabetic autonomic neuropathy) [28], scleroderma (52–73%) [29, 30], and intestinal pseudo-obstruction [31]. In old age patients, motility disorders are probably the major cause of development of SIBO [32]. Recent study found that prolonged small bowel transit time was more common in patients with typical complaints and positive lactulose breath test. This was demonstrated using the wireless motility capsule. In this study, colonic transit and whole gut transit were prolonged. However, gastric emptying was normal [33].

Anatomical defects include small intestinal diverticulosis (especially jejunal diverticula) [31]. Postoperative changes include gastrectomy [34, 35] which may cause hypochlorhydria or achlorhydria (pending on the extent of resection), secondary changes in motility, creation of blind loops and diverticula. Intestinal strictures, fistulae, and anastomosis may cause stagnation of intestinal content, thus enhancing bacterial flourishing. Hypochlorhydria has been associated with the extensive worldwide use of proton pump inhibitors (PPIs) [32]. A meta-analysis revealed a pooled odds ratio of 2.82 for SIBO among PPI users. This was proved only in studies using small intestinal aspirates and not breath tests [36]. This cause is still controversial as few reports failed to establish this association [37]. SIBO has been described in patient suffering from immunodeficiencies such as hypogammaglobulinemia as well as HIV [38]. SIBO has been linked to other conditions (e.g., Parkinson's disease, esophagitis, rosacea, and obesity),

however, the most controversial is it's relation to IBS. Pimental et al. reported a 84% prevalence of SIBO among IBS patients using lactulose breath test in diagnosis [39, 40]. Other studies using lactulose report figures ranging between 34 and 84% [41, 42]. Studies using glucose breath test report a much lower percentage of 6–16% [43, 44].

Diagnostic Tests

A detailed medical history, dietary and lifestyle assessment, followed by clinical investigations in accordance with national guidelines should be committed. Investigations may include blood and fecal tests, endoscopy, and radiological imaging to rule out any organic disease. In the absence of organic disease, patients will often be diagnosed with a functional gastrointestinal disorder [45]. However, there are a few clinically useful tests in the identification of specific carbohydrate intolerance.

Exclusion diets to achieve symptom improvement followed by gradual food reintroduction to identify tolerance can be the first diagnostic modality for carbohydrate malabsorption. In patients suspected of having IBS, an exclusion diet avoiding several dietary components might be required. Low short chain fermentable carbohydrates (low FODMAP) diet is considered the most successful of the exclusion diets for IBS, with expected resolution of symptoms within 3–4 weeks of dietary change [45]. However, this is a very restrictive diet, difficult to follow for long periods of time.

Hydrogen and/or methane breath testing are useful, noninvasive measurements to assess carbohydrate malabsorption in the gastrointestinal tract. In these tests, a measured amount of lactose or fructose is given to the patient. The unabsorbed carbohydrate is metabolized by the gastrointestinal microbiota producing hydrogen or methane which is absorbed into the bloodstream and expired via the lungs.

Lactulose, a nonabsorbable synthetic disaccharide of fructose and galactose, is used for SIBO diagnosis, as this carbohydrate is metabolized solely by the microbiota, a high hydrogen/methane reading of the test is diagnostic for SIBO.

The test protocols vary highly; strict breath test protocols require 14-day abstinence from antibiotics, colonoscopy preparations, laxatives, or probiotics. A diet low in fermentable carbohydrates 48 hours prior to each breath test and an overnight fast prior to commencement of the test is advised. Some protocols require brushing the teeth and use of an antiseptic mouthwash prior to testing to ensure that oropharyngeal fermentation is not contributing to measurements.

The most common protocols for lactose / fructose / sorbitol entails drinking 25-100 g of the investigated carbohydrate, taking a baseline sample and thereafter exhaling into a tube every 15 min up to 3 h. A deviation of >20 ppm (part per million) over baseline reading is a marker of a positive test.

Risks and Benefits

Although the tests have an excellent safety profile, being easy to use and noninvasive, the benefit of the tests is debatable. There appears to be huge individual inter- and intra-variability in the amount and duration of gas production, however, this does not correlate to symptom profile or severity [45].

Therapeutic Options

Lactose Intolerance

Treatment should be aimed at improving digestive symptoms, not treating malabsorption [46]. Reduction of lactose intake rather than exclusion is recommended as most patients with self-reported lactose intolerance can ingest at least 12 g of lactose (=250 mL milk) without experiencing symptoms [47, 48]. Symptoms after intake of small amounts of dairy products should raise the suspicion of a true food allergy to cow's milk protein rather

than malabsorption [46]. Lactase enzyme replacement is another option; however, it changes the taste of the food when mixed with the dairy products.

Although lactase expression is not upregulated by lactose ingestion, tolerance may be induced by repeated lactose dosing due to adaptation of the intestinal flora [49].

Another option is dividing the same amount of ingested lactose. With this strategy, reducing the daily amount or using low lactose dairy products may be unnecessary.

Result on the use of probiotics in lactose-intolerant individuals is conflicting [50, 51]. Attempts to change colonic response to lactose (colonic adaptation) by adding increasing amount of lactose was tested. The rationale for this procedure is that colonic bacteria will adapt by favoring proliferation of lactase-producing bacteria such a bifidobacteria which can decrease H2 production by beta-galactosidase. Results of studies testing this approach were inconclusive [52, 53]. A single randomized controlled study tested the effects of rifaximin in relieving symptoms of lactose intolerance. Most patients responded but there was no difference from the group that had a lactose-free diet over that period. The clinical significance of these results is unclear [54]. To the best of our knowledge, no further attempts to use either locally active or systemic antibiotics were published ever since.

Fructose Intolerance

Compliance with a fructose-restricted diet may significantly improve symptoms: abdominal pain, belching, bloating, fullness, indigestion, and diarrhea [55], especially in patient primarily diagnosed with IBS. Recently, an Australian group led by Gibson PR and Shepherd SJ introduced the low FODMAP diet concept [56–58]. FODMAPs conceivably should be considered as whole and not as individual items, because it is possible to point out subjects with substantial combined intakes of these substances.

SIBO

The primary goal of therapy in SIBO should be the treatment of any underlying disease or structural defect [10]. Management should include correction of nutritional deficiencies, supplemental fat-soluble vitamins, vitamin B12, and minerals. Use of prokinetic agent may be considered for patients with gastroparesis or intestinal dysmotility. Promotility drugs such as motilin receptor agonists (e.g., erythromycin and azithromycin) and 5-HT4 agonists (e.g., tegaserod, cisapride, and prucalopride) can induce phase III MMCs (migrating motor complexes) in a fasting state [59] and potentially decrease the recurrence of bacterial overgrowth. Treatment for SIBO aims to modify the GI microbiota; thus, many different antibiotic regimens have been advocated for use in SIBO, including ciprofloxacin, metronidazole, neomycin, norfloxacin, and doxycycline [10]. However, choice of antibiotic remains primarily empiric. Effective treatment generally includes one or more drugs with activity against both aerobic and anaerobic enterobacteria. In a meta-analysis of 10 placebo-controlled trials, antibiotics were shown to be superior to placebo with a combined normalization rate of 51% (95% confidence interval (CI), 47–56%) for antibiotics compared with 10% (95% CI, 5–18%) for placebo [60].

SIBO is a relapsing disease, especially when there are predisposing factors. The frequency of repeat therapy is ranging from none to monthly and for 4–6 months. Rifaximin (a nonabsorbable rifamycin analogue) is of a growing interest in SIBO management. Rifaximin was found better than metronidazole in normalizing breath test in patients suffering from SIBO. The number of dropouts was significantly greater in the metronidazole group. Clinical response was not reported in that study [61]. Rifaximin efficacy was tested in the TARGET 1 and 2 studies evaluating its effects on non-constipated IBS patients. SIBO presence was not assessed in these studies. After a month, more patients in the treatment group had an improvement in global symptoms than the placebo group [62]. TARGET 3 study evaluated the repeat treatment effects in D-IBS patients.

Significantly more patients had a clinical response after the first round of repeat treatment with rifaximin compared to placebo [63]. Rifaximin alone was not found to be effective in treating methane-producing bacteria such as *Methanobrevibacter smithii*. However, systematic review of the use of rifaximin in patients with SIBO has not yet been published. Recently, statins were found to have an inhibitory effect on *Methanobrevibacter smithii* [64]. Its clinical significance in SIBO remains to be proved [65]. Pilot studies address use of probiotics in SIBO. An open-labelled pilot study assessed the effect of *Lactobacillus casei* Shirota on SIBO patients by lactulose ingestion on hydrogen breath test. Following a 6-week intervention 64% of patients no longer had a positive breath test, but there was no significant improvement in abdominal symptoms [66]. A low FODMAP diet significantly affects the gut microbiota [67]. However, to date, no study has systematically addressed the role of diet in SIBO patients.

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Small Intestinal Tests: Small Bowel Follow Through, CT Enterography, and MR Enterography

33

Charles Marn and Naveen Kulkarni

Introduction

Small bowel intestinal motility disorders may result in prolonged or accelerated transit and can present with wide range of symptoms including but not limited to abdominal distention, colicky pain, recurrent vomiting, diarrhea, or obstruction. However, the small bowel remains a challenging anatomical site to image accurately (due to long length of approximately 6 m) and nonspecific clinical presentations from motility disorders that can confound successful imaging approaches. Selecting the right imaging modality to answer a specific clinical question is an important component of patient workup. The conventional approach to imaging begins with the small bowel follow through which can identify small bowel mucosal abnormalities, dysmotility, and abnormal transit time. CT and MRI techniques are more expensive and mainly indicated to evaluate diseases that mimic or contribute to small bowel motility disorders. This chapter will provide an overview of small bowel follow through, CT and MRI techniques and their indication in small intestinal motility disorders.

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Small Bowel Follow Through

The small bowel follow through is the original and traditional radiology test of the small bowel [1–4]. This test began in the first half of the twentieth century, and is based on the simple principle of filling the small bowel with barium, an element that is dense to X-rays. The test is done with a combination of large still images of the abdomen, accompanied by fluoroscopic observation of the small bowel in real time by a radiologist. With these techniques, a radiologist can see anatomic details of the small bowel such as surface (mucosal) features, small bowel diameter, and the time it takes for barium to leave the stomach and reach the colon (Fig. 33.1). Sometimes, this test can be combined with detailed images of the stomach (an Upper GI series), but most often, a small bowel study is done separately after the stomach has been evaluated by endoscopy [1–4].

The small bowel follow through is performed for a wide variety of clinical problems. Along with CT enterography and MR enterography (see below), the small bowel follow through is an important test to diagnose and manage Crohn's disease (Figs. 33.2 and 33.3). It is also commonly used for patients with possible bowel blockage from adhesions (scar tissue) or cancer. Patients with diarrhea, malabsorption or protein loss or pain are often studied with a small bowel study. SBFT is occasionally helpful to evaluate gastrointestinal blood loss, and to evaluate anatomy after surgery [3, 4].

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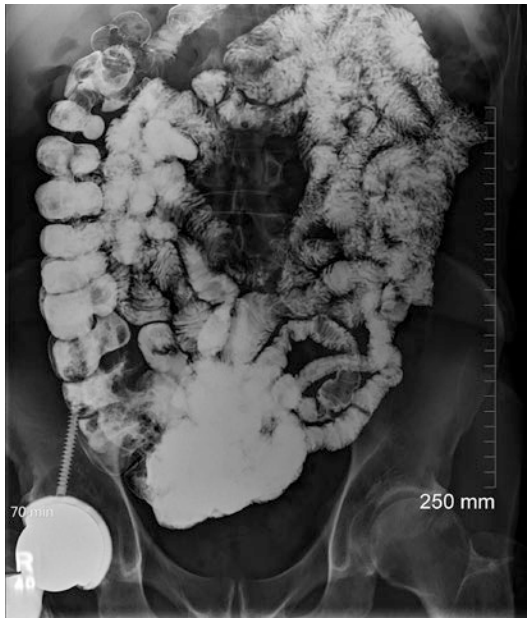

Fig. 33.1 Normal small bowel follow through

The small bowel study is usually initiated early in the day after an overnight fast. No other preparation is necessary. In most practices, the patient will discuss his or her symptoms with the radiologist at the start of the exam. The study begins with a regular X-ray before any barium is given, to see if any abnormalities are present which would later be lost behind the barium. This is followed by the administration of a large cup of thin barium. This is the chalky, white, nearly tasteless material that is dense to X-rays. The progress of the barium through the small bowel is monitored with still images of the abdomen obtained by a radiology technologist at 10–30 min intervals. As the barium moves through the small bowel, the radiologist will chose the appropriate times to do a real-time, detailed evaluation with fluoroscopy. These are "live" X-ray images of the intestine, much like watching a video clip on the internet. This step allows the radiologist to observe how well the small bowel contracts, and may help him see abnormalities that are not apparent on still images. The radiologist can sometimes find abnormalities

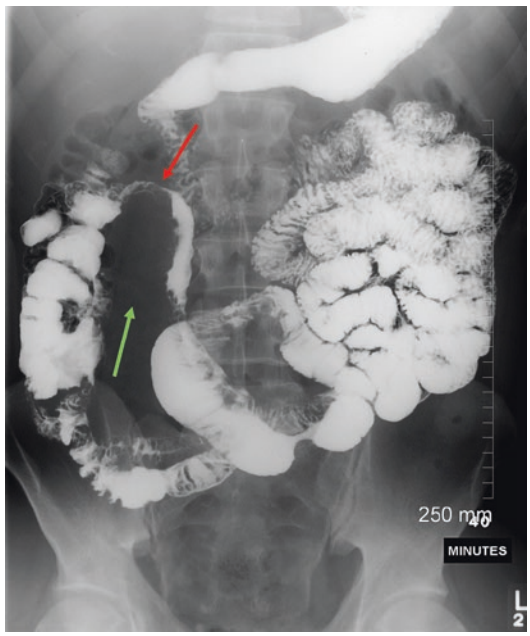

Fig. 33.2 Small bowel follow through shows terminal ileal strictures and abdominal separation of small bowel loops in the right lower quadrant secondary to mesenteric fat proliferations

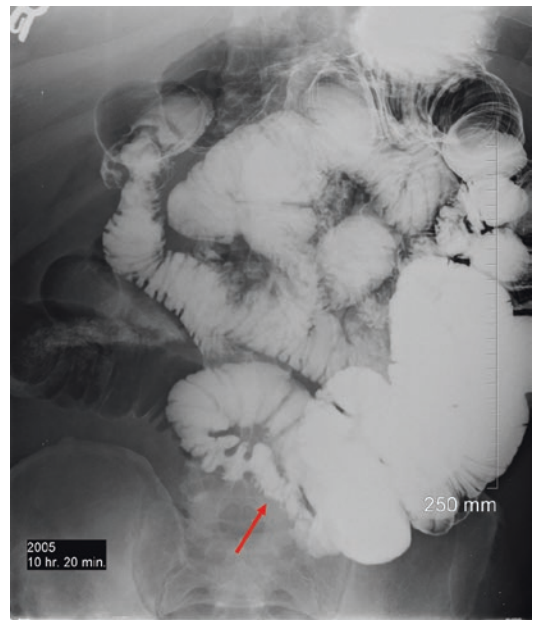

Fig. 33.3 Small bowel follow through demonstrates abnormally dilated small bowel loops consistent with small bowel obstruction secondary to stricture (*red arrow*, transition point). (I am assuming we are showing a stricture in right lower quadrant with delayed transit time)

by asking the patient to point to areas of discomfort or pain during fluoroscopy. The radiologist will likely ask the patient to drink more barium during the exam. This helps keep the small bowel well distended, making abnormal areas more obvious (Fig. 33.3). Some radiologists may have the patient take gas crystals during the exam. Gas in the small bowel can help show abnormalities not well seen in dense areas of barium, like the pelvis. The entire exam is usually done in 45 min to 2 and one-half hours, depending on how fast the small bowel fills and empties. The only discomfort experienced by patients is a mild sense of bloating, particularly if gas crystals are used [3–6].

While there is extensive research on radiation exposure and cancer risk, the best and most comprehensible risk assessment is only available for humans who have received moderate to high doses of radiation [6, 7]. Real and measurable risk is well documented for survivors of the atomic blasts of Hiroshima and Nagasaki, and for the occurrence of second cancers in patients who receive large doses of radiation to treat cancers such as lymphoma, thyroid cancer, cervical cancer, and other neoplasms. The risk from a single radiology exam such as a CT scan or small bowel follow through is so small as to be nearly unmeasurable, and certainly falls into other acceptable risks such as travelling by car, swimming, or being a pedestrian in a city. Further, risk only has meaning when balanced by benefit, and the value of accurate disease detection and monitoring almost always outweighs the small risk of radiation. However, it is prudent to exercise care for patients who may require many exams over the course of a chronic disease process such as Crohn's disease or young patients. In these cases, MR exams may give fairly similar information with no known biologic risk. Finally, pregnancy status should be clear in women of childbearing age before exams using ionizing radiation.

CT Enterography

Over the last 15 years, a specific set of modifications to routine CT scanning of the abdomen and pelvis have been devised to make CT more sensitive for the detection of disease in the small bowel. CT enterography is accomplished with three modifications to routine CT technique. First, a large volume (up to 2 L) of neutral oral contrast (fluid) is given to distend bowel. The fluid can contain sorbitol, locust bean gum, polyethylene glycol, or small amounts of barium. Unlike water, these agents are chosen because they are not rapidly absorbed in the small bowel. As such, they distend the small bowel, making abnormalities of the wall more obvious—consider the analogy of the difficulty in reading a crumpled newspaper versus a page that has been spread out. The oral contrast is ingested over 60 min with last 200–300 mL given immediately before the scan. Glucagon has been used by some investigators, but unlike MR enterography its efficacy has not be well established with CT enterography. Second, IV contrast is given and timed to show blood flow to the bowel wall, approximately 45 s after IV contrast injection. Disease states such as inflammation or tumor will often alter blood flow, and increased or decreased flow can be detected with CT enterography (Fig. 33.4). Finally,

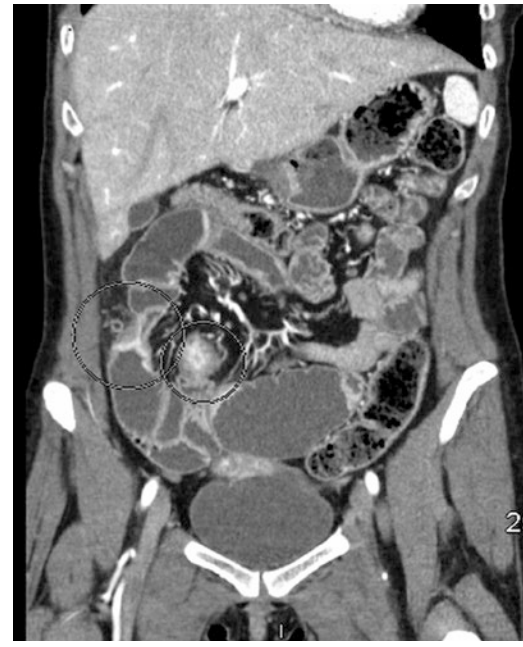

Fig. 33.4 Coronal image from CT enterography in a 32-year-old patient with Crohn's disease shows two short segment strictures with mucosal hyperenhancement (circles) suggesting active disease

computer techniques are used to display images in three planes, which often makes abnormalities more detectable [8–10].

The patient experience for CT enterography is similar to other CT tests that use IV contrast (X-ray dye). First, the patient's past experience with IV contrast must be reviewed for allergies. Blood work is usually needed to assure that kidney function is normal, since IV contrast can worsen kidney function in patients with kidneys that do not work well. Large volume of liquid ingested before the exam can make some patients bloated. The CT exam itself is quite fast—the images are obtained in as little as 20 s. Modern scanners are high speed devices that can generate detailed images even if some motion is present. In certain situations, more than one trip through the scanner is necessary. For instance, X-ray contrast from the blood supply may pool in a bowel loop at a site of bleeding, and this collection may be most apparent a minute or two after the contrast was given [10, 11].

MR Enterography

Overview

Over the past several years, MRI has become an increasingly popular modality in evaluation of small bowel owing to lack of ionizing radiation, improved soft tissue contrast, ability to provide dynamic information regarding distention and motility, and relatively safer intravenous contrast agent profile. Continuing improvements in MR software and hardware have enabled small bowel MR to assume a major role in the evaluation of the small bowel. Optimal distention of the small bowel loops is crucial for the correct evaluation of the bowel wall because collapsed bowel loops may hide lesions or mimic disease by mistakenly suggesting that the collapsed segments are actually an abnormality-related thickened bowel wall. Two techniques are currently performed: MR enteroclysis and MR enterography. Although MR enteroclysis produced better distention of small bowel, it is less well tolerated as it requires nasoenteric intubation (often needing sedation) and infusion of 1500–2000 mL of contrast agent. Although there are few studies indicating better performance of MR enteroclysis over MR enterography, from an evidence-based medicine point of view, the overall level of evidence is weak. Because MR enteroclysis is more time intensive and less efficient than enterography, it is not widely performed. In comparison, MR enterography requires that patient ingest large volume of oral contrast material (up to 1.0–1.5 L) but is better tolerated. A limitation of MR enterography is variability in bowel distension, especially jejunal loops. Although the debate of MR enteroclysis vs MR enterography will continue, the decision of using one technique over other must take into account indication, performance of one technique over other, patient acceptance, resources, and institutional expertise. At our institution, MR enterography is routinely used for evaluation of small bowel disease [11–13].

Technique

MR enterography of the small bowel is performed using enteric contrast agent to achieve bowel distention and these agents are classified based on signal intensity produced on T1- and T2-weighted images: negative (low/dark signal intensity), positive (high/bright signal intensity), or biphasic [low signal (dark) intensity on images of one type and high (bright) signal intensity on images of the other type]. Biphasic agents are most commonly used and show low signal intensity on T1-weighted images and high signal on T2-weighted images. Low signal on T1-weighted images allow good visualization of bowel wall/mucosal enhancement and abnormalities. Several different biphasic contrast agents have been used (e.g., water, low-density barium, polyethylene glycol, mannitol) and dosing algorithm is determined by the type of agent used. In comparison, negative contrast agents (low signal on both T1- and T2-weighted images) and positive contrast agents (high signal on both T1- and T2-weighted images) are either not readily available or costly, hence not widely used. Of note, positive contrast agents may allow assessment of contrast progression and transit

time through the bowel. A typical oral preparation includes patient fasting for 4–5 h before examination and approximately 1–1.5 L of enteric contrast agent is ingested over 1 h. At our institution, VoLumen (barium sulfate suspension 0.1% w/v, 0.1% w/w) is used as the enteric contrast agent. Since in many cases oral contrast would have reached colon by the time of imaging, routine use of rectal contrast is not advocated. During scanning, patient can be positioned in supine or prone. The prone position helps to separate bowel loops and decrease the imaging volume (bowel loops are elevated out of pelvis and provide maximal bowel coverage on coronal images) and motion artifact from anterior abdominal wall are also reduced. Despite these possible advantages, the prone position does not perform better in terms of detecting abnormality. The supine position affords greater patient comfort and is thus indicated in patients with abdominal pain, stomas, and/or abdominal wall fistulas [11, 13].

For the MR enterography a thick-slab of T2-weighted MR is initially performed to assess small bowel distention. If distention of the small bowel, particularly ileum is suboptimal, the patient can drink more oral contrast material. The key sequences in interpretation of MR enterography include series of T2-weighted and contrast-enhanced T1-weighted series. T2-weighted sequences are critical in evaluating bowel wall thickening, mucosal fold, and mesenteric structure. Fat-saturated T2 sequences are good at delineating inflammatory changes. The T2-weighted sequence commonly used include half-Fournier acquired single shot turbo spin (HASTE) and true fast imaging with steady precision (true FISP) [Note that HASTE and FISP sequence name are vendor specific and are named differently for different vendors]. Both of these are single slice acquisition in approximately 1 s per slice and acquired in combination of axial and coronal plane. Although these provide excellent image quality and overall information on anatomy, mesentery, and mesenteric vessels (structure supporting and supplying blood to small bowel), they lack resolution and hence limited in evaluation of small bowel lesions. For contrast-enhanced acquisition, two- or three-dimensional spoiled gradient-echo fat-saturated T1-weighted sequences are used. If patient is cooperative, contrast-enhanced three-dimensional volumetric sequences which provide better spatial resolution and allow multiplanar reconstruction are preferred. When patients have difficulty in remaining still, a two-dimensional T1-weighted sequence, which is less susceptible to motion artifacts but has reduced spatial resolution, is employed. Gadolinium-based contrast material is injected (0.2 mmol per kilogram of body weight at a rate of 2 mL/s), followed by a bolus injection of 20 mL of saline. Although there is no consensus about scanning delay, typically coronal gradient-echo fat-saturated T1-weighted sequences are performed before and 40–45 s after contrast injection to acquire three sequential phases to image during peak bowel enhancement (each acquisition take about 15 s). An axial sequence beginning 90 seconds after contrast injection is also performed. Since gradient T1-weighted sequences are particularly susceptible to motion artifacts, antiperistaltic agents such as hyoscine butylbromide or glucagon can be used to reduce motion artifact from bowel peristalsis and improve study quality. Antiperistaltic agents are administered immediately before IV contrast injection. In addition to above sequences, multiphase balanced gradient echo sequence can be used to assess bowel peristalsis which is altered in the area of inflammation and fibrosis. This is acquired as a stack in coronal plane to cover entire abdomen and has been shown to aid detection of abnormal small bowel segments when findings on routine MR sequences are overlooked. Since administration of antiperistalsis agents can affect bowel peristalsis, it should be taken into account before running multiphase sequence [14–16].

MR Enterography Performance, Advantages, and Disadvantages

Unlike CT, performance of MR is dependent on many factors: patient cooperation, scanner capabilities, reader's experience and complexity related to image artifacts and image contrast from different kinds of image sequences. Although CT

enteroclysis produces more high quality exams as compared to MR enterography, better soft tissue contrast profile of MR enterography results in sensitivity which is similar to or better than CT enterography in detection of small bowel disease. Also, the safety profile of intravenous (IV) MR contrast agent makes MR enterography feasible in patients with contraindications to IV dye used for CT. In patient with decreased renal function where both CT and MR IV contrast agents are contraindicated, non-contrast MR enterography rather than non-contrast CT is preferred as it can still detect many abnormalities. Important limitations of MR imaging are longer scan time (up to 30–40 min for entire study) with multiple short breath holding sessions (as compared to CT which is complete in 20 s), scanner availability and access, cost of the examination, and variability in examination quality. The resolution of MR is lower than CT [12, 13].

Indications of CT Enterography and MR Enterography

Unlike small bowel follow through which provides real-time information on small bowel motility and transit time making it optimal for studying motility disorders, CT enterography and/or MR enterography is usually reserved to rule out conditions like inflammatory small bowel disease, mechanical obstruction, and small bowel tumors that can mimic primary small bowel motility disorders related to neuropathic/myopathic cause. CT enterography and MR enterography however provide entire evaluation of bowel wall thickness, its surface, and also the tissues that support the bowel. The first and most common use of CT and MR enterography is the evaluation of bowel inflammation, especially Crohn's disease (Figs. 33.4 and 33.5). Although both CT and MR enterography perform well in detecting bowel damage and monitoring treatment response in Crohn's disease, MR is being increasingly preferred due to lack of ionizing radiation and need of repeated follow-up imaging. A unique advantage of MR is better evaluation of fistula (an abnormal connection between bowel and adjacent structure or between two bowel segments), especially perianal disease. In addition, CT enterography and MR enterography can also be used to search for sites of intestinal bleeding, patients with bowel obstruction (CT being the modality of choice and MR reserved as problem solving tool) those suspected to have tumors and polyps of small bowel [8, 9, 11, 13].

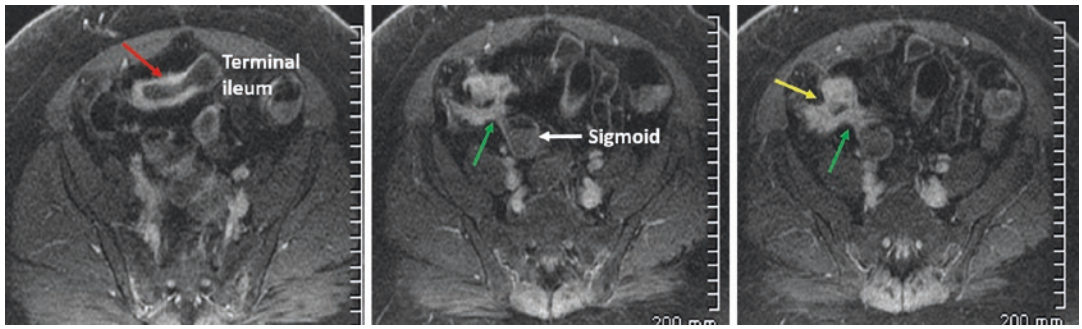

Fig. 33.5 MR enterography in a 35-year-old female. Axial post gadolinium-enhanced images at the level of pelvis shows terminal ileum wall is thickened with intense hyperenhancement (*red arrow*) and there is complex fistula to the sigmoid colon (*green arrow*) and entero-enteric fistula (*yellow arrow*)

Conclusion

In summary, a successful imaging approach to small bowel motility disorders depends on the local availability of different services and clinical expertise. Small bowel follow through is the mainstay for evaluating small bowel motility. Consideration should always be given to CT and MR enterography to rule out other conditions that can mimic bowel motility disorder. Ultimately, diagnostic yield is determined by accurate clinical assessment and the appropriate choice of investigations.

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The Wireless Motility Capsule

34

Dan Carter and Eytan Bardan

What Is Wireless Motility Capsule?

Gastrointestinal (GI) tract transit and motility exams are performed in order to define the underlying abnormal physiology in common functional GI disorders as gastroparesis, functional dyspepsia and chronic constipation failing empiric medical therapy. Traditionally, motility testing is limited to the specific region of the GI tract consistent with the chief complaint [1–3]. These exams include scintigraphy or breath test for the diagnosis of gastroparesis and radiopaque marker (ROM) study or, less frequently, scintigraphy for the assessment of colonic transit. The assessment of small bowel transit is usually limited to few academic centers and involve barium radiography, scintigraphy, and lactulose breath test.

The wireless motility capsule (WMC) is a novel technique that enables the measurement of regional and whole gut transit time in a single standardized ambulatory test. The wireless motility and pH monitoring system consists of a single-use capsule, a receiver, and data processing software (Fig. 34.1). The capsule is indigestible and measures 26 mm × 13 mm,

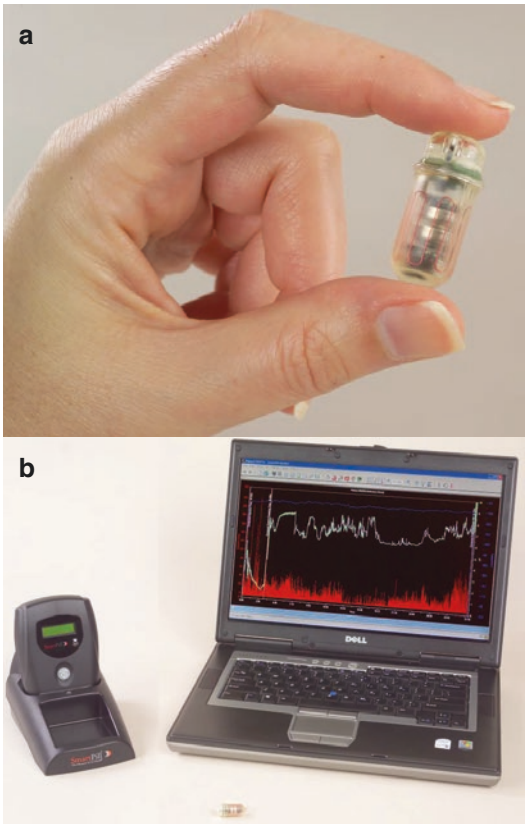

Fig. 34.1 The wireless motility capsule system (Smartpill). (**a**) The capsule. (**b**) The data receiver and the display software. Used with the permission of Medtronic, Dublin, Ireland

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and holds sensors for pH, temperature, and pressure. The pH measurement is accurate to 0.5 pH units and pressure measurement is accurate to ±5 mmHg below 100 mmHg [4]. Both the capsule and receiver have a battery life rated for 5 days of use after activation. The capsule transmits the data to the external receiver that is positioned within 1.5 m of the body. Anatomic positioning is determined using measuring for pH, temperature, and pressure, enabling the definition of time of entering the stomach, time of leaving the stomach and entering the small intestine, the time of reaching the cecum, and the time of exit from the body.

Indications for the Use of Wireless Motility Capsule

In 2011, the American and European Neurogastroenterology and Motility Societies have released a position paper concerning the evaluation of gastrointestinal transit in clinical practice [5]. WMC testing was recommended for the following indications:

(a) Assessment of gastric emptying and regional and whole gut transit time in individuals with suspected gastroparesis, symptoms of upper GI dysmotility, or suspected alterations of GI motility in multiple regions.
(b) Detection of small bowel dysfunction in subjects with a more generalized GI motility disorder.
(c) Assessment of colonic transit time (CTT) in subjects with symptoms of chronic constipation.

Similarly, the United States Food and Drug Administration (FDA) approved the SmartPill WMC GI Monitoring System for the evaluation of gastric emptying time in patients with suspected gastroparesis, for the evaluation of CTT in patients with suspected slow transit constipation, and for the measurement of temperature, pressure, and pH throughout the GI tract [6].

Study Protocol

The preparations for the study include a 6 h fast, avoidance of alcohol and tobacco, and discontinuation of medications potentially altering GI motility and gastric pH (Table 34.1). The study begins with consumption of a standardized meal consisting of a low fat egg meal (120 g eggbeaters, two slices of bread, 30 g of strawberry jam and 120 ml of water) or a 250 ml Ensure meal (250 kcal, protein 9 g, carbohydrates 40 g, fat 6 g, fiber 0 g) (Abbott Laboratories, Abbott Park, Il, USA) or a 260-kcal nutrient bar (17% protein, 66% carbohydrates, 2% fats, and 3% fiber) that is available through the manufacturer along with 50 ml of water. On completion of the meal, the WMC is activated and swallowed immediately. It is essential not to deviate from the protocol meal and not to swallow the capsule prior to the meal, as changes in the gastric empting and colonic transit can occur [7]. An external data recorder is attached to the waist for the period of the exam. Fasting should be continued for 2 h following the ensure meal or 6 h fast following the low fat egg meal or the nutrient bar meal. During the test period, the patients record (using an event button positioned on the recorder) special activities as

Table 34.1 Medications and products altering GI motility and gastric pH

Medications slowing GI motility (stop 3 days before the exam)
Narcotic agents
Antidiarrheal agents
Anticholinergic agents
Antiemetic agents
Medications accelerating GI motility
Prokinetic agents (stop 3 days before the exam)
Laxative agents (stop 2 days prior before the exam)
Medications raising gastric pH
Proton pump inhibitors (stop 7 days before the exam)
Histamine receptor antagonists (stop 3 days before the exam)
Antacids (Stop 1 day before the exam)
Other medications and products
Nonsteroidal anti-inflammatory agents (stop 3 days before the exam)
Tobacco (stop 12 h before the exam)
Alcohol (stop 24 h before the exam)

meals, sleep, and bowel movements. Abstention from the use of tobacco products for 8 h and the ingestion of alcohol for 72 h after the swallowing of the capsule as well as from strenuous exercise during the exam is required. The recorder is returned after 5 days and the data is downloaded and are analyzed using the display software (MotiliGI, Given Imaging Corp).

Data Analysis

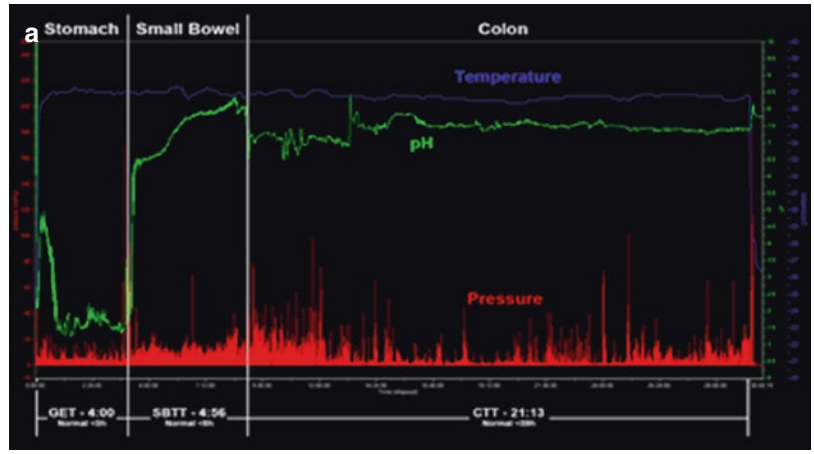
Data analysis and report are prepared by the display software. Typical result chart is presented in Fig. 34.2. Normative motility transit times are presented in Table 34.2. Gastric emptying time is defined as the duration of time from capsule ingestion to a pH rise of >3 pH units, representing the passage of the capsule from the acidic stomach to the alkaline duodenum. The sensitivity and specificity of WMC in identifying delayed gastric empting in comparison to a 4 h scintigraphic data were 0.87 and 0.92, respectively, with a correlation coefficient of 0.73 [8]. In another study, WMC was found to have 100% sensitivity and 50% specificity in diagnosing gastroparesis as compared to scintigraphic study of gastric emptying. In this study, the WMC detected motor abnormalities in 17 patients compared with 10 patients assessed by antroduodenal manometry [9]. Small bowel transit time (SBTT) is measured by using the capacity of the capsule to measure changes in pH profile [10, 11]. The SBTT is defined as the period that takes the capsule to move from entering the duodenum and until passing into the colon. In a study involving 66 healthy adults (18–65) and 34 adults with gastroparesis (18–66), the results of the SBTT measured by WMC were similar to the SBTT measured by scintigraphy in both the healthy and the gastroparetics [3]. Significant correlation of SBTT values obtained with WMC in comparison to whole gut scintigraphy ($r = 0.69$; $p = 0.05$) was demonstrated in another study [12]. The determination of SBTT was not possible in 5–10% of the patients due to the inability to accurately identify pH landmarks [13, 14]. Colon transit time (CTT) is defined as the time from the cecal entry and until the capsule leaves the body. A sustained (>10 min) pH drop of >1 unit that occurs more than 30 min after gastric emptying defines cecal entry, and loss of signal or a sudden temperature drop defines the capsule's exit from the body. In a study performed on 78 constipated and 87 healthy subjects, CTT measured by WMC had good correlation to that measured by a ROM study ($r = 0.78$ at day 2 and $r = 0.59$ at day 5) and comparable specificity (0.95) and sensitivity (0.46) [14]. In another multicenter study performed on 158 constipated adults, CTT measured by WMC demonstrated an overall agreement of 87% with that of 5-day ROM [13].

Contraindications and Adverse Events

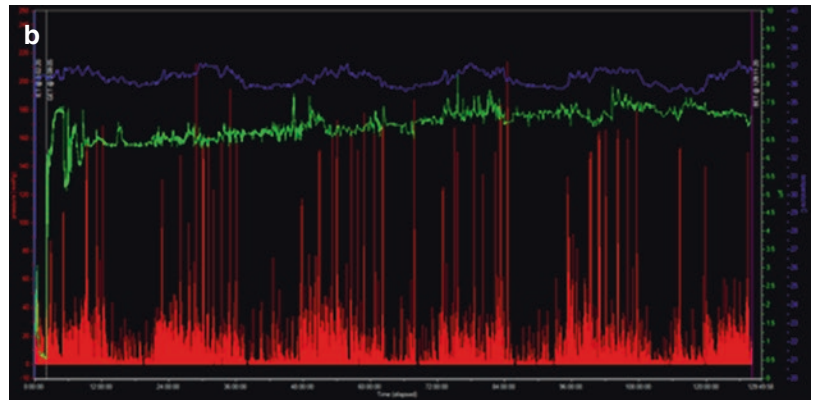
The main risk attributed to the use of the WMC relates to retention of the capsule in the GI tract. Therefore, WMC should not be performed in patients with suspected or known strictures or fistulas within the GI tract, Crohn's disease, history of gastric bezoar, history of diverticulitis, history of surgery on the gastrointestinal tract, or any abdominal or pelvic surgery within the last 3 months before the exam. Swallowing difficulties and dysphagia to pills and food may limit the use of WMC. In these cases, capsule insertion can be aided by PillCam delivery device and fluoroscopic guidance to ensure the positioning of the capsule in the stomach.

Due to the possible interference with the transmission of data to the receiver, WMC is partially contraindicated in patients with a cardiac pacemaker, defibrillator, or a left ventricular assist device. On the other hand, electronic simulators (as gastric stimulator, spinal stimulator, or infusion pumps for medication) do not hamper with the transmission and therefore their use is permitted during the exam. The use of WMC Capsule during magnetic resonance exam is contraindicated, and expulsion of the capsule must be confirmed prior to this exam.

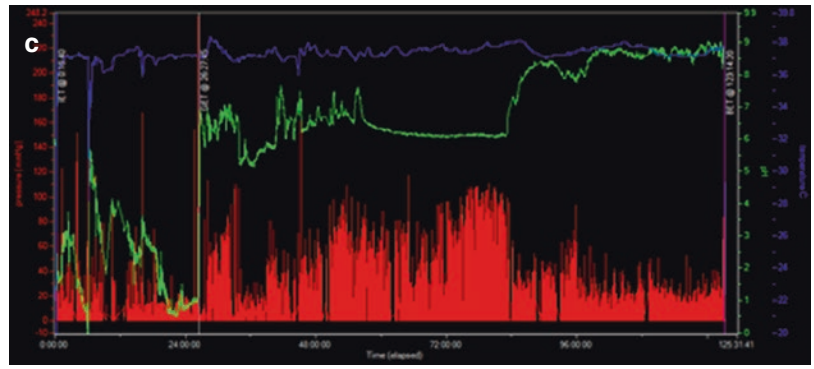
The reported incidence of sustained retention of the capsule (>2 weeks) is 0.33% [5]. Capsule retention can be detected by radiological



Normal transit



Slow transit contipation



GP and Slow CTT

Fig. 34.2 Typical wireless motility capsule results. (**a**) Normal transit, (**b**) slow transit constipation, (**c**) gastroparesis and slow transit constipation. Courtesy of Dr. Rita Brun

Table 34.2 Normal WMC transit times

Parameter	Time (h)
Gastric emptying	2–5
Small bowel transit	2–6
Colon transit	10–59

identification, although the pH data may also provide information on locating the retained capsule. In most cases the capsule will eventually be excreted without any intervention. In some cases, endoscopic retrieval is required. Facilitation of the capsule excretion can be achieved with the

use of Prokinetics (e.g., Prucalopride) and laxatives. The reported rate of capsule retention requiring intervention is low (0.01%) [15].

Bowel obstruction due to capsule retention is the most serious potential adverse event of WMC. In the case of clinical suspicion of obstruction (symptoms of abdominal distension, abdominal cramps, nausea, and vomiting), immediate abdominal imaging and capsule retrieval should be pursued.

The incidence of mechanical causes for test failure is low, reported in 0.6% in clinical trials and in 0.8–0.9% of post-marketing exams.

WMC in Special Populations

Although not FDA approved, the WMC system demonstrated efficiency in pediatric population. In a study involving 22 children (8–17 years), the WMC proved to have 100% sensitivity and 50% specificity in diagnosis of gastroparesis as compared to scintographic studies [9]. WMC demonstrated effectiveness also in elderly population (65–78 years), where device agreement between WMC and 5-day ROM in the diagnosis of colonic slow transit constipation was 88% [16]. WMC was found to be effective and safe in critically ill patients [17] as well as in patients with cystic fibrosis [18].

Strengths and Limitations

The main strength of the WMC system lays in the possibility of a reliable measurement of gastric emptying time, small bowel transit time, and colon transit time at the same exam. The fact that the test is office based, radiation free and relatively easy to perform and interpret is another strong point.

As any technology, WMC has limitations. The fact that the pressure measurement is produced using a non-stationary, single point transducer, limits the ability to detect and measure the pressure wave front. This fact may limit the efficacy of the WMC in association to other manometric testing. However, the invasive nature and the fact that small bowel and colonic manometry are performed in small number of centers, limit the use of these modalities. Another limit results from the inability of the WMC to distinguish between gastric liquid and solid emptying.

The fact that the capsule is nondigestible and needs to be ingested may limit the use due to danger of retention, especially in patients with suspected strictures, fistulas, GI obstructive symptoms, history of gastric bezoars, disorders of swallowing, recent GI surgery, Crohn's disease, and diverticulitis.

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Chronic Constipation

35

Walter Hogan

Patient Question: "*Why am I having problems with my bowel movements***?"**

"I am Experiencing Difficulty Having a Bowel Movement. What is Wrong?"

Answer

If you are in good health, you may be functionally constipated. Constipation is defined as a difficulty in the passage of stool (defecation); it can occur with a variety of symptoms associated with the stooling activity such as straining, not experiencing a sensation of "relief," or manual maneuvers required to expel stool. Infrequent eliminations of hard formed stools is a classic expression of constipation.

Two basic conditions explain the cause of constipation:

1. Impairment of movement of stool through the colon and/or
2. Dysfunction of the pelvic muscles obstructing passage of stool

Constipation is a common condition afflicting the general population. The frequency of occurrence has been reported to be as high as 40% in some studies.

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The formal definition of functional constipation by experts in this field includes the following criteria: two or more of the following conditions which occur >25% of the time with fewer than three spontaneous eliminations weekly during the last 3 months [1].

1. Straining at stool
2. Lumpy hard stool
3. Feeling of incomplete evacuation
4. Sensation of rectal blockage
5. Manual maneuvering required

"I am Not in Control of My Bowel Movements. What is Happening?"

Recurrent, uncontrolled passage of fecal material over a period of at least 3 months has been identified as fecal incontinence [2]. The causes of fecal incontinence are multiple ranging from gross loss of stool with diarrhea to fecal staining of undergarments related to impaired rectal storage or a weakened pelvic floor.

Prevalence of fecal incontinence ranges from 7% to 15% in the general population to as high as 50–70% in nursing care facilities.

Clues to the loss of stool can be aided by the patients assessment of the quantity, frequency and association or lack of association of sensation with defecation. For example, "urge" incontinence is a feeling of impending defecation but

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inability to reach a toilet on time. "Passive" incontinence on the other hand connotes an absence of awareness or diminished sensation preceding the loss of stool.

Pelvic Floor and Anorectum (Fig. 35.1)

Anatomy

The pelvic floor is a dome-shaped structure of striated muscle responsible for storage and evacuation of stool. A portion of the pelvic floor includes the puborectalis muscle which is a thick, sling-link muscle that is responsible for maintaining forward reinforcement of the anorectal angle.

The anorectum is the terminal portion of the large intestine. The rectum is approximately 15 cm in length with the anal canal (2.3–3.5 cm) occupying the most distal segment and surrounded by internal and external sphincters.

Innervation

The internal anal sphincter is an extension of the circular smooth muscle surrounding the rectum. It is an "involuntary" structure supplied by parasympathetic nerves. The external anal sphincter is a "voluntary" structure innervated primarily by S4 through the inferior rectal nerve. The external sphincter blends into the more proximal puborectalis muscle (Fig. 35.2).

Sensation

Rectal distention is perceived by the patient as a localized "fullness" associated with the urge to pass flatus or defecate. The anal canal, on the other hand, from the proximal dentate line

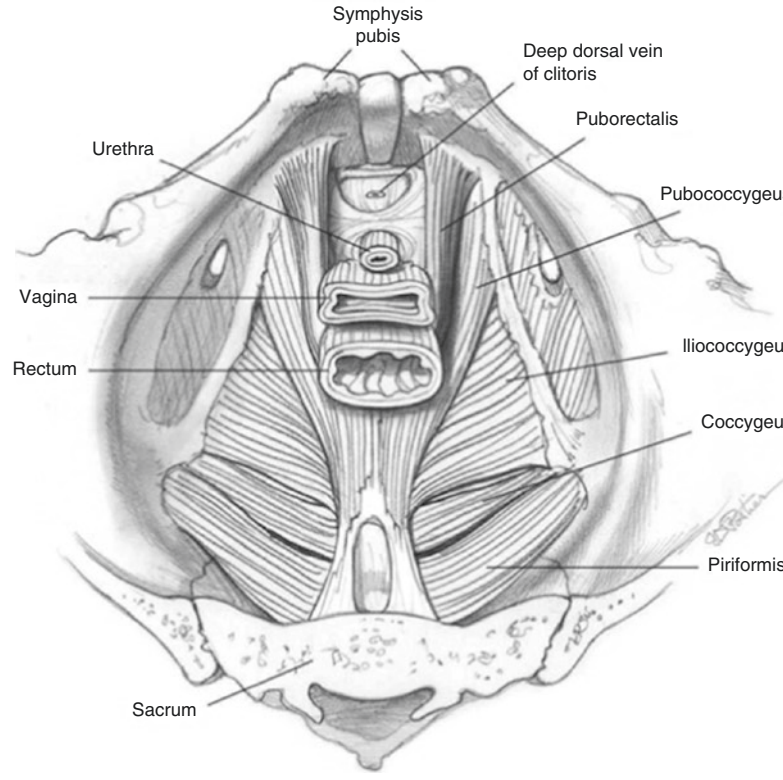


Fig. 35.1 Sagittal section of pelvic anatomy demonstrating pelvic musculature and puborectalis "sling" around the sphincters. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved)

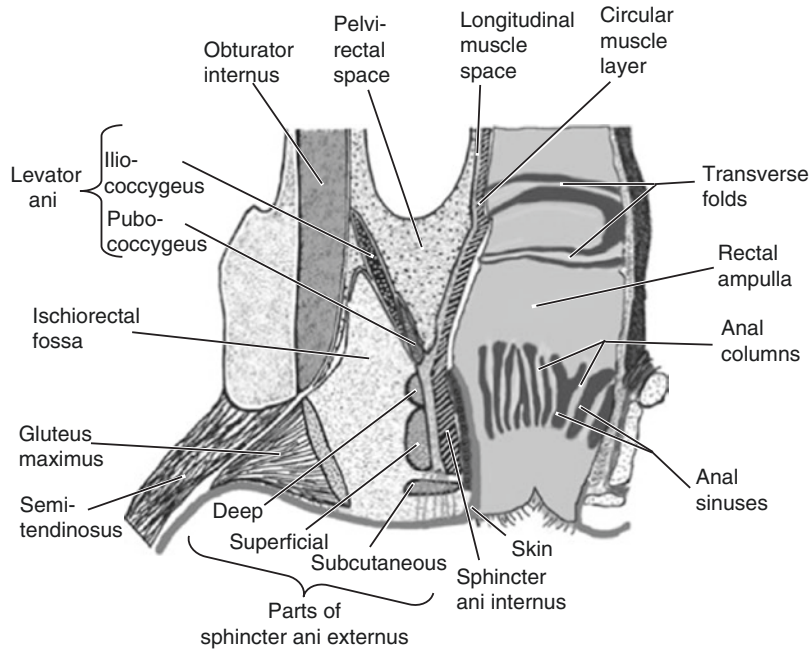


Fig. 35.2 Anatomic juxta position of internal anal sphincter (ani internus) and external anal sphincter (ani externus) surrounding the rectum (Sagittal view). (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved)

(mucocutaneous line) is exquisitely sensitive to light touch, pain, and temperature.

Physiology of Defecation/Continence

During defecation stool is transferred into the rectum by a series of propagated colonic contractions. Distention of the rectum subsequently prompts relaxation of the internal anal sphincter and the sensation of fullness. There is an associated urge for relief with voluntary contraction of the puborectalis and external sphincter muscle.

Anorectal continence (stool retention) is a combination of competent anosphincter function, anal sealing caused by distal anovascular tissue and maintenance of the angle formed between the rectum and sigmoid by the levator ani and puborectalis and external sphincter muscle.

Perineal Inspection/Anorectal Exam

Valuable information concerning the patient's defecatory problem can often be obtained by inspection and digital rectal examination of the patient. The appearance of scars, fistula tracks, asymmetry or "bulging" of perineal fold, rectal tissue eversion or prolapse, prominent hemorrhoids or perianal excoriations can provide evidence of defecatory problems. Visualization of perineum during a straining maneuver may demonstrate excessive pelvic descent (>3 cm) or bilateral gluteal infolding. This observation of a paradoxical "squeeze" while supposedly straining is tantamount to a diagnosis of dyssynergia!

Four quadrant testing of perineal sensation with a cotton Q-tip should elicit an anocutaneous reflex ("anal wink") attesting to perineal nerve function.

The digital rectal exam, performed with the gloved finger, adequate lubricant and with the patient in the left lateral posture can assess the sphincteric resting tone and squeeze pressure. The strength of the puborectalis sling pressure and sensation can be demonstrated during a "squeeze" maneuver. The presence of a rectocele or mass can be detected and evaluation of the prostate is essential in the male patient.

Clinical Tests

The majority of patients with defecatory problems do not require a battery of sophisticated

tests to answer their difficulty. A detailed history, physical exam, and endoscopic inspection of the colon may be all that is needed in eliminating a structural cause for the patient's problem and directing appropriate conservative treatment.

Patients with more severe difficulty with elimination may be candidates for clinical testing to help elucidate an answer. It should be noted at the outset that the specificity and sensitivity of any one test currently in use in clinical practice to detect the etiology of a defecation disorder is either unsubstantiated or questionable.

Anorectal Manometry

This test of anorectal function and sensation involves placement of a small catheter containing a distal balloon into the patient's rectum. Two Fleets enemas prior to the test are usually sufficient to cleanse the rectum but the preliminary digital exam will verify this fact.

Currently a solid-state probe with high-resolution manometry microtransducer is the recording instrument of choice. One version contains 12 circumferentially placed sensors which permits radial pressure recording over a 2 cm length of the anal canal [3]. An additional two sensors placed proximal record pressure within the rectum and within the small balloon. The resulting pressure averages can be displayed as both an isobaric contour plot as well as a basic pressure profile (Fig. 35.3).

The anorectal manometry test assesses internal and external sphincter function, rectal sensation, anorectal reflex, and rectal compliance. The following data points are determined from the study.

(a) Resting (basal) Sphincter Pressure.
This pressure measures predominantly (70%) internal (involuntary) sphincter tone.
(b) Squeeze Pressure.
The amplitude/duration of maximal external (voluntary) sphincter and puborectalis contraction is recorded during brief voluntary squeezing and during a sustained one-minute contraction. The influence of coughing on external sphincter contraction provides a maximal "provoked" measurement for comparison with the patient's voluntary effort.
(c) Rectal Sensation.
The patient response to incremental increases in rectal balloon volumes (up to 150 ml depending on patient tolerance) is recorded for an initial "sensation" and subsequent "urge" sensation felt by the patient.

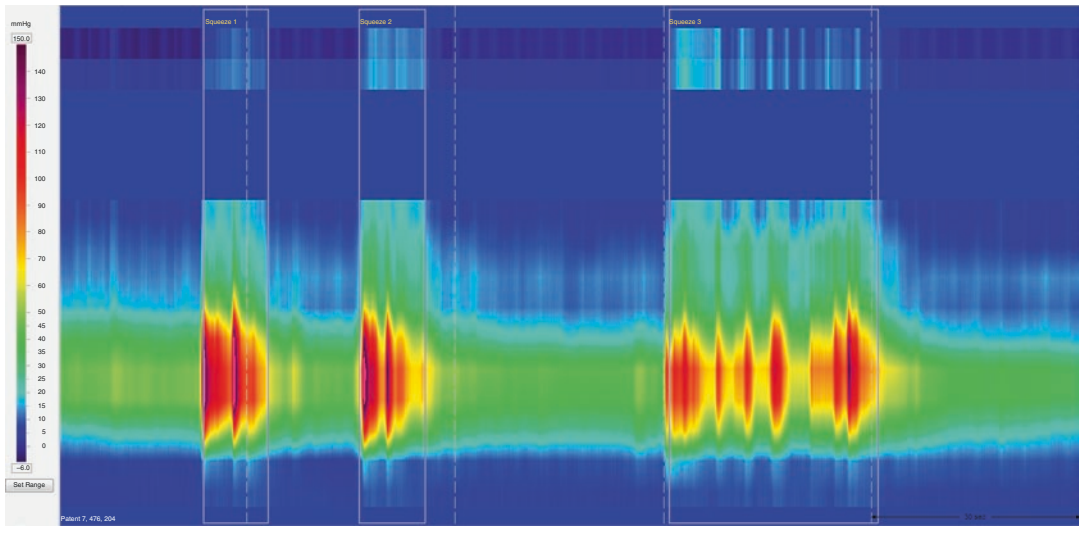


Fig. 35.3 High-resolution solid-state manometry (isobaric contour plot) display demonstrating external sphincter contraction during to ansient and sustained squeeze (top)

(d) Anorectal Inhibitory Reflex
The internal anal sphincter relaxes at a point during graded volume inflation of a rectal balloon. This demonstrates the integrity of the myenteric plexus communication between the rectum and anal canal. This reflex is classically absent in Hirschsprung's disease [4].

(e) Rectal Balloon Expulsion.
This test monitors simulation defecation by expulsion of a 50 ml rectal balloon over a period of 1 min. The test is best performed with the patient seated on a toilet facility. The ratio of the intraabdominal pressure vs. the relaxation pressure of the pelvic floor and external sphincter required to expel the balloon provides a value called the defecatory index.

(f) Rectal Compliance
Pressure–volume relationship between the rectal wall and graded balloon volumes approximates a measure of rectal compliance.

Clinical Usefulness of Anorectal Manometry Test

Anorectal manometry is most useful in determining a pattern of obstruction defecation as the cause for the patient's distress [5].

Normally during simulated defecation there is an increase in intrarectal pressure associated with relaxation of the anosphincter. In many patients an obstructive defecation pattern is characterized by inadequate relaxation or contraction of the pelvic floor during simulated defecation. The term dyssynergia has been used to describe this apparent paradox. Several reproducible variations between the rectal and anorectal pressures have been recorded in patients with obstructive defecation disorders defined as dyssynergia [6].

A recent report in a large population of woman with defecatory disorders described three manometric patterns indicative of dyssynergia (hypertensive anosphincter (basal) pressure (Fig. 35.4); low rectal pressure or a hybrid) [2]. These findings correlated with abnormal rectal balloon expulsion times.

No one test result is sufficiently predictive to diagnose dyssynergia however. For example, contraction of the anosphincter during simulated defecation has been observed in 20% of patients without apparent problems with defecation. While unsuccessful passage of a rectal balloon is important for the diagnosis of dyssynergia, successful expulsion does not obviate the diagnosis either. For this reason, the positive results from several tests are necessary to fulfill the diagnosis of dyssynergia. In our laboratory, we require three abnormal test results to define the criteria for dyssynergia, i.e., obstructive features on manometry, inability to expel a rectal balloon, and an abnormal defecatory index (<1.2%). Some authorities also require an abnormal defecography study to complete the criteria for dyssynergia.

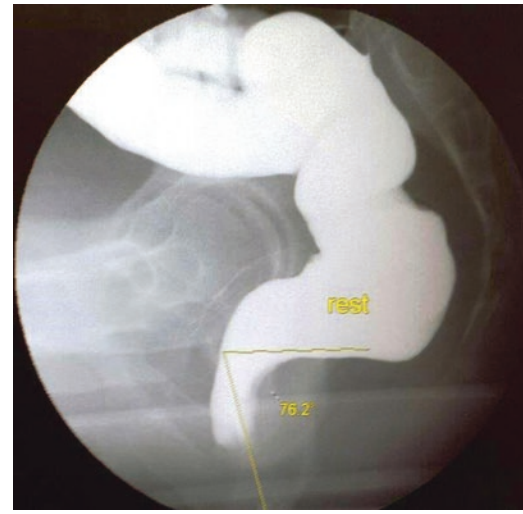


Fig. 35.4 Defecography image showing the anorectal angle at rest (76.2° angle)

Defecography

Defecography is a radiologic examination observing the rectal expulsion of barium paste by the patient during simulated defection [7]. The anorectal angle at rest and during straining can be measured (Figs. 35.5 and 35.6). The perineal descent is estimated and contrast emptying noted. In addition to evaluating rectal and pelvic floor dynamics structural abnormalities can be detected, e.g., rectocele, enterocele, rectal prolapse, and megarectum. Recently defecography has been performed during real-time magnetic

resonance imaging. This technique provides more information concerning sphincteric and soft tissue visualization but is more costly. Defecography provides important information about these pelvic structural abnormalities which might benefit from surgical therapy. An adequate defecography study requires an interested and experienced radiographer and cooperative patient

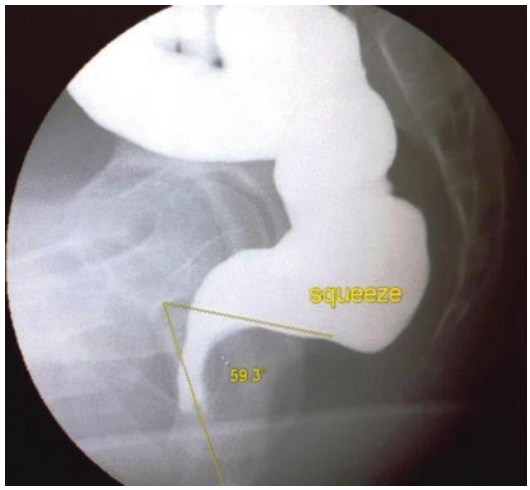


Fig. 35.5 Defecography image and abnormal reduction of anorectal angle (59.3°) during "squeeze" maneuver

Colonic Transit Studies

Colonic transit time has been classically investigated utilizing radiopaque markers monitored radiographically over a standardized time period.

The Sitzmarker capsule has been the most frequently used test to determine an approximation of stool transit in patients [8]. A capsule containing 24 markers is ingested following a colonic purge by the patient. A baseline abdominal X-ray series is obtained and repeated in 5 days. Retention of ≥6 markers is considered to be diagnostic of "slow transit" constipation. Positive test results have been reported in two-thirds of patients with functional constipation. However colonic slow transit can be diagnosed only after dyssynergia has been excluded since 60% of patients with this problem have abnormal marker retention. More recently sophisticated scintigraphy techniques and the smart pill (a wireless novel motility capsule) have been introduced to access colonic transit [9]. These tests provide radiation-free methods of measuring colonic transit and test results correlate with standard marker studies. Current availability and costs have limited extensive use of these newer techniques to date.

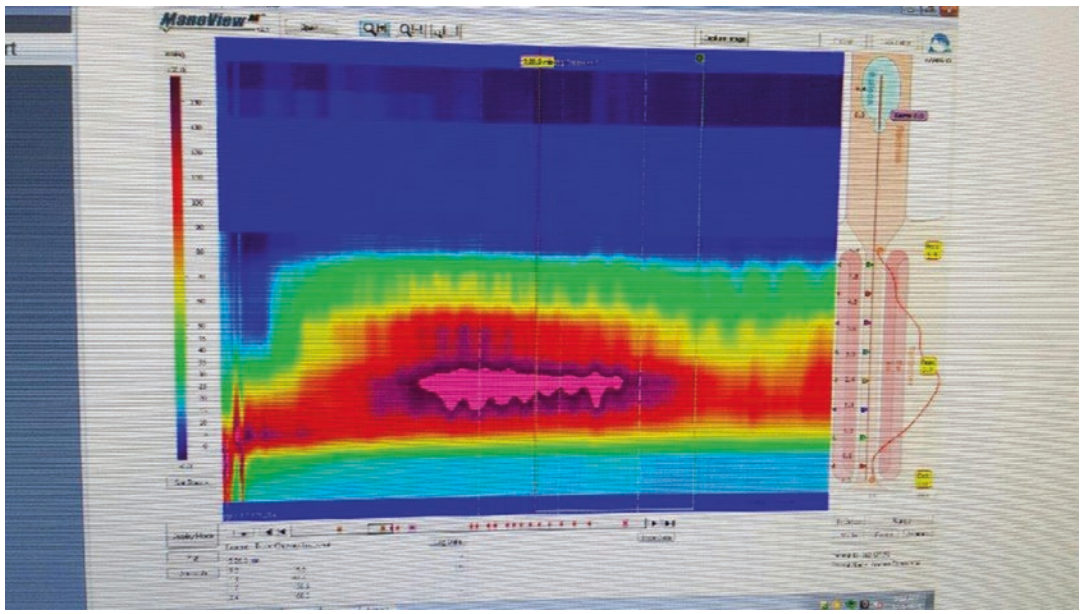


Fig. 35.6 High-resolution manometry (isobaric plot) display of hypertonic resting (internal sphincter) pressure. The intense middle coloration reflects the vertical pressure scale on the left

Anorectal Ultrasound (US) (Fig. 35.7)

Anorectal US can assess the structural integrity of the anosphincters [5]. Structural defects, loss of mass or adjacent abnormalities can often be detected. The study can distinguish internal from external sphincter. In our experience, this test is useful in targeting Botox injections directly into the sphincter zone of patients with hypertensive basal sphincter pressure [10]. However, Botox injection in patients with levator ani syndrome has not yielded successful results.

Electromyographic Tests (EMG)

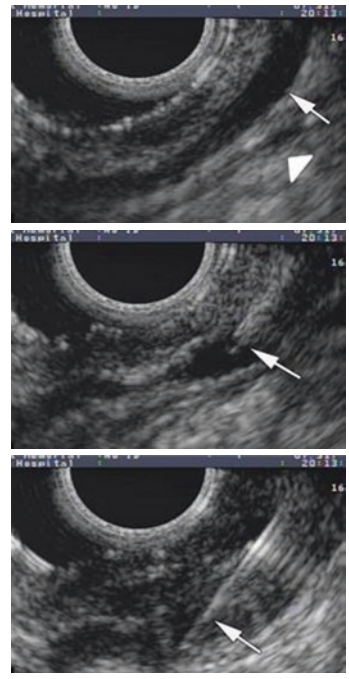
EMG and pudendal nerve testing is useful in determining anorectal injury and neuropathy [12]. EMG technology utilizing needle or surface electrodes is available in most units with neurologic facilities and physician expertise. This test may be diagnostic in detecting causes of incontinence following spinal injury, disease, or traumatic injury.

Fecal Incontinence

The causes of fecal incontinence are multiple and range from anorectal weakness resulting from trauma, neuropathy, and specific prundal nerve injury. Pelvic floor disorders with enhanced descending perineum and rectal prolapse are major sources of incontinence. Problems affecting rectal capacity and sensation are common in patients with anorectal incontinence also. Disorders of the central nervous system are often responsible for incontinence but more difficult to diagnose and treat. Finally, chronic constipation and stool retention with overflow is perhaps the most underappreciated cause of anorectal incontinence and rectal leakage. An abdominal X-ray series demonstrating significant stool retention in a patient with "incontinence" can usually resolve this quandary.

Clinical Evaluation

A careful history is perhaps the most important element in providing clues to the patient's fecal incontinence. A patient stooling diary and identification of the elimination form using the



Internal anal sphincter (arrow)
External sphincter (arrow-head)

22 gauge FNA needle (arrow) inserted into the internal anal sphincter under EUS guidance

Twenty units of Botox injected into the internal anal sphinter

Fig. 35.7 Ultrasound images at anorectal zone. The tissue layers of the internal anal sphincter are well demarcated. Botox injection is accitrated targeted

Bristol stool scale are useful tools for helping with this situation [13]. Concurrent drug use, dietary habits (artificial sweeteners), and timing of stooling may be important clues. For example, frequent postprandial (clustered) stooling interspersed with an "incomplete" sensation is more commonly related to constipation issues in our experience.

A most informative clue is whether the patient experiences an intense urge or passive (unawareness) associated with stool incontinence. Urge incontinence is associated with a severe sensation to defecate which prompts leakage or loss of liquid stool volume before reaching the toilet. This is a frequent story from the patient with stool retention and subsequent overflow (a delivery problem not a sphincter problem). Passive loss of stool is more indicative of significant sphincter weakness, deficient rectal sensation, or structural alteration.

Physical Examination

A thorough digital exam of the unprepped rectum in the patient with anorectal incontinence provides helpful information concerning the cause [14]. A stool-filled rectum suggests a retention issue not necessarily a sphincter problem per se. Rectal digital exam can be a relatively accurate method of identifying hypotensive basal sphincter and voluntary squeeze pressure. Observing the patient during a sustained valsalva maneuver may be necessary to detect an underlying rectal prolapse or patulous opening of the anosphincter or excessive pelvic descent.

Clinical Tests

Anorectal manometry can confirm the clinical impression of the patients' gross anorectal incontinence. The test does quantify sphincter tone and rectal sensation but its most important value is often confirming normal function of these elements. However patients with "urge" incontinence may demonstrate reduced sphincteric squeeze pressure or increased rectal compliance.

Anorectal ultrasound, defecography and pelvic magnetic resonance imaging are important tools in detecting dynamics and alterations of the pelvic floor and associated structures. Information provided by these tests may identify structural abnormalities that may respond to surgery.

Neurophysiological tests such as EMG or pudendal nerve motor latency are useful in detecting neurologic impairment as the cause or contributor to the incontinence.

Functional Pelvic Pain

Excluding obvious inflammatory or structural abnormalities in the pelvic floor, functional anorectal pain syndromes have been characterized as levator ani syndrome or proctalgia fugax. These two clinical entities are defined by the duration of pain and the presence or absence of anorectal tenderness on digital examination [2].

Levator ani symptoms are frequently described as a dull ache or pressure sensation felt in the upper rectal area. The painful episodes can last for a half hour or longer. The pain pattern may be improved temporarily with defecation or passage of flatus. Rectal exam can elicit tenderness when traction is applied to the puborectalis muscle. A symptom pattern occurring for at least 9 months is necessary to meet current diagnostic criteria.

Proctalgia fugax is defined as a recurrent rectal pain unrelated to defecation which persists for periods of seconds to minutes. The pain episodes rarely last beyond 30 min and classically awaken the patient from sleep at nighttime. The patient experiences no pain between episodes. Conventional manometric and radiologic studies have only been useful in excluding other causes for these disorders.

Treatment Regimens

At the point in time when patients with significant defecatory disorders require sophisticated diagnostic tests, they have been exposed to dietary restrictions, laxatives, antidiarrhea drugs, and colonoscopy exam.

Patients with chronic constipation may require a more regulated use of laxatives to be clinically effective. The majority of physicians are still concerned about "laxative dependency" and limit the duration and dosage of these drugs. Periodic and inconsistent use of laxatives is often the explanation for apparent "ineffectiveness." It needs repetition: laxatives do not cause a megacolon which has been an unproven fear of clinicians.

The standard addition of fiber supplements, e.g., psyllium in adequate amounts (≥30 mg/d) to the diet of the patient with chronic functional constipation and slow transit is frequently unsuccessful and adds to the bloating sensation. Miralax has become the first-line trial laxative medication for constipation. Improved effectiveness can be enhanced by twice daily dosing or the graded implementation of Senna or Dulcolax tablets with the Miralax. In addition, several new laxative medications have been introduced for the treatment of constipation, e.g., Lubiprostone 24 mg bid and Linaclotide 145 mg qd.

The patient needs to maintain a diary of the stooling pattern and the use of laxatives on a daily bases to effectively manage the problem. Unfortunately, laxatives may lose their efficiency and require dosage adjustment or the patient decreases frequency of intake. A stool diary will help adjust this situation.

Patients with diarrhea and anorectal incontinence may benefit from dietary alteration. For example, elimination of dietary lactose, fructose, or sorbitols may be the answer. Removal of gluten, unless the patient has celiac disease, has questionable effectiveness.

Patients with frank anorectal incontinence or soilage require a far different therapeutic approach. The use of antidiarrheal medications (e.g., one or two tablets of Loperamide) on a daily bases may be effective in stopping the diarrhea but in some situations may provoke constipation. (If the patient with "uncontrolled diarrhea" does not experience an elimination for 24 h after taking a tablet of Loperamide, the problem is decidedly functional and probably an issue with constipation.) Patients with overflow incontinence often cannot control their eliminations with taking laxatives. The inconvenience and unexpectedness of defecation adds to the patient's anxiety and social problems. These patients, particularly those burdened by spinal damage or rectal structural abnormalities, may respond to large volume enemas administered on a routine basis. Rectal suppositories or small enemas may be helpful also. The rational associated with this type of therapy is to provide a programmed, anticipated elimination.

Pelvic Floor Retraining (Biofeedback)

Biofeedback training techniques have been developed to enhance/alter striated muscle activity monitored by perianal EMG or pressure sensors placed inside the anus and rectum. Simulated defecation using an artificial stool model has been used in some situations.

Biofeedback programs advocate several steps in their treatment algorithm. The therapeutic goal is often directed by the pattern of dyssynergic defecation recorded manometrically.

The standard Pelvic Training Program involves both biofeedback techniques plus simulated defecation:

1. Patient education and awareness
   The paradoxical situation of squeezing the sphincter voluntarily or being unable to relax during the act of defecation is thoroughly explained to the patient.
2. Increased intraabdominal wall pressure technique
   Strengthening exercises to augment abdominal support with various pushing techniques during simulated defecation (push technique).
3. Pelvic relaxation technique
   Pelvic floor muscular relaxation during straining monitored by devices visually provides feedback and reinforcement for the patient.
4. Rectal devices
   Simulated defection is monitored usually involving an inflated lubricated rectal balloon.

Biofeedback therapy is the primary choice of therapy for patients with functional defecation disorders. However, a formal biofeedback

program performed by dedicated, experienced personnel is essential but not always locally available!! Some programs require a series of weekly visits while others require a more stringent dedicated and compact schedule. The overall success rates for biofeedback training range from 70 to 80% based on randomized controlled studies.

Surgical Treatment

Anosphincter surgery generally is ineffective over long-term follow-up. Recently, sacral nerve stimulation and anal sphincter submucosal injection of a bulking agent have been approved by the US Food and Drug Administration for treatment of structural anosphincter incontinence. A 5-year uncontrolled study of 16 patients receiving sacral nerve stimulation reported complete continence in 30% and satisfaction in 89% [2]. However, no controlled study has been reported using this therapeutic modality.

Injection of a bulking agent into the anal sphincter has been successful in achieving a reduction of a rectal incontinence in 52% of patients with fecal incontinence vs. 31% of the sham patient group of 206 patients followed for 3 years.

Other Treatments

A variety of therapies have been advocated for treatment of patients with functional anorectal pain ranging from digital massage, sitz baths, and psycho therapeutics. In one study of 157 patients with chronic proctalgia, digital massage of the levator ani was compared to pelvic floor biofeedback. Patients with tenderness on palpation of the levator reported 87% relief of pain vs. 22% in the massage group [2].

In a small group of patients botulinum A toxin injection in the anosphincter was unsuccessful [11]. However in a small uncontrolled series of botulinum injections in patients with hypertonic basal sphincter pressures, the results have been encouraging [10].

Patients with proctalgia fugax can often be treated effectively with insertion of a glycerin or morphine suppository during the pain episode. This form of treatment is less effective in patients with chronic proctalgia.

Conclusions

Defecation disorders are extremely prevalent in the population and often cause significant symptoms and social disability. The majority of patients with elimination problems can be treated effectively with conservative measures. However many patients require more definitive evaluation and sophisticated testing to help determine the cause of their problems. Knowledge of the defecatory process, pelvic muscle structures, physical exam and information concerning the available testing modalities and their efficacy is necessary in dealing with this situation. This chapter has reviewed these issues and suggested treatment approaches.

Acknowledgements *Disclosures:* Nothing to disclose.

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Functional Anorectal Pain/Tenesmus

36

Arnold Wald

Introduction

In a United States population survey published almost 25 years ago, the prevalence of anorectal pain was 6.6% [1]. Rectoanal pain was reported more often by women and tended to decline after age 45. Persons with anorectal pain reported missing an average of 17.9 days from work or school during the previous year.

There are many causes of chronic or recurrent anorectal pain—these include organic diseases such as anal fissure, prostatitis, coccygodynia, and inflammatory bowel diseases. However, many patients have no evidence of organic disease and are diagnosed to have chronic or recurrent proctalgia. Lastly, there are patients who report a frequent urge to defecate in the absence of stool in the rectum. This symptom, known as tenesmus, may be associated with organic diseases (proctitis/proctosigmoiditis) or can occur as a functional disorder. Another definition of rectal tenesmus is a feeling of incomplete defecation, even though the person may have just had a bowel movement.

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Chronic Proctalgia

Clinical situation: After extensive testing to determine the cause of a dull aching pain high in the rectum which has occurred intermittently for the past 9 months, the patient is given a diagnosis of levator ani syndrome.

Question: Why do I have this pain when the tests are all normal? What treatments can make it better?

Answer: There are many names for the condition you have, including levator ani syndrome, levator spasm, and puborectalis syndrome. The cause is poorly understood but is thought to be associated with overly contracted pelvic floor muscles, also known as the levator ani or puborectalis muscle. The diagnosis is based on the symptoms, the tenderness of that muscle on my examination and the exclusion of other causes by imaging studies such as ultrasonography and pelvic CT scans, such as you had.

There are many treatments for this disorder, but little evidence to support their use. On the basis of the results of your anorectal manometry, one study suggests that biofeedback may be helpful to you. I am going to refer you to a physical therapist who specializes in treatment of this type. Studies suggest that you have a 70–80% chance of success and the treatment, which generally involves 5–6 sessions, carries no risk of complications.

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Commentary

Chronic proctalgia is also called levator ani syndrome, levator spasm, puborectalis syndrome, pyriformis syndrome, and pelvic tension myalgia. As in any syndrome, there are no biologic disease markers to establish the diagnosis. There are no published data on the frequency with which chronic proctalgia is seen in medical or gastroenterology practice.

According to the Rome IV criteria, chronic proctalgia may be divided into **levator ani syndrome** or **unspecified anorectal pain** [2]. This is based on whether or not there is tenderness during posterior traction on the puborectalis muscle on digital examination. For unknown reasons, tenderness is more often predominantly left sided [3] and palpation generally elicits the characteristic discomfort. If there is no puborectalis discomfort on palpation, the default diagnosis is "unspecified anorectal pain." This distinction has important implications for treatment (see below). It must also be emphasized that in order to make the diagnosis, symptoms should be chronic or recurrent, last 30 min or longer, and other causes of rectal pain have been excluded by appropriate testing.

An algorithm for approaching these patients is shown (Fig. 36.1).

Many treatments, largely directed at reducing tension of the striated muscles of the pelvic floor, have been used with little supporting evidence. These include electrogalvanic stimulation [4, 5], biofeedback training [6], muscle relaxants [3], digital massage of the levator ani muscles [7], and sitz baths. There is no evidence to support the use of botulinum toxin A injections [8], and surgery to cut the puborectalis muscle should be avoided.

The most rigorous study to date evaluated biofeedback, electrogalvanic stimulation, and digital massage in a group of patients with chronic proctalgia [9]. Patients were stratified into those with "levator ani syndrome" or "unspecified functional anorectal pain" on the basis of the examination. Patients in each group were further divided into those who exhibited a dyssynergic defecation pattern on the basis of anorectal manometry and balloon expulsion testing. The results were impressive. In the levator ani group, those with evidence of dyssynergia had an 87% response to biofeedback treatment (consisting of 5 weekly sessions) at 1 month but no benefit was observed in patients who did not have this finding. Response to biofeedback exceeded that of 9 sessions of electrogalvanic stimulation (45%) which in turn exceeded the response to 9 sessions of digital massage (22%). There were no differences in patients with either levator ani syndrome or unspecified anorectal pain if they did not exhibit dyssynergia. While this single center study was impressive, future studies are needed to confirm these findings. However, this study suggests a therapeutic pathway for many of these patients.

Future Studies

More studies of this difficult disorder are needed to determine best treatments. The results of the Chiarioni study need to be confirmed by independent centers. Electrogalvanic stimulation should be studied further as a possible alternative to biofeedback for patients who reside in areas where biofeedback expertise is not available.

While chronic proctalgia is not a fatal illness, quality of life is significantly impaired, as it is in most patients with chronic pain syndromes. Above all, selecting a treatment without harmful risks should remain paramount.

Proctalgia Fugax

Clinical situation: An otherwise healthy man presents with a several year history of recurrent self-limited attacks of severe anal pain lasting up to 15 min. He has had at least six episodes during the past 2 years and feels well between episodes.

Question: What is the cause of my pain and is there anything that can prevent these attacks from occurring?

Answer: You have a condition called proctalgia fugax. While the pain is very uncomfortable, it is not associated with permanent damage to the rectum or surrounding muscles.

It is thought that the pain is a result of spasm of some of the muscles of the anus or pelvic floor.

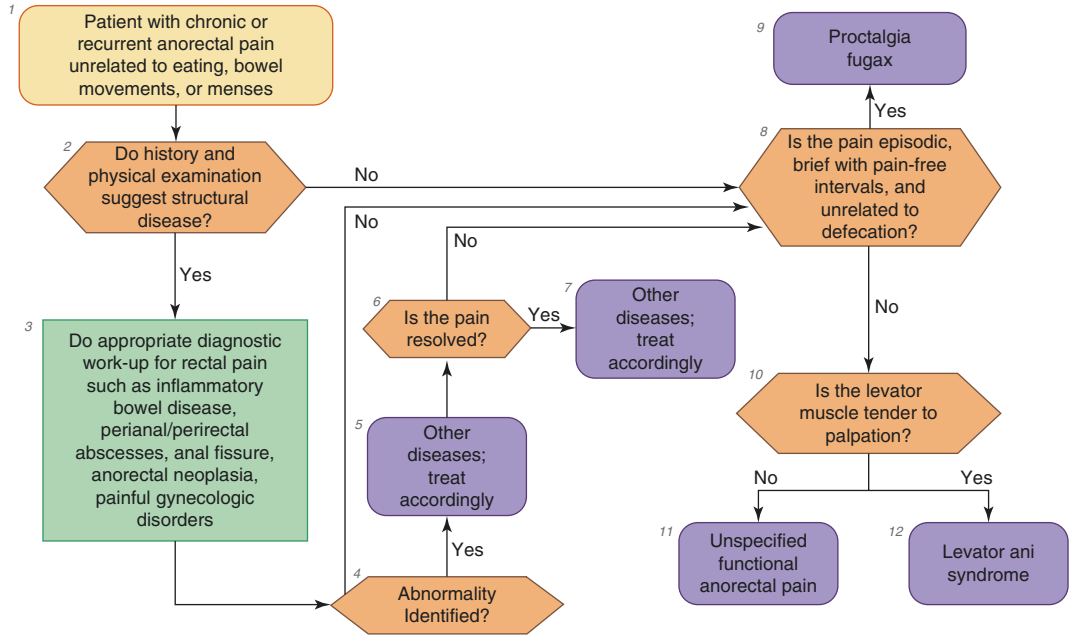

Fig. 36.1 Chronic or recurrent rectal pain. *1*. Pain present for at least 6 months is required for a diagnosis of functional anorectal pain syndrome. Pain associated with bowel movements, menses, or eating excludes the diagnosis of functional anorectal pain. *2–3*. The history and physical exam should identify alarm and other features suggesting structural disease, such as severe throbbing pain, sentinel piles, fistulous opening, anal strictures, induration, and anal tenderness during digital examination or while gently parting the posterior anus. Relevant organic causes of pain including inflammatory bowel disease, perianal abscesses, anal fissure, and painful gynecological conditions should be considered and identified by appropriate testing. If pain is associated with and worsened by menses, conditions that may include endometriosis, dysfunctional uterine bleeding, or another gynecological pathology should be evaluated by pelvic examination, pelvic ultrasound, and/or referral to a gynecologist. The minimum diagnostic workup (in the absence of alarm signs) includes the following: CBC, ESR, biochemistry panel, flexible sigmoidoscopy, and perianal imaging with ultrasound or MRI. If there is a high index of suspicion for anal fissures, anoscopy should be considered. *4–7*. If the diagnostic workup for alarm signs or symptoms identifies an abnormality (i.e., evidence of another disease explaining the anorectal pain), treat accordingly. If treatment of the other disease resolves the pain, this excludes the diagnosis of proctalgia fugax or levator ani syndrome. If treatment does not resolve the pain, go to Box 8. However, if the diagnostic workup for alarm signs or symptoms does not identify an abnormality, continue evaluation for proctalgia fugax or levator ani syndrome (Box 8). *8*. An important feature of the history is whether the pain is episodic with pain-free intervals. *9*. Patients with proctalgia fugax have brief episodes of pain lasting seconds to minutes with no pain between episodes. *10–12*. Patients with levator ani syndrome and unspecified functional anorectal pain have chronic or recurrent anorectal pain; if recurrent, the pain lasts for 30 min or longer during episodes. Levator ani syndrome, unlike unspecified functional anorectal pain, is associated with tenderness during posterior traction of the puborectalis. Used with permission from: Bharucha AE, Rao SC, Wald A. Anorectal Disorders. In Kellow J, Drossman DA, Chang L, Chey W, Tack J, Whitehead WE (eds). Rome IV Diagnostic Algorithms for Common GI symptoms. Chap. 6, pp. 112–131. Rome Foundation, Raleigh, NC, 2016

Because most persons do not consult with physicians and because it is uncommon to see patients when they are symptomatic, there are no studies to determine how or why these attacks occur. Also, there is no clear evidence for treatment which is often not necessary if the attacks are brief or infrequent. Some physicians recommend albuterol inhalants, amylnitrate or diltiazem ointment or clonidine in patients whose episodes last more than 30 min, but there is little or no evidence that they are effective.

Although the episodes are unpleasant, there is no permanent damage and the disorder is considered "harmless."

Commentary: The prevalence of proctalgia fugax in the population may be as high as 18%,

but only about one in five patients consult a health care professional [10]. The diagnosis is made on clinical criteria, which specify that episodes of pain are unrelated to defecation and last no more than 30 min, and by the exclusion of other disorders such as prostatitis, coccygodynia, and major structural alterations of the pelvic floor [2] (Fig. 36.1).

The short duration and episodic nature of these attacks have made this disorder virtually impossible to study and characterize. Studies have suggested that abnormal smooth muscle contractions may be responsible for the pain [11]. Several families with a hereditary form of proctalgia fugax were found to have hypertrophy of the internal anal sphincter [12, 13]. If this finding were universal, drugs to reduce internal anal sphincter tone would be theoretically appropriate, but there is no data to support this in the vast majority of cases.

The appropriate approach to patients is an explanation about the disorder, that it is unpleasant but harmless and to provide reassurance. For patients who have frequent attacks with a duration more than 20 min, the use of an albuterol inhalant (a beta adrenergic agonist) has been reported to shorten attacks [14]. Others have recommended clonidine [15], or nitrate ointments and diltiazem ointments based upon anecdotal reports. There are no studies of anxiolytic or antidepressant agents in proctalgia fugax but these may be indicated in patients exhibiting depression, anxiety, and other mood disorders.

Tenesmus

Clinical situation: A patient presents with longstanding complaints of an urge to defecate, often not resulting in a bowel movement. Even after having a bowel movement, the patient continues to feel that she has not emptied the rectum completely. An extensive workup has excluded infectious, inflammatory, and other known causes for tenesmus.

Question. Why do I have this problem when all the tests have been negative? Is there anything that can make me feel better?

Answer: As we discussed during the initial consultation visit, there are many diseases which can produce these symptoms, including infections and other causes of inflammation of the rectum. You underwent a colonoscopy and there is no evidence of inflammation. We have also looked for conditions that could cause inflammation outside the rectum using imaging studies, and these have been negative as well.

My assumption is that some event caused the nerves of the rectum to become hypersensitive or irritated. This is something that you cannot see with scopes or imaging studies. When this happens, the nerves sense signals which are usually too weak to be felt normally. These signals are carried to the spinal cord and brain and make you feel uncomfortable in that area. But it is a misperception by the brain that something (like stool) is in the bowel when, in fact, there is none.

Since we think that this involves changes in nerve chemistry, I am going to try certain medications that can desensitize the rectal nerves so that they won't send the wrong signals to the brain. I hope that they will be effective but they do act slowly and there may be some side effects. These drugs are also known as tricyclic agents which have been used for depression in the past but they do not have an antidepressant effect in the small doses that we use. I want to emphasize that we do not consider these symptoms imaginary or associated with a mood disorder. We will start at the lowest dose and increase the levels slowly according to side effects and clinical improvement.

Commentary: There are few concepts that are more difficult to convey to patients than that of visceral hypersensitivity and abnormal central nervous system (CNS) processing of gastrointestinal symptoms. Rectal hypersensitivity is easy to comprehend in the presence of inflammation caused by ulcerative colitis, Crohn's disease, radiation treatment, or infectious processes such

as herpes proctitis. When there is no inflammation, how does hypersensitivity evolve and be maintained?

When acute visceral inflammation or injury arises, such as with acute cholecystitis, pain clearly arises from a peripheral nerve injury and nociceptive signals are carried by afferent nerves to the brain. However, if discomfort or pain becomes chronic, it is increasingly influenced by the CNS which can become dysregulated; this amplifies the pain and becomes associated with gut dysfunction. This can be further influenced by cognitive and emotional centers and even autonomic dysregulation. Both of these processes have been demonstrated in patients with irritable bowel syndrome [16, 17].

There are many examples of visceral hypersensitivity involving the esophagus to the colon [18]. A traditional way to study this phenomenon has been the use of visceral distension (barostat) models but it remains uncertain whether the findings relate to alterations in rectal tone, altered peripheral or central nervous system processing or even psychological issues such as anticipatory bias in the laboratory setting [16, 17].

While there are no studies on the treatment of functional tenesmus, I often use an approach based largely on the treatment of functional disorders such as irritable bowel syndrome, noncardiac chest pain, and functional abdominal pain. This involves both pharmacological and behavioral measures [19–21]. It is critically important to emphasize to the patient that the choice of certain drugs should not convey the idea that the health care provider is dismissive of the complaint or suspects an emotional basis for tenesmus. This discussion must be done before treatment is started and will improve compliance.

In general, I prefer to start with a tricyclic agent (TCA) in the lowest available dose. This is because TCAs appear to be most effective for reducing pain in irritable bowel syndrome [21] and in disorders such as noncardiac chest pain [19]. Starting at the lowest dose helps to minimize side effects (most often drowsiness, dry mouth, and dizziness) and many patients will respond at this dose. The dose is increased every 2–3 weeks as tolerated and it is emphasized to the patient that improvement may take several weeks to occur. If the patient is intolerant to one agent, they may be tried on another (for example, switching from amitriptyline to desipramine, imipramine, or nortriptyline). If there is underlying depression or other mood disorder, selective serotonin uptake inhibitors (SSRIs) may be helpful by improving emotional factors that may amplify the symptoms and improving quality of life. If successful, I will treat for 9–12 months before attempting to taper the agent.

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Fecal Incontinence

37

Subhankar Chabkraborty and Adil E. Bharucha

What Is Fecal Incontinence (or Accidental Bowel Leakage)?

Suggested Response to the Patient

Fecal incontinence (accidental bowel leakage) is the inability to control your bowel movements, causing stool (feces) to leak unexpectedly from your rectum. Also called bowel or anal incontinence, fecal incontinence (FI) can range from occasional leakage of a small quantity of stool while passing gas to a complete loss of bowel control.

The ability to hold stool (called continence) requires the rectum, anus, and nervous system to be working normally. Two groups of muscles in the wall of the anus are responsible for holding the stool in the rectum, the outer muscle group (external anal sphincter) and the inner muscle group (internal anal sphincter). In addition, your ability to sense the presence of stool in the rectum (called rectal sensation), the ability of the rectum to relax and store stool (called rectal compliance), and the physical and mental capabilities to recognize the urge to defecate, and go to the toilet are necessary for continence.

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Is It a Common Condition?

Suggested Response to the Patient

Yes. More than 5.5 million Americans have fecal incontinence. It is more common in older people and in women. However, many people do not like to talk about fecal incontinence, perhaps due to a loss of confidence, self-respect, modesty, and composure. If you have fecal incontinence and have not discussed the symptom with a physician or family members, you are not alone. Sharing the symptom with your family and physician is the first step to getting help.

What Causes Fecal Incontinence? Did This Occur Because My Anal Sphincter Was Damaged During Vaginal Delivery?

Suggested Response to the Patient

Fecal incontinence is commonly caused by altered bowel habits (especially diarrhea) and conditions that affect the ability of the rectum and anus to

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hold stool. The sphincters muscles or the nerves supplying them can be damaged during vaginal delivery in women, by trauma, or during anal surgery. The sphincter muscles become weaker as you grow older. Most women with FI develop the symptom at the age of 60 years or older, i.e., several decades after vaginal delivery. Hence, while anal sphincter injury during vaginal delivery may explain FI that occurs shortly after delivery, it is unlikely that injury during a vaginal delivery several decades previously is responsible for FI.

Nerve malfunction can also happen in people who strain excessively, in patients with diabetes, or after a stroke. The rectal wall is stiffer after radiation treatment or in patients with Crohn's disease. In these patients, the rectal reservoir may be smaller, predisposing to leakage. Other conditions where the rectum drops down into the anus (rectal prolapse) or when the rectum protrudes into the vagina (rectocele) can also cause fecal incontinence.

Brief Review of the Literature

Table 37.1 lists the conditions that are associated with FI and Table 37.2 highlights the key features of a comprehensive history in FI [1].

Table 37.1 Etiology and risk factors for fecal incontinence

Anal sphincter weakness
• Injury—obstetric trauma, related to surgical procedures, e.g., hemorrhoidectomy internal sphincterotomy, fistulotomy, anorectal infection
• Non-traumatic—scleroderma, internal sphincter thinning of unknown etiology
Neuropathy—stretch injury, obstetric trauma, diabetes mellitus
Anatomical Disturbances of Pelvic Floor—fistula, rectal prolapse, descending perineum syndrome
Inflammatory Conditions—Crohn's disease, ulcerative colitis, radiation proctitis
Neurological diseases—dementia, stroke, brain tumors, spinal cord lesions, multiple system atrophy (Shy Drager's syndrome), multiple sclerosis
Diarrhea—irritable bowel syndrome, post-cholecystectomy diarrhea
Other risk factors—obesity and smoking

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Table 37.2 Components of a comprehensive history in fecal incontinence

Question	Rationale
Elucidate whether a patient has FI	• Patients may not volunteer the symptom spontaneously
Onset, natural history and risk factors	• Relationship of symptom onset/deterioration to other risk factors may suggest etiology • Natural history, e.g., recent symptomatic deterioration may reveal reason for seeking medical attention
Bowel habits and type of leakage	• Disordered bowel habits are critical to pathogenesis of FI • FI for solid stool suggests more severe sphincter weakness than for liquid stool • Management should be tailored to specific bowel disturbance
Degree of warning before FI	• Urge and passive FI are associated with more severe weakness of the external and internal anal sphincter, respectively • Urge FI is associated with reduced rectal capacity and increased rectal sensation • These rectal sensory disturbances are potentially amenable to biofeedback therapy
Diurnal variation in FI	• Nocturnal FI occurs uncommonly in idiopathic fecal FI, and is most frequently encountered in diabetes and scleroderma
Impact of fecal FI on quality of life	• Critical to ascertain severity of FI
Urinary FI – presence and type	• Association between urinary and fecal FI • Same therapy (e.g., pelvic floor retraining) may be effective for both conditions

Table 37.2 (continued)

Question	Rationale
Evaluate possible causes of FI	• A careful characterization of bowel habits with a questionnaire or bowel diary is very useful • The obstetric history must inquire specifically for known risk factors for pelvic trauma, e.g., forceps delivery, episiotomy, and prolonged second stage of labor • Medications, including laxatives, artificial stool softeners may cause or exacerbate FI • Neurological diseases that cause FI invariably cause other, i.e. non anorectal manifestations before patients develop FI

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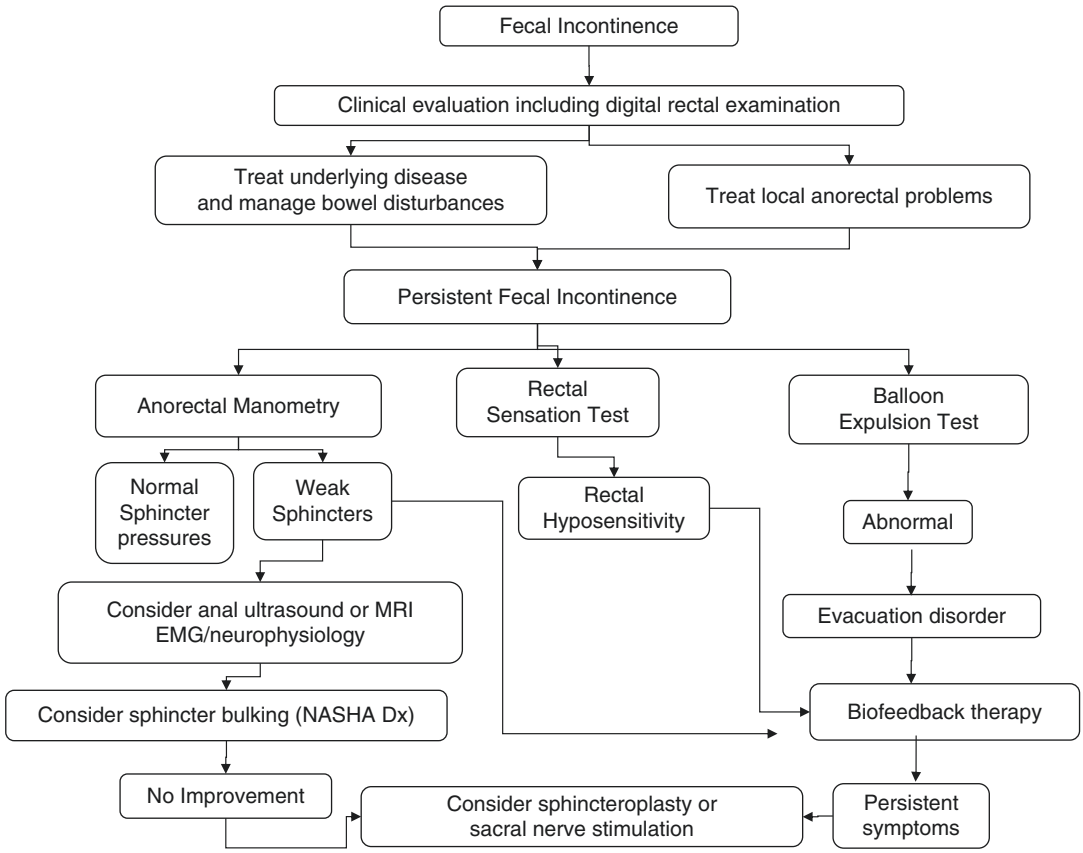

Fig. 37.1 Algorithm for managing fecal incontinence. Reproduced with permission from Bharucha AE, Rao SSC. An update on anorectal disorders for gastroenterologists. (Brief Review). Gastroenterology 2014;146(1):37–45. *Abbreviation*: *EMG* electromyography, *NASHA Dx* non-animal stabilized hyaluronic acid/dextranomer

To emphasize, obstetric anal sphincter injury is not, after adjusting for bowel disturbances, a major risk factor for FI occurring many decades after vaginal delivery in women [2, 3]. FI in the immediate postpartum period is more likely following third-degree (i.e., involving the external anal sphincter) and fourth-degree lacerations (i.e., extending through the external and internal anal sphincters) and with forceps or vacuum extraction [4].

What Diagnostic Tests Are Necessary?

Brief Review of the Literature

An algorithm for managing FI is shown in Fig. 37.1. Diagnostic tests are necessary when symptoms do not improve with treatment of the underlying disease, bowel disturbances, and local

anorectal problems. An anorectal manometry with assessment of rectal sensation and rectal balloon expulsion is the initial step. The findings guide subsequent management. Endoanal imaging with ultrasound or MRI, occasionally supplemented with anal electromyography, should be considered in patients with anal weakness, especially when surgery is being considered.

What Can I Do to Control My Accidents?

Suggested Response to the Patient

- First, it is important to consult your physician to ensure there is no serious underlying disorder responsible for FI.
- Dietary modifications are often helpful in patients with diarrhea
- Consider reducing or eliminating the consumption of foods that contain artificial sweeteners (e.g., sorbitol, high fructose corn syrups) and caffeine-containing foods (e.g., coffee, colas, and chocolate) for a brief period (e.g., 1 month) and observe for changes in your bowel movements and FI. High fructose corn syrups contain fructose and glucose. Certain sugars such as fructose and sorbitol are poorly absorbed from the intestine. Hence, they exert osmotic effects and predispose to formation of soft or loose stools. While breath tests can identify people who incompletely absorb fructose, a simpler approach is to eliminate foods containing such sweeteners (e.g., sodas) and markedly curtail consumption of caffeine.
- Another option is to consider reducing consumption of dairy products (milk, cheese, chocolate milk, and cream), high gas producing vegetables (broccoli, onions, cabbage, cauliflower, garlic, artichoke), or vegetables containing insoluble fiber (salad, lettuce, tomatoes, raw vegetables, carrot, and corn).
- If you have accidents with loose or watery stool, antidiarrheal agents such as loperamide (non-prescription) or lomotil (prescription) can be very helpful. When feasible, it is important to take loperamide (2 mg) 30 min before meals. Perhaps start by taking one or, if necessary, two tablets 30 min before meals, and supplement as necessary after each runny stool, up to a maximum of eight tablets daily.
- Agents which bind bile salts (e.g., cholestyramine, colestipol, and colesevelam) also reduce diarrhea in patients with diarrhea due to irritable bowel syndrome or after cholecystectomy (gall bladder surgery). Normally, bile acids are almost completely absorbed in the small intestine. When not, they travel to the colon, where they irritate the colonic lining, causing diarrhea. Bile salt binders prevent diarrhea due to this mechanism.
- If you have constipation and accidents, then your doctor may suggest that you eat fiber-rich foods, and prescribe fiber supplements or an osmotic laxative (e.g., polyethylene glycol).
- It may be beneficial to go to the toilet at a specific time of day. For example, your doctor may recommend that you make a conscious effort to have a bowel movement after eating. This helps you gain greater control by establishing with some predictability when you need to use the toilet.
- Physical therapy is effective for patients with accidental bowel leakage.
  - If the incontinence is due to a lack of anal sphincter control or decreased awareness of the urge to defecate, you may benefit from a bowel retraining program and exercise therapies that will help you improve muscle strength in the vicinity of your anus.
  - In other cases, bowel training involves an exercise therapy called biofeedback. Biofeedback involves inserting a small pressure-sensitive probe into your anus. This probe registers the strength of your anal sphincter. You can practice sphincter contractions and learn to strengthen your own muscles by viewing the scale's readout as a visual aid. These exercises can strengthen your rectal muscles. It is also possible to improve rectal sensation with biofeedback therapy. Some patients have constipation and fecal incontinence. The constipation may be caused by pelvic floor

dysfunction, also known as a defecatory disorder. This can be remedied with a different type of biofeedback therapy that is designed to improve coordination between movement of the abdomen and pelvic floor muscles during defecation.
– If you have substantial symptoms after treatment with medications and biofeedback therapy, your physician may consider other options such as sacral nerve stimulation, perianal injection of a bulking agent, or as a last resort, a colostomy.

Brief Review of the Literature

- Conservative therapies will benefit approximately 25% of patients and should be tried first (Fig. 37.1, Table 37.3) [5]. These conservative measures include reduced intake of foods (e.g., poorly absorbed carbohydrates such as fructose, sorbitol, and others, caffeine) that can cause or aggravate diarrhea and/or rectal urgency, urge suppression techniques, and antidiarrheal agents (e.g., loperamide). For those failing to respond to medical therapy, biofeedback therapy remains the mainstay. Randomized controlled trials show that biofeedback therapy is superior to Kegel exercises [6].
- Older studies suggest that, among antidiarrheal drugs, loperamide was more effective than diphenoxylate and both are better than placebo for diarrhea-associated FI [7]. In a randomized controlled trial (RCT) of patients who were incontinent for loose or liquid stools, psyllium (16 g/day), but not carboxymethylcellulose or guargum reduced the frequency of FI [8]. An uncontrolled study observed that psyllium was as effective as loperamide in reducing weekly episodes of FI and improving quality of life (QOL) [9]. Loperamide also increases internal anal sphincter tone [10] and is generally regarded as a first-line approach in patients with diarrhea and FI.

Table 37.3 Summary of fecal incontinence

Question	Suggested approach
How common is FI in the community?	Approximately one in 10 adults suffers from FI
Do all patients need to be asked about FI?	Yes. Patients may not volunteer to report the problem, so they must be asked about it, particularly in patients with diarrhea
What tests should I order in my patients with FI?	Limited testing to rule out inflammation or neoplasms if necessary. If these have been ruled out, no further testing is needed and conservative treatment should be tried first
What pharmacologic therapies can I use?	For patients with diarrhea—loperamide, diphenoxylate-atropine, bile acid binding agents (e.g., cholestyramine and colesevelam), and clonidine For constipation—soluble fiber (e.g., psyllium)
What physical therapy options are available?	Pelvic floor exercises can be recommended initially. If symptoms do not improve, consider biofeedback therapy
Does sacral nerve stimulation help?	Yes. In certain patients it can be useful, up to a third achieve complete continence, but up to a third also require device replacement, revision or explant SNS is probably not useful for those with (a) Large sphincter defects (b) Chronic diarrhea (c) Chronic IBD (d) Ongoing anal inflammation (e) Significant peripheral neuropathy (f) Visible sequelae of pelvic radiation (g) Complete spinal cord injury
Are there other non-surgical therapies?	Perianal bulking agents may be considered However, further research is needed to identify the patient group most likely to benefit from this approach
When is surgery indicated?	For postpartum FI, anal sphincteroplasty can be considered in the postpartum period

- Biofeedback therapy. Norton et al. observed that symptoms improved in approximately 54% of patients with FI who received standard care (i.e., instruction in diet, fluids, techniques to improve evacuation, a bowel training program, titration of antidiarrheal medication if necessary, and practical management) in nine 40- to 60-minute sessions over 3–6 months by a specialist nurse [11]. Incremental measures (i.e., instructions in pelvic exercises, face-to-face pelvic floor biofeedback therapy, and a home electromyographic device) did not provide additional benefit over standard care. These findings question the utility of pelvic floor biofeedback therapy for FI. However, a subsequent study observed that among patients who do not respond to medical therapy, biofeedback therapy designed to improve anal sphincter and puborectalis tone, strength and endurance, and anorectal coordination is superior to Kegel exercises [6]. Objective benefits of biofeedback therapy include increased rectal sensation in patients with reduced rectal sensation and shorter latency between rectal distension and contraction of the external anal sphincter [12]. There are no consistent effects of biofeedback therapy on anal resting and squeeze pressures.

My Skin Is red and Sore from Frequent Wiping Due to the Accidents. Is There Anything You Recommend to Treat This?

Suggested Response to the Patient

- A skin cleanser rather than soap and water should be used to cleanse soiled skin. Methods to clean the skin include a cotton cloth moistened with a hydrating skin cleansing foam, incontinence clean-up cloths, or baby wipes. Products that contain alcohol should not be used as they can cause drying of the skin and discomfort if skin is denuded. The skin should be patted dry or use a blow dryer on a cool setting. Do not rub the skin dry.
- When in bed, absorbent incontinence pads may be used. These pads should be highly absorbent, wick moisture away from the skin and breathable. Adult briefs or diapers should only be used during ambulation or when sitting in a chair.
- Barrier products may be used to keep skin hydrated and intact. There are different products depending on the degree of incontinence.
- Infrequent incontinence with intact skin may be treated with a skin sealant spray or wipe or a petrolatum-based cream.
- Infrequent incontinence with non-intact skin should be managed with a zinc-based ointment. Apply the ointment generously on the skin after it has been cleansed. Place a cotton-based absorbent dressing, such as a fluff gauze, make-up remover pad or an anorectal dressing between the skin folds of the buttocks to absorb and wick any drainage. The same recommendations apply to patients with frequent incontinence who have intact or non-intact skin.

For Physicians

A Cochrane systematic review concluded that "little evidence, of very low to moderate quality, exists on the effects of interventions for preventing and treating incontinence-associated dermatitis in adults" [13]. Soap and water performed poorly for preventing and treating such dermatitis. Preferred options include a washcloth with cleansing, moisturizing, and protecting properties. Applying a product (e.g., moisturizer, skin protectant, or a combination) might be more effective than not applying a leave-on product. Some of these products contain polymers, which conduct moisture away from the skin. Topical antifungal agents are used to treat perianal fungal infections.

Incontinence pads protect the skin and prevent clothing and bedding from soiling. Randomized trials indicate that disposable products are superior to nondisposable products in providing skin protection.

What Options Do I Have if Medications and Biofeedback Therapy Do Not Work?

Suggested Response to the Patient

Yes. If the measures above do not work, then there are several surgical options. Perhaps the first and most widely used option is sacral nerve stimulation, in which the nerves that supply the rectum and anal sphincters can be stimulated by a stimulator.

A second option is to inject a polymer into the anal canal to help improve the anal seal. However, in 1 study, this procedure did not increase anal pressures nor was it better than biofeedback therapy.

The third option is an anal sphincteroplasty, which is an operation to repair a damaged anal sphincter. While fecal continence improves in many patients shortly after surgery, the benefits are generally not sustained over time. Hence, this surgery is typically suggested for women who have accidental leakage after delivery. A colostomy is the last resort for accidental bowel leakage.

For Physicians

While fecal continence improves in many patients shortly after surgery, the benefits are generally not sustained over time. For example, only 28% were continent at 40 months in one study [14]. Hence, anal sphincteroplasty is primarily reserved for women with postpartum FI.

Sacral nerve stimulation (SNS) and anal submucosal injection of a "bulking agent" (dextranomer in stabilized hyaluronic acid [NASHA Dx]) are now approved by the Food and Drug Administration for the treatment of FI. In the pivotal US multicenter trial of SNS, 90% of 120 patients proceeded to implantation of a permanent stimulator [15]. At five-year follow-up in 76 patients (63%), 36% reported complete continence [16]. Patients with chronic diarrhea, large sphincter defects, chronic inflammatory bowel disease, visible sequelae of pelvic radiation, active anal inflammation, neurologic diseases such as clinically significant peripheral neuropathy or complete spinal cord injury, and anatomic limitations preventing the successful placement of an electrode were excluded from the study.

By comparison, only 6% and 13% of 206 patients randomized to the NASHA Dx bulking agent were completely continent at 6 and 36 months, respectively [17]. That response rate is lower than the proportion (40%) who were completely continent at 12 months after SNS [15]. In contrast to SNS, NASHA Dx did not improve QOL relative to placebo at 12 months. Another trial found no difference in efficacy among patients who were randomized to either pelvic floor biofeedback therapy or treatment with NASHA/Dx; NASHA/Dx did not increase anal resting or squeeze pressures in this study [18].

Percutaneous tibial nerve stimulation (PTNS) is a new ambulatory therapy for fecal incontinence that is less invasive than SNS. A multicenter double-blind RCT in 144 FI patients observed that transcutaneous stimulation was not significantly better than sham stimulation [19]. This option is not approved for treating FI in the United States.

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Irritable Bowel Syndrome

38

Yehudith Assouline-Dayan

Do I Have IBS?

Many patients experience discomfort originating in their digestive tract from time to time, but patients with IBS have ongoing symptoms. According to the Rome criteria for diagnosing IBS, patients experience abdominal pain related to defecation with altered bowel habits associated with change in the frequency or the consistency of stool. They should report pain at least 1 day a week in the last 3 months while symptoms should exist for at least 6 months.

Patient with IBS with constipation or IBS-C report hard or lumpy stools in at least 25% of their bowel movements (BM) and loose Stools in less than 25% of their BM, while patients with IBS diarrhea or IBS-D will report the opposite.

Patients might also report cramping, alternating bowels with constipation, diarrhea, or both, urgency, incomplete defecation, mucus in the stool, abdominal bloating, and gas, but these are not part of the inclusion criteria according to Rome. The Rome criteria are international standard criteria used to diagnose functional gastrointestinal disorders and the last version of Rome IV was published in May of 2016. The criteria are widely considered by experts to be 98% accurate in diagnosing IBS based on symptoms without the need for extensive testing for most people [1].

Is It a Common Disorder?

IBS is very common and affect about 10–20% of the population, however, most of the patients with IBS have mild symptoms that they manage with lifestyle and diet changes and OTC medications and they do not seek medical help. About 20% of the patient with IBS will have more significant symptoms that impair global function and quality of life and they are the ones primary care providers and gastroenterologists will see in clinic. This group of patient tends to have multiple doctor appointments, they undergo numerous tests and procedures, and they have greater chance of having multiple surgeries, not necessarily GI related, which results in morbidity, dysfunction, and increased health care expenses [2].

IBS is 1.5–2 times more common among females, and it cannot be explained solely by the fact that females seek more medical help and tend to report symptoms more than males. It is well established that hormones play a role in the disorder and many female patients will report different or worse symptoms during their period.

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The disorder also harbors a genetic and environmental component, since patients who have first, second, or third degree relative with IBS are at increased risk of developing IBS. Comorbidity with other functional gastrointestinal disorders (FGID), as well as non-GI conditions such as psychiatric conditions, mainly depression and anxiety, fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain are observed in this group of patients [3]. A history of recurrent abdominal pain or headache during childhood and a history of physical or emotional abuse are also risk factors [4].

Why Did This Happen to Me? What Is the Cause for IBS?

The pathophysiology of IBS is complex and incompletely understood, as central and peripheral pathways are involved in the development of this common disorder. There is abundant data to show that visceral hypersensitivity, alterations in the gut microbiome, intestinal permeability, gut immune function, motility, brain-gut interactions, and psychosocial status are all involved in the development of IBS. It is beyond the scope of this chapter to go through all the data that is available, moreover, the different mechanisms interplay in a sophisticated network of gut brain interactions and are not truly separable.

Studies which used a rectal balloon distention as stimulus showed that patients with IBS had v*isceral hypersensitivity*, meaning that they experienced greater pain for the same balloon volume as compared to healthy controls [5]. Patients with IBS also have dysregulated hypothalamic-pituitary-adrenal axis (HPA) mediated by CRH secretion when visceral pain is induced during sigmoidoscopy [6].

A subgroup of patient with IBS report abdominal pain or cramping following a meal due to *altered motility*. While postprandial colon contractions are a physiological response to meal, some IBS patients are experiencing heightened gastro-colic reflex. Others may have blunted response to meal resulting in hard pebbly stool and constipation.

Increased permeability is another mechanism involved in the development of IBS. Studies conducted on post infectious IBS have shown disrupted tight junction between colonocytes which leads to increased permeability [7]. This process increases exposure of enteric nerve endings to stimuli such as toxins and microorganisms. This in return can lead to altered motility and visceral hypersensitivity. The severity of the enteric infection, preexisting anxiety, and female gender have been diagnosed as risk factors for the development of post infectious IBS. From long-term follow-up of this group we have learned that the majority of patients can expect complete resolution of symptoms within several years [8].

Altered gut microbiota is associated with altered gut immune function, altered gut motility, and altered neurological function that in IBS patients could lead to hypersensitivity. Several studies have demonstrated different microbiota composition in IBS compared to control, and although some of the data is conflicting, most of the studies support decreased levels of fecal Lactobacillus and Bifidobacterium in IBS patients compared to controls. We also know that manipulating the microbiota changes bowel function, as there is some evidence that probiotics improve bloating and abdominal pain [9] and that antibiotic such as Rifaximin relieves IBS-D symptoms. There is even limited data showing that fecal microbiota transplant can cure IBS [10]. Overall, data is limited and this field will need further exploration before we can offer a safe and effective microbiota manipulation.

Early life stress is involved in the development of exaggerated pain perception. Many patients with IBS report history of abuse either emotional or physical, anxiety or depression. Not only stress underlies the mechanism of hypersensitivity, but it can also aggravate symptoms and induces anxiety [11].

Will My IBS Progress? Am I at Increased Risk for Colon Cancer? What Tests Should Be Done?

Although the diagnosis of IBS is based on symptoms and fulfilling Rome criteria with an accuracy of 95–98%, most primary care providers and gastroenterologists believe this is a diagnosis of exclusion [12, 13].

IBS guidelines do no support extensive workup for patient with FGID; however, in reality providers and patients who seek GI consultation expect testing and will not be satisfied without completing additional tests. Workup is also driven by exposure to media and the remote possibility of missing a significant diagnosis. In fact, colonoscopy in individuals with suspected IBS has low yield and there is not an increased risk for colon cancer [14]. In regard to bowel disease inflammatory (IBD), in the presence of normal inflammatory markers such as CRP and fecal calprotectin, and in the absence of alarming symptoms, fewer than 1% of patients undergoing a colonoscopy will be diagnosed with IBD.

Additional tests are indicated in the presence of alarming symptoms such as rectal bleeding, iron deficiency anemia, unintentional weight loss, fever, vomiting, family history of colon cancer, or in patient older than 50 years.

Symptoms of IBS and celiac disease overlap and differentiating them by taking the history is not accurate. Blood tests can help rule out this disease with high sensitivity, and it is cost effective to screen for celiac disease when the prevalence of celiac is greater than 1% [15].

What Should I Eat When I Have IBS?

Most if not all patients with IBS believe that their symptoms are affected by their diet. Up to 80% of patients are able to identify food trigger of which the most common are fatty food, fiber, dairy products, legumes, caffeine, and alcohol. Moreover, the majority of the patients have tried to eliminate trigger foods from the diet along the course of their disease. Food triggers were more commonly reported by women, and patients who identified high number of triggers had reduced quality of life [16].

In general, if the patient can point to specific food that triggers symptoms, the best would be to avoid the food, unless the diet becomes very limited and there is concern for malnutrition or nutrients deficiency. Eating large volume meals can trigger abdominal distention, fatty of fried food delays gastric emptying and might increase gas production and diarrhea. Consuming non-absorbable sugars, legumes, and cruciferous vegetables (broccoli, cauliflower, etc.) can cause gas, bloating, and diarrhea.

In the past several years we were introduced to the low FODMAP diet, which is a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols. Several randomized controlled trials showed improvement of abdominal pain, bloating, flatulence, and altered bowel movements in IBS patients who followed a low FODMAP diet. When guided by a dedicated dietician and with good adherence, success can be up to 80%. Since the diet is relatively new, there is no data on the long-term consequences mainly in regard to nutrient deficiencies and altered gut microbiota [17].

Many of our patients find the diet hard to follow and there is some encouraging data regarding a more simple traditional diet. In one randomized study that was recently published, "traditional IBS diet" was as effective a low FODMAP diet [18]. The standard diet consisted of three average size meals and three snacks spread through the day with reduced fat, spicy foods, coffee, alcohol, onions, cabbage, beans and discontinuing carbonated beverages and artificial sweeteners that are made of poorly absorbable sugars.

Recommending gluten-free diet is still debatable, since the symptoms of IBS and non-celiac gluten sensitivity overlap. In the only double-blind randomized controlled trial of gluten-free diet (GFD) in IBS patients with no celiac disease, Biesiekierski JR and colleagues reported significant improvement of GI symptoms on GFD [19]. If a patient is already on a low FODMAP diet it is unlikely that adhering to gluten-free diet will have additional benefit [20].

Doctor, Can You Fix Me? What Are the Treatment Options?

There is not a definitive cure for IBS, since it is a chronic disorder that is the consequence of multiple processes. Our goal when treating IBS is to establish good rapport with the patient and it is a major factor in treatment success and in patient satisfaction. During the interview we should listen to the patient and believe his symptoms. One

should not let the patient feel that his symptoms are imaginary nor that we believe that everything he says is driven by anxiety and somatization. Patient also needs to understand that the responsibility for treatment is mutual and it is not the sole responsibility of the provider, and the patient should be fully engaged in the treatment plan. Next would be to set realistic expectations. We do not "fix the bowel function," we can't "take the IBS away," rather we can work together and set a treatment plan that we both agree upon.

This is a process that will not happen overnight, but with good patient and physician relationship we have a good chance of helping and improving symptoms and function [21].

There are several treatment options including medications and nondrug interventions which can help improve symptoms of IBS. The choice depends on the severity of symptoms, the impact of quality of life and global function, and on the provider and patients preferences. Treatment is individually tailored to meet the patient needs after good rapport was established.

Medications and Supplements for IBS

Fibers

Fibers change the consistency of the stool and improve colonic transit time, thus increasing the amount of fiber in the diet can help symptoms in 20% of the patient with IBS. Fibers can be divided between soluble fibers like psyllium/isphagula, linseed (flaxseed), calcium polycarbophil, Metamucil, and methylcellulose (Citrucel) and insoluble fibers like wheat bran, corn fiber, and vegetable fibers and it seems that soluble fibers do a better job [22]. Consuming fibers can result in gas and bloating and it is recommended to gradually increase the dose and increase water consumption.

Antispasmodics

This category includes dicyclomine, hyoscyamine, peppermint oil, and pinaverium. The first two have anticholinergic properties and the last two hold calcium channel blockers properties. Antispasmodic have been studied in several controlled trials and were shown to alleviate abdominal cramping and pain with a number needed to treat of 3 [23]. The medications with anticholinergic properties may result in constipation, drowsiness, dizziness, blurred vision, or urinary retention and are preferably used in IBS-D.

Antidepressants

Antidepressant, mainly selective serotonin releasing inhibitors (SSRIs) and tricyclic antidepressants (TCAs), have been studies a lot in IBS. These medications improve pain and global assessment in IBS patients regardless of coexisting anxiety or depression [23]. These medications are used in other chronic pain conditions such as chronic pelvic pain, fibromyalgia, and neuropathic pain and involve central pain pathways. In a functional MRI study of IBS patients, amitriptyline reduced brain activation in anterior cingulated cortex and parietal association cortex during painful rectal distention [24].

IBS-C Specific Medications

Lubiprostone (Amitiza). Lubiprostone enhances water flow into the large bowel by activating chloride channels in the colonic wall and helps with constipation. It accelerates colonic transit time and improves the severity of constipation, stool consistency, degree of straining, abdominal pain, and bloating. Its efficacy was proven in several studies and it is FDA approved for adult women with IBS-C. The most common side effects are nausea, diarrhea, and abdominal pain.

Linaclotide (Linzess) is a guanylate cyclase C agonists, which results in increased secretion of chloride and water into intestines lumen. Not only it accelerates colonic transit time, but it also inhibits colonic nociceptors, thus relieving abdominal pain. It was FDA approved for IBS-C and chronic constipation in 2012. Potential side effects include diarrhea in up to 20% of patients that can be severe, abdominal pain, and gas [25].

Experimental

Plecanatide, an analog of the natural peptide uroguanylin that acts as a guanylate cyclase C agonists is currently in phase III trials in patients with IBS-C. Data from a phase II are encouraging.

Elobixibat (A3309) is an ileal bile acid transporter inhibitor which increases bile acid concentration in the colon resulting in enhanced fluid and electrolytes secretion and accelerated contractions. Phase III clinical trial was recently completed. Results are pending.

IBS-D Specific Medications

Anti-diarrheal medications such as Imodium, Lomotil, and Pepto Bismol can be used at the lowest dose needed. Imodium may be helpful if taken 20–30 min before eating, before leaving the house, or before dining out. Several studies looked into the efficacy of loperamide in IBS-D and, in fact, loperamide was superior to placebo in regard to stool frequency and consistency but in majority of the studies it had no effect on abdominal pain [26].

Bile Acid sequestrants (binders), such as cholestyramine (Prevalite), colestipol (Colestid), or colesevelam (Welchol). Up to 25% of the patients with diarrhea might have bile salts malabsorption leading to increased water and electrolyte secretion and accelerated colon transit. There is not yet a wildly available test for stool bile acid and it is reasonable to try bile acid binders for several weeks, especially when diarrhea has become more prominent following a cholecystectomy. Common side effects are constipation, bloating, and a non-appealing taste.

The tricyclic antidepressant, such as Amitriptyline, Nortriptyline, and Desipramine, are usually given in small doses (starting at 10 mg st bed time and with gradual increase up to 50–75 mg) since increasing the dose will result in increased anticholinergic SE which were mentioned in the antispasmodic section.

Since constipation is a common side effect of TCA, they are usually prescribed for IBS-D. One of the studies that looked into low dose (10 mg) amitriptyline in 54 patients with IBS-D showed that at 2 months the medication was well tolerated, and was more effective than placebo in improving frequency of loose stool, sensation of incomplete defecation, and overall symptoms [27].

Alosetron (Lotronex). Alosetron blocks the action of the serotonin receptor 5-HT3 on the nerve system of the bowel. It slows the movement of waste through the large intestine, which allows more time for the water to get absorbed and results in decreasing the moisture and volume of the remaining waste. In a 48 weeks trial of Alosteron vs placebo, the Alosetron group had greater adequate relief and less urgency than the placebo group [28]. It is approved for severe IBS-D in women who have exhausted all treatment options. Its prescription is limited due to potential rare serious side effects including ischemic colitis, perforation, and death.

Ramosetron is another 5HT3 receptor antagonist that showed efficacy in men and women, but is currently only approved in Japan and selected Southeast Asian countries.

Rifaximin (Xifaxan) is a nonabsorbable antibiotic which has been studied in patients with IBS-D. In two randomized, double-blind, placebo-controlled phase III trials, rifaximin 550 mg tid for 14 days was shown to be better than placebo (40.7% vs 31.7%, $p < 0.001$, number needed to treat ~11) in achieving relief of global IBS symptoms. Patients who responded well to rifaximin can benefit from retreatment in case of symptoms recurrence [29]. Common side effects include peripheral edema, flatulence, abdominal pain, and nausea.

Eluxadoline (Viberzi) was recently approved for IBS-D since it has an antidiarrheal effect and it also improved abdominal pain. It has μ and κ opioid receptor agonist properties, and δ opioid receptor antagonist properties. In large randomized, double-blind, placebo-controlled phase III studies, eluxadoline 100 mg tid was more efficacious than placebo in improving the worst abdominal pain score and stool consistency. Common side effects are constipation in less than 10% and nausea. Pancreatitis was reported in 0.3% with risk factors being concomitant alcohol use and a history of cholecystectomy [30].

Ibodutant, a Tachykinin NK2 Receptor Antagonists, decreases smooth muscle contractions. Recently a phase 3 trial has been completed. Results are pending.

Does Alternative or Nondrug Treatments Work?

The medications that are used for treating IBS have modest benefit and potential side effects, when combined with the chronic nature of the condition, it is not surprising that many patients and providers seek nondrug therapies. In fact, many nondrug therapies were studied in IBS.

Psychological interventions such as hypnotherapy, cognitive behavioral therapy, and relaxation techniques improve IBS symptoms. There is data to support moderate long-term effect that lasts at least 6–12 months following the completion of the intervention. The life span of such interventions is especially important in chronic, relapsing lifelong conditions such as IBS.

Psychological intervention was more effective than placebo in a recent meta-analysis of 32 randomized controlled trials comparing various psychological therapies with control therapy. About 50% of patients in the intervention group improved compared with about 25% improvement in the control group with a number needed to treat of 4 [31]. Unfortunately, cost and availability of skilled providers limits the use of these techniques in patient with functional GI disorders.

Acupuncture, overall, the effectiveness of acupuncture was studies in more than 17 randomized controlled trials with over 1800 participants. Although, the larger study which included 230 patients did not find acupuncture to be superior to sham acupuncture [32], other studies did find acupuncture to be of benefit. It is possible that it may help improve symptoms for people with IBS, especially when it matches their personal beliefs.

Homeopathy showed benefit over placebo in two studies with small number of participants and with a very short follow-up of 2 weeks. With the increased placebo rate that is seen in IBS patient, 2 weeks follow-up prevents us from drawing any conclusion [33].

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Part IV

Commonly Used Drugs for GI Motility Disorders

Top 10 Drugs Most Commonly Used for GI Motility Disorders

39

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Case: Diffuse Esophageal Spasm

Distal or diffuse esophageal spasm (DES) is a rare disorder of the esophagus characterized by symptoms of esophageal dysphagia and/or chest pain [1]. The etiology of DES remains unclear; however, the premature contractions or esophageal spasm are thought to be due to an impairment in inhibitory signaling possibly from loss of ganglion cells which in turn leads to uncoordinated contractions [2]. High resolution manometry is the gold standard for the diagnosis of DES with findings of greater than 20% premature contractions and a normal relaxing lower esophageal sphincter [3].

Treatment of DES begins with avoidance of potential trigger foods based on the patient's history and control of gastroesophageal reflux [1, 4]. Most studies on the treatment of DES have been small and predate the use of high definition manometry. However, if the patient remains symptomatic, then pharmacologic therapy is warranted and often is chosen based on the patient's symptoms, comorbidities, and side effect profile of the medication. Patients who are refractory to medical therapy or who are intolerant to their side effects are then considered for endoscopic botox injections. Lastly, a keen clinician should be watchful of patients with DES as it has been reported that 8% transitioned to achalasia in a prospective cohort study with a mean follow-up of 5 years [5].

Calcium Channel Blockers

Calcium channels blockers are a class of medications widely used in the management of cardiovascular disorders. The exerts the effect by interfering with calcium availability and use within the myocardium and smooth muscle. This leads to changes in myocardial contractility, blood pressure, and smooth muscle contractility [6]. The latter effect has made these medications attractive for the treatment of DES. In patients with DES, nifedipine demonstrated a rapid onset of action (within 10 min), a reduction of lower esophageal pressure by 31%, decreased strength of the spasm by 39%, and overall improvement in the frequency of spasm. However, the effects of nifedipine were short, with observed contractility patterns returning to baseline within the hour [7]. Clinical studies have been mixed, though most have shown an improvement of symptoms, in particular when administered prior to meals [8, 9]. Diltiazem has also shown benefit, with select patients showing marked relief in dysphagia and chest pain [10].

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The use of calcium channel blockers in the treatment of DES is limited by their side effect profile. The minimum required dose should be used, as up to 60% of patients reported symptoms of headaches and dizziness [7, 9, 10]. In patients with underlying hypertension already on antihypertensive medical therapy, a calcium channel blocker could be substituted. The development of longer acting, once daily diltiazem preparations have made calcium channel blockers into a first-line agent in the treatment of DES.

Nitrates

Nitric oxide (NO) is thought to play an important role in the coordination of esophageal peristalsis. It is the dominant inhibitory neurotransmitter that is found in the esophagus leading to smooth muscle relaxation. Studies on healthy volunteers treated with infusions of NO scavengers elicited symptoms and manometric findings of DES [11]. Based on this evidence, nitrates were trialed for the treatment of esophageal motility disorders. Early in its use, most trials evaluated the effect of nitrates in the setting of esophageal achalasia. Manometric studies using short-acting nitrates such as sublingual nitroglycerin demonstrated a rapid relaxation of the lower esophageal sphincter, although it was of short duration [12]. Long-acting nitrates such as isosorbide dinitrate demonstrated similar but longer lasting results. Studies of nitrates on DES soon followed and demonstrated manometric as well as clinical improvement, with the most pronounced benefit in those without gastroesophageal reflux disease; patients remained asymptomatic from 6 months to 4 years [13, 14].

The pathophysiology of DES supports the use of nitrates in its management. However, there have been no reported randomized trials to this date. Studies have been small and the use of nitrates has been limited by the side effect profile including headaches and rarely syncope. Despite these limitations, patients with intermittent symptoms may benefit from short-acting nitrates that can be used on an as-needed basis.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors are a new option available for the treatment of DES. These medications work by blocking the effect of phosphodiesterase which normally inactivates production of nitric oxide by degrading 3'5'-cyclic monophosphate [15]. Sildenafil, a phosphodiesterase inhibitor initially developed for the treatment of erectile dysfunction, has been effective in treating of DES. First studied in healthy adults without esophageal motility disorders or esophageal complaints, sildenafil decreased the lower esophageal sphincter tone, strength, and velocity of contractions [16, 17]. These findings make the use of phosphodiesterase inhibitors promising in the treatment of DES. Sildenafil was then demonstrated to decrease lower esophageal sphincter pressures and decrease contractility strength in the distal esophagus in patients with a hypertensive motility disorders [18]. A case report of two patients with esophageal spasm published in 2007 demonstrated a near resolution of dysphagia and chest pain as well as manometric abnormalities. Patients were followed for up to 8 weeks and had continued symptom control [19].

In addition to the symptom improvement, the effect of sildenafil can approach 8 h with one dose and has been associated with minimal side effects [18]. Despite the favorable evidence for the use of phosphodiesterase inhibitors in esophageal motility disorders, long-term use has been limited by its high cost and lack of insurance coverage. It is promising as a leading agent in the management of DES but further research is needed on its efficacy.

Botulinum Toxin

Botulinum toxin A (BTX) inhibits neuromuscular transmission and has many uses in medicine. In the esophagus, it inhibits acetylcholine release, thereby inhibiting contractility [20]. Endoscopic injection of BTX to the gastroesophageal junction has been a treatment option for patients with achalasia who are unable to undergo a surgical

approach. In a double-blind placebo-controlled trial for the treatment of DES, patients were injected with 100 units of BTX diluted in 4 ml of normal saline into the distal esophagus. Patients in the placebo arm were injected with saline alone. Patients in the BTX arm of the study demonstrated a significant improvement in dysphagia but not to chest pain when compared to the placebo group. Response to treatment was also observed up to 6 months after the initial therapy [21].

The method of injecting the esophagus with BTX, specifically the amount and exact location, has not been standardized across practicing gastroenterologists and centers. Although generally thought to be a safe procedure, there has been a case report of fatal mediastinitis following BTX injection, highlighting that all procedures carry some risk [22]. Ultimately, this therapeutic option is available for patients who have severe symptoms or are refractory to medical therapy.

Future Trends

Peroral endoscopic myotomy (POEM) is a novel treatment for DES. POEM is a procedure typically intended for the treatment of achalasia. In 2015, a multicenter collaboration published their experience in the treatment of achalasia and other spastic esophageal disorders. 73 patients were treated with the POEM procedure, 9 of which had DES. 100% of patients with DES responded to the treatment and those with repeat manometry post procedure had resolution of their manometric abnormalities. The role of POEM in the treatment in DES is yet to be defined, however early experiences are promising and may become a standard treatment for medically refractory patients [23].

Case: Gastroparesis

Treatment of gastroparesis begins with a careful review of the patient's comorbidities and current medications which can impact gastric motility. This would include optimization of glycemic control in patients with diabetes and reduction of opioid type medications. Thereafter a treatment plan can be outlined based on severity of symptoms, which can include lifestyle and pharmacologic interventions. Dietary therapy includes eating more frequent and smaller meals that are low in fat and soluble fiber [24]. This has been supported by study demonstrating symptom improvement with a low particle diet (no husks, peels, rinds, etc.) among diabetics with gastroparesis [25]. Pharmacologic therapy has included metoclopramide, domperidone, and erythromycin but currently only metoclopramide is FDA approved for the treatment of gastroparesis. Goals of pharmacological management include using the minimum required dose to improve symptoms, close monitoring for side effects, and limiting the length of therapy to no more than 12 weeks at a time.

Prokinetics

Prokinetics are the first pharmacological line of therapy for patients with gastroparesis. Metaclopramide is a dopamine receptor antagonist which has prokinetic and antiemetic properties. Several studies have demonstrated effectiveness in improving symptom control and gastric emptying compared to placebo [26–28]. However there is poor correlation between improvement in gastric emptying and symptoms. These initial short-term studies demonstrated mild side effects which resolved with discontinuation of the medication. However, with the increased frequency of use adverse reaction registries have demonstrated an increased risk of reversible and irreversible movement disorders. Tardive dyskinesia is the most concerning irreversible side effect of metoclopramide. This has led to the placement of a black box warning from the FDA [29, 30].

Domperidone is a dopamine antagonist with similar efficacy to metoclopramide. However, compared to metoclopramide it does not readily cross the blood brain barrier and has been associated with fewer central nervous system related

side effects (e.g., somnolence, akathisia, anxiety, depression). Most frequent side effects include nausea, vomiting, headaches, diarrhea, and prolactin related effects [31]. At doses greater than 30 mg daily, it has also been associated with QTc prolongation which may lead to cardiac arrhythmias [32]. Currently it is not an FDA-approved medication and therefore is not readily available. Domperidone can be prescribed for patients who are refractory to treatment through the FDA investigational new drug application.

Erythromycin, a macrolide antibiotic, has also been used for the treatment of gastroparesis. Erythromycin is a motilin receptor agonist and has a strong effect on the rate and strength of gastric antral contractions by inducing the migrating motor complex [33]. After treatment with intravenous erythromycin patients with idiopathic and diabetic gastroparesis had a significant decrease in retained stomach material on gastric emptying studies from a baseline of 85% to 20%. When continued on an oral formulation and followed for 8 weeks of therapy patients had continued reduction in total symptom scores [34]. The use of erythromycin is limited by the development of tolerance to the medication and drug–drug interactions which have been associated with an increased risk of sudden cardiac death [35].

Future Therapies

Based on the significant side effect profile and lack of available therapeutic options further drug development is underway. Novel medications which show promise are selective motilin receptor agonists. A clinical trial on the effects of camicinal on gastric emptying and symptoms has been completed, but results have yet to be reported (clinical trials.gov, NCT01262898).

Colon Motility and Constipation

The function of the colon is to store fecal matter and absorb water. Nonpropulsive colonic contractions help delay transit of fluid and promote adequate time for absorption of water. Stool transit averages around 30 hours from ileocecal valve to defecation. High amplitude sequential contractions propagate down the colon 6–8 times per day which propels stool distally and provides the urge to have a bowel movement. Chronic constipation is a subjective sensation of incomplete or inability of evacuation for more than 4 weeks. The working definition of chronic constipation is generally described as less than three bowel movements per week. Chronic constipation can be divided into slow-transit constipation, normal-transit constipation, or pelvic floor dysfunction and is defined by radiographic colon transit study. Initial strategies in treating constipation involves designing a bowel regimen with dietary measures, increased fluid intake, laxatives, and stool softeners. Osmotic or contact cathartics can be instigated with appropriate dose escalation as indicated. Medications that patients take or are prescribed should be reduced or stopped if necessary for relief. If initial strategies don't work, then second tier pharmacologic treatments are considered.

Pharmacologic Management of Slow Transit Constipation

Linaclotide

Linaclotide is a minimally absorbed 14 amino acid peptide agonist of guanylate cyclase 2C (GC-C) that increases fluid secretion into the colon, improving stool consistency, and subsequently reducing colon transit time. Linaclotide has been effectively used in the treatment of constipation-predominant irritable bowel syndrome (IBS-C) and chronic idiopathic constipation (CIC) [36]. Although linaclotide is not generally considered a direct pro-motility agent, there are minor effects on motor nerves of the gastrointestinal tract and it has been a useful option for treating patients with constipation, therefore, warrants discussion in this chapter.

The mechanism of action of Linaclotide is through activation of the GC-C receptor located on the intestinal epithelial cells [36]. Linaclotide mimics the endogenous peptides guanylin and

uroguanylin, both of which activate the cell surface receptor of GC-C. Activation of GC-C increases both intracellular and extracellular second messenger, cyclic guanosine monophosphate (cGMP). Increasing cGMP effectively facilitates chloride and bicarbonate secretion into the intestinal lumen and inhibits absorption of sodium ions [36, 37]. Water secretion follows the ion flow resulting in more fluid within the bowel, improved stool consistency, and results in improved colon transit. The increased intestinal transit is dose dependent and reflected in the amount of fluid secreted into the colon. Four large randomized controlled trials showed increased bowel movements in IBS-C and CIC patients. A double-blinded phase III randomized trial showed some improvement in pain in addition to constipation compared to placebo within the first week of use [38].

It has also been shown that linaclotide influences visceral nerve function by decreasing sensory nerve activity. It has been suggested that decreased neural feedback reduces intestinal distension-induced pain by decreasing sensory nerve activity. Linaclotide may also influence motor nerve activation, which enhances smooth muscle contraction, increasing bowel movement frequency [38, 39].

A phase III, double-blind, placebo-controlled trial in IBS-C patients compared linaclotide 290 μg once daily to placebo for a 26-week treatment period. The study showed that Linaclotide once daily significantly improved the spontaneous bowel movements (47.6% vs. 22.6% endpoint responders, $P < 0.001$) and abdominal pain (48.9% vs. 34.5% endpoint responders). Adverse events were similar between groups, except for diarrhea, which occurred in 4.5% linaclotide patients vs. 0.2% of placebo patients [40].

Linaclotide was ultimately FDA approved in August 2012 for treatment of IBS-C and CIC. Linaclotide is marketed with the trade name of Linzess or Constella [41].

Linaclotide is available in 145 mcg and 290 mcg. The approved dose for IBS-C is 290 mcg daily and for CIC is 145 mcg daily. Dosing should be scheduled once per day on an empty stomach at least 30 min prior to the first meal.

Linaclotide has an excellent safety profile, as there is no evidence of systemic exposure to linaclotide or its active metabolites after oral administration; thus it has limited bioavailability. The most commonly reported side effect is diarrhea [42]. No drug–drug interaction studies have been conducted to date as it is not found in plasma, thus no interactions are anticipated. Due to increased intestinal expression of GC-C, children under 6 years may be more likely than adults to develop significant diarrhea and dehydration, thus a relative contraindication in children under age 6 years of age. Patients with known or suspected mechanical obstruction should avoid Linaclotide.

Specific Treatments for Opioid-Induced Constipation

Opioids are commonly used medications for the treatment of pain and are generally thought of as safe, effective, and easily titrated. Whether used acutely or on a more chronic basis, side effects can be problematic, including opioid-induced constipation (OIC) and decreased mental acuity. Additional symptoms of bloating, early satiety, and distension pain are also precipitated by the opioid effects on decreasing intestinal motility. Opioid pain medications bind specific opioid receptors in the intestinal tract and central nervous system and effectively diminish motility in both a direct and anticholinergic mechanism. Opioid-induced constipation therefore ensues due to nonpropulsive contractions and inhibition of water and electrolyte secretion. When opioids are required for prolonged pain control, addressing the limiting constraints of the side effects is often required. If opioid medications are required for pain management and refractory constipation ensues, then opioid antagonists can be prescribed. Recently, several opioid antagonists have been FDA approved and do not compromise pain modulation or effect mental acuity. Included in the options are naloxegol, which is in oral form, and methylnaltrexone, which is available both in the injectable and oral forms.

Naloxegol

Naloxegol is a peripherally acting selective opioid antagonist used to treat opioid-induced constipation. Naloxegol effectively blocks the binding of the mu-receptor and is a PEGylated derivative of naloxone. The PEGylation confers P-glycoprotein transporter-substrate properties, thus limiting crossing of the blood–brain barrier. Naloxegol is FDA approved for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain [43].

The mechanism of action of naloxegol is through the preferential binding of the mu-opioid receptors found in the intestinal tract. Naloxegol binds to mu-receptors with greater affinity than the delta- or kappa opioid receptors, therefore considered "selective." By preferentially binding up the mu-receptor, Naloxegol limits the opioid receptor activation by the agonist medications, thus limiting the nonpropulsive contractile motility, preserving motility, and therefore reducing constipation. A primary advantage of this opioid antagonist is that it does not effectively cross the blood brain barrier and does not block the central nervous system mechanism for pain control when given concomitantly with opioid analgesics, thus naloxegol improves constipation while not reducing levels of analgesia [44].

Studies show that naloxegol is associated with a shorter morphine-induced delay in oral-cecal transit time than placebo in healthy volunteers and that central opiate effects are not reduced. Naloxegol demonstrated an increase in the number of spontaneous bowel movements per week compared to placebo in two phase III trials. A shorter time to first post-dose bowel movement was observed on both trials for 25 mg dose ($P < 0.001$). Pain scores for opioid dosing did not differ from baseline. Naloxegol may be effective for short-term use in patients who have failed non-pharmacologic strategies. Efficacy was studied for up to a 52 week treatment period. A 12.5 mg dose was also studied but did not have the same benefit in both trials [43, 45].

Naloxegol is available under the trade names of Movantik and Moventig. Movantik was approved by the FDA in 2014 for use in adult patients with constipation due to chronic cancer related narcotic pain medication use. Movantik is available in both 12.5 and 25 mg oral tablets and are recommended for a daily dosing. The oral formulation is a preference advantage compared to other mu-receptor antagonists that are injected. Onset of action is expected within 6–12 h following administration [43]. The recommended adult dosage of Movantik is 25 mg once per day in the morning.

Naloxegol has a good safety profile with most common adverse events being reported as abdominal pain, diarrhea, nausea, and vomiting. These adverse events were mild to moderate and there were no life-threatening events found in the trials, including bowel perforation or cardiac events. Side effects appeared to be dose dependent and seen more commonly in the 25 mg dose [43, 45, 46]. No data beyond 12 months' use exists for comparison.

Contraindications include patients with known compromised intestinal obstruction or wall integrity such as Ogilvie's, diverticular disease, or gastrointestinal malignancy. Concurrent use with CYP3A4 inhibitor medications, diltiazem, verapamil, quinidine, cimetidine, rifampin, carbamazepine, St. John's wort or consuming grapefruit or grapefruit juice are contraindicated.

Methylnaltrexone

Methylnaltrexone is a peripherally acting mu-opioid antagonist used to treat opioid-induced constipation (OIC). Similar to naloxone, methylnaltrexone blocks some of the effects of opioid medications such as constipation without diminishing analgesia or causing withdrawal syndrome.

The mechanism of action of methylnaltrexone is to reduce OIC through binding the same opioid receptors that opioid agonists would, thus preventing morphine receptor activation and decreased colon motility that results in constipation. Methylnaltrexone chemically differs from the earlier developed opioid antagonist, naltrexone, in that it is a quaternary ammonium cation which leads to greater polarity and lower lipid solubility. These pharmacological properties

appear to limit the drug crossing of the blood brain barrier, although this has been debated [47]. With minimal drug moving across the blood brain barrier, central nervous system effects, such as pain control or withdrawal symptoms, are not experienced by the patients. Three randomized trials and two meta-analyses have shown increased stool frequency in patients concomitantly using morphine and methylnaltrexone [48, 49]. A placebo crossover analysis revealed little or no gastrointestinal tolerance developing with longer use [50]. Some studies have questioned whether some of the analgesia of opioids has a peripheral sensory mechanism, thus suggesting that opioid antagonists may result in decreased pain control related to peripheral mechanisms; however this remains controversial [51, 52].

Methylnaltrexone is marketed as Relistor and was cleared by the FDA in 2014 for OIC patients with non-cancer chronic pain and continues to be used in patients with cancer pain receiving palliative care, which had been introduced in 2008. It was initially available only in an injectable form, based on weight-based determination, which was the dosing form in previous clinical trials. Most doses range between 8 and 12 mg (or 0.15 mg/kg) subcutaneously once every other or every third day. Dosing should not exceed once daily. Methylnaltrexone can be used safely for an extended time and likely with escalating doses [53]. In July 2016, the FDA cleared the oral form of Relistor for OIC in adults with chronic non-cancer pain. Efficacy of the oral methylnaltrexone was comparable for improvement in constipation and with a similar safety profile as studies found with the injectable form. Dosing is recommended at 450 mg once daily.

The side effect profile of methylnaltrexone is low and generally includes nonspecific gastrointestinal symptoms of nausea, abdominal pain, vomiting, and sweating. The FDA does have a warning cautioning the use of methylnaltrexone in patients with known or suspected bowel obstruction or lesions in the intestinal wall such as diverticulitis, colitis, or intestinal cancers. Bowel perforations have been found in patients with advanced cancer receiving methylnaltrexone for OIC [54].

Alosetron

Alosetron is a selective 5-HT3 (serotonin) antagonist found to slow intestinal transit, and to decrease intestinal secretion and colon tone [55, 56]. 5-HT3 receptors are present on both sensory and motor neurons, and have represented an attractive target for treatment of bowel disturbance [56]. Subsequent randomized trials demonstrated effectiveness in women with severe diarrhea-predominant irritable bowel. Improvement was seen in both the primary endpoint of pain (41% vs. 29 and 26 the placebo arms in two trials) and the secondary endpoints of diarrhea and urgency [57, 58]. Improvement in quality of life measures was also seen [55]. Interestingly, not enough men were included in the trials initially; the drug was therefore approved in women only. Subsequent trials were positive in men [56].

Unfortunately, ischemic colitis began to be reported following release, including a death. A summary of risk estimated the risk to be 0.15% vs. 0.0% in the placebo group [59, 60]. Post-marketing surveillance found ischemic colitis to occur in 1.1 per 1000 patients and serious problems with constipation in 0.66 per 1000. The drug was withdrawn in 2000. However, adverse events were almost all brief and responded to drug withdrawal [55]. The drug was therefore reintroduced to the market in 2002 with a risk management program designed to protect patients: this included a mandatory test for physicians, written consent, specific stickers for prescriptions, and reporting of serious adverse events, among other requirements. In January 2016, because of new information suggesting stable, low-level incidence of bad outcomes, the FDA substantially reduced the above requirements, significantly improving patient access, and acknowledging the overall safety of the drug [61].

Thus, alosetron is an excellent drug for women (and likely men) with D-IBS who have failed standard treatment consistent of antidiarrheals (loperamide up to eight a day, or diphenoxylate), fiber such as psyllium and perhaps a bile binder such as cholestyramine or colestipol. If pain is a component, anticholinergics should be used;

alosetron is then the next drug to be tried in most situations. The drug is started at 0.5 mg a day, (trials have shown efficacy at this dose [56]) building slowly up to 1 mg bid as needed. Careful and comprehensive patient education is mandatory. If the patient develops constipation or symptoms of ischemic colitis, the drug must be stopped immediately. Under these conditions, it is a safe and effective treatment of D-IBS [62].

The black box warning should be respected concerning ischemic colitis ("discontinue immediately" for constipation or symptoms of ischemic colitis—rectal bleeding, bloody diarrhea, worsening of abdominal pain). The drug is only approved for women with severe D-IBS whose symptoms have lasted at least 6 months and failed to respond to conventional therapy. There is a long list of drug–drug interactions, and the practitioner must be careful to avoid these [63].

Other 5-HT3 drugs are being tested for use in D-IBS including ondansetron, cilansetron, and ramosetron. This will be an interesting area of drug development.

Thus, alosetron is a highly effective drug in selected patients. It must be used carefully with significant time spent in patient education.

Lubiprostone

Lubiprostone is a bicyclic fatty acid derived from a metabolite of prostaglandin E1. It works via chloride channels including the CIC-2 channel as well as (possibly) the CFTR channel [64]. The end result is to increase electrolyte and fluid secretion. It also affects the intestinal smooth muscle likely via prostaglandin effects, which might increase its efficacy in IBS. Thus, both fluid secretion and transit are affected in a positive way. It has been shown to be active both in chronic idiopathic constipation and constipation-predominant IBS [55, 64–67].

Lubiprostone was first studied in constipation. A randomized, dose finding trial (12, 24, 36 mcg sid v. placebo) showed improvement in spontaneous daily bowel movement number at week two with 24 mcg sid approved by the FDA [64, 68]. Additional phase 3 randomized trials showed efficacy of 24 mcg bid in inducing an initial stool as well as reducing straining, improving stool consistency, and global patient satisfaction.

Demonstrating efficacy in IBS-C was more difficult. Two phase 3 studies were conducted in IBS-C at a dose of 8 mcg bid for 12 weeks in 1154 patients [69]. The design was complex with relief of symptoms being the primary endpoint. Patients were "responders" or "non-responders" depending on moderate relief for all 4 weeks of the trial or significant relief of 2 weeks. The lubiprostone arm demonstrated a 17.9% response vs. 10.1% in the placebo arm. Nausea and diarrhea were the main side effects in all of these trials (8% nausea vs. 4% in the placebo arm in one trial).

Lubiprostone has also been studied in opioid-induced constipation. A randomized double-blind multicenter trial using the 24 mcg bid dose showed significant improvement vs. placebo. This indication was subsequently approved by the FDA. Interestingly, morphine inhibits chloride channels, an effect reversed by lubiprostone [63].

Thus, lubiprostone is effective for IBS-C (8 mcg bid) or idiopathic constipation (24 mcg bid). The IBS dose can be increased depending on response. The indication is for women primarily as adequate studies in men have not been done. Safety in pregnant women has not been established; the drug is a category C so that a pregnancy test in appropriate patients is recommended prior to initiating therapy. Nausea has been the limiting side effect in our experience. Long-term safety has not been established.

The role of lubiprostone is as a second-line agent. For constipation, the best treatment approach begins with fiber and laxatives. It is important to acknowledge that laxatives are safe without risk for habituation, "addiction" or damage to the intestine—"laxative abuse colon". Glycolax (polyethylene glycol) is also used at this stage, with some advocating for a role for probiotics. This would be stage 1 therapy: lubiprostone is one excellent choice for stage 2 therapy.

Antispasmodics

It is somewhat ironic that the most widely used drugs for the pain and cramps of IBS are also the least studied. Dicyclomine and hyoscyamine are the anticholinergic agents in widespread use in this country with multiple other anticholinergic agents used in other countries [70]. There is only one randomized trial of dicyclomine (and none of hyoscyamine) in the literature, that of Page et al. published in 1981. In this study, a double dose of dicyclomine (40 mg qid) was compared to placebo with a significant improvement in symptoms found in the drug arm [71, 72]. Subsequent meta-analyses have included multiple drugs used in other countries to achieve significance with the family of anticholinergics found to be effective. For example, a recent meta-analysis studied ten different antispasmodics in a total of 2585 patients and found efficacy [73]. Peppermint oil has also been studied and has a similar mechanism, but is not in widespread use (if used, knowledge of the kinds of peppermint oil available is important as this is not a regulated product) [68, 74].

Dicyclomine and hyoscyamine are safe and inexpensive. Dicyclomine is started at a low dose of 20 mg up to four times a day (and is available in a 10 mg pill as well for patients having trouble tolerating it). If side effects are not too troubling, the dose can be increased to 40 mg four times a day. Hyoscyamine is more flexible, coming both in a long-acting form 0.375 which is dosed up to three times a day, and a sublingual 0.125 pill which can give faster relief and given up to four times a day. Anticholinergic side effects can be troublesome for both drugs. However, dry mouth, although almost universal, can be managed with sips of liquid through the day. Likewise, constipation is easy to manage in our experience. Blurred vision, sedation, and urinary retention are uncommon, fortunately, but require stopping the drug.

As scant as the evidence of efficacy of these drugs, they remain the first-line treatment for IBS with discomfort and bloating [55]. The best use is intermittent, as some have noted a reduced potency with maintenance use. Use in the elderly should be avoided if possible; both agents are listed in the Beers Criteria as potentially inappropriate in patients over 65 years old [75]. Specific problems include memory impairment, cognitive decline, dementia, confusion, hallucinations, and others. Thus, use in the elderly should be cautious, if used at all.

Thus, these drugs are used in stage 1 therapy in average risk individuals for treatment of IBS with abdominal pain, bloating, and cramping. Fiber such as metamucil, citrucel, or bran is typically started at the same time. Fortunately, most patients respond to such low-level therapy, with newer drugs coming quickly [76].

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