Diagnosis and Treatment of Gastroesophageal Reflux Disease

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Editor
Michael F. Vaezi, MD, PhD, MSc
Department of Gastroenterology
Vanderbilt University School of Medicine
Nashville
Tennessee
USA

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To my wife, Holly, who is not only my kids' hero but also mine.

Preface

Gastroesophageal reflux disease is a common clinical entity encountered by all specialties in medicine. Over the past few years, there has been increasing understanding of the pathophysiology of this disease, and treatment options are vast. Improved and novel diagnostic tests are providing an easier way for clinicians to establish the diagnosis and offer patients the latest treatment options. This book is a constellation of information from the world's experts in the field of esophagology and reflux disease. The chapters are organized so that the reader systematically learns about the disease definition, recognizes the current challenges in diagnosis, and then is provided with the latest information about medical, endoscopic, and surgical options for patients with reflux disease. We are grateful to the contributors and hope that the book provides useful insight into this commonly encountered disease and can pave the way for optimal patient care.

Michael F. Vaezi, MD, PhD, MSc

Contents

Contributors

Ali Akbar Divison of Gastroentrology, University of Tennessee Health Science Center, Memphis, TN, USA

Dan E. Azagury Department of Bariatric and Minimally Invasive Surgery, Stanford University School of Medicine, Stanford, CA, USA

Tom R. DeMeester Department of Surgery, Keck Medical Center of University of Southern California, Los Angeles, CA, USA

Ronnie Fass Esophageal and Swallowing Center, Division of Gastroenterology and Hepatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, USA

C. Prakash Gyawali Department of Medicine, Division of Gastroenterology, Barnes-Jewish Hospital/Washington University School of Medicine, St. Louis, MO, USA

Colin W. Howden Divison of Gastroentrology, University of Tennessee Health Science Center, Memphis, TN, USA

John W. Jacobs Department of Internal Medicine, Division of Digestive Diseases and Nutrition, Joy McCann Culverhouse Swallowing Center, University of South Florida Morsani College of Medicine, Tampa, FL, USA

Robert Kavitt Section of Gastroenterology, Hepatology and Nutrition, Center for Esophageal Diseases, University of Chicago, Chicago, IL, USA

Carla Maradey-Romero Esophageal and Swallowing Center, Division of Gastroenterology and Hepatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, USA

Dejan Micic Section of Gastroenterology, Hepatology and Nutrition, University of Chicago Medical Center, Chicago, IL, USA

Amit Patel Department of Medicine, Division of Gastroenterology, Barnes-Jewish Hospital/Washington University School of Medicine, St. Louis, MO, USA

Joel E. Richter Department of Internal Medicine, Division of Digestive Diseases and Nutrition, Joy McCann Culverhouse Swallowing Center, University of South Florida Morsani College of Medicine, Tampa, FL, USA

George Triadafilopoulos Department of Medicine, Stanford University, Stanford, CA, USA

Stephanie G. Worrell Department of Surgery, Keck Medical Center of University of Southern California, Los Angeles, CA, USA

Patrick Yachimski Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, Nashville, TN, USA

Chapter 1
Definitions of Gastroesophageal Reflux Disease (GERD)

Amit Patel and C. Prakash Gyawali

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal outpatient diagnoses and carries a significant clinical impact and disease burden worldwide [1]. A systematic review of population-based studies suggested that the prevalence of GERD is 10–20% in the Western world and 5% in Asia [2]. Prevalence rates are higher than incidence rates worldwide, implying that the condition is chronic [2]. Estimates of the annual direct cost burden of GERD on the USA healthcare system alone top US$ 9 billion [3]. GERD is well documented to adversely affect quality of life, and patients with persistent GERD symptoms suffer from reduced physical as well as mental health-related quality of life (HRQOL) [4]. This is mainly from symptomatic presentations, hence the importance of symptom-based definitions of GERD [1]. As the population ages, the severity of reflux esophagitis and the prevalence of Barrett's esophagus (BE) increase while symptoms become less prevalent, highlighting the importance of diagnostic definitions of GERD on investigative studies [5]. In this chapter, we explore different approaches to defining GERD—symptomatic definitions, endoscopic definitions, parameters on ambulatory reflux testing (acid and impedance monitoring) defining GERD, diagnostic implications of structural and anatomic abnormalities, and the impact of newer diagnostic modalities on the definition of GERD.

Spectrum of GERD

Gastroesophageal reflux (GER), or the retrograde flow of gastric content across the esophagogastric junction (EGJ) and the lower esophageal sphincter (LES), can be physiologic, especially in the postprandial setting. Inherent mechanisms are in

C. P. Gyawali (✉) · A. Patel
Department of Medicine, Division of Gastroenterology, Barnes-Jewish Hospital/Washington University School of Medicine, Campus Box 8124, 660 S. Euclid Avenue,
St. Louis, MO 63110, USA
e-mail: cprakash@wustl.edu

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place for the LES to relax transiently in response to distension of the fundus of the stomach, resulting in venting of air (belching) [6]. The resting LES tone, inspiratory diaphragmatic crural pinch at the same level as the LES, and the angle between the long axes of the esophagus and the stomach prevent significant retrograde movement of gastric content across the EGJ and LES in the physiologic setting. However, transient LES relaxations (TLESRs) can result in small amounts of gastric content refluxing into the esophagus; in health, esophageal secondary peristalsis is efficient in stripping any refluxed material back into the stomach [7].

GER becomes pathologic (GERD) when associated with symptoms (typically heartburn or regurgitation) or mucosal injury (typically esophagitis or BE) [8, 9]. Symptoms and mucosal injury are not mutually exclusive, and each can occur in the absence of the other. Therefore, subjective symptom analysis, and, indeed, endoscopic inspection of the esophageal mucosa, may not always be indicative of GERD. Symptoms related to GERD can be atypical (noncardiac chest pain, NCCP) or even extra-esophageal (cough, asthma, dental erosion), further complicating the diagnosis of GERD in these settings [1]. Beyond symptom assessment and inspection of the esophageal mucosa at upper endoscopy, the availability of diagnostic tests to quantify reflux and to assess the association of symptoms with reflux episodes affords further insight into the definition of GERD.

Symptom-Based Definition

The clinical presentation of GERD is predominantly symptom based, as the vast majority of patients present to their physicians with typical symptoms of heartburn and regurgitation. However, there is a significant and growing recognition of atypical symptoms defining GERD, particularly when these atypical symptoms occur in the absence of typical symptoms or endoscopic evidence of mucosal damage. Given the diagnostic challenges associated with the spectrum of clinical symptoms that may be related to GERD with varying definitions across geographic regions, the Montreal classification International Consensus Group was formed to develop a global definition for GERD [1]. Utilizing a modified Delphi process over a 2-year period, this group proposed 50 consensus statements pertaining to GERD definition, published in 2006. At the core, the Montreal group agreed that GERD develops from reflux of stomach contents into the esophagus and proximally, causing troublesome symptoms and/or complications [1].

Symptomatically, the Montreal classification suggested that reflux symptoms must be “troublesome” to meet the definition of GERD. Specifically, this threshold required adverse effects on patient well-being; population-based studies have suggested mild symptoms occurring at least 2 days weekly or moderate-to-severe symptoms occurring at least 1 day weekly may approximate this threshold [10, 11]. Others have suggested that heartburn symptoms occurring more than twice a week

negatively impact quality of life [12]. However, in practice, clinicians rely on patients themselves to determine if their reflux symptoms are troublesome, rather than rely on frequency or duration thresholds to meet this definition of GERD. In the absence of esophageal mucosal injury, episodic heartburn not deemed troublesome by the patient does not meet the Montreal criteria for a symptomatic esophageal GERD syndrome [13].

The Montreal classification concluded that heartburn and regurgitation constitute the characteristic symptoms of the typical reflux syndrome, allowing suspicion of GERD based on presence of these symptoms alone, a position adopted by the American Gastroenterological Association in 2008 [14]. However, typical GERD symptoms (heartburn, regurgitation) by themselves are only modestly predictive of GERD. In a large cohort of 33,000 patients undergoing endoscopy for typical GERD symptoms, 27.8% had erosive esophagitis, 9.1% had BE, 3.7% had esophageal strictures, and 44.8% had a hiatal hernia, leaving 39% with a normal endoscopy [15]. When compared to endoscopic evidence of GERD, the performance characteristics of these typical symptoms demonstrated sensitivity of only 44%, but with specificity of 87%, in another study [16]. When ambulatory reflux monitoring is used as the gold standard, performance characteristics are better. In a selected population of over 300 patients referred for 24-h ambulatory pH monitoring, typical symptoms had 78% sensitivity and 60% specificity for GERD [17]. Likewise, in a cohort of 228 patients who had previously undergone laparoscopic anti-reflux surgery, only heartburn significantly correlated with abnormal acid exposure on pH testing, with a positive predictive value of 43%, negative predictive value of 82%, and overall accuracy of 78% [18]. The addition of a further step, the proton pump inhibitor (PPI) test, adds additional confidence in the symptomatic diagnosis of GERD with typical symptoms, as discussed below.

A significant advance in defining GERD over the past two decades consists of the distinction between esophageal and extra-esophageal syndromes. In the Montreal classification, esophageal syndromes were further subdivided into symptomatic syndromes (typical reflux syndrome, reflux chest pain syndrome), and syndromes with esophageal injury (reflux esophagitis, reflux stricture, BE, and esophageal adenocarcinoma) [1]. Extra-esophageal syndromes were subdivided into established associations (reflux cough, reflux laryngitis, reflux asthma, and reflux dental erosion syndromes) and proposed associations (pharyngitis, sinusitis, idiopathic pulmonary fibrosis, and recurrent otitis media).

With extra-esophageal reflux symptoms, the diagnostic yield of documentation of GERD on endoscopy and ambulatory reflux monitoring is lower than that established for typical GERD. The accuracy of available diagnostic tests, including laryngoscopy, upper endoscopy, pH-metry, and pH-impedance testing, for the evaluation of suspected extra-esophageal reflux symptoms is suboptimal [19], and contributes substantially to health-care expenditures. In fact, the initial year's cost for the workup and management of suspected extra-esophageal reflux symptoms may be more than five times than that for typical GERD [20].

Definition Based on Symptom Response to PPI

At initial presentation, an empiric therapeutic trial of PPI constitutes a commonly employed approach to diagnosis, with symptomatic response to this trial confirming clinical suspicion of GERD. Initial reports of this approach used omeprazole 40 mg before breakfast and 20 mg before dinner for 7 days, and 80% of GERD patients with heartburn reported symptom improvement, compared to 42% of patients with heartburn in the absence of GERD [21]. When symptom response to 7 days of twice-daily omeprazole is compared to abnormal acid exposure or erosive esophagitis on endoscopy, the PPI trial has a sensitivity of 75–80%, but specificity of 55% [21, 22]. In one study with GERD defined as the presence of erosive esophagitis on endoscopy, a PPI trial had similar sensitivity to acid exposure and symptom index (SI) on 24-h pH monitoring (83 vs. 80%) [23]. In a meta-analysis incorporating 15 studies investigating the accuracy of empiric PPI trials as a diagnostic strategy for GERD (using ambulatory pH monitoring as the reference standard), the positive likelihood ratio was 1.63–1.87, sensitivity 78%, and specificity 54% [24].

Response to PPI trials in non-GERD heartburn has to be interpreted with caution, since there is overlap with other processes that may also improve with antisecretory therapy (such as eosinophilic esophagitis, EoE) or as a placebo effect (such as functional heartburn). Further, antisecretory therapy may not be as effective at improving GERD symptoms in nonerosive disease compared to erosive esophagitis, and PPI nonresponders could still have reflux-triggered symptoms [1, 14, 25]. Nevertheless, lack of response to PPI therapy carries a high negative predictive value for the diagnosis of GERD, and it at least suggests need for further esophageal investigation. Despite the limited specificity of empiric PPI trials, simplicity and limited cost have established their universal utility in the initial evaluation and management of suspected GERD symptoms [26].

The diagnostic yield of empiric PPI therapy for most atypical symptoms, apart from NCCP, is worse than for typical symptoms. Two meta-analyses assessing the accuracy of PPI treatment as a diagnostic test for NCCP (with pH monitoring and/or endoscopy serving as reference standards) found a sensitivity of 80% and specificity of 74% [27, 28]. In contrast, the yield of empiric PPI for suspected extra-esophageal symptoms of GERD is abysmal. For example, a Cochrane meta-analysis found no apparent significant differences in symptomatic improvement between 2 and 3 months of PPI therapy and placebo for nonsmokers with chronic cough and normal spirometry [29]. Similarly, in nonsmokers with chronic cough randomized to twice-daily PPI or placebo for 3 months, no differences were found between PPI and placebo in cough-related quality of life or symptoms, even in a subset with positive pH monitoring [30]. These data highlight the fact that extra-esophageal symptoms often have multifactorial etiologies; GERD may represent a cofactor rather than the sole etiology for symptom generation.

Endoscopic Definition

Endoscopic definitions of GERD hinge on identification of esophageal mucosal injury visible to the endoscopist. The Montreal classification defined esophageal complications of GERD to include reflux esophagitis, hemorrhage, stricture, BE, and adenocarcinoma. Reflux esophagitis, the most common form of mucosal injury, may be seen as breaks in the distal esophageal mucosa immediately proximal to the squamocolumnar junction on upper endoscopy. Developed by the International Working Group for the Classification of Oesophagitis (IWGCO), the Los Angeles (LA) classification (named for an initial presentation at the 1994 World Congress of Gastroenterology in Los Angeles) is widely used to grade the severity of reflux esophagitis, with its definitive form published in 1999 [31, 32]. The LA classification describes increasing endoscopic grades of severity of esophagitis as follows: grade A, mucosal break(s) < 5 mm in length and not extending between the tops of two mucosal folds; grade B, mucosal break(s) > 5 mm in length, extending across the tops of two mucosal folds; grade C, mucosal break(s) continuous between tops of at least two mucosal folds but not involving > 75 % of esophageal circumference; and grade D, mucosal break(s) involving > 75 % of the esophageal circumference.

There are limited data to suggest that LA grade A esophagitis may rarely be encountered in healthy asymptomatic individuations (e.g., in as many as 8 % of control subjects in one study [33]), but higher grades are rarely seen in the absence of pathologic GERD. The LA grade of esophagitis at presentation has been described to predict healing with PPI therapy, with the highest healing rates described for LA grade A, and lowest for LA grade D. The likelihood of relapse following discontinuation of therapy is highest with LA grade D [34, 35]. The increasing popularity of empiric PPI trials and over-the-counter availability of these agents have further reduced the likelihood of finding esophagitis on endoscopy, limiting the role of endoscopy to the evaluation of treatment failures and complications in the presence of alarm symptoms [14].

While the identification of esophagitis defines erosive GERD (ERD), a significant proportion of reflux disease is nonerosive (with no mucosal breaks visible at endoscopy), termed nonerosive reflux disease (NERD). With the increase in popularity of empiric PPI therapy resulting in high likelihood of healing of esophagitis, there has been a diagnostic shift towards NERD in recent decades, since patients on PPI therapy are significantly more likely to be classified as NERD compared to PPI-naïve patients [36]. Population-based estimates suggest only about one third of GERD patients have ERD, with the remaining two thirds falling under the umbrella of the NERD phenotype [9, 37]. While the presence of erosive esophagitis can confirm GERD, the converse is not true: the absence of esophagitis on endoscopy does not rule out GERD, and pH monitoring is necessary to diagnose NERD. In the presence of endoscopically normal mucosa, histologic findings have poor diagnostic yield in GERD [38] (see section “Esophageal Histopathology and Mucosal Integrity”).

However, the finding of intestinal metaplasia on histopathology from suspected esophageal BE segments has a high concordance with abnormal esophageal acid exposure [39], but not necessarily with reflux symptoms [37, 40]. BE develops in patients with presumed genetic predisposition in the setting of prolonged esophageal reflux exposure, as a protective mechanism against corrosive injury and symptoms; therefore, BE segments are less sensitive to acid-triggered symptoms. Population screening suggests BE prevalence of 1.6% in an adult asymptomatic Swedish population, while the prevalence of BE in diagnosed GERD can be up to 13% in high-risk groups (chronic GERD, older age, white men) [37]. Although BE is a premalignant condition, risk estimate of development of esophageal adenocarcinoma is approximately 0.5% per year [41]. Therefore, while targeted screening for BE is recommended in predisposed individuals, population screening is not cost-effective, in terms of both diagnosing reflux disease and esophageal cancer prevention. Nevertheless, the confirmation of BE on histopathology from endoscopic biopsies defines the presence of GERD and establishes the need for therapy of GERD [26].

Ambulatory Reflux Monitoring-Based Definition: Acid Exposure Time

Ambulatory pH monitoring assesses and quantifies esophageal acid exposure times, and it helps determine if symptoms co-occur in close proximity to reflux events in assessing symptom–reflux association [42]. Catheter-based ambulatory pH monitoring was introduced in the 1970s for determining esophageal acid exposure over the course of a 24-h period. The most intuitive metric from ambulatory pH monitoring is the acid exposure time (AET, or the fraction of total recording time at pH < 4.0). AET thresholds defining abnormal acid exposure off PPI therapy fall into a narrow range around 4–5% [42, 43]. While there has been a recent interest in differentiating asleep and awake acid exposure, the analysis of pH monitoring has traditionally been separated by body position—upright or supine. Because acid reflux events occur more frequently in the upright compared to the supine position, in both asymptomatic controls and patients with GERD, acid exposure times are higher in the upright position compared to the supine position [44, 45]. Consequently, the thresholds defining abnormal esophageal acid exposure in the upright position (range of ~6–10%) are much greater than those for the supine position (in a range of ~1–6%) [46–51].

For patients tested on PPI therapy, a more stringent total distal AET threshold of 1.6% has been proposed and studied [52, 53]. Wireless pH systems are now available with longer monitoring periods, better patient acceptance, and less restriction of daily activities during the ambulatory study [54]. With these wireless pH systems, recordings of 48–96 h are possible with extended battery life in the portable recording device, but swallowed acidic material cannot be reliably differentiated from acidic reflux events without stringent patient diary recordings of oral intake. With wireless pH monitoring, the 95th percentile for distal esophageal

AET for controls over 2-day recordings was 5.3 %, slightly higher than that reported for catheter-based pH systems [55]. Day-to-day variation in AET has been well characterized using wireless pH monitoring, raising questions about the validity of borderline AET elevations on a 24-h study or on any one day of a multiple-day wireless pH study [43, 55]. Nevertheless, abnormal AET is commonly utilized for quantitation of acid exposure in patients with symptoms incompletely responding to antisecretory therapy, or when documentation of acid exposure is needed prior to anti-reflux surgery.

The DeMeester score was developed to quantify esophageal acid exposure as a composite of six measurements extracted from an ambulatory pH study: (1) percentage of total recording time with pH < 4, (2) percentage of upright recording time with pH < 4, (3) percentage of supine recording time with pH < 4, (4) total number of reflux events, (5) number of reflux events > 5 min in duration, and (6) duration of longest reflux event [46]. DeMeester scores of > 14.7–14.9 are commonly considered abnormal [56].

pH testing off antisecretory therapy is typically utilized for evaluation of patients with a low index of suspicion for GERD or to document reflux in patients being evaluated for endoscopic or surgical anti-reflux therapies. pH testing on therapy does not have as much clinical utility, as pH-impedance testing can provide additional information regarding weakly acidic reflux episodes which may not be detected by pH testing alone. This option is typically utilized to assess patients with known reflux disease with refractory symptoms incompletely responsive to antisecretory therapy, primarily to investigate the presence of persistent reflux parameters despite appropriate antisecretory therapy.

Impedance-Based Definition

Impedance monitoring is based on recording resistance to flow of tiny electrical currents across pairs of electrodes on an esophageal catheter. Reflux episodes are identified when retrograde decreases of > 50 % in impedance values (corresponding to the presence of refluxate adjacent to the electrodes) are detected across at least three consecutive distal pairs of impedance electrodes [43]. Therefore, the primary advantage of impedance testing over traditional pH testing lies in its ability to detect reflux events regardless of pH, thus detecting weakly acidic reflux and allowing testing on antisecretory therapy.

The first consensus on the use of esophageal multichannel intraluminal impedance (MII) in the evaluation of reflux episodes was published in 2004 [57]. This consensus proposed a distinction between acid (pH < 4), weakly acid (pH 4–7), and nonacid (or weakly alkaline; pH > 7) reflux. Combined MII–pH monitoring thus has greater sensitivity over traditional pH testing alone to detect reflux events. The gain in detection of reflux over pH monitoring is mainly from detection of weakly acid and nonacid reflux episodes, thereby allowing the test to be performed on PPI therapy. Since neutralization of mucosal acidification typically lags behind clearance of

refluxate from the esophagus, pH-detected reflux events tend to be longer than impedance-detected events. Hence, bolus contact time with a pair of impedance electrodes in the distal esophagus tends to be significantly shorter than acid exposure times [49]. The impedance correlate of AET is the reflux exposure time (RET), or the fraction of time refluxate is in contact with the distal esophageal impedance electrode 5 cm above the LES (corresponding to the distal esophageal pH sensor). A multicenter examination of healthy controls helped establish a threshold of 1.4% for an abnormal RET [49]. Despite this development of normative thresholds, RET has not been shown to represent a robust predictor of treatment outcome following reflux therapy [58].

Number of Reflux Events

The total numbers of reflux events on ambulatory reflux monitoring have been proposed as a means of defining GERD. Two studies (one American, one European) found very similar 95th percentile values of 73–75 reflux events on 24-h pH-impedance monitoring in healthy volunteers, implying that higher numbers of reflux events suggest the diagnosis of GERD [49, 50]. Recent data suggest that lower thresholds for total reflux events may identify GERD as low as 53 off PPI may be distinctive of GERD [59].

In the setting of antisecretory therapy, acid reflux events decrease while weakly acid reflux events are detected more often. In a landmark study utilizing pH-impedance monitoring before and after omeprazole therapy, acid reflux events significantly decreased, but the numbers of nonacid reflux events almost doubled, despite similar total numbers of reflux events [60]. While heartburn improved following omeprazole therapy, regurgitation events were reported more often. Other reports suggest a reduction in numbers of reflux events with antisecretory therapy in patients with GERD, presumed from reduced volume of gastric secretion [61]. Consequently, the thresholds utilized for numbers of reflux events indicative of GERD are lower when pH-impedance monitoring is performed on PPI therapy. The 95th percentile of normal values for total numbers of reflux events when testing is performed on PPI therapy have ranged from 48 to 57 [49, 59].

Outcome studies with characterization of reflux solely based on numbers of reflux events in the absence of abnormal AET or other reflux parameters are limited. While numbers of reflux events do decrease significantly with anti-reflux surgery in these instances [62], the thresholds alone may not necessarily segregate those with good response to therapy [63]. This may be partly related to the fact that duration of individual reflux events may vary dramatically, and patients with low numbers of reflux events could have significant acid or reflux exposure in the esophagus if prolonged. However, reflux events do have relevance in assessing correlation of symptoms with reflux events.

Symptom–Reflux Association

In addition to quantitation of esophageal acid exposure and reflux events, pH and pH-impedance monitoring can assess correlation of reflux events with esophageal symptoms. The two tests used most often are SI and symptom association probability (SAP). For pH-impedance testing, these symptom–reflux parameters may be calculated for acid-detected reflux events as well as impedance-detected reflux events. The SI is calculated as a simple ratio of the number of reflux-related symptoms to the total number of symptom episodes [64]. Analyses utilizing receiver operating characteristic curves designated a threshold of SI > 50 % as positive for heartburn episodes [65].

Two methods of calculating SAP have been proposed. The Weusten method, used most commonly, involves dividing the 24-h recording time into consecutive 2-min periods [66]. Next, 2×2 contingency tables are constructed, depicting the presence or absence of symptoms versus the presence or absence of reflux for each period. Fisher's exact test is then used to calculate the p value across the contingency table, representing the probability that symptoms and reflux are related by chance alone [66]. The SAP can also be calculated using the Ghillibert probability estimate (GPE), which represents the sum of partial probabilities for the exact numbers of reflux-associated symptoms within the context of the total number of symptoms, taking the total duration of the study and the total exposure time into account [67]. Regardless of how the SAP is calculated, it is considered positive if > 95 %, corresponding to $p < 0.05$, or a < 5 % chance that the observed association between symptoms and reflux occurred by chance. The Weusten and Ghillibert approaches to SAP can be used virtually interchangeably (with major discordance found in less than 3 % of cases), though the SI may be discordant with SAP, especially in the setting of limited or frequent symptoms [68]. Because of its ability to detect more reflux events, pH-impedance testing increases the yield of detecting a positive symptom–reflux association over traditional pH testing alone [69], especially when performed off pH therapy [58].

Symptom–reflux association is the weakest link in ambulatory pH and pH-impedance monitoring, since it is heavily reliant on patients promptly designating presence of symptoms on their event logger [70]. However, symptom–reflux association has value when positive in particular settings. It contributes to the strength of reflux evidence identified on ambulatory monitoring, especially since patients with strong GERD evidence (both abnormal acid exposure and positive symptom–reflux association) have the best symptomatic outcome with anti-reflux therapy [71, 72]. In the setting of physiologic reflux parameters, positive symptom–reflux association identifies a subgroup of patients with characteristics more akin to functional esophageal disease than GERD. Even though previously classified under the NERD umbrella or termed "acid sensitive," these patients share psychosomatic and HRQOL characteristics similar to patients with functional heartburn than to true GERD [73]. Reflux hypersensitivity has been used to describe settings where symptom–reflux association is positive on pH-impedance testing that detects all

reflux episodes regardless of pH, shifting patients previously diagnosed as functional heartburn with a negative pH study into this category using pH-impedance monitoring [73].

There are several factors that impact the clinical utility of symptom–reflux association. The calculations are highly reliant on symptom episodes, which can vary widely depending on symptom perception, and patient compliance with symptom reporting [74]. Specifically, very high or very low numbers of symptom episodes can significantly influence the calculation of SI [68]. SAP estimates may have better value in these instances because they take into account periods without symptoms (where reflux exposures may also be limited). SI and SAP indices can be over-interpreted, especially in the absence of high rates of reflux [70]. Therefore, a positive symptom–reflux correlation result is much more clinically useful than a negative result in evaluating GERD.

Barium Radiography

Barium esophagrams are often performed in the setting of esophageal symptoms, but have limited utility in the diagnosis of GERD. Although the overall sensitivity for detection of esophagitis (seen as a reticular or finely nodular pattern) may be around 65%, the sensitivity decreases for milder grades of esophagitis [20]. Barium radiology without any provocative maneuvers detects one third to one half of patients with GERD [75, 76]; evidence of reflux can be seen with provocative maneuvers in as many as 70% [77]. The main issue with barium esophagography in GERD is that the most important mechanism of GERD, TLESR, can occur in the normal subject, which can result in reflux of barium from the stomach high into the esophagus in the supine position. On the other hand, if no TLESR is provoked during the study, a patient with reflux disease may have a normal study. Therefore, the sensitivity and specificity of barium studies for diagnosis of GERD make this test inadequate to serve as a screening procedure for GERD [26, 78]. However, barium radiograms provide excellent anatomic detail and are important in assessing complications of GERD (such as a stricture or ring) or evaluating the anatomy of the esophagus prior to intervention [26, 79].

Although hiatal hernia is a common finding in patients with GERD, its presence alone does not define GERD. Many patients with hiatal hernia do not have symptoms of GERD, and many patients with GERD do not have hiatal hernias. Proportions with abnormal acid exposure may not significantly differ between GERD patients who have a hiatal hernia and those who do not [78]. In another study of over 300 patients, most patients had normal pH monitoring parameters regardless of the presence of a hiatal hernia, but those with larger hernias were more likely to have abnormal pH-monitoring parameters [80]. The presence of a hiatal hernia does appear to decrease the likelihood of symptom response to PPI in patients with GERD [81].

Although hiatal hernias may not define GERD, presence of a hiatus hernia impacts LES basal pressure, esophageal emptying, and TLESR. Sloan and Kahrilas employed concurrent videofluoroscopy and esophageal manometry to assess the impact of hiatal hernias on esophageal emptying, finding impaired esophageal emptying in nonreducing hernias compared to controls due to "late retrograde flow," suggesting impaired EGJ competence [82]. Likewise, the presence of hiatal hernias in GERD is associated with higher extent of reflux and lower amplitude of distal esophageal body peristalsis [83], while large hiatal hernias (>3 cm) are associated with a shorter and weaker LES compared to small or no hiatal hernias [84].

A hiatus hernia may be detected on upper endoscopy or esophagram; high-resolution manometry (HRM) can also identify separation between the LES and the diaphragm, which defines a hiatus hernia [85]. However, no investigation has a definable sensitivity for detection, especially when the hernia is small and intermittent [86].

The concept of the acid pocket is important to understanding the relevance of a hiatus hernia in the diagnosis of GERD. The acid pocket consists of a pool of meal-stimulated gastric acid that floats at the proximal aspect of ingested food close to the EGJ. This was first demonstrated in 2001 by investigators using a stepwise pull through of a pH catheter from the proximal stomach across the EGJ in the postprandial state [87]. In patients with GERD, the acid pocket may act as a reservoir for reflux into the esophagus, potentially leading to symptoms or mucosal injury [88]. When compared to healthy volunteers, patients with GERD have increased acid pocket length, as well as a more proximal location of the acid pocket within a hiatal hernia [89]. Hiatal hernias appear to facilitate entrapment of the acid pocket above the diaphragm, representing a major risk factor for increased reflux.

Esophageal Histopathology and Mucosal Integrity

Although random biopsies from endoscopically normal-appearing mucosa were discouraged in the past, the increasing recognition of EoE as a mechanism for esophageal symptoms makes it important to biopsy even normal-appearing esophageal mucosa at endoscopy [38]. Histologic findings attributed to reflux include increased papillary length, basal cell hyperplasia, and infiltration by leukocytes and/or eosinophils. These have poor sensitivity (30%) despite adequate specificity (78%) for a diagnosis of GERD, compared to symptoms and endoscopic changes [90].

Assessment of esophageal mucosal integrity has advanced to the evaluation of dilated intercellular spaces (DIS), which may represent disruption of the protective barrier at the esophageal squamous epithelium. DIS has been identified in both ERD and NERD, and it is thought to be induced by acid exposure; it may resolve with antisecretory therapy [91]. Increased permeability may contribute to esophageal symptom generation [92]. However, its specificity may be limited, since it has been recognized in almost one third of asymptomatic controls [93]. Therefore, it would be premature to use DIS as a clinical tool to diagnose GERD at this time.

Esophageal baseline impedance (BI) is another novel means of assessing esophageal mucosal integrity. Distal esophageal BI values are lower in GERD compared to healthy controls or symptomatic patients with normal esophageal acid exposure. Further, antisecretory therapy increases BI levels in GERD patients, suggesting that BI levels reflect reflux-induced changes in the esophageal mucosa that may reverse with acid suppression [94]. A BI threshold of 2100 Ω may differentiate GERD patients from functional heartburn with sensitivity and specificity surpassing 70%, suggesting that BI may have clinical utility in evaluating PPI-refractory reflux symptoms [95]. However, BI has not been widely evaluated as a metric for the diagnosis of GERD at present.

Strength of Reflux Evidence

The diagnostic tests described in this chapter may increase confidence in a reflux diagnosis when combined together, as evidenced by better symptomatic outcomes with anti-reflux therapy in patients with stronger reflux evidence. For instance, NERD presenting as heartburn has significantly higher rates of complete heartburn resolution (72%) when pH testing is positive, compared to heartburn alone or with negative endoscopy (50%) [96]. Similarly, the combination of abnormal pH parameters and positive symptom–reflux association predicts a higher likelihood of symptom response to anti-reflux therapy, for both typical and atypical reflux symptoms. These findings suggest that confidence in the diagnosis of GERD increases when the definition of GERD is fulfilled on multiple test modalities.

Conclusion

Definitions of GERD—symptomatic, endoscopic, through ambulatory reflux monitoring, anatomic, or through newer diagnostic modalities—have evolved significantly over the past decades. Despite these advances in the evaluation of reflux, in most clinical settings, symptoms and/or the response of these symptoms to therapeutic PPI trials define GERD, especially with typical symptoms of heartburn or regurgitation [26]. The popularity of PPI therapy has largely shifted the concept of refractory GERD from unhealed mucosal disease towards persisting symptoms despite PPI therapy, sometimes with implication of weakly acidic or nonacid reflux [97]. Diagnostic tests can complement clinical diagnosis, especially with atypical symptoms or when the diagnosis remains in question despite a PPI trial.

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Chapter 2
Complications of Gastroesophageal Reflux Disease

Patrick Yachimski

Acute esophageal exposure to gastric and/or duodenal refluxate can result in pyrosis and symptomatic gastroesophageal reflux disease (GERD), as well as erosive esophagitis. The pathophysiology underlying GERD and the esophageal response to acute acid exposure, including esophageal defense mechanisms, are discussed elsewhere in this book. Chronic esophageal acid exposure can result in anatomic and structural changes to the esophagus—ranging from benign lesions (peptic stricture), to premalignant lesions (Barrett's esophagus), to esophageal adenocarcinoma. These esophageal complications of chronic GERD will be discussed in the following chapter.

Peptic Stricture

Peptic strictures describe a fixed luminal narrowing of the distal esophagus. Strictures develop as a result of collagen deposition and fibrosis generated in response to the healing of erosive esophagitis. Peptic strictures are typically located at or just above the gastroesophageal junction, the region of esophagus in closest proximity to gastric refluxate. Etiologies of cicatricial disease other than peptic injury must be considered for isolated strictures involving the mid or proximal esophagus.

Characteristic symptoms of peptic stricture include dysphagia, chiefly for solids, and also esophageal food impaction. Diagnosis of peptic stricture can be confirmed by either barium esophagram (Fig. 2.1) or upper gastrointestinal endoscopy (Fig. 2.2a). Endoscopy has emerged as the preferred diagnostic modality in patients with a suggestive clinical history, as endoscopy simultaneously offers the opportunity for therapeutic intervention. Treatment for symptomatic strictures consists of

P. Yachimski (✉)
Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, 1660 The Vanderbilt Clinic, Nashville, TN 37232-5280, USA
e-mail: Patrick.yachimski@vanderbilt.edu

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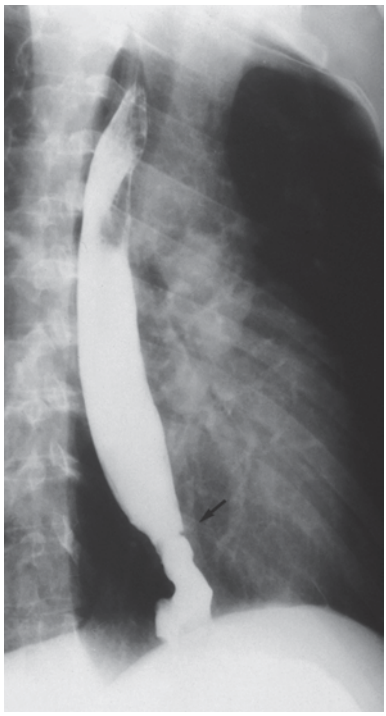

Fig. 2.1 Barium swallow peptic stricture

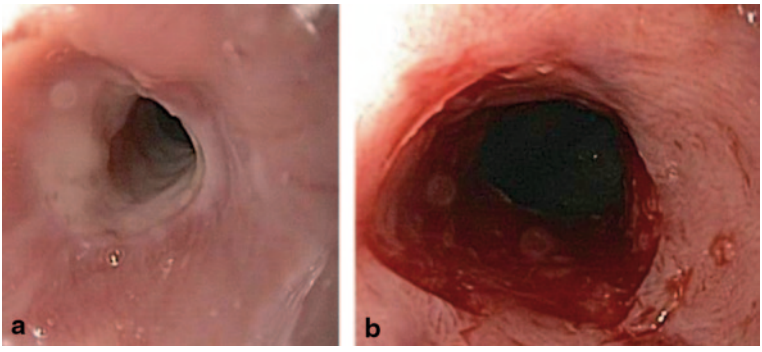

Fig. 2.2 **a**, **b** EGD images. Peptic stricture (pre- and post-dilation)

dilation, using either a bougie-type dilator (Maloney or Savary) or a through-the-scope pneumatic dilator. The goal of dilation is to provide mechanical disruption of fibrosis (Fig. 2.2b). Clinical axiom suggests that achieving a luminal diameter of 14–15 mm is typically sufficient to palliate dysphagia. Current clinical guidelines associate endoscopic pneumatic or bougie dilation with a higher procedural bleeding risk than a diagnostic endoscopic examination, and this may require

modification of periprocedural antiplatelet and anticoagulant therapy in order to minimize bleeding risk [1]. Transmural esophageal perforation is an uncommon adverse event of peptic stricture dilation when proper technique is utilized, with an estimated incidence rate of less than 1 in 250 cases [2, 3].

Multiple dilation sessions may be required in order to achieve durable symptom palliation for some patients. A refractory stricture is defined as a fibrotic luminal narrowing resulting in dysphagia for which a luminal diameter of 14 mm cannot be achieved following five consecutive dilation sessions at 2-week intervals, whereas a recurrent stricture is defined as a stricture for which luminal diameter cannot be maintained for 4 weeks following dilation to 14 mm [4]. Adjunctive options for the subset of patients with refractory or recurrent peptic strictures may include temporary placement of an esophageal endoprosthesis (stent) or providing instruction in home dilation techniques [5].

While most gastroenterologists will encounter patients with peptic strictures in the course of general clinical practice, the incidence of peptic stricture is declining overall [6]—likely as a result of the widespread use of prescription and over-the-counter medications which suppress gastric acid production. Following diagnosis of a peptic stricture, proton pump inhibitors (PPI) are typically prescribed to patients not already on chronic antisecretory therapy, in order to reduce the likelihood of stricture recurrence.

Barrett's Esophagus

Definition

Barrett's esophagus (BE) was initially described in 1950 by Norman Barrett, a thoracic surgeon, as esophagus with columnar epithelium. Current definitions emphasize both the visible endoscopic presence of salmon-colored mucosa populating the tubular esophagus proximal to the anatomic gastroesophageal junction (Fig. 2.3) and the histopathologic presence of columnar epithelium (Fig. 2.4) as requisite for the diagnosis of BE—this is to be distinguished from columnar epithelium identified in biopsies of an irregular squamocolumnar junction (Z line) or gastric cardia, neither of which constitutes BE. Given these important distinctions, overdiagnosis of BE may be common in clinical practice [7]. Communication and collaboration between the gastrointestinal endoscopist and pathologist may be necessary to ensure that both criteria are met and for confirmation of diagnosis in questionable cases.

Classic histopathologic findings requisite for the diagnosis of BE have included the presence of columnar epithelium with intestinal metaplasia, as characterized by the presence of goblet cells on Alcian blue stain. This is currently a matter of some controversy. The ability to detect goblet cells may be in part a function of adequate biopsy sampling, with one study suggesting that a minimum of eight forceps biopsies are needed to limit random sampling error and enable optimal detection [8].

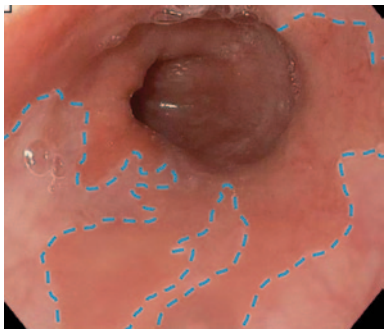

Fig. 2.3 Endoscopic image of BE. The *blue line* demarcates the borders of the *salmon-colored* Barrett's epithelium in the distal esophagus, compared with the *lighter pink* epithelium of normal squamous mucosa

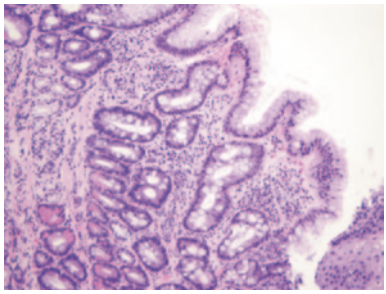

Fig. 2.4 Barrett's esophagus, characterized by the presence of columnar epithelium with goblet cells, with maturing surface epithelium (original magnification, 100×). (Image courtesy of Chanjuan Shi, MD)

Current American Gastroenterological Association (AGA) guidelines require the presence of intestinal metaplasia in the diagnosis of BE [9]. On the other hand, recently updated British Society of Gastroenterology (BSG) guidelines suggest that columnar epithelium without intestinal metaplasia may qualify for the diagnosis of BE [10], under the presumption that columnar epithelium with or without goblet cells is at risk for neoplastic progression.

A common endoscopic stratification system for BE is based on length of visible BE. Short-segment BE (SSBE) is defined as BE with a maximal length of less than 3 cm above the gastroesophageal junction, whereas long-segment BE (LSBE) is defined as BE with a maximal length of ≥3 cm. The distribution of BE may not be uniform in all cases, and a validated (Prague) classification scheme endorses endoscopic description of BE by both its circumferential (C) and maximal total (M) length [11]. The development of LSBE is felt to be reflective of a greater pathologic burden of esophageal acid exposure compared with development of SSBE [12], and there are data to suggest that long-term esophageal adenocarcinoma (EAC) risk is greater for LSBE than SSBE [13].

Cellular Origin and Pathophysiology

Metaplastic transformation of native squamous esophageal epithelium is thought to be induced by chronic inflammation. Development of BE is therefore an esophageal

defense mechanism, as the columnar epithelium of BE is relatively acid resistant when compared with squamous mucosa.

Identifying the cellular origin of BE has been a focus of considerable investigation. One rat model of reflux induced by surgical esophagojejunostomy identified progenitor cells of bone marrow origin as candidates for initiation of esophageal metaplasia [14]. An alternative transgenic mouse model implicated stem cells residing in the gastric cardia, activated by bile acid, as progenitors of BE [15].

Rodent models of BE employing reflux disease induced by esophagojejunostomy, with subsequent profound small-bowel esophageal reflux, may not perfectly mimic GERD in humans with intact foregut anatomy. Nonetheless, it is likely that in addition to gastric reflux, duodenal reflux containing bile acids contributes to the pathogenesis and natural history of esophageal neoplasia. Unique effects of bile acids, including deoxycholic acid, on esophageal epithelium include generation of oxidative stress and DNA damage which may contribute to carcinogenesis [16, 17].

It is difficult to pinpoint precisely when BE develops in the course of chronic GERD. In other words, there are no observational data reporting baseline endoscopy in patients with GERD documenting the absence of BE, followed by longitudinal endoscopic surveillance documenting interval development of BE. The potential for development of BE has long been recognized in pediatric patients [18]. BE in pediatric patients has been reported in patients with neurodevelopmental conditions including mental retardation [19] and congenital tracheoesophageal abnormalities. The prevalence of BE in a general pediatric population appears to be less than 1 % [20, 21].

Prevalence and Risk Factors

Not all patients with chronic GERD develop BE. As a corollary, not all patients with BE report regular or frequent heartburn symptoms. In a study of individuals invited to undergo upper endoscopy at the time of screening colonoscopy, BE was detected in 8 % of patients with GERD and 6 % of patients without GERD [22]. The finding of a relatively comparable prevalence of BE among patients with and without GERD has been replicated in multiple studies [23].

Careful review of this data, however, reveals a wide range across studies in the overall prevalence of BE among individuals without GERD, from 1 to 25 % [23]. The high-end estimate of 25 % was obtained from a Veteran's Affairs population [24], and is reflective of the fact that BE disproportionately affects Caucasian males in the sixth decade of life and older. Consequently, current practice guidelines endorse consideration of age, gender, and ethnicity when determining the appropriateness of screening for BE among individuals with GERD [9].

Anatomic factors associated with development of BE include the presence of a hiatal hernia and obesity. The association between obesity and BE appears to be stronger for central adiposity, defined by such variables as waist circumference and waist-to-hip ratio, than elevated body mass index per se [25–28]. The mechanism underlying the pathway from obesity to BE may not be solely a function of the

mechanical effects of obesity in exacerbating GERD. An additional role may be played by the hormonal milieu of obesity, as, for instance, elevated levels of insulin and insulin-like growth factors have been associated with BE [29].

While genetic factors responsible for development of BE have yet to be fully elucidated, familial clustering of BE has been described. Individuals with BE may be diagnosed at a younger age than individuals with sporadic BE. Familial BE likely accounts for less than 10% of all BE cases [30–33].

Risk of development of BE is almost certainly multifactorial, with likely contributions from environmental as well as host factors. While speculation has focused on the role of alcohol consumption and specific types of alcohols (beer vs. wine vs. liquor), a recent population-based analysis found no evidence of an association between alcohol consumption and risk of development of BE [34]. An intriguing theory involves the evolution of hygiene, the practice of *Helicobacter pylori* eradication, and emergence of BE. An inverse association has been reported between BE and active *H. pylori* infection or sequelae of prior *H. pylori* infection such as chronic atrophic gastritis and gastric intestinal metaplasia [35]. This has led to the hypothesis that *H. pylori* is protective with respect to the esophagus, and the question as to whether indiscriminate eradication of *H. pylori* is appropriate in all circumstances [36]. More recent data have identified an altered esophageal microbiome in individuals with GERD and BE compared to normal controls [37].

Esophageal Adenocarcinoma

Incidence and Risk Factors

EAC is the fourth most common gastrointestinal tract malignancy, and the incidence of EAC in the USA and Western Europe has risen considerably over the past several decades. Emerging data suggest that the overall rate of increase in EAC incidence appears to be slowing since the late 1990s [38]. Nonetheless, the rise in incidence of EAC coupled with the decline in incidence of esophageal squamous cell carcinoma has rendered EAC the most commonly encountered esophageal tumor in Western gastroenterology practice.

BE is the major risk factor for EAC. However, the overwhelming majority of cases of EAC are diagnosed in individuals without a known prior diagnosis of BE—presumably because the majority of individuals diagnosed with EAC never experienced GERD symptoms sufficient to warrant earlier endoscopic investigation. In the Northern Ireland Barrett's Oesophagus Registry, prior diagnosis of BE was present in only 7.3% of patients diagnosed with EAC [39]. Moreover, while EAC-related mortality is increased considerably among individuals with BE compared to individuals without BE, EAC-specific mortality accounts for only a minority of all-cause mortality in patients with BE. In a meta-analysis of more than fifty studies, EAC accounted for 7% of deaths among patients with BE. Patients with

BE were more than twice as likely to die of a non-esophageal malignancy, which accounted for 16% of deaths. More than 50% of deaths were due to cardiovascular or pulmonary disease [40]. Data from such studies challenge the practice of current symptom-targeted screening and surveillance strategies, as shall be discussed.

Risk factors for EAC are similar if not identical to risk factors for BE. Caucasian males are disproportionately represented among individuals diagnosed with EAC. Trends in EAC incidence have paralleled an increasing prevalence of obesity. A recent study investigating trends of EAC and obesity in the USA, the Netherlands, and Spain demonstrated, however, that the increase in incidence of EAC in each of these three nations could not be explained solely by the increasing prevalence of obesity [41]. Additional environmental factors which have been proposed as etiologic agents include dietary nitrogen-containing compounds and *H. pylori*. Epidemiologic analyses suggest that nonsteroidal anti-inflammatory drugs [42, 43] and statins [44] may have a protective effect.

Progression from BE to EAC

A long-standing estimated progression rate from BE to EAC of 0.5% per year was based on a study designed to assess for publication bias in the cancer risk of BE [45]. More recent epidemiologic investigations have reported considerably lower progression rates from nondysplastic BE to EAC: 0.38% per year in an Irish registry [46], 0.30% per year in a Netherlands registry [47], and as low as 0.12% per year in a Danish registry, after excluding prevalent cases of EAC diagnosed during an initial period of follow-up [48].

Intermediate steps in the progression from intestinal metaplasia (BE) to EAC can result in histopathologic findings of dysplasia. These features may include nuclear crowding and pleomorphism, hyperchromatism, and emergence of a disorganized epithelial architecture. Dysplasia is currently classified according to one of two grades, based on severity of histopathologic findings: low-grade dysplasia (LGD; Fig. 2.5a) or high-grade dysplasia (HGD; Fig. 2.5b). Based on meta-analysis data, the estimated progression rate from HGD to EAC is between 6 and 7% per year [49]. The finding of HGD has therefore served as a trigger for therapeutic intervention.

Conflicting estimates have been reported for progression rates from LGD to EAC. In a multicenter US cohort, the progression rate from LGD to the combined end point of HGD/EAC was less than 2% per year [50]. This estimate was supported by a recent meta-analysis, in which the annual progression rate from LGD to HGD/EAC (1.7%) was exceeded by annual mortality due to non-esophageal disease (4.7%) [51]. On the other hand, studies from the Netherlands have demonstrated that among patients referred with a diagnosis of BE LGD, the majority (80%) are downstaged to less advanced pathology following expert histopathology review [52]; yet among patients with confirmed LGD, progression rates to HGD/EAC exceed 9% per year [52, 53].

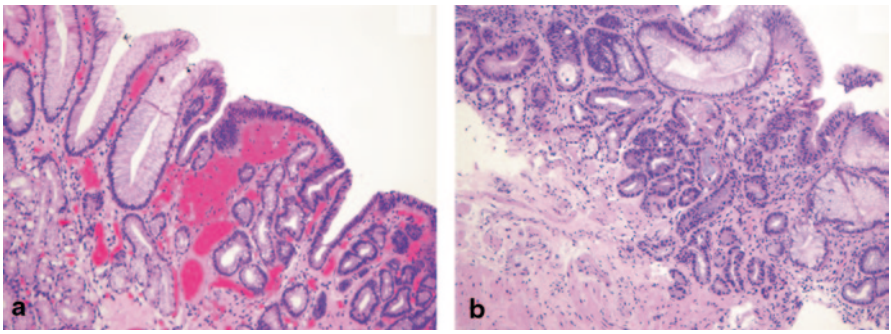

Fig. 2.5 **a** Barrett's esophagus with low-grade dysplasia (original magnification, 100×). **b** Barrett's esophagus with high-grade dysplasia (original magnification, 100×). (Images courtesy of Chanjuan Shi, MD)

As reflected by the disparate estimates of cancer risk associated with LGD, achieving reliable estimates of risk of progression is contingent upon accurate assessment of baseline prevalent histopathology. Unfortunately, the detection and grading of dysplasia are fraught with numerous challenges. Endoscopic evaluation can fail to detect prevalent dysplasia, as the heterogeneous, nonuniform distribution of dysplasia within a BE segment [54] may elude detection even by systemic biopsy sampling protocols. In addition, the histopathologic grading of dysplasia is by some measure subjective, and interobserver agreement among pathologists is poor [55].

Current Endoscopic Management Approaches to BE and EAC Prevention

A triumvirate approach to management of BE has consisted of endoscopic screening of patients with GERD for diagnosis of BE, endoscopic surveillance of patients with established BE to identify progression to dysplasia and enable early cancer detection, and intervention (historically, surgical esophagectomy) for patients with HGD or early-stage cancer. Numerous factors including revised estimates of BE progression rates, increased recognition of the limitations of symptom-targeted screening and surveillance strategies, and the emergence of endoscopic therapy for BE HGD and stage T1 EAC have all had major impacts on endoscopic management of disease.

Screening

An ideal screening test is an examination with high sensitivity and specificity, an examination which is easy to perform and available at reasonable cost, an examination which is acceptable to patients and clinicians, and an examination which

following disease detection offers early treatment of a disease which would otherwise have caused considerable morbidity if diagnosed at a later, symptomatic stage. There are no controlled prospective or retrospective data to suggest that endoscopic screening fulfills all these criteria or prevents or reduces EAC-related mortality.

A rationale for endoscopic screening for BE and EAC has been based on cost-utility analyses, which suggest that a one-time endoscopic screening examination at age 50 or age 60 among individuals with GERD may be cost-effective relative to a no-screening strategy [56, 57]. Such analyses are based on simulated disease models which predict the likelihood of transition between competing health states, and may be sensitive to estimates of BE prevalence, cancer incidence rates, and cost of endoscopy.

One of the major challenges to this screening strategy for EAC prevention is the fact that, as previously discussed, the overwhelming majority of EAC cases are identified in individuals without a known prior diagnosis of BE [39]. Restricting screening to only individuals with symptomatic GERD fails to account for a large asymptomatic population at risk.

Viewed in the context of other accepted cancer screening tests (colonoscopy for colorectal cancer screening, mammogram for breast cancer screening), a one-time screening endoscopy at age 60 may be reasonable among men with GERD—but is difficult to justify in women at any age, given the overall lower age-adjusted incidence rates of EAC among women compared to men [58]. The ambivalence of recent practice guidelines may be viewed as an initial shot across the bow of the current practice of endoscopic screening for BE and EAC. The AGA now recommends against screening for BE among the general population with GERD, albeit with consideration of screening for individuals with risk factors including age 50 years, male gender, white race, and elevated BMI or central adiposity [9]. The BSG states that endoscopic screening for BE is not justified for all individuals with GERD, but can be considered in individuals with chronic symptoms and multiple risk factors [10].

While diagnostic endoscopy has a low overall risk of patient morbidity, the costs of endoscopy are not inconsequential. Both direct costs and indirect costs (i.e., missed time from work) can be significant when considered on a large scale. There may be a future role for disruptive technologies such as unsedated transnasal endoscopy [59] or non-endoscopic methods of tissue acquisition [60] in screening for BE.

Surveillance

The practice of surveillance endoscopy among patients with BE has been similarly justified on the basis of cost-effectiveness analyses. Disease simulation models have demonstrated that a strategy of surveillance at 5-year intervals can be cost-effective compared to a strategy of no surveillance, with the assumption that intervention (esophagectomy) can be offered as an option to those who develop HGD or cancer [61, 62]. These models are sensitive to estimates of cancer risk—and as such,

epidemiologic data resulting in lower revised estimates of risk of progression from BE to EAC [46–48] may undermine justification for surveillance.

A recent US-based case-control study reported no evidence of reduced EAC-related mortality among patients with BE who undergo endoscopic surveillance [63]. Alternatively, a recent European study assessed the impact of endoscopic surveillance on all-cause and EAC-specific mortality after stratifying according to endoscopic surveillance intervals. No mortality reduction was identified among individuals receiving "inadequate" surveillance, defined as a time interval 1.5 times expected between initial BE diagnosis and EAC diagnosis accounting for baseline histopathology and grade of dysplasia; there was, however, evidence of 2- and 5-year mortality reduction among those undergoing "adequate" surveillance with endoscopic examination at appropriate frequency [64].

Current AGA practice guidelines recommend surveillance endoscopy at 3–5 year intervals for BE without dysplasia [9]. The BSG guidelines call for modification of the recommended surveillance interval for nondysplastic BE according to length of the BE segment: every 3–5 years for BE length less than 3 cm and every 2–3 years for BE length ≥3 cm [10]. The recommended surveillance interval for BE containing LGD is every 6 months [9, 10]. In cases of HGD in which endoscopic therapy is not pursued, the recommended surveillance interval is every 3 months [9].

Given that the majority of patients with BE never develop EAC, a major challenge is to identify individuals with BE who are at risk of development of dysplasia or EAC (progressors) in contrast to those not at risk (nonprogressors). Current risk estimates are based largely on the presence/absence of dysplasia, an imperfect histopathologic marker. Either novel biomarkers or clinical prediction models will be necessary to achieve future optimal risk stratification among individuals with BE.

Endoscopic Therapy

The emergence of endoscopic eradication therapy has had a monumental impact on the management of BE-associated neoplasia. Whereas patients with BE containing HGD or intramucosal EAC once faced surgical esophagectomy as the only treatment option, an increasing proportion of patients are now undergoing endoscopic therapy. In a US cohort from the Surveillance Epidemiology and End Results (SEER) database, for instance, the proportion of patients undergoing endoscopic therapy for HGD or T1 EAC increased from 3% in 1998 to 29% in 2009 [65].

The emergence of endoscopic therapy has been facilitated not only by development of endoscopic techniques for mucosal eradication but also by refined endoscopic staging protocols. Whereas historical cohorts reported high rates of occult invasive cancer among patients undergoing esophagectomy with a preoperative diagnosis of HGD, the rate of occult invasive malignancy has been dramatically reduced with use of endoscopic ultrasound (EUS) for tumor staging [66]. EUS has the ability to both examine the esophageal wall layers for evidence of tumor penetration

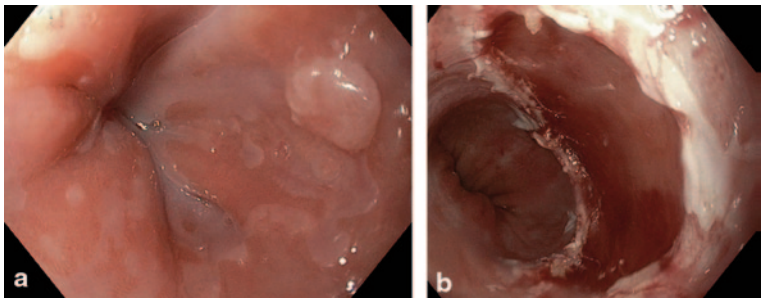

Fig. 2.6 **a** Endoscopic view of Barrett's esophagus with a nodule in the 3 o'clock location. **b** Endoscopic view following endoscopic mucosal resection. Pathology demonstrated T1a adenocarcinoma

and assignment of T stage, and also has the ability to identify and sample by fine needle aspiration regional lymph nodes for assignment of N stage.

The development of esophageal endoscopic mucosal resection (EMR) techniques has had even more considerable impact in the staging of intramucosal neoplasia. This technique allows the *en bloc* removal of large segments of the esophageal mucosa and submucosa (Fig. 2.6a, b). This provides a considerable mucosal surface area for histopathologic assessment, overcoming the potential sampling error of limited-size forceps biopsies. In cases of T1 EAC, the resected specimen also enables critical assessment of depth of invasion. The likelihood of lymph node involvement is low (less than 2%) for T1a (intramucosal) EAC [66]. In many instances, therefore, patients with T1a EAC may undergo endoscopic therapy with reasonable expectation of complete cancer eradication and durable disease remission. The likelihood of lymph node involvement increases considerably, however, for patients with T1b (submucosal invasive) EAC [67].

Current guidelines recommend endoscopic staging with EMR for dysplasia associated with focal endoscopic abnormalities within a BE segment [9, 10]. Liberal use of EMR for this purpose may result in a change of diagnosis, either by downstaging or by upstaging histopathology based on initial interpretation of forceps biopsies, in more than 50% of cases [68].

Following resection of lesions containing advanced pathology, typical practice is to proceed with endoscopic eradication of all intestinal metaplasia, as the risk of metachronous neoplasia arising from residual BE can exceed 20% [69]. While widefield EMR can be used for complete eradication of BE, the risk of post-EMR stricture is approximately 40% following this approach [70]. Alternatively, ablative options available for treatment of BE and for which there are strong controlled data in treatment of HGD include photodynamic therapy (PDT) and radiofrequency ablation (RFA).

PDT consists of systemic administration of a photosensitizing agent, followed by endoscopic application of laser energy to the esophagus. In a randomized controlled trial of PDT with porfimer sodium photosensitizer plus omeprazole versus omeprazole alone for treatment of HGD, eradication of HGD at 5-year follow-up

was observed in 77% of the PDT arm versus 39% of the PPI arm. Progression to EAC at 5-year follow-up decreased by nearly 50% among those receiving PDT [71]. In a randomized controlled trial of RFA plus PPI versus PPI alone, remission of HGD was observed in 81% of subjects at 12-month follow-up. Remission of all intestinal metaplasia was observed in 77% of subjects. Progression from HGD to EAC was observed in 2.4% among those undergoing RFA compared with 19% in the PPI arm [72]. In most centers, RFA has supplanted PDT as the ablative modality of choice given a lower overall stricture rate compared to PDT and the absence of prolonged posttreatment phototosensitivity.

While such endoscopic eradication therapies may once have been reserved for HGD/T1 EAC patients unfit for surgery due to advanced age or comorbid illness, accumulating efficacy data have allowed consideration of endoscopic therapy as first-line treatment in lieu of surgery for a wide range of HGD/T1a patients. Practice guidelines now recommend endoscopic therapy as the preferred treatment for the majority of patients with HGD [9]. In a series of 1000 consecutive patients with T1a EAC treated with endoscopic resection, initial complete response was achieved in 96%, and complete remission was achieved in 94% over a median 56.6 months of follow-up. EAC-specific mortality was responsible for less than 2% (2/113) of overall deaths [73].

The efficacy and relative safety of RFA, in particular, has prompted consideration of whether endoscopic therapy should be offered to BE patients with pathology less advanced than HGD. A randomized trial of RFA versus endoscopic surveillance for LGD reported progression at 3 years to the combined end point of HGD/EAC in 1.5% of subjects undergoing ablation compared to 26.5% of subjects undergoing surveillance [74]. Reported progression rates of LGD have been highly variable, with at least one study reporting that low progression rates of LGD to HGD/EAC are well exceeded by non-EAC-related mortality [51]. RFA of nondysplastic BE has been reported, and some have taken the position that offering intervention to this larger pool of patients with early stage BE may become analogous to the practice of screening colonoscopy and resection of colonic adenomas for prevention of colorectal cancer [75]. Whether such practice can be supported from a resource utilization standpoint may be sensitive to refined estimates of malignant progression, as well as the need for posttreatment endoscopic surveillance.

Conclusion

Patients with chronic GERD are at risk for development of esophageal pathology. While the prevalence of peptic esophageal stricture has become less common in the era of potent pharmacologic antisecretory therapy, attention is now instead focused upon premalignant and malignant esophageal pathology in the context of an increasing prevalence of EAC. BE is the precursor lesion for EAC and may develop in individuals with or without symptomatic GERD. While recent epidemiologic data suggest that the risk of malignant progression from BE to EAC may be lower

than previously believed, a symptom-targeted endoscopic screening strategy fails to diagnose a large burden of asymptomatic individuals at risk, and current clinical criteria are limited in their ability to stratify patients as either low or high risk for neoplastic progression.

For patients diagnosed with early-stage neoplasia including T1a (intramucosal) cancer, endoscopic resection and ablation techniques have revolutionized therapy and now offer many patients an alternative to surgical esophagectomy. Future advances in the management of EAC may depend upon the development and application of disruptive screening technologies for early cancer detection.

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Chapter 3
Diagnostic Approaches to GERD

Dejan Micic and Robert Kavitt

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common disorders of the gastrointestinal tract and is defined as symptoms or mucosal damage secondary to the abnormal reflux of gastric contents into the esophagus [1]. While the reflux of gastric contents into the esophagus is a physiologic event, given the definition requiring mucosal damage or abnormal symptoms, the diagnosis of GERD can be made using a combination of presenting symptoms and/or objective testing [2]. When defined by using patient-centered symptoms, prevalence rates of GERD in North America range from 18.1 to 27.8%, indicating a common disease process requiring diagnostic methods to objectively define GERD when initial empiric regimens fail to control symptoms [3].

GERD occurs when the normal antireflux barrier between the stomach and the esophagus is impaired, either transiently or permanently. Therefore, defects in the esophagogastric barrier, such as lower esophageal sphincter (LES) incompetence, transient LES relaxations, and hiatal hernia, are the primary factors involved in the development of GERD [4]. Symptoms develop when the offensive factors in the gastroduodenal contents, such as acid, pepsin, bile acids, and trypsin, overcome several lines of esophageal defense, including esophageal acid clearance and mucosal resistance. As more components of esophageal defense break down, the severity of reflux increases.

The lack of a standard criterion for measuring GERD combined with the definition including mucosal damage and/or clinical symptoms leads to inaccuracies in

R. Kavitt (✉)
Section of Gastroenterology, Hepatology and Nutrition, Center for Esophageal Diseases, University of Chicago, 5841 S. Maryland Avenue, MC 4080, 60637 Chicago, IL, USA
e-mail: rkavitt@medicine.bsd.uchicago.edu

D. Micic
Section of Gastroenterology, Hepatology and Nutrition, University of Chicago Medical Center, Chicago, IL, USA

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the diagnosis and subsequently diagnostic studies. A systematic review of seven studies assessing the accuracy of clinical opinion in the diagnosis of esophagitis found a sensitivity of clinical opinion to vary between 30 and 76% and specificity between 62 and 96% [5]. Limitations in clinical history and response to therapy highlight the need for improved diagnostic methods while limiting patient inconvenience. This chapter reviews both the historical and current diagnostic methods available in the diagnosis of GERD.

Proton-Pump Inhibitor Test

The symptomatic response to a short course of treatment with an inhibitor of gastric acid secretion has become known as the proton-pump inhibitor (PPI) test [6]. Typically, a reduction in a symptom assessment of 50% has been defined as a positive test result and indicative of a diagnosis of GERD [6, 7]. However, the lack of an optimal cutoff in symptom improvement, PPI dose, test duration, and gold standard reference for GERD hampers the diagnostic accuracy of the test.

In a study of 43 consecutive patients presenting with episodes of heartburn in whom upper endoscopy and ambulatory 24-h esophageal pH monitoring were performed, Fass et al. were able to define the test characteristics of a PPI test using omeprazole at a dose of 60 mg daily as well as the optimal definition for a reduction in symptoms. Patients were treated with omeprazole (40 mg in the morning and 20 mg in the evening) or placebo for 7 days, followed by a washout period and randomization to the comparator arm. Overall, 35 patients were classified as GERD positive (based on abnormal endoscopy or 24-h esophageal pH monitoring), and among GERD-positive patients, 28 (80%) had a positive response to the omeprazole test using a symptom improvement definition of 50%. Omeprazole test specificity was 57.1% with a positive predictive value of 90.3% and a negative predictive value of 36.4%. Subsequently, a receiver-operating curve (ROC) was performed to assess the degree of symptom improvement associated with the optimal test characteristics demonstrating that a 75% symptom reduction was associated with 85.7% sensitivity, 90.9% positive predictive value, and 81% accuracy. In comparing the PPI test to a conventional diagnostic strategy of upper endoscopy followed by 24-h esophageal pH monitoring if erosive disease was not demonstrated, the PPI test saved US$ 348 per average patient undergoing diagnostic evaluation which was attributable to a 64% reduction in the performance of upper endoscopies and 53% reduction in 24-h esophageal pH monitoring, highlighting the benefits of an initial empiric PPI trial [8].

Multiple PPI doses have been used in therapeutic trials for the diagnosis of GERD ranging from 40 to 80 mg of omeprazole daily with study durations from 1 to 4 weeks [7]. Schindlbeck et al. demonstrated an improvement in test sensitivity for the diagnosis of GERD among patients with abnormal 24-h esophageal pH monitoring when receiving omeprazole 40 mg twice daily (sensitivity 83.3%) compared to those receiving omeprazole 40 mg once daily (sensitivity 27.2%) for 7 days while using a 75% reduction in symptoms as the definition of a positive test [9].

A meta-analysis assessing an empiric PPI trial as a method of diagnosis of GERD using 24-h esophageal pH monitoring as a reference standard found a combined sensitivity of 78 % and specificity of 54 %, which was comparable to a GERD definition based on esophagitis as the reference standard, which demonstrated a combined sensitivity of 71 % and specificity of 41 % [10]. This is in concordance with a systematic review demonstrating a higher likelihood of a 50 % reduction in clinical symptoms among those with unexplained chest pain when objective evidence with positive pH-monitoring test or endoscopic evidence of reflux esophagitis is demonstrated compared to those without objective evidence of GERD [11].

Therefore, a PPI trial does not confidently establish or exclude a diagnosis of GERD, although optimal test characteristics have not been defined. Improved test characteristics can be obtained with higher PPI doses, greater improvement in symptoms and in those with objective evidence of GERD. When used in a defined short course, most patients will have an improvement within 3 days, thereby forgoing the need for advanced diagnostic testing [12].

Provocative Testing

Provocative testing of the esophagus is mostly of historical value. Such testing arose because of the difficulty in evaluating patients with noncardiac chest pain. The Bernstein test, introduced by Bernstein and Baker in 1958, is an acid perfusion test used as an objective method to reproduce symptoms of acid-related injury [13]. In performing the test, the patient sits upright with a nasogastric tube placed 30 cm from the nares, and normal saline is infused for a period of 15 min followed by a 0.1 N hydrochloric acid solution for 30 min or until symptoms are produced. Solutions are infused at a rate of 100–120 drops (6–7.5 mL) per minute, and the test is considered positive when the patient's symptoms or substernal burning is reported twice during acid perfusion and relieved by saline [14]. While the original description reported 19 of 22 patients with gastroesophageal reflux having a positive test (86 % sensitivity) and 20 of 21 controls having a negative test (95 % specificity), subsequent studies have demonstrated lower sensitivities, especially in comparison with 24-h esophageal pH monitoring as the reference standard, making for the Bernstein test to be now rarely used [13, 15, 16].

Radiographic Studies

Radiographic studies have the ability to assess for conditions predisposing to a diagnosis of GERD, underlying damage to the esophageal mucosa, as well as the actual presence of liquid reflux [14]. When compared to endoscopic findings, in a study of 266 individuals, radiographic examination was able to detect 22 % of patients with mild esophagitis, 83 % with moderate esophagitis, and 95 % with severe

esophagitis, therefore limiting the utility of a radiographic assessment simply for the diagnosis of GERD [17]. Further enhancement of the esophageal mucosal lining can be performed with a double-contrast technique, although the overall sensitivity of this test remains low [2].

Further assessment of gastroesophageal reflux can be demonstrated with the use of fluoroscopy after gastric loading of barium. In a review of three series, gastroesophageal reflux at the time of fluoroscopy had an average sensitivity of 40% and specificity of 85% [14, 18, 19]. Therefore, when present, the demonstration of reflux by fluoroscopy has specificity but lacks sensitivity for a diagnosis of GERD as defined by the presence of esophagitis [18]. When changing the reference standard to esophageal pH monitoring, the proportion of patients with a positive pH test did not differ among those with or without spontaneous reflux as demonstrated on barium study, thus limiting the use of gastric loading of barium as a screening procedure [20].

While radiographic imaging has the ability to exclude alternative diagnoses and identify for complications of chronic reflux (stricture or esophageal ulceration), many patients with GERD show no abnormalities on barium studies and therefore cannot rule out the presence of reflux disease [14].

Endoscopy

Endoscopy is the test of choice to evaluate the mucosa in patients with symptoms of GERD. Endoscopy is indicated in those who do not respond to initial therapy, when there are alarm symptoms suggesting complicated disease (dysphagia, odynophagia, bleeding, weight loss, or anemia) and when sufficient duration of disease places an individual at risk for Barrett's esophagus [1]. Cross-sectional studies of patients undergoing endoscopy have suggested that approximately 20% of patients with upper gastrointestinal symptoms have esophagitis, 20% have endoscopy-negative reflux disease, 10% have peptic ulcer disease, 2% have Barrett's esophagus, and 1% may have malignancy [5].

Findings related to a diagnosis of GERD include the presence of erosive esophagitis, peptic strictures, and a columnar-lined esophagus (Barrett's esophagus) [2]. Reflux esophagitis is present when erosions or ulcerations are present at the squamocolumnar junction (SCJ; interface between the light pink esophageal squamous mucosa and the red columnar gastric mucosa). There are many grading systems to characterize the severity of erosive esophagitis, the most common of which is the Los Angeles (LA) classification (Fig. 3.1) [21]. Given the presence of esophagitis as well as the finding of Barrett's esophagus as diagnostic of GERD, endoscopy has excellent specificity in the diagnosis of GERD with correlation to symptom severity and response to treatment [21].

However, similar to the use of radiographic studies for the diagnosis of GERD, sensitivity remains low. In a population-based study from northern Sweden using a validated questionnaire for gastroesophageal reflux symptoms, the prevalence of

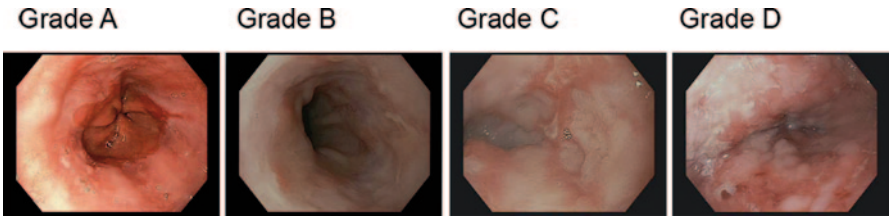

Fig. 3.1 Los Angeles (LA) classification of erosive esophagitis. *Grade A:* One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds. *Grade B:* One (or more) mucosal breaks more than 5 mm long that does not extend between the tops or two mucosal folds. *Grade C:* One (or more) mucosal break that is continuous between the *tops* of two or more mucosal folds but which involved less than 75 % of the circumference. *Grade D:* One (or more) mucosal break which involves at least 75 % of the esophageal circumference [21]

symptoms was 33.6 %. Endoscopy was performed on a random subset of the responders demonstrating mucosal breaks and erosive esophagitis in a total of 15.5 % of the sample population. Among those with gastroesophageal reflux symptoms as the reference standard, only 24.5 % had evidence of erosive esophagitis [22]. Therefore, with the recognition that 70–85 % of patients with symptoms of GERD have nonerosive reflux disease (NERD), the role of endoscopy for the detection of erosive esophagitis as the basis for the diagnosis of GERD is limited and not cost-effective [8, 23–25]. Furthermore, initial empiric diagnostic and treatment strategies for GERD limit the utility of endoscopy in the diagnosis of GERD as independent predictors for the demonstration of NERD include PPI use prior to endoscopy, the absence of nocturnal symptoms, age ≥ 60, and the absence of a hiatal hernia [26].

Although endoscopy has limited sensitivity in the diagnosis of GERD, endoscopy allows for a detailed evaluation to rule out alternative diagnoses such as eosinophilic esophagitis, infection, or pill-induced injury, as well as for sampling of rings and strictures and for screening of Barrett's esophagus [2, 6]. While screening for Barrett's remains controversial, a number of studies highlight similar risk factors associated with the presence of Barrett's esophagus to include male sex, older age (> 40 years), and prolonged duration of symptoms (> 13 years) [27–29]. Barrett's esophagus is suspected endoscopically when the pale pink squamous mucosa of the distal esophagus is replaced to various lengths with salmon-pink columnar mucosa (Fig. 3.2). In Barrett's esophagus, the SCJ is displaced proximal to the gastroesophageal junction (GEJ or Z line; defined by the proximal margin of the gastric folds), and the diagnosis is confirmed with a biopsy finding of intestinal metaplasia, which is different from normal esophageal mucosa lined by stratified squamous mucosa. Intestinal metaplasia is characterized by mucin-containing goblet cells, which can be detected by routine hematoxylin and eosin stain or accentuated with an alcian blue stain. Barrett's esophagus may be divided into short-segment Barrett's esophagus (SSBE) and long-segment Barrett's esophagus (LSBE) types according to whether the metaplasia is longer or shorter than 3 cm. It is more common to find dysplasia and cancer in a patient with LSBE, but patients with SSBE are also at increased risk.

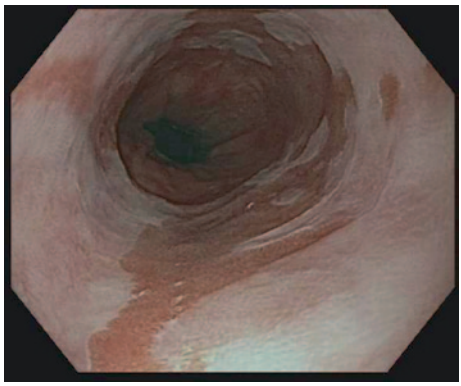

Fig. 3.2 Endoscopic appearance of long-segment Barrett's metaplasia extending proximally from the gastroesophageal junction (*salmon-pink* columnar mucosa)

Advanced endoscopic imaging techniques have been evaluated as a method of improving the sensitivity of endoscopy in the diagnosis of GERD. Narrow-band imaging (NBI) utilizes a blue/green wavelength of light to illuminate the mucosa and preferentially enhance the superficial tissue structures emphasizing features such as capillary and mucosal patterns without the use of dyes. The use of NBI has been used to improve the visualization of the SCJ and thus improving the ability to assess for erosive disease. In a prospective study of 80 patients (50 with GERD as defined by validated questionnaire, of which 30 had endoscopically erosive esophagitis), the use of NBI magnified images demonstrated that an increased number and presence of dilated intrapapillary capillary loops were the best predictors for a diagnosis of GERD with a 92 % sensitivity and 100 % specificity (when combined with the presence of microerosions). In addition, an increased number and presence of dilated intrapapillary capillary loops were able to differentiate patients with NERD compared to a control group [30]. A second study assessing the role of NBI in examination of the SCJ included 107 subjects (36 with NERD, 41 with erosive esophagitis, and 30 controls). A combination of increased vascular pattern and absence of round pit pattern was able to distinguish NERD from controls with a sensitivity of 86.1 % and specificity of 83.3 % [31]. Therefore, advanced imaging techniques may provide endoscopy with an improved sensitivity for the diagnosis of GERD.

Esophageal Biopsy

The addition of esophageal biopsies to endoscopy allows for histologic assessment in order to assess for microscopic mucosal injury, rule out alternative diagnoses such as eosinophlic esophagitis, and assess for disease complications such as the development of Barrett's esophagus or neoplasia. Early histologic studies in asymptomatic patients and in whom no reflux was demonstrated by pH studies detailed the normal histologic appearance of the esophageal mucosa characterized by dermal papillae that extended less than halfway to the free luminal margin and a basal cell

layer occupying less than 15% of the total thickness of the epithelium. Polymorphonuclear leukocytes were never found in the lamina propria, and eosinophils were uncommon. However, in those with symptomatic reflux and positive pH studies, the dermal papillae extended more than 50% of the distance to the epithelial surface and the basal cell layer accounted for more than 15% of the epithelial thickness. Polymorphonuclear cells and eosinophils were seen in the lamina propria in severe cases of esophagitis [14]. In the initial study by Ismail-Beigi, 28 of 33 patients with reflux had at least one abnormal biopsy (85% sensitivity) while 19 of 21 control subjects had normal biopsies (90% specificity) [32]. However, a subsequent study defining GERD patients based on 24-h ambulatory pH monitoring was unable to replicate the sensitivity of basal zone thickness or papillary length for the diagnosis of GERD [33].

Outside of the use of light microscopy for a diagnosis of GERD, transmission electron microscopy has been used to evaluate the dilated intercellular space (DIS) diameter. In a study of 11 patients with heartburn (6 with erosive esophagitis) and 13 controls, 8 of the 11 with heartburn and no controls demonstrated an intercellular space diameter of $\geq$2.4 μm, demonstrating a 73% sensitivity and 100% specificity as a histologic discriminator for GERD [34].

In a more recent analysis of 258 subjects with GERD diagnosed based on the presence of reflux esophagitis, abnormal distal pH monitoring or $\geq$95% symptom association probability (SAP), the presence of eosinophils, total epithelial thickness, and papillary length were significant predictors of GERD. Total epithelial thickness measured 0.5 cm above the Z line demonstrated a sensitivity of 77% and specificity of 52% for the diagnosis of GERD [24]. Furthermore, combining histologic features has the ability to improve the test characteristics of esophageal biopsy for the diagnosis of GERD as demonstrated in a study of 119 patients with GERD symptoms and 20 control patients with normal 24-h ambulatory pH monitoring in which biopsies were obtained at the Z line, 4 cm from the Z line, and 2 cm from the Z line. A combination of histologic assessment was performed for basal cell layer, length of papillae, and DIS, which were semiquantitatively scored 0–2 and combined with the presence of intraepithelial eosinophils, neutrophils, and necrosis/erosions resulting in a final histologic "reflux score." ROCs demonstrated that for a score of >2, the "reflux score" had 84% sensitivity and 85% specificity for the diagnosis of GERD [35].

The optimal use of histologic parameters in the diagnosis of GERD remains in the ability to rule out alternative diagnoses as the use of esophageal biopsy for the diagnosis of GERD is limited by interobserver variability in identifying and grading relevant features [24]. In a review of five studies, regardless of histologic criteria, esophageal biopsy for a diagnosis of GERD had an overall sensitivity of 77% and specificity of 91% [14]. Given the insensitive test characteristics of histology in the diagnosis of GERD, the routine use of biopsy of the esophagus cannot be recommended in a patient with heartburn and normal endoscopy and therefore should only be taken when other causes of esophagitis are suspected [2, 6].

Manometry

Esophageal manometry is a diagnostic test that measures intraluminal pressures and coordination of the pressure activities of the three functional regions of the esophagus: LES, esophageal body, and upper esophageal sphincter (UES). Manometry is performed with the use of either a water-infusion catheter or a solid-state catheter system. Solid-state catheters contain embedded microtransducers that directly measure the esophageal contractions. Water-perfused catheters contain several small-caliber lumens that are perfused with water from a low-compliance perfusion device. When a catheter port is occluded by an esophageal contraction, water pressure builds within the catheter, exerting a force that is conveyed to an external transducer. With either catheter system, the electrical signals from the transducers are transmitted to a computer, which produces a graphic record.

Manometry is commonly used in the assessment of patients with symptoms suggestive of esophageal motor dysfunction, such as dysphagia and noncardiac chest pain. The role of manometry in the evaluation of GERD is limited to the accurate placement of catheter-based ambulatory 24-h esophageal pH monitoring and evaluation of esophageal peristalsis prior to antireflux surgery. Patients with achalasia can present with heartburn and regurgitation mimicking a diagnosis of GERD, and achalasia is a manometric contraindication to antireflux surgery [36, 37]. Manometry may also be helpful in patients with a primary symptom of regurgitation as it can help differentiate rumination syndrome from GERD [6].

Ambulatory Reflux Monitoring

Ambulatory 24-h esophageal pH monitoring is an important tool in the diagnosis and management of GERD. Esophageal pH monitoring can detect and quantify gastroesophageal reflux and correlate symptoms temporally with reflux. The primary indications for ambulatory 24-h esophageal pH monitoring are (1) to document excessive acid reflux in patients with suspected GERD but without endoscopic esophagitis, (2) to assess reflux frequency, and (3) to assess symptom association.

Standard ambulatory 24-h esophageal pH monitoring measures distal esophageal acid exposure by using a single pH electrode catheter that is passed through the nose and positioned 5 cm above the superior margin of the manometrically determined LES. Although other techniques for electrode placement exist, such as pH step-up (rise in pH from stomach to esophagus) and endoscopic and fluoroscopic placement, they are less accurate and not standardized [38, 39]. After catheter placement, the patient is encouraged to conduct a typical day without dietary or activity limitations. Because ingestion of foods or liquids with a pH < 4.0 can mimic reflux events and produce false-positive results, acidic foods or drinks should be excluded from the analysis period or accurately noted in the pH diary [40, 41]. In using a catheter-based system, the pH is recorded every 4–6 s, and the data are transmitted

to an ambulatory data logger. Faster sampling frequencies up to 1 Hz can lead to the detection of a greater number of reflux events but do not change the overall acid exposure values [42].

Typical ambulatory esophageal pH monitoring units have an event marker that can be activated by the patient during the study to indicate the timing of symptoms, meals, and recumbent positioning. The patient also records these events on a diary card so that specific symptoms can later be correlated with the esophageal acid exposure as recorded by the pH probe. At the end of the study, data are downloaded to a computer, which generates a pH tracing and a data summary. The typical duration for clinical esophageal pH monitoring catheter-based systems is 24 h. Shorter study periods ranging from 3 to 16 h have been studied as a result of poor patient tolerance to the pH catheters; however, shorter study durations have resulted in decreased sensitivity compared to 24-h monitoring [41, 43–45].

When performing study interpretation, a reflux episode is defined when the esophageal pH drops below 4.0. This value is chosen on the basis of the proteolytic activity of pepsin, which is most active at and below this pH. Additionally, a pH value less than 4.0 best distinguishes between symptomatic patients and asymptomatic controls [46–49]. Although many scoring systems and parameters have been evaluated, the percentage of time that the pH is less than 4 is the single most important parameter to measure and is calculated in most software programs used in the analysis of pH monitoring. Results are generally considered abnormal when the total time that the pH is less than 4 exceeds 4.2 % of the study period [50,51]. Stratification by supine time and upright time is also reported by all software programs.

Although the pH software automatically calculates the total, upright, and supine reflux times, manual review of the pH tracing to exclude artifact is essential for precise interpretation. A typical reflux event involves an abrupt drop in pH. This must be distinguished from a slowly drifting pH value, which may be secondary to the probe's losing contact with the esophageal mucosa and drying out. Probe dysfunction or disconnection can result in a reading that drops to zero. In addition, some patients may sip on acidic carbonated or citrus beverages, causing prolonged periods during which pH is less than 4. These artifacts should be identified, and their corresponding time excluded from the calculation of acid exposure times.

Multiple-probe catheters have additional pH electrodes located more proximally in the esophagus or the hypopharynx. These electrodes allow for the detection of proximal esophageal and pharyngeal acid reflux events, which may be useful in the evaluation of extraesophageal GERD symptoms, particularly laryngitis, chronic cough, and asthma. The conventional location of the proximal esophageal pH probe is 15–20 cm above the LES, with a normal value for total time with pH below 4.0 being less than 1 % [52, 53]. The hypopharyngeal probe is usually placed 2 cm above the manometrically determined UES. Although normal values are not clearly defined, more than two or three episodes of hypopharyngeal reflux are considered abnormal. It is again critical to review the pH tracings to be sure that proximal esophageal or hypopharyngeal reflux events are accompanied by distal esophageal reflux and are not secondary to artifact.

Given limitations in patient tolerance to ambulatory catheter-based esophageal pH monitoring systems and difficulties with prolonged measurement periods, an ambulatory wireless capsule-based pH monitoring system has been developed (Fig. 3.3). Upon placement, a standard upper gastrointestinal endoscopy is performed to locate the GEJ. The endoscope is removed, and an introducer with an attached pH capsule probe is inserted. The introducer is advanced, and the capsule probe is placed 6 cm above the GEJ. Recording data are then transmitted to a device worn on the patients' waist. The wireless system has the advantage of recording 48–96 h of pH data. The capsule pH probe falls off after several days and is passed in the stool.

The wireless capsule-based pH monitoring system may be better tolerated, causing less interference with daily activities, and has a higher overall satisfaction rate for patients with GERD. In a randomized study of 50 patients receiving catheter-based or wireless pH monitoring, wireless capsule-based pH monitoring was associated with less nose pain, runny nose, throat pain, throat discomfort, and headache as compared with those with the traditional pH probe, whereas the wireless capsule-based pH monitoring was associated with more chest pain [54]. An additional advantage of wireless pH testing is its greater sensitivity for detecting reflux events due to (1) prolonged monitoring, (2) improved patient compliance, (3) reduced impairment of patients' daily activity, and (4) decreased likelihood of catheter movement during the study [55]. However, disadvantages of the wireless pH testing system exist including the risk of early capsule detachment. A report from two centers described early detachment in 3/85 patients at 24 h and poor data reception in 3/85 patients at 48 h, where erroneous interpretation of acid exposure time could result due to intragastric pH monitoring [55].

A number of comparison studies have been performed assessing the simultaneous capture of acid reflux using the wireless pH system and catheter-based pH monitoring [56–58]. While strong correlations were observed between acid exposure recorded, a significant offset was noted in the pH values reported by the two systems with the wireless capsule-based pH monitoring system under recording reflux events compared to the catheter-based system [56, 58, 59]. When using a reference

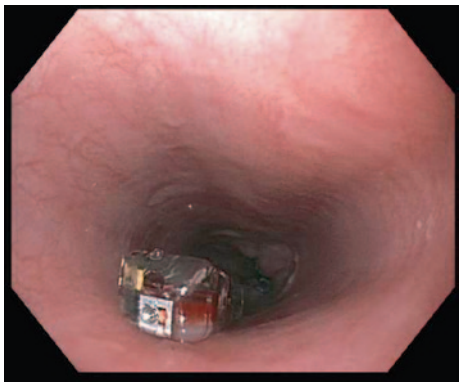

Fig. 3.3 Endoscopic appearance of the Bravo wireless pH capsule (Given Imaging, Yoqneam, Israel) attached to the esophageal mucosa after deployment

standard of swallowed orange juice measured ex vivo, differences in calibration of the catheter-based system due to a thermal calibration correction factor error in the software (which has since been corrected) accounted for differences in offset of pH values and reflux events [59]. Although the number of reflux events could only be partly explained by differences in the thermal correction factor, increased numbers of short reflux events were detected by the catheter-based system likely secondary to the lower sampling rate of the wireless capsule-based pH monitoring system [58].

The standard duration of recording for esophageal pH monitoring catheter-based systems is 24 h; however, with the introduction of wireless capsule-based pH monitoring, recording times can occur from 48 to 96 h [60]. The routine 48-h data acquired by wireless pH systems can be interpreted using an average of the 48-h collection or using only the 24-h period with the greatest acid exposure. In a study of 85 patients, 39 control subjects and 37 patients with GERD, the use of a definition of abnormal acid exposure as greater than 5.3 % of the study time, using only the 24-h period with the greatest acid exposure had 83.8 % sensitivity for a diagnosis of GERD and 84.5 % specificity compared to 67.5 % sensitivity and 89.7 % specificity when using only the first 24 h of data collection [55].

Monitoring of pH can be performed on or off medical therapy. In monitoring performed without medical therapy, patients are asked to stop PPI therapy for at least one week, histamine H2 blocker therapy for 48 h, and antacid use for 2 h [61]. Whether the study should be performed on or off acid-suppressive therapy depends on what information the clinician desires to gain. A pH study performed off therapy documents whether acid reflux is present at baseline, such as in a patient considering antireflux surgery or in those with atypical GERD symptoms in order to rule out the presence of acid reflux. A study performed in a patient on therapy documents whether continued acid reflux is the cause of refractory symptoms in patients with a poor or incomplete response to medical therapy.

One potential advantage of the ambulatory esophageal monitoring system is the ability to correlate symptoms with reflux episodes. However, even in patients with well-documented GERD, only half of symptomatic events are related to reflux episodes [62]. This observation has led to the development of several symptom scoring systems which can be calculated for individual symptoms attributed to reflux including heartburn, regurgitation, or chest pain [59]. The symptom index (SI) is defined as the percentage of symptom episodes related to reflux events defined by the number of symptoms associated with $pH < 4$ divided by the total number of symptoms during the study period [63]. Good symptom correlation is considered to be an SI over 50 % for the definition of a positive association. The second scoring system developed includes the symptom sensitivity index (SSI) in which the number of reflux events associated with symptoms is divided by the total number of reflux events during the study period [64]. The symptom-based scoring system with the greatest statistical validity is the SAP, a statistical probability calculation in which the entire pH tracing is separated into 2-min intervals and each segment is evaluated for reflux and symptom episodes; a modified chi-square test is used to calculate the probability that the observed distribution of symptoms and reflux events could have occurred by chance [65]. A SAP value of > 95 % indicates that the probability that

the observed association between reflux and symptom occurred by chance is <5% [59]. While the SAP provides information on the statistical validity of the reflux and symptom association, the SI and SSI provide information on the strength of the association [66]. Unfortunately, no clinical trials prove that the symptom-based scoring systems predict a cause-and-effect relationship and therefore should be used as complimentary information that links a particular symptom to reflux events without a defined ability to predict response to medical or surgical therapy [59].

Ambulatory 24-h Bile Monitoring

Duodenogastroesophageal reflux (DGER) refers to regurgitation of duodenal contents through the pylorus into the stomach, with subsequent reflux into the esophagus. DGER may be important because factors other than acid, namely bile and pancreatic enzymes, may play a role in mucosal injury and symptoms in patients with GERD [67–70]. Initially, esophageal pH greater than 7.0 during pH monitoring was considered a marker of such reflux, but alkaline reflux was later proved to be a poor marker for DGER. This finding led to the development of a fiberoptic spectrophotometer (Bilitec 2000, Synectics, Stockholm) that detects DGER in an ambulatory setting independent of pH [71]. This instrument utilizes the optical properties of bilirubin, the most common bile pigment. Bilirubin has a characteristic spectrophotometric absorption band at 450 nm. The basic working principle of this instrument is that absorption near this wavelength implies the presence of bilirubin and, therefore, represents DGER.

As in pH monitoring, data from the bilirubin spectrophotometer are usually measured as percentage of time that bilirubin absorbance is greater 0.14 and can be analyzed separately for total, upright, and supine periods. Percentage of time bilirubin absorbance exceeds 0.14 is commonly chosen as a cutoff because studies show that values lower than this number represent scatter owing to suspended particles and mucus present in the gastric contents [71]. In a study using 20 healthy controls, the 95th percentile values for percentage of total, upright, and supine times that bilirubin exceeded 0.14 were 1.8, 2.2, and 1.6%, respectively [72]. Several reports have indicated a good correlation between Bilitec fiberoptic spectrophotometer readings and bile acid concentration measured by duodenogastric aspiration studies [71, 73–75]. Validation studies have found that this instrument underestimates bile reflux by at least 30% in an acidic medium because of bilirubin isomerization with a shift in wavelength absorption [72]. Therefore, the instrument's measurement of DGER must always be accompanied by simultaneous measurement of esophageal acid exposure by means of prolonged pH monitoring. Furthermore, a variety of substances may result in false-positive readings by this instrument, because it indiscriminately records any substance with an absorption band around 470 nm. This fact necessitates the use of a modified diet to avoid interference and false readings [71, 75]. As the Bilitec spectrophotometer measures reflux of bilirubin and not bile

acids or pancreatic enzymes, it must be assumed that the presence of bilirubin in the refluxate is accompanied by other duodenal contents.

Development of this instrument was an important advancement in the assessment of DGER, but its clinical role is limited, and it is no longer available. While initial studies demonstrated the role of bile acids in animal models contributing to mucosal damage, further studies with this device were instrumental in showing that acid reflux and bile reflux occur together, making it difficult to incriminate duodenal contents alone as the cause of damage to the esophagus [70, 72]. Moreover, studies demonstrated a decrease in esophageal bilirubin exposure with omeprazole treatment, thereby further limiting the clinical utility of the assessment of DGER as a contributor to the development of GERD [76].

Impedance

Multichannel intraluminal impedance (MII) is a technology that measures both acid and nonacid reflux of liquid or gas consistency [77]. Impedance, a measure of the total resistance to current flow between adjacent electrodes, is capable of differentiating between liquid and gas refluxate on the basis of their inherent current and resistance properties. By incorporating multiple electrodes along the axial length of the impedance catheter, the proximal extent of the reflux event is able to be captured, as well as the differentiation of antegrade from retrograde refluxate [66]. Catheters commonly employ six or more impedance measuring segments to detect changes along variable lengths of the esophagus with placement standardly 5 cm above the LES (similar to conventional catheter-based pH testing systems) [41]. Current impedance technology has been validated against esophageal manometry studies and is sensitive for the detection of liquid boluses where drops in impedance are observed with boluses as small as 1 and 10 mL [78, 79]. The combined impedance/pH recorder is capable of also measuring characteristics of gastroesophageal reflux that are not detectable by standard ambulatory 24-h esophageal pH monitoring alone. Clinically, this approach may be useful for further evaluation of typical or atypical reflux symptoms refractory to acid suppression therapy, in assessing the role of nonacid and/or nonliquid reflux.

Although there is no doubt that MII–pH measurement is currently the most accurate and detailed method to detect reflux of all kinds, the clinical indications for its use are still evolving, and its role in the management of patients with GERD awaits further definition for two main reasons: (1) the relevance of nonacid reflux in specific clinical settings has to be further discerned and (2) there is a paucity of high-quality blinded, randomized, controlled studies examining the benefit of treating nonacid reflux.

Combining impedance with esophageal pH monitoring allows for identification of all of the parameters measured by standard pH monitoring while adding the total number of reflux events, proximal extent of reflux event, and characterization of the reflux events as acid (pH < 4) or nonacid [80]. Normal values have been established

for reflux events in healthy adults, and as with ambulatory esophageal monitoring systems, symptom-scoring systems can be applied in order to correlate symptoms with reflux episodes [81]. Based on impedance values 5 cm above the LES, the median number of reflux episodes in a 24-h period was 30 of which two thirds were acid and one third was weakly acidic [81]. Identification of reflux episodes requires manual visual interpretation as current automated impedance–pH analysis software overestimates the number of reflux episodes [41].

The role of nonacid reflux in the contribution to mucosal damage was reviewed in a prospective study of patients with GERD symptoms and healthy controls that underwent combined impedance/pH monitoring off medical therapy. Among 300 individuals with GERD symptoms, erosive esophagitis was identified in 58, Barrett's esophagus was identified in 18, and no mucosal damage was seen in 224 patients. Compared to healthy controls, those with erosive esophagitis and NERD had longer distal esophageal acid exposure time and a higher median number of acid reflux episodes. All groups had a similar median number of nonacid reflux episodes suggesting that acid reflux episodes, refluxate volume, and acid clearance are important factors in the pathogenesis of GERD, whereas nonacid reflux contributes less to esophageal mucosal damage [82].

The role of nonacid reflux in the development of symptoms was characterized in a study of 60 patients with symptoms of heartburn and regurgitation that underwent combined impedance/pH monitoring off therapy. In using 11 definitions of reflux, the proportion of patients with a positive SAP varied from 62.5 to 77.1%, and a higher proportion of patients had a positive SAP when reflux was identified using combined impedance/pH monitoring as opposed to pH monitoring alone (77.1% vs. 66.7%) detailing that nonacid reflux can contribute to symptoms. Furthermore, among symptomatic reflux events, 85% were associated with acid reflux while 15% were associated with weakly acidic reflux [83].

In order to characterize a treatment effect on reflux events, a laboratory-based study of 12 patients with symptomatic heartburn was performed, and combined impedance/pH monitoring was performed for 2 h in the right lateral decubitus position following a meal in order to promote reflux events both before and after 7 days of omeprazole therapy, 20 mg twice daily. Prior to medical therapy, 217 reflux events were recorded, of which 98 (45%) were acidic and 119 (55%) were nonacid. During treatment with omeprazole, the total number of reflux events increased to 261 while the number of acid reflux events decreased to 7 (3%) and the nonacid reflux events increased to 254 (97%). In five individuals, symptom-scoring association was studied with heartburn and acid taste more common with acid reflux events while regurgitation occurred with both acid reflux and nonacid reflux [84]. However, the clinical significance of nonacid-related regurgitation in the setting of medically treated acid reflux remains to be defined [59].

Given the lack of esophageal mucosal damage attributed to nonacid reflux and the role of nonacid reflux in the development of primarily regurgitation symptoms, the utility of combined impedance/pH monitoring has been assessed in studies performed on PPI therapy. A study including 168 patients with persistent GERD symptoms on twice daily PPI therapy demonstrated a negative SI in 52% of patients

that recorded a clinical symptom over the course of the study day suggesting that alternative factors other than acid or nonacid reflux are involved in the persistence of symptoms on PPI therapy. Additionally, of the patients with typical reflux symptoms, 11% had a positive SI for acid reflux and 31% had a positive SI for nonacid reflux. Again, the primary symptom with a positive SI for nonacid reflux was regurgitation [85]. Similarly, in a study of 79 patients off PPI therapy and 71 on PPI therapy, a positive SAP was identified for nonacid reflux among 4.1% of patients off PPI therapy and 16.7% of patients on PPI therapy indicating an increased diagnostic yield for nonacid reflux symptoms on PPI therapy. Importantly, the two most common symptoms associated with nonacid reflux remained regurgitation and cough [86].

The above studies demonstrate that combined impedance/pH monitoring has the greatest sensitivity for the identification of reflux events and for the ability to characterize the events as acid or nonacid. However, the clinical application of combined impedance/pH monitoring in patients with persistent symptoms on PPI therapy is hindered by the high rate of negative symptom scoring systems in individuals with persistent symptoms and the association of nonacid reflux events with regurgitation, which lacks evidence as a primary endpoint in therapeutic trials.

A novel minimally invasive device has been recently described as a method to diagnose chronic reflux and GERD utilizing a mucosal impedance catheter through the working channel of an upper endoscope (Fig. 3.4). In a study comparing 61 patients with erosive esophagitis, 81 with NERD, 93 without GERD, 8 with achalasia, and 15 with eosinophilic esophagitis, mucosal impedance values were significantly lower in patients with GERD or eosinophilic esophagitis compared to those without GERD or with achalasia (Fig. 3.5). Importantly, the pattern of mucosal impedance was different in those with GERD compared to those with eosinophilic esophagitis.

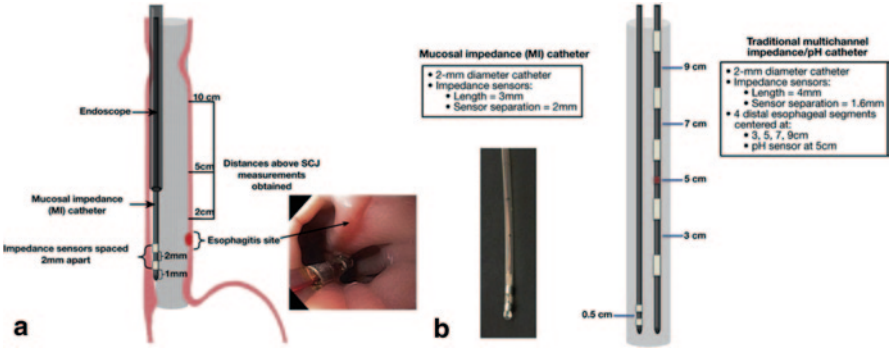

Fig. 3.4 Mucosal impedance (MI) catheter. **a** Two 2-mm long impedance sensing electrodes positioned 1 mm from the tip of a 2-mm soft catheter are advanced through an upper endoscope. Mucosal impedance measurements are obtained by direct mucosal contact of sensors at the site of esophagitis (if present) and 2, 5, and 10 cm above the squamocolumnar junction *(SCJ)*. **b** Photograph of the MI catheter *(inset)* and schematic comparison of the MI catheter to the traditional multichannel impedance pH catheter along the esophageal lumen. Measurements represent distances from the *SCJ*. (Adapted from Ref. [87], with permission from Elsevier)

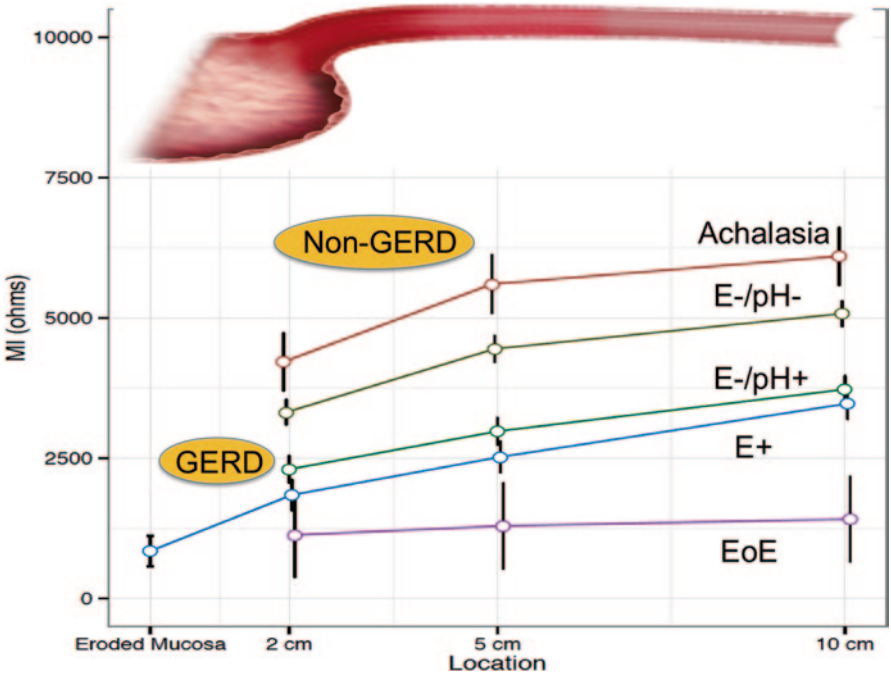

Fig. 3.5 Median (IQR) mucosal impedance values are shown in an axial distribution along the esophagus for five study groups. GERD and non-GERD patients exhibited lower MI values at the distal esophagus with a progressive increase along the esophagus, with the former group having lower MI values at all levels than the latter group. The MI pattern in EoE is distinct from GERD in showing low MI values all along the esophagus. *IQR* interquartile range, *EoE* eosinophilic esophagitis ,*GERD* gastroesophageal reflux disease, MI mucosal impedance (Adapted from Ref. [87], with permission from Elsevier)

When utilizing erosive esophagitis as a reference standard, mucosal impedance had a sensitivity of 76 % and specificity of 95 % compared to 75 and 64 %, respectively, for wireless capsule-based pH monitoring [87]. Therefore, novel minimally invasive techniques are being developed and will require further validation in the diagnosis of GERD, as well as in the performance of such techniques in patients with atypical symptoms of GERD and persistent symptoms.

Conclusion

Given the high prevalence of GERD in North America combined with the lack of a standard criterion for measuring GERD, multiple diagnostic strategies have been developed and evaluated in order to improve our ability to recognize and diagnose GERD. A number of limitations to the diagnostic methods include patient intolerance and duration and interpretation of diagnostic studies leading to inaccuracies

in the individual diagnostic methods. It is neither practical nor necessary to initiate diagnostic testing on every patient with symptoms of GERD and therefore clinical symptom-based and empiric medical therapies remain as the frontline evaluation in patients suspected to have GERD. Further testing is only required when disease complications are suspected, patients fail therapy, or the diagnosis must be confirmed due to atypical symptoms or before a change in treatment strategy is initiated [41]. Novel techniques such as advanced endoscopic imaging techniques, combined impedance/pH monitoring, and mucosal impedance will require further validation before becoming standard tools in our armamentarium for the diagnosis of GERD.

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Chapter 4
Lifestyle Modifications in GERD

Ali Akbar and Colin W. Howden

The Montreal consensus conference defined gastroesophageal reflux disease (GERD) as "a condition, which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [1]. GERD therefore constitutes the symptom complex that is related to the reflux of acidic gastric juice into the esophagus and more proximally. One of the main, physiological anti-reflux mechanisms is competence of the lower esophageal sphincter (LES). Transient LES relaxations (TLESRs) are a known underlying mechanism of reflux in GERD. Factors affecting LES relaxation can potentially ameliorate or worsen reflux and, hence, the typical GERD symptoms of heartburn and regurgitation. Similarly, body weight and intra-abdominal pressure may also play important roles. Based on this concept, various lifestyle modifications (including attention to posture, diet, and body weight among others) have been thought to be helpful in the management of symptoms related to GERD. On the basis of "fair" quality evidence, the American Gastroenterological Association (AGA) has recommended certain lifestyle modifications that can be tailored to particular patients' symptoms instead of recommending routine recommendations for all patients [2].

This chapter discusses various lifestyle modifications and assesses their impact on overall symptom control related to GERD. It is, however, important to note that these modifications, alone or in combination, are complimentary to pharmacologic therapy. Before the era of effective pharmacological treatment of GERD (as discussed elsewhere in this book), it is likely that lifestyle modifications were of greater importance in overall GERD management than they now appear. Nonetheless, patients and primary care providers often ask about adjustments to lifestyle that may help to improve symptoms. As discussed here, while many of these make sense for overall patient health, their impact on the management of GERD symptoms may be minor or absent due to the major impact that modern therapeutics has on symptom control.

C. W. Howden (✉) · A. Akbar
Divison of Gastroentrology, University of Tennessee Health Science Center,
Suite H210, Memphis, TN, USA
e-mail: chowden@uthsc.edu

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Smoking

Clearly, it is sound medical practice to recommend smoking cessation in all patients. Smoking cessation is often particularly recommended to patients with GERD, although whether this has any direct benefit to the management of their GERD symptoms—as opposed to their general well-being—has been debated for some time. Cigarette smoking has been linked to GERD symptoms. In 1972, Stanciu et al. [3] described reduced LES pressure in 25 chronic smokers (consuming 15–60 cigarettes daily) who complained of heartburn. All subjects also had reduced (i.e., more acidic) measured intraesophageal pH. Tobacco smoking also reduces salivary bicarbonate secretion, which is probably important for the neutralization of acidic gastric contents that have refluxed into the esophagus and are in contact with the esophageal mucosa [4, 5]. Impaired esophageal acid clearance, coughing, and deep inspiration are additional underlying mechanisms [6, 7]. Worsening GERD symptoms have been reported with longer duration of smoking. This was reported in a case–control study showing an odds ratio (OR) for reflux of 1.7 (95% confidence interval (CI), 1.4–2.0; $P<0.001$) in daily smokers with a tobacco use history of over 20 years as compared with those who smoked daily for less than one year [8]. In a study of 30 subjects [9], using 24-h intraesophageal pH monitoring, more reflux episodes were detected in subjects who smoked than in those who did not. However, that did not translate into a greater esophageal acid exposure time. Another study [10] (measuring reflux episodes and then correlating those with reflux symptoms) showed that smoking significantly increased the percentage time that the intraesophageal pH was <4 during a 24-h period, attributed to increased reflux events and decreased acid clearance. While smoking, the patients noted a 114% increase in daytime heartburn episodes that immediately followed an acidic reflux event identified by a fall in pH. Smit et al. [11] showed similar findings (i.e., the amount of time that intraesophageal pH was <4) in both the upper and lower esophagus (measured by dual probe pH monitoring) in smokers during periods of active smoking compared to when they were not smoking. This suggests variation in the degree of reflux related to periods of active smoking.

Despite the known effect that smoking has on LES relaxation (and hence increased esophageal acid reflux), two reviews of earlier data did not show improvement in GERD symptoms after smoking cessation [12, 13]. However, the included studies looked at very short-term effects of smoking on GERD symptoms.

More recently, a large, prospective, population-based study (the Nord-Trøndelag Health or HUNT study) [14] was conducted from 1995–1997 to 2006–2009 in Norway and the results were reported in 2014. The study included more than 29,000 individuals. The association between smoking cessation and improvement in GERD symptoms was assessed by logistic regression. Cessation of daily tobacco smoking (along with taking anti-reflux medication at least once weekly) was associated with improvement in GERD symptoms from “severe” to “no” or “minor” complaints (adjusted OR 1.78; 95% CI 1.07–2.97), when compared to persistent daily smoking. This association was particularly strong among individuals within the normal range of BMI (OR 5.67; 95% CI 1.36–23.64), but not among overweight individuals.

Therefore, there is some evidence that smoking cessation may help to alleviate GERD symptoms. This may be particularly important for non-overweight individuals when given in combination with appropriate pharmacotherapy.

Weight Loss

Obesity is a known risk factor for the development of GERD symptoms. Multiple studies in the USA, the UK, Norwegian, and Spanish populations have shown positive associations between being overweight or obese and GERD symptoms [15–19]. Furthermore, GERD symptoms tend to be worse with increasing body weight, thereby demonstrating some evidence of a "dose–response" effect. Based upon the association of obesity and GERD symptoms, it is logical to assume that GERD symptoms would improve with weight loss and consequent reduction of BMI. However, an earlier study from Sweden [20], in 20 obese GERD patients with daily symptoms despite regular daily use of anti-reflux medications found that weight reduction did not improve subjective (reflux symptoms) or objective (intraesophageal pH) manifestations of GERD. Another prospective study in GERD patients who were morbidly obese examined the effect of a liquid, low calorie diet, and vertical band gastroplasty on 24-h, ambulatory intraesophageal pH before and after surgery; it found no beneficial effect of either measure on reflux [21].

Kaltenbach et al. [13] performed a systematic review in an attempt to identify lifestyle measures that have an impact on GERD symptoms. Weight loss in the obese and elevation of head end of the bed were the only interventions resulting in improvement of intraesophageal pH profiles and symptoms.

Another systematic review published in 2009 [22] looked at various weight-reducing modalities (including dietary/lifestyle modifications and surgical procedures such as Roux-en-Y gastric bypass and vertical band gastroplasty) on symptomatic and/or objective manifestations of GERD in obese patients. Four of seven studies reported an improvement in GERD symptoms as well as pH-metry outcomes with diet/lifestyle interventions. For Roux-en-Y gastric bypass, an improvement in GERD symptoms was found in all (mainly evaluated by questionnaires). In contrast, for vertical-banded gastroplasty, no change or even an increase of GERD manifestations (measured by pH-metry and symptoms) was noted. The results for laparoscopic adjustable gastric banding were conflicting.

The impact of a structured weight loss program on GERD symptoms in overweight and obese subjects (BMI 25–39.9 kg/m^2) was assessed in a prospective cohort study [23]. BMI and waist circumference were measured at baseline and at 6 months, and all participants completed a validated reflux disease questionnaire. Mean weight loss at 6 months was 13 ± 7.7 kg. A total of 65 % had complete resolution and 15 % had partial resolution of reflux symptoms. There was a small but statistically significant correlation between percentage of body weight loss and reduction in GERD symptom scores ($r = 0.17$; $P < 0.05$).

Most recently, in a set of quality measures that are suggested for the care of GERD patients [24], eight clinical experts ranked potential measures for validity on the basis of the RAND/University of California, Los Angeles Appropriateness Methodology. They identified 24 valid GERD care quality measures (identified from literature, guidelines, and experts) related to initial diagnosis and management, monitoring, further diagnostic testing, proton pump inhibitor (PPI) refractory symptoms, symptoms of chest pain, erosive esophagitis (EE), esophageal stricture or ring, and surgical therapy of this condition. Weight loss recommendation in any obese patient with reflux symptoms was the only quality lifestyle modification with high validity.

Based on the evidence present to date, weight loss seems to improve GERD symptoms in obese and overweight individuals. This appears true whether achieved through conservative weight loss strategies or surgical management.

Head of Bed Elevation

The recumbent position has been associated with an increase in esophageal acid exposure and a worsening of GERD symptoms. Stanciu et al. [25], measured intra-esophageal pH in GERD patients when in different body positions. They reported percentage of time during which pH was below five and the number of reflux episodes. These were both significantly reduced when patients were in the head-up position than when sitting or lying. Their results suggested that elevation of the head end of the bed would improve GERD symptoms, decrease reflux episodes, and promote acid clearance. Later, another randomized crossover study by Hamilton et al. [26] compared different lying positions and their effect on esophageal pH, reflux episodes, and distal esophageal acid clearance times in 15 individuals with moderate-to-severe acid reflux symptoms. Three lying positions (flat, head elevation with 8-in. bed blocks, and head elevation by a foam wedge) were compared. The wedge caused a statistically significant decrease in the time that distal esophageal pH was less than 4 as compared to the flat position. It also decreased the longest episode experienced by the subjects. Both head elevation positions (by wedge and on blocks) showed a trend towards a decrease in acid clearance time as compared to the flat position.

In contrast to the above two studies, results of a multicenter trial [27] showed no difference in reflux scores and use of antacids after all included patients were randomly assigned to either sleeping with horizontal bedhead or having the bedhead raised by 15 cm. However, this 2-week study did not use esophageal pH monitoring and some patients were allowed use of a PPI twice a day while others were not.

More recently, a small study [28] showed that nocturnal GERD symptoms improved with elevation of the head end of the bed on a 20 cm block. Esophageal pH measurements were obtained in supine position on day 1 and then obtained on day 2 and 7 (while head end elevated). Mean supine reflux time, acid clearance time, number of reflux episodes lasting at least 5 min, and symptom score all improved.

Twenty patients completed this 7-day study and there was statistically significant improvement in all measures.

Thus, there is evidence of both objective and subjective improvement in acid reflux with bedhead elevation. However, many patients and/or their spouses or sleeping partners find this impractical and unacceptable. Despite evidence to support it, a recommendation to elevate the head end of the bed is not routinely given or followed.

Avoidance of Late-Night Meals

Nocturnal reflux symptoms have a greater impact on quality of life (QoL) compared with daytime symptoms. Both nocturnal symptoms and sleep disturbances are critical to elucidate when evaluating a patient with GERD [29]. They can improve with avoidance of late-night meals. In an older study, nocturnal intragastric pH was higher with an early dinner (6 p.m.) than with a late dinner (9 p.m.) and hence acid reflux symptoms were thought likely to improve as a result [30].

The most recent guidelines [31] for the diagnosis and management of GERD from the American College of Gastroenterology (ACG) suggested avoidance of late-night meals within 2–3 h of reclining (as well as elevation of the head end of bed) for the management of nocturnal reflux symptoms (conditional recommendation, low level of evidence).

Despite lack of substantive evidence to support it, it is common practice—and probably sensible—to advise GERD patients (particularly those with nocturnal symptoms) to avoid eating for the 2–3 h period before bedtime. This is a simple intervention that should be easily understood by patients once explained.

Breathing Exercises

Cammarota et al. [32] showed more severe GERD symptoms in a study of 351 professional opera choristers when compared to 578 age- and sex-matched non-singers. Theoretically, at least, singers who practice and concentrate on deep inspiration might be better protected against GERD symptoms since they contract their diaphragm during inspiration to allow for chest expansion (abdominal breathing). This protective effect is based on the assumption that the diaphragmatic crura contribute to the reflux protective mechanism (along with the LES). This raises the possibility that the type of breathing could play some role in the management of GERD symptoms.

In fact, Eherer et al. [33] developed a training program to raise patients' consciousness of their breathing as they learned to shift from thoracic movements to abdominal wall movements. They had excluded patients with anatomical abnormalities like large hiatal hernia or endoscopically diagnosed EE. Nineteen patients

were included in this randomized trial (ten in the breathing exercise group and nine in the control group). QoL, pH-metry, and on-demand PPI usage were assessed at baseline and after 4 weeks of training. There was a significant decrease in time with a pH < 4.0 in the training group (9.1 ± 1.3 % vs. 4.7 ± 0.9 %; $P < 0.05$) but no significant change in the control group. Similarly, QoL scores improved significantly in the training group (13.4 ± 1.98 before and 10.8 ± 1.86 after training; $P < 0.01$) but no improvement in the control group. QoL improvement and reduced use of PPI was maintained during nine months of follow-up in 11 of 19 patients who continued breathing exercises.

Thus, based on very limited evidence, there is evidence for both subjective and objective improvement following a course of breathing exercises. However, this would be difficult to implement routinely and the results of the above study may not be generalizable to the GERD population at large. Apart from highly selected subgroups of GERD patients, as indicated above, it is doubtful that this would influence routine clinical practice.

Dietary Influences

In general, dietary modifications have not been shown to have a great impact on the alleviation of GERD symptoms. There are, however, instances when selective elimination can be recommended [31].

Some non-epidemiological studies have reported that coffee causes a relaxation of the LES, which in turn can increase reflux episodes and symptoms [34, 35]. Some studies have suggested a role of caffeine in the development of GERD symptoms. In one study, involving 17 GERD patients who ingested, in a double-blinded manner, either regular or decaffeinated coffee, decaffeination was shown to decrease the amount of time that reflux occurred [36]. Wendl et al. [37] showed that regular coffee induced significantly ($P < 0.05$) more reflux compared with tap water and normal tea, which were not different from each other. Decaffeination of coffee significantly diminished reflux. Interestingly, decaffeination of tea or addition of caffeine to water did not have any effect, thereby raising the possibility that some other component(s) of coffee apart from caffeine might be responsible for promoting GERD symptoms.

However, data from a randomized, crossover study [38] involving healthy subjects and GERD patients showed that coffee had no effect on postprandial acid reflux time or on the number of reflux episodes in either group. Furthermore, coffee was noted to increase percentage reflux time in the fasting state in GERD patients but not in healthy subjects. This may suggest that avoidance of coffee ingestion while in a fasting state might be beneficial in patients with GERD.

More recently, a study of over 8000 patients from Japan [39] evaluated the effect of coffee in different upper gastrointestinal (GI) disorders including reflux esophagitis (RE) and non-erosive reflux disease (NERD). There were 994 RE patients, 1118 with NERD, and 5901 non-GERD controls. (It is unclear whether the control

subjects were age and sex matched.) Coffee consumption did not show any association with RE or NERD.

In a meta-analysis published in 2014, Kim et al. [40] specifically looked at the effect that coffee intake has on GERD. Among 15 case–control studies that were included, no significant association was found (OR 1.06; 95% CI 0.94–1.19). In a subgroup analysis, the amount of coffee intake also had no impact on GERD symptoms.

An older study has suggested that fried and spicy foods cause more GERD symptoms, although this study was uncontrolled and did not quantify the intake of dietary items [41]. Similarly, El Serag et al. conducted a cross-sectional study on 371 volunteers to elucidate the relationship between diet and GERD symptoms. They used a dietary questionnaire to estimate the amount of food intake in the previous year and then a GERD questionnaire plus upper endoscopy (performed on 164 of 371) to assess reflux severity. EE was found in 40 of 164 subjects. High fat intake was associated not only with more GERD symptoms but also with EE. This finding, however, was statistically significant only in obese individuals [42]. In another study of 58 subjects with heartburn [43], dietary cholesterol and saturated fat intake were significantly associated with increased likelihood of reflux events. Other studies have not shown an association between fat intake and reflux symptoms [44] and have concluded that it is only BMI, as opposed to dietary composition, that most influences symptoms of GERD [45].

A more recent study from Poland [46] used a questionnaire about dietary habits in 221 healthy subjects and 292 patients with GERD. Both groups had a mean BMI < 26. Patients with GERD reported more symptoms with certain foods than healthy subjects ($P < 0.001$). In the GERD group, foods that were high in fat ($P = 0.004$), fried ($P = 0.022$), sour ($P = 0.003$), or spicy ($P = 0.014$) caused more symptoms. Eating one to two meals a day, drinking peppermint tea every day, and eating one large meal in the evening were found to be risk factors for GERD on univariate logistic regression analysis. The authors actually recommended eating more frequent (at least three but up to five) and appropriately timed meals to avoid eating a large meal at a given time and hence avoid reflux symptoms. These findings have not been replicated elsewhere.

Avoidance of carbonated drinks has been suggested to improve GERD symptoms. Fass et al. [47] looked at a large cohort of patients with heartburn. More than 15,000 patients completed a questionnaire about heartburn during sleep; of these, 3806 (24.9%) reported having this symptom. On multivariate analysis, increased BMI, carbonated soft drink consumption, and use of benzodiazepines were strong predictors of nocturnal heartburn.

In conclusion, there is sparse high-quality data regarding the role of different diets and/or drinks in clinical manifestations of GERD. However, there may be some role of the timing of food intake and the volume of each meal in producing GERD symptoms.

Alcohol

Alcohol consumption has been associated with reflux through its effects on LES pressure and esophageal motility [48]. In animal studies, alcohol was noted to directly inhibit contractility of the esophagus and to decrease LES pressure and the amplitude of lower esophageal peristaltic contractions [49, 50].

Vitale et al. [51] studied the effect of alcohol on nocturnal gastroesophageal reflux in 17 healthy volunteers with or without 120 mL of Scotch whisky after the evening meal. Esophageal acid clearance in the supine position was impaired after moderate amounts of alcohol ingestion.

The relationship between ethanol and gastric acid secretion has been previously investigated with inconsistent findings. Alcoholic beverages with alcohol concentrations <5%, vol/vol can stimulate gastric acid secretion, whereas drinks with higher concentrations of alcohol (i.e., 5–40%, vol/vol) have no demonstrable stimulatory effect and may actually inhibit gastric acid output [52]. The effect of chronic alcohol consumption on gastric acid secretory capacity is not as predictable as that of acute ingestion.

In a study to look at the effect of alcohol on gastric pH, esophageal motility, and acid exposure, 14 healthy volunteers were given 360 mL of red wine or tap water during lunch or dinner in a randomized manner. All underwent ambulatory 24-h esophageal motility and esophagogastric pH monitoring. Percent reflux time—and hence esophageal acid exposure—increased during the postprandial period after wine ingestion in comparison with water. No significant changes in gastric pH or esophageal motility were noted [53].

The total amount of alcohol consumption has also been associated with GERD symptoms and RE. In a study [54] involving 463 Japanese men, heavy drinkers (>50 g ethanol/day), moderate drinkers (25–50 g ethanol/day), and light drinkers (<25 g ethanol/day) had ORs for EE of 1.99 (95% CI 1.12–3.53; $P=0.019$), 1.88 (95% CI 1.02–3.48; $P=0.044$), and 1.11 (95% CI 0.55–2.23; $P=0.769$), respectively, when compared to people who never drank alcohol. Baseline characteristics were similar between drinkers and nondrinkers except for smoking, which was more common in those who consumed alcohol (61.6 vs. 50.3%; $P=0.016$).

On the other hand, a Swedish case–control study, using data from public health surveys, involving 3153 GERD patients and more than 40,000 controls determined that alcohol consumption was not associated with any increase in the risk of GERD [55]. There was insufficient evidence to support a direct effect of alcohol abstinence on pH or GERD symptoms on a subsequent systematic review [13].

Thus, there is conflicting and inconsistent evidence for the role of alcohol in promoting GERD symptoms and the effects of alcohol avoidance on relieving GERD symptoms. In the clinical setting, attention should be focused on the identification of individuals with excessive alcohol intake. They should obviously be counseled about this aspect of their lifestyle although largely for general health reasons rather than as part of GERD management.

Medications

Many medications can unmask or worsen GERD symptoms. Calcium channel blockers, nitrates, beta-blockers, theophylline, and benzodiazepines have all been reported to worsen the symptoms of GERD through their pharmacological relaxation of the LES. The study mentioned above by Fass et al. [47], identified benzodiazepines (multivariate analysis) to be among the strong predictors of nocturnal heartburn. Similarly, anticholinergic medications (e.g., scopolamine, Ditropan, benztropine) and tricyclic antidepressants (via their anticholinergic action) can also promote LES relaxation. While these medications may be prescribed for legitimate indications, patients with GERD should be counseled about possible worsening of symptoms and appropriately monitored.

Conclusion

Many of the lifestyle modifications that have been recommended for patients with GERD are based on common sense and sound medical practice. It is appropriate to recommend smoking cessation, a sensible diet, appropriate weight reduction in the overweight and obese, and avoidance of excess alcohol consumption to all of our patients. This is as true for GERD patients as it is for any others. The evidence that these reasonable and appropriate measures make a substantive impact on GERD management is far less clear. They should be offered as part of routine health promotion regardless of a patient's primary diagnosis. For GERD patients in particular, sensible weight reduction in the overweight and obese, avoidance of eating before bedtime, and consideration of bedhead elevation appear to be the most likely to be associated with subjective or objective improvement. However, given the proven effectiveness of medicines for GERD, the availability of surgical anti-reflux procedures for carefully selected patients and—possibly—the advent of newer endoscopic approaches to the condition, lifestyle modifications are likely to continue to play only a minor role in the management of this highly prevalent and troubling condition.

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Chapter 5
Role of H_2RA and Proton Pump Inhibitor Therapy in Treating Reflux Disease

John W. Jacobs, Jr. and Joel E. Richter

The retrograde passage of gastric contents into the esophageal lumen occurs as a normal physiologic event. It is only when this process leads to the development of symptoms or complications that it is labeled gastroesophageal reflux disease (GERD). Heartburn and regurgitation are the most typical symptoms of GERD. Contributing factors to the development of these symptoms include anti-reflux barriers, luminal acid clearance, acidity of the refluxed contents, and gastric emptying. Optimal medical therapy therefore would target lower esophageal sphincter (LES) pressure, facilitate esophageal lumen acid clearance, increase esophageal mucosal resistance to the effect of acid, augment gastric emptying, and limit transient LES relaxations (TLESRs). Given that such perfect therapy does not exist, treatment must be tailored to each individual patient to obtain maximum benefits.

Some GERD patients respond to "as needed" strategies of medication, but the course of GERD is variable and many patients will require longer term medical therapy. The two mainstay medical interventions in GERD are H_2-receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs). Clinicians often use these medications alone, or in combination, to achieve symptom relief and to heal esophagitis. In this chapter, we review these two drug classes, explain their mechanisms of action, discuss a typical approach to treatment, and explore their use in unique clinical situations, specifically the patient with nonerosive reflux disease (NERD), Barrett's esophagus, peptic stricutres, extraesophageal symptoms, and the pregnant patient. Lastly, we address both the potential side effects of these medications, along with the ongoing, increasingly publicized concern regarding the long term use of PPIs.

J. E. Richter, Jr. (✉) · J. W. Jacobs
Department of Internal Medicine, Division of Digestive Diseases and Nutrition, Joy McCann Culverhouse Swallowing Center, University of South Florida Morsani College of Medicine, 12901 Bruce B. Downs Blvd., MDC 72, 33612 Tampa, FL, USA
e-mail: jrichte1@health.usf.edu

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Acid Production

H_2RAs and PPIs comprise the two classes of acid suppressive medications that are most commonly prescribed to GERD patients today. To understand these two classes and their respective mechanisms of action, we first review the mechanism of gastric acid production.

Gastric acid is composed of hydrochloric acid (HCl), potassium chloride (KCl), and sodium chloride (NaCl). The stomach produces approximately 2 L of gastric acid per day, and its production has traditionally been divided into three interrelated phases. The first, the cephalic phase, is activated by the thought, smell, sight, and taste of food. The brain processes these stimuli and stimulates gastric acid production predominantly via the vagus nerve. The majority of gastric acid is produced during the second phase, the gastric phase, when food present in the stomach distends the gastric wall, activating mechanoreceptors. This, in turn, triggers a neural reflex to secrete gastric acid. Throughout this phase, amino acids and peptides in food further stimulate acid secretion. The third phase, the intestinal phase, occurs when chyme enters the small intestine. Small-bowel distension and amino acids stimulate negative feedback mechanisms that decrease further acid secretion.

Gastric acid production is a closely regulated process involving four principle cells: parietal cells, gastrin-expressing cells (G cells), enterochromaffin-like cells, and somatostatin-secreting D cells. Primarily located in the gastric fundus, parietal cells are responsible for secreting gastric acid. During the cephalic phase, the vagus nerve releases acetylcholine. Upon ingesting a meal during the gastric phase, G cells in the gastric antrum release gastrin into the blood. Both acetylcholine and gastrin stimulate parietal cells to secrete acid. In addition, both ligands also stimulate enterochromaffin-like (ECL) cells, which are located in close proximity to the parietal cells. Upon activation, ECL cells degranulate and release histamine, which promptly binds to its receptor on the nearby parietal cell. Histamine is the principle paracrine stimulator of gastric acid secretion.

Parietal cells contain secretory canaliculi from which HCl is secreted into the apical lumen of the stomach via H^+/K^+-ATPase, which is known as the "proton pump." When the parietal cell is not stimulated, the H^+/K^+-ATPases are located within vesicles inside the cell. Once the parietal cell is stimulated, intracellular levels of calcium and cyclic adenosine 3′, 5′ monophosphate (cAMP) increase, activating the proton pump, transporting it to the plasma membrane, and fusing the vesicles with the secretory canaliculi at the apical surface. The H^+/K^+-ATPase then exchanges H^+ for a K^+ ion against a steep concentration gradient. This is the final step of gastric acid secretion. A model of a parietal cell is seen in Fig. 5.1 [1].

Inhibition of either of the acetylcholine, histamine, or gastrin receptors will decrease acid production to a degree. Importantly, inhibition of the H^+/K^+-ATPase enzyme acts upon the final common pathway, and is the reason for the selective superiority of PPIs. However, by interfering at different points along the pathway of acid secretion, both H_2RAs and PPIs inhibit gastric acid secretion and raise intragastric pH levels.

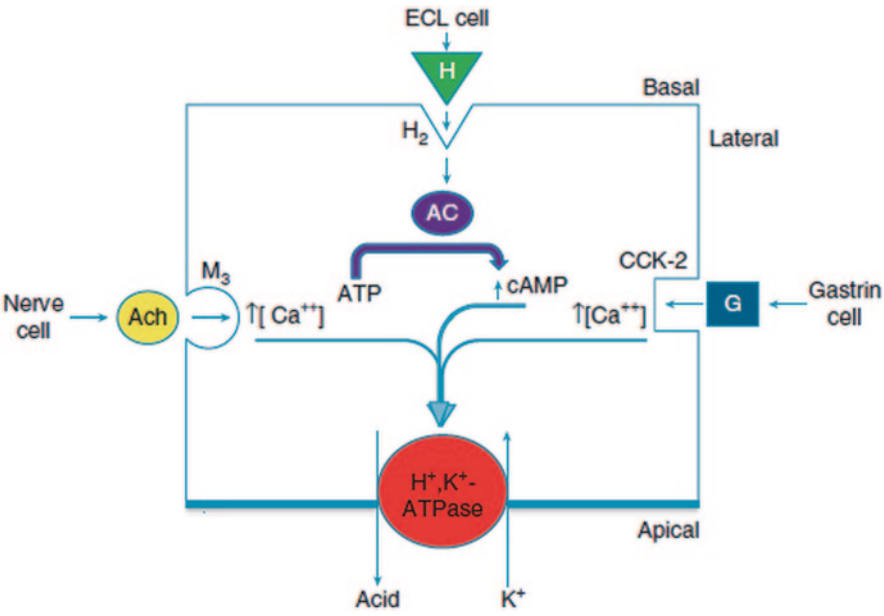

Fig. 5.1 Model of a parietal cell showing stimulatory receptors on its basal–lateral plasma membrane and their second messengers. *AC* adenylate cyclase, *Ach* acetylcholine, Ca^{2+} calcium ion, *cAMP* cyclic adenosine monophosphate, *CCK* cholecystokinin, *ECL* enterochrommafin like, *G* gastrin, *H* histamine, H^+, K^+-*ATPase* hydrogen, potassium-ATPase (proton pump), *M* muscarinic. (Reprinted by permission from Macmillan Publishers Ltd.: Feldman MJ 2013)

H_2-Receptor Antagonists

Prior to the development of PPIs, H_2RAs were the primary class of medication prescribed for treating GERD. There are four H_2RAs currently available on the market: cimetidine, famotidine, nizatidine, and ranitidine (Table 5.1) [2–5]. The first medication, cimetidine, was developed in the 1960s, first marketed in 1976 and became one of the first "blockbuster drugs." H_2RAs became available as over-the-counter (OTC) medications in 1995 and are still widely used today, especially in patients who are not able to take PPIs or in patients who take it in combination with PPI therapy. As a class of medication, H_2RAs competitively antagonize histamine at the level of the parietal cell's H_2 receptor, and their effectiveness comes as a sole result of inhibiting acid secretion. They do not effect LES pressure, decrease TLESRs, or augment either esophageal or gastric emptying. In general, the efficacy of gastric acid inhibition is best at night, when the medication is taken before dinner or at bedtime.

Among patients on H_2RA therapy, symptom relief and endoscopic improvement of esophagitis varies significantly, ranging from 32 to 82% and 0 to 82%, respectively [6]. One review showed that complete healing was seen endoscopically in only 27–45% of patients, and this was primarily in those patients with milder

Table 5.1 Currently available H_2RAs

Generic name	Brand name	Oral dosage strengths	Half-life (h)	Cost[a]
Cimetidine [2]	Tagamet	Tablets: 200 and 400 mg	2	Strength: 200 mg Quantity: 30 tablets OTC cost: US$ 13.99
Famotidine [3]	Pepcid	Tablets: 10, 20, and 40 mg Oral solution: 40 mg/5 mL	2.5–3.5	Strength: 20 mg Quantity: 25 tablets OTC Cost: US$ 12.99
Nizatidine [4]	Axid	Capsules: 150 and 300 mg Oral solution: 15 mg/mL	1–2	Strength: 150 mg Quantity: 30 tablets Cost: US$ 69.99
Ranitidine [5]	Zantac	Tablets: 75, 150, and 300 mg Oral solution: 15 mg/mL	2.5–3	Strength: 75 mg Quantity: 30 tablets OTC cost: US$ 10.99

OTC over the counter

[a] Cash price to purchase this medication at Walgreens, Tampa, Florida on March 31, 2015

degrees of esophagitis [7]. Increasing the strength or the frequency of H_2RA dosing up to two to four times per day may increase esophageal mucosal healing. One large study of 696 patients with GERD showed that ranitidine 150 mg four times per day produced significantly higher mucosal healing rates at 12 weeks than ranitidine 150 mg twice per day or cimetidine 800 mg twice per day (77 vs. 71 and 68 %, respectively) [8]. In another study of 474 patients with erosive esophagitis comparing famotidine 20 mg twice per day versus 40 mg twice per day, relief of symptoms was significant in all patients at 6 and 12 weeks, but did not differ between treatment groups. Endoscopic healing was significantly better in the famotidine 40 mg twice per day group compared with 20 mg twice per day at both week 6 (58 vs. 43 %) and week 12 (76 vs. 67 %) [9]. Overall, the wide variability in the literature, especially with regard to symptom and endoscopic improvement, is likely due to inconsistency in symptom end points and variability in interpreting endoscopic baselines.

Side Effects

As a drug class, H_2RAs are well tolerated, have few side effects, and are generally safe to use. The most common side effects are gastrointestinal, including nausea, vomiting, abdominal pain or bloating, diarrhea, and constipation. Other side effects include headaches, dizziness, and rashes. H_2RAs are metabolized through the liver cytochrome P450 pathway. This raises the possibility of drug–drug interactions, especially with other agents that are also metabolized through the same pathway. This is particularly the case with cimetidine, the first H_2RA. Serum concentrations of several drugs are altered following administration of cimetidine including warfarin, theophylline, phenytoin, lidocaine, procainamide, tramadol, and beta-blockers. Ci-

metidine is also a competitive antagonist of the dihydrotestosterone (DHT) receptor. This was shown to lead to galactorrhea in women and gynecomastia in men. The more recently developed H_2RAs are not as potent inhibitors of the cytochrome P450 pathway and appear less likely to significantly alter the metabolism of other agents. It does not appear that H_2RAs affect the serum concentration of clopidogrel.

Proton Pump Inhibitors (PPIs)

PPIs are the most widely used class of medications for treating patients with GERD and are the most effective agents. There are currently seven PPIs available on the market (Table 5.2) [10–16]. Five are delayed release medications: omeprazole, esomeprazole, pantoprazole, lansoprazole, and rebeprazole. Another is omeprazole immediate release-sodium bicarbonate, which is a combination of non-enteric-coated omeprazole with sodium bicarbonate (OME-IR). The last is dexlansoprazole, which is the R-enantiomer of lansoprazole and utilizes a dual-release technology with two types of enteric-coated granules that dissolve at different pHs. This drug first dissolves in the duodenum and produces a peak plasma level approximately 1 h after administration. The second component dissolves in the distal small intestine and produces a second peak approximately 4 h later [17]. Four PPIs are available OTC: omeprazole, omeprazole with sodium bicarbonate, esomeprazole, and lansoprazole.

PPIs are all highly selective and concentrate in the strongly acidic environment of the secretory canaliculi of the parietal cells. Once the PPI is present in the acidic environment, the inactive benzimidazole converts to a cationic sulfonamide, which then binds to the H^+/K^+-ATPase preventing gastric acid production [18, 19]. However, it is important to recognize that gastric acid inhibition following PPI administration is delayed because these drugs need time to build up in the secretory canaliculi and inhibit the H^+/K^+-ATPases. Therefore, to achieve maximal effect, it is recommended to take PPIs 30 min before the first meal of the day, and not with the meal. Given that PPIs bind to H^+/K^+-ATPases irreversibly, new proton pump enzymes must be produced for gastric acid secretion to continue. PPIs block approximately 70–80 % of active pumps, as new H^+/K^+-ATPases are continuously being produced. As a result, a single dose of a PPI does not prevent all acid secretion. When a PPI is taken twice daily, more H^+/K^+-ATPases become irreversibly bound to the drug, thus the effect on gastric acid inhibition is potentiated. Given the dual-release technology of dexlansoprazole, medication administration prior to meals is not as necessary as with the delayed-release PPIs.

pH Control

PPIs demonstrate superior pH control over H_2RAs over a 24-h period. While omeprazole, OME-IR, rabeprazole, pantoprazole, and lansoprazole all provide a

Table 5.2 Currently available PPIs

Generic name	Brand name	Oral dosage strengths	Half-life (h)	Cost[a]
Over the counter (OTC)				
Omeprazole [10]	Prilosec	Delayed-release capsules: 10, 20, and 40 mg Delayed-release oral suspension: 2.5 mg, 10 mg	0.5–1	Strength: 20 mg Quantity: 28 tablets OTC cost: US$ 21.99
Omeprazole and Sodium bicarbonate [11]	Zegerid	Capsules: 20 mg omeprazole and 1100 mg sodium bicarbonate 40 mg omeprazole and 1100 mg sodium bicarbonate Powder for oral suspension: 20 mg omeprazole and 1680 mg sodium bicarbonate 40 mg omeprazole and 1680 mg sodium bicarbonate	1	Strength: 20/1100 mg Quantity: 14 capsules OTC cost: US$ 12.99
Esomeprazole magnesium [12]	Nexium	Delayed-release capsules: 20 and 40 mg Delayed-release oral suspension: 2.5, 5, 10, 20, and 40 mg	1–1.5	Strength: 20 mg Quantity: 28 capsules OTC cost: US$ 21.99
Lansoprazole [13]	Prevacid	Capsules and tablets: 15 and 30 mg	1.5	Strength: 15 mg Quantity: 28 tablets OTC cost: US$ 21.99
Prescription medications				
Rebeprazole sodium [14]	Aciphex	Delayed-release tablets: 20 mg Delayed-release capsules: 5 and 10 mg	1–2	Strength: 20 mg Quantity: 30 tablets Cost: US$ 306.99
Pantoprazole sodium [15]	Protonix	Delayed-release tablets: 20 and 40 mg Delayed-release oral suspension: 40 mg	1	Strength: 20 mg Quantity: 30 tablets Cost: US$ 119.99
Dexlansoprazole [16]	Dexilant	Delayed-release capsules: 30 and 60 mg	First Peak at 1–2 Second Peak at 4–5 T1/2 = 1–2	Strength: 30 mg Quantity: 30 tablets Cost: US$ 264.99

[a] Cash price to purchase this medication at Walgreens, Tampa, Florida on March 31, 2015

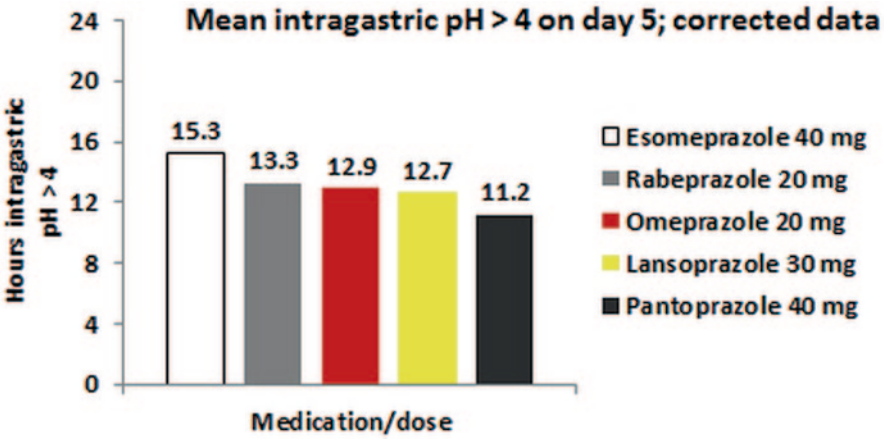

Fig. 5.2 Percentage time intragastric pH above 4 for five delayed-release proton pump inhibitors given once daily before breakfast. (Adapted with permission from Richter JE, Castell D 2012)

similar degree of intragastric pH control (11–13 h with pH > 4), esomeprazole at 40 mg daily dosing does provide a slightly longer duration of control (Fig. 5.2) [20, 21]. The newest PPI, dual-release dexlansoprazole, has been shown to maintain pH > 4 for up to 17 h with once-daily administration [16].

Healing of Erosive Esophagitis and Control of Symptoms

While PPIs may not lead to complete symptom relief in all patients, they are superior to H_2RAs in their capacity to improve symptoms [22]. In addition, compared with H_2RAs, PPIs have shown superior healing rates in patients with erosive esophagitis [23]. A large meta-analysis of 43 articles in 1997 showed superior healing of all grades of erosive esophagitis and heartburn relief when using PPIs, as compared with H_2RAs, sucralfate, or placebo [22]. The mean overall healing percentage irrespective of drug dose or treatment duration (≤12 weeks) was the highest with PPIs (83.6 ± 11.4 %) versus H_2RAs (51.9 ± 17.1 %), sucralfate (39.2 ± 22.4 %), or placebo (28.2 ± 15.6 %). The mean heartburn-free proportion of patients was highest with PPIs (77.4 ± 10.4 %) versus H_2RAs (47.6 ± 15.5 %), and PPIs showed a significantly faster healing rate (11.7 %/week) versus H_2RAs (5.9 %/week) and placebo (2.9 %/week).

While all PPIs have similar healing rates of erosive esophagitis after 8 weeks of treatment, esomeprazole 40 mg has shown a small advantage when compared with omeprazole 20 mg, pantoprazole 40 mg, and lansoprazole 30 mg [24–26]. Esomeprazole's advantage is mostly seen with LA grades C and D esophagitis. Another large meta-analysis in 2006 compared rates of esophagitis healing and symptom relief with esomeprazole versus alternative PPIs (except OME-IR and dexlansoprazole) [27]. The analysis included 10 studies and 15,136 patients. At 8 weeks, there

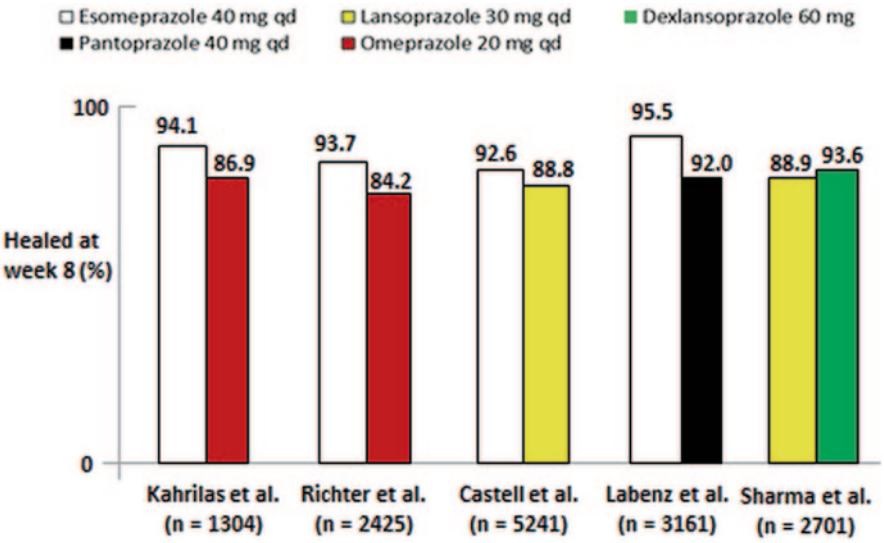

Fig. 5.3 Healing of erosive esophagitis at 8 weeks with various delayed-release proton pump inhibitors. (Adapted with permission from Richter JE, Castell D 2012)

was a 5% (relative risk, RR, 1.05; 95% CI 1.02–1.08) relative increase in the probability of erosive esophagitis healing with esomeprazole, which led to an absolute risk reduction of 4% and a number needed to treat (NNT) of 25. The calculated NNTs by LA grades A through D were 50, 33, 14, and 8, respectively. Esomeprazole also led to an 8% (RR, 1.08; 95% CI 1.05–1.11) relative increase in the probability of GERD symptom relief at 4 weeks.

In a comparative trial of dexlansoprazole 60 or 90 mg daily with lansoprazole 30 mg daily for 8 weeks, dexlansoprazole achieved non-inferiority to lansoprazole [28]. Dexlansoprazole achieved healing rates of 92–95% of patients in individual studies versus 86–92% for lansoprazole, but the difference was not statistically significant ($p > 0.025$). However, in an integrated analysis of healing in patients with moderate-to-severe erosive esophagitis (LA grades C and D), dexlansoprazole was superior to lansoprazole at healing severe disease. Figure 5.3 shows a summary of healing rates at 8 weeks among various PPIs [21, 24–26, 28, 29].

General Treatment Approach

Most delayed-release PPIs are taken once daily and administered in the morning. With its dual-release technology, dexlansoprazole is approved for dosing without regard to the timing of food intake. The rationale behind morning dosing for delayed-release PPIs stems from an intragastric pH study which assessed the effects of different dosing schedules on pH [30]. This crossover study treated 21 healthy patients with either omeprazole 20 mg or lansoprazole 30 mg daily for 7 days, with

the dose given 15–30 min before breakfast, and also on an empty stomach without any food until lunch. Intragastric pH was monitored from 8:00 a.m. to 4:00 p.m. to determine the percentage time gastric pH was below 4.0. Administering the PPI before breakfast led to significantly improved daytime intragastric pH control compared to taking the PPI on an empty stomach and then not eating for several hours. Backed by this data, along with clinical experience, we suggest that PPIs should be taken 30 min before a meal, ideally breakfast, and that this once-daily dosing regimen leads to improvement in symptoms in the majority of patients.

While once-daily PPI dosing is usually very effective, some patients require an increase in dosage, usually given just before the evening meal. This may be due to the presence of persistent GERD symptoms, Barrett's esophagus, or extraesophageal symptoms. When this is the case, increasing the PPI to twice daily does lead to increased pH control. Maintenance PPI therapy should be considered in patients who have recurrent GERD symptoms once a PPI is discontinued, and in patients with complications such as erosive esophagitis or Barrett's esophagus [31]. When patients require long-term PPI therapy, the medication should be taken at the lowest effective dose.

Switching a patient from one PPI to another PPI is very common in clinical practice. However, there is very little data to support this approach. One multicenter, randomized, double-blind trial evaluated patients with persistent heartburn while on lansoprazole 30 mg daily [32]. Patients were randomized to 8 weeks of lansoprazole 30 mg twice daily or esomperazole 40 mg daily. The primary end point was the percentage of heartburn-free days from day 8 to the end of treatment. The data showed that both treatment arms were equally effective for heartburn-free days (55% esomeprazole vs. 58% lansoprazole), symptom score improvement (for heartburn, acid regurgitation, and epigastric pain), and rescue antacid use (0.4 tablets/day in the esomeprazole group vs. 0.5 tablets/day in the lansoprazole group). The authors concluded that switching to a different PPI was just as effective as increasing patients' PPI to twice daily. Currently, there is not any data that supports switching to a different PPI more than once.

Nocturnal Reflux

Many GERD patients suffer from nocturnal symptoms, which is likely an underappreciated problem. While sleeping, the body's natural defense mechanisms against GERD, such as saliva production and peristalsis, are significantly reduced. Nocturnal reflux can significantly impact quality of life and lead to sleep disturbances. Critical to symptom control is maintaining a gastric pH > 4. However, intragastric pH monitoring studies show that despite being on twice-daily PPI therapy, overnight pH can drop to less than 4 for over an hour [33]. This is called nocturnal acid breakthrough (NAB).

Patients with NAB have several treatment options: (1) single-dose PPI can be administered before the evening meal, (2) patients can be placed on a PPI before breakfast and OME-IR or an H_2RA at bedtime, or (3) patients can be placed on

twice-daily PPI plus an H_2RA at bedtime. One study of 49 patients found that bedtime administration of OME-IR had superior overnight intragastric pH control compared with lansoprazole and esomeprazole [34]. H_2RAs are used most commonly to optimize overnight pH control when given at bedtime as an adjunct to PPI therapy. One small study of 12 volunteers found that omeprazole 20 mg twice daily plus ranitidine (150 mg or 300 mg) at bedtime provided superior overnight pH control compared with omeprazole 20 mg twice daily plus an additional omeprazole dose at bedtime [35]. Another study of 105 GERD patients on PPI twice daily (60 patients) or PPI twice daily plus an H_2RA at bedtime (45 patients) showed that the median percentage time that gastric pH remained >4 was 51% in the twice-daily PPI group compared with 96% in the twice-daily PPI plus bedtime H_2RA group [36]. This contrasts with another study of 22 patients (13 with GERD and 9 controls) which evaluated pH control after each of four treatment regimens: (1) omeprazole 20 mg twice daily for 2 weeks, (2) omeprazole 20 mg twice daily plus ranitidine 300 mg at bedtime for 4 weeks, (3) omeprazole 20 mg before breakfast and at bedtime for 2 weeks, and (4) omeprazole 20 mg every 8 h for 2 weeks [37]. Results showed that the treatment regimens resulted in NAB elimination in 9–41% of patients. However, no single treatment regimen resulted in more significant NAB control than the others and there were not any differences in percentage time that pH was <4 for any treatment regimen.

There is concern over H_2RA tolerance, that is, the potential that H_2RAs may lose their effect following prolonged use. One study of 20 GERD patients and 23 healthy volunteers obtained baseline pH testing and then administered 2 weeks of omeprazole 20 mg twice daily before meals [38]. pH testing was then repeated. Subjects next received 4 weeks of PPI plus ranitidine 300 mg at bedtime, and pH testing was obtained on days 1, 7, and 28. Results showed that combination PPI and H_2RA therapy reduced NAB only with the introduction of therapy. No difference in acid suppression between the twice-daily PPI and twice-daily PPI plus H_2RA groups was seen following 1 week of combination therapy. In the majority of patients following 1 month of H_2RA therapy, gastric acidity returned to pre-H_2RA levels.

While many patients may develop tolerance to H_2RAs, clinical experience has shown that some patients have a sustained response. The most recent American College of Gastroenterology (ACG) guidelines state that a bedtime H_2RA can be added to daytime PPI therapy in patients with evidence of nighttime reflux [31]. To reduce the chance of drug tolerance, as-needed use of an H_2RA at night might be more practical if the patient eats late or has an unusually large evening meal.

Special Clinical Situations

Nonerosive Reflux Disease

The majority of GERD patients have a normal endoscopy and, therefore, NERD. Among patients who experience symptoms of heartburn with NERD, PPI therapy has been shown to be superior to H_2RAs and prokinetics. In a large Cochrane

systematic review of 32 trials, the RR for heartburn remission in placebo-controlled trials for PPIs was 0.37 (two trials, 95% CI 0.32–0.44), for H_2RAs was 0.77 (two trials, 95% CI 0.6–0.99), and for prokinetics was 0.86 (one trial, 95% CI 0.73–1.01) [39]. In a direct comparison of PPIs and H_2RAs, PPIs were more effective at achieving heartburn remission (seven trials, RR 0.66, 95% CI 0.6–0.73). In the treatment of endoscopy-negative reflux disease, the RR for heartburn remission for PPI versus placebo was 0.71 (ten trials, 95% CI 0.65–0.78) and for H_2RA versus placebo was 0.84 (two trials, 95% CI 0.74–0.95). The RR for PPI versus H_2RA was 0.78 (three trials, 95% CI 0.62–0.97). The authors' conclusion was that PPIs are more effective than H_2RAs in relieving heartburn in patients with endoscopy-negative reflux disease, although the magnitude of benefit was greater for those treated empirically [39].

Interestingly, however, early studies have also shown that patients with NERD may not respond as well to PPIs as patients with erosive disease. One study compared omeprazole 10 or 20 mg once daily with placebo in patients with heartburn, but without endoscopic signs of esophagitis [40]. Following 4 weeks of treatment, only 46 and 31% of patients in the 20 and 10 mg groups, respectively, reported complete absence of heartburn, while 13% in the placebo arm reported absence of heartburn. While superior to placebo, the rate of symptomatic relief was lower than reported in most erosive esophagitis trials. A second study of 209 patients comparing omeprazole 20 mg daily to placebo found similar results [41]. Following 4 weeks of treatment, only 43% of patients were completely asymptomatic from heartburn and regurgitation, again a lower rate than most erosive esophagitis trials. Another study compared a 4-week trial of omeprazole 20 mg and 10 mg once daily in 277 patients with erosive esophagitis and 261 patients without erosive esophagitis [42]. Only 29% of patients with nonerosive disease reported complete symptom relief on omeprazole 20 mg at 4 weeks, while 48% of patients with erosive esophagitis reported relief.

Later studies with esomeprazole and lansoprazole do show higher rates of symptom improvement as compared with earlier studies [43, 44]. However, clinical experience has shown that patients with NERD can be difficult to manage overall, often because symptom response to PPIs is variable. In the subset of NERD patients who do not have an adequate response to PPI therapy, pH and esophageal function testing should be considered.

Barrett's Esophagus and Peptic Strictures

Barrett's esophagus and peptic strictures are well-known complications of long-standing GERD. Metaplastic columnar cells replace healthy epithelium as a result of continued exposure to the acid refluxate. Clinical studies have shown a decreased risk for the development of dysplasia in patients on PPI therapy. One study of 236 veteran patients found that over 1170 patient-years of follow-up, the incidence of dysplasia was significantly lower in those patients placed on PPI therapy following their diagnosis of Barrett's than in those patients who either took an H_2RA or no therapy [45]. PPI use was independently associated with a decreased risk

of dysplasia. A recently published study of 1830 Barrett's patients found that PPI use was associated with a lower risk of progression to any grade of dysplasia or esophageal carcinoma [46]. The current ACG guidelines state that maintenance PPI therapy should be given to patients with Barrett's esophagus [31].

Peptic stricture formation is due to chronic, reflux-induced inflammation that leads to collagen deposition. It occurs in up to a quarter of patients with untreated severe GERD [47]. Clinical reports over the past 20 years find that the number of reflux-induced peptic strictures is decreasing with the widespread availability of PPIs. In addition, studies have shown that PPI therapy in patients with peptic strictures can decrease the need for esophageal dilation [48]. While the use of PPIs in peptic strictures was not addressed in the 2013 ACG guidelines, we believe all patients with peptic strictures need maintenance PPI therapy.

Extraesophageal Disease

While heartburn and regurgitation are the predominant symptoms of GERD, the clinical spectrum of symptoms may involve an array of extraesophageal complaints, such as pulmonary or laryngeal symptoms. However, physicians must be mindful of the fact that one cannot infer causality, as extraesophageal symptoms are often multifactorial in etiology. Studies have shown that GERD may contribute to over 20% of cases of chronic cough [49] and a large VA study found increased odds ratios (OR) for pharyngitis (OR 1.48, 95% CI 1.15–1.89), aphonia (OR 1.81, 95% CI 1.18–2.80), and chronic laryngitis (OR 2.01, 95% CI 1.53–2.63) in patients with esophagitis or esophageal stricture [50]. The Montreal Consensus also recognized the possible associations between GERD and asthma, chronic cough, and laryngitis [51]. However, all patients with these symptoms need to be carefully evaluated and individual patients may need pH testing to objectively identify the role of GERD as a contributing factor.

PPIs, usually in BID dose regimens have been extensively studied in patients with extraesophageal symptoms. One randomized, double-blind trial compared omeprazole 40 mg twice daily to placebo for 3 months, showing a reduction in nocturnal cough while on omeprazole [52]. However, a large meta-analysis of nine randomized controlled trials comparing PPI to placebo, found no overall significant difference between treatment and placebo in total resolution of cough, although sensitivity analysis did show improvement in cough scores in those patients on PPI therapy [53]. Another large meta-analysis of eight randomized controlled trials comparing PPI to placebo in the treatment of suspected GERD-related chronic laryngitis found that PPI therapy led to a nonsignificant reduction in symptoms compared to placebo (RR 1.28, 95% CI 0.94–1.74) [54].

One 26-week randomized, double-blind, placebo-controlled study of 828 patients with moderate-to-severe asthma and symptomatic GERD found that esomeprazole 40 mg daily improved pulmonary function and asthma-related quality of life, but the improvements were minor [55]. A large meta-analysis of 11 trials comprising 2524 patients showed that PPI therapy in adults with asthma led to statistically

significant improvement in peak expiratory flow rate [56]. However, the improvement was small and was not felt to be clinically significant.

Many patients with unexplained chest pain have GERD as a possible contributing factor and numerous studies support PPI use in GERD-related noncardiac chest pain. One large meta-analysis of eight studies comparing PPI therapy (omeprazole, lansoprazole, or rebeprazole) with placebo found that PPIs reduce symptoms of noncardiac chest pain and may be useful as a diagnostic test in identifying reflux [57]. The pooled risk ratio for persistent pain following PPI therapy was 0.54 (95% CI 0.41–0.71) and the overall NNT was three (95% CI 2–4). The pooled sensitivity, specificity, and diagnostic OR for the PPI test versus 24-h pH monitoring and endoscopy were 80%, 74%, and 13.83%, respectively. Empiric PPI treatment is also a less expensive initial approach before upper endoscopy and pH testing.

In clinical practice, PPIs benefit some patients with chronic cough, laryngitis, asthma, and atypical chest pain, especially those with marked heartburn, acid regurgitation, and esophagitis on endoscopy. While extraesophageal symptoms usually are multifactorial, PPIs can improve the GERD component contributing to the overall complaint. However, whether or not PPIs will lead to complete resolution of symptoms is not predictable. In patients not responding to 3 months of PPI therapy, once or twice daily, or who do not have concomitant typical GERD symptoms, we recommend pH testing and further evaluation for non-GERD etiologies of their symptoms.

Pregnancy

Many pregnant women develop GERD symptoms, especially in the first trimester of pregnancy. One concern that many patients and providers have is the potential teratogenicity of antireflux medications. For mild symptoms, the first step is lifestyle and dietary modifications, including eating smaller meals, not eating late at night, avoiding trigger foods, avoiding tobacco, and elevating the head of the bed. For patients with refractory symptoms, the physician must discuss the risks and benefits of antireflux medication with the patient as not all agents have been extensively evaluated in pregnant women.

H_2RAs are the most commonly used and safest medications for pregnant women. All four H_2RAs (cimetidine, famotidine, nizatidine, and ranitidine) are the Food and Drug Administration (FDA)-approved category B drugs (meaning that animal studies show no risks, but human studies are inadequate, or animal studies show some risk not supported by human studies). Cimetidine and ranitidine have been used extensively in pregnant women over the past several decades and have a good safety profile. Famotidine also appears to be safe in pregnancy. Nizatidine was previously classified as category C because of animal studies showing spontaneous abortions and low fetal birth rate, but recently was reclassified as category B. For this reason, the other H_2RAs may be a safer option. All H_2RAs are excreted into breast milk. Famotidine has the lowest concentration in breast milk of all H_2RAs. With the exception of nizatidine, H_2RAs are safe to use during lactation [58].

PPIs are categorized as FDA class B medications, with the exception of omeprazole, which is class C because of older studies showing fetal toxicity. While more recent studies suggests that omeprazole is likely safe in pregnancy, the medication remains class C and therefore is not routinely recommended [58, 59]. One of these studies evaluated pregnant women exposed to omeprazole, lansoprazole, or pantoprazole, and the rate of major congenital abnormalities did not differ between the exposed and control groups [59]. The most recent ACG practice guidelines state that PPIs are safe in pregnant patients if clinically indicated (conditional recommendation, moderate level of evidence) [31]. In general, management of GERD in pregnancy must be individualized, and PPIs can be considered in pregnant women with intractable symptoms or who have complicated disease. In general, PPIs are not recommended in lactating mothers [58].

Long-Term Concerns Surrounding PPI Use

As a class of medications, PPIs are generally well tolerated and safe to use. As with H_2RAs, the most common side effects are gastrointestinal and include nausea, abdominal pain, and diarrhea. Other side effects include headaches and rashes. Over the past decade, however, significant well-publicized concerns have been raised regarding possible complications in patients who are on either short-term or chronic PPI therapy. These include vitamin B12 deficiency, hypomagnesemia, an increased risk of bone disease, an increased risk of infection, specifically *Clostridium difficile* colitis and community acquired pneumonia, and drug–drug interactions with clopidogrel. As a consequence, the FDA has issued warnings for many of these concerns regarding long-term PPI use.

Vitamin B12 Deficiency

Vitamin B12 (cobalamin) absorption occurs after the enzyme pepsin releases B12 from dietary protein. Pepsin however requires an acidic environment for its own activation and, as a result, there has been concern that gastric acid suppression could lead to B12 malabsorption [60]. While some published data suggest an increased risk, most studies are small, not well controlled, and results are not consistent. One small study found a significant difference in mean serum B12 and methylmalonic acid levels between 17 long-term PPI users who were older, institutionalized patients, compared with 19 nonusers [61]. Another study evaluating 125 patients on long-term (>3 years) PPI therapy found no association between long-term PPI use and vitamin B12 levels [62]. Currently, a relationship between chronic PPI therapy and B12 deficiency has not been firmly established. Therefore, there are no formal recommendations that providers check vitamin B12 levels in patients on PPI therapy.

Hypomagnesemia

Hypomagnesemia has now become a well-established but rare side effect of long-term PPI use. In March 2011, the FDA released a safety announcement regarding low magnesium levels in patients on PPIs for prolonged periods of time (typically more than 1 year) [63]. Hypomagnesemia has been associated with all PPIs and this is a class effect. However, the FDA stated that the risk is lower when OTC PPIs are used according to their OTC labels. The mechanism behind PPI-induced hypomagnesemia is not established. In the most severe cases, patients with hypomagnesemia may present with ataxia, parasthesias, tetany, and arrhythmias. In many cases, magnesium supplementation alone does not correct serum magnesium levels, and patients have to discontinue PPI therapy. While hypomagnesemia was not addressed in the 2013 ACG GERD guidelines, the FDA has suggested that physicians consider checking serum levels prior to initiating PPI therapy, and periodically while on treatment, especially in patients taking other medications that are known to lower serum magnesium levels, such as digoxin or diuretics [63].

Bone Disease

Significant concern exists, primarily among women, regarding the role PPIs play in inhibiting bone resorption, leading to an increased risk of osteoporosis and bone fractures. While osteoclasts have proton pumps in their cell membranes, clinical trial data show mixed results. One meta-analysis of 10 studies with 223,210 fracture cases found that among PPI users the OR for hip fracture was 1.25 (95% CI 1.14–1.37), vertebral fracture 1.50 (95% CI 1.32–1.72), and wrist/forearm fracture was 1.09 (95% CI 0.95–1.24) [64]. Interestingly, however, in subgroup analysis, there was no duration effect, as short-term PPI use was associated with a higher risk of hip fracture, but long-term PPI use was not. Other studies also show an increased risk of fracture associated with PPI use [65], even after adjustment for potential confounders [66].

Importantly, however, other studies have not shown this association. One large study evaluated changes in bone mineral density in 207 new PPI users, with changes in bone mineral density in 185 new H_2RA users, and among 1676 patients who did not take either class of medications [67]. After a medium follow-up period of 9.9 years, adjusting for known risk factors for osteoporosis (demographics, body mass index, lifestyle factors, comorbidities, and menopausal transition stage), there was no difference in bone mineral density change in the hip, femoral neck, or lumbar spine in PPI users compared with the other two groups. Another study using the large Manitoba Bone Mineral Density Database evaluated the relationship between PPI use and osteoporosis, matching cases with osteoporosis at the hip or lumbar vertebrae with three controls with normal bone mineral density [68]. Researchers found that PPI use over a 5-year period was not associated with osteoporosis of the

hip (OR 0.84; 95% CI 0.55–1.34) or lumbar spine (OR 0.79; 95% CI 0.59–1.06). In addition, PPI use could not account for any significant decrease in bone mineral density at either site.

The current ACG guidelines state that patients with known osteoporosis can remain on PPI therapy. In addition, unless a specific patient has other known risk factors for osteoporosis, the concern for developing bone fractures or osteoporosis should not impact the decision about using a PPI long term if a strong indication exists (strong recommendation, moderate level of evidence) [31].

Clostridium difficile Colitis

Clostridium difficile colitis is one of the most common and feared causes of diarrhea in hospitalized patients. Numerous studies have shown that PPI use is a risk factor for the development of *C. difficile*. It is likely that the lack of gastric acid not only leads to the inability to neutralize *C. difficile* spores, but it also affects the balance of gut flora, making patients more susceptible to infection. This is particularly the case in critically ill patients where PPI use has been showed to be an independent risk factor for the development of *C. difficile* [69]. In addition, PPI use is an independent risk factor for recurrent *C. difficile* infection [70, 71]. The ACG guidelines state that PPIs should be used with care in patients at risk for *C. difficile* infection (strong recommendation, moderate level of evidence) [31]. In clinical practice, hospitalized patients should be continually evaluated for their need for PPI therapy, and when needed, the lowest dose used.

Pneumonia

A relationship between chronic PPI therapy and an increased risk for pneumonia has not been firmly established. A meta-analysis of eight observational studies showed that both PPIs and H_2RAs increased the overall risk of pneumonia [72]. However, a meta-analysis of 23 randomized controlled trials in that same article found that only H_2RAs were associated with an increased risk of hospital-acquired pneumonia. Another large meta-analysis of six nested case–control studies observed that a short course of PPI therapy was associated with an increased risk of pneumonia, but chronic use was not [73]. Similar findings were also shown in another study finding that the risk for community-acquired pneumonia increased if PPI therapy was started within the previous 2, 7, and 14 days [74]. However, no significant relationship was found between the development of pneumonia and longer term PPI use. The most recent ACG guidelines state that while short-term PPI usage may increase the risk of community-acquired pneumonia, the risk does not appear increased in long-term users (conditional recommendation, moderate level of evidence) [31].

Concomitant Use of PPIs and Clopidogrel

Since the initial FDA advisory in 2009, much has been publicized and investigated regarding the potential drug-drug interactions between clopidogrel and PPIs. This concern is relevant as both agents use the same CYP 2C19 pathway for metabolism, leading to the fear that concomitant PPI use may interfere with clopidogrel's ability to inhibit platelet aggregation. Much of this initial fear was based on in vitro studies. Since then, this issue has been extensively researched and data now show that the fear regarding concomitant medication administration was overblown. In 2010, the American College of Cardiology Foundation (ACCF), ACG, and the American Heart Association (AHA), published an updated expert consensus article which stated that in the setting of PPI and thienopyridine co-prescription, the evidence remains weak for diminished antiplatelet activity [75]. In addition, the most recent 2013 ACG guidelines state that the available clinical data do not support an increased risk for cardiovascular events during medication coadministration [31].

Conclusion

H_2RAs and PPIs are the mainstay of medical treatment in patients with GERD and its complications. PPIs demonstrate superior symptom control and healing of esophagitis when compared to H_2RAs. Sometimes these drugs are used together to control NAB as H_2RAs are more effective at controlling acid secretion at night. Both classes of medication are safe, well tolerated, and carry a low risk of adverse events. Nevertheless, these medications are generally overused and may have long-term consequences in selected patients, especially older women and patients with a history of *C. difficile* infection. Therefore, PPIs need to be used more selectively and have the best indications in patients with severe complications of GERD (severe esophagitis, peptic stricture, and Barrett's esophagus), or intractable symptoms only responding to PPIs with frequent breakthrough on alternative medications. Otherwise, patients with mild-to-moderate symptomatic GERD or NERD can be treated with as needed antacids, H_2RAs, or PPIs.

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Chapter 6
Novel Upcoming Therapies

Carla Maradey-Romero and Ronnie Fass

Introduction

Currently, the main medical therapeutic modalities for gastroesophageal reflux disease (GERD) are proton pump inhibitors (PPIs) and histamine type 2 receptor antagonists (H_2RAs). The effect of both classes of drugs is mediated through gastric acid suppression, albeit with different potency. Other underlying mechanisms for GERD treatment include neutralizing gastric acidity (antacids), creating a foamy raft in the stomach that prevents or replaces gastric acid reflux (alginate-based formulations), and improving esophageal clearance and gastric emptying (prokinetics).

The main goals of GERD treatment are to relieve symptoms, heal, and maintain remission of erosive esophagitis (EE), prevent complications, and improve health-related quality of life (HRQL) [1]. Presently, PPIs provide unsurpassed clinical efficacy in GERD patients, primarily due to their profound inhibitory effect on acid secretion. However, even in patients receiving PPI therapy, the resolution of esophageal mucosal inflammation is much more predictable than resolution of symptoms [2].

The different GERD phenotypes demonstrate varied degrees of response to antireflux treatment. Nonerosive reflux disease (NERD) patients, for example, have a significantly lower response rate to PPI therapy as compared with other GERD groups and consequently constitute the majority of patients with refractory heartburn. Failure of PPI therapy is the most common presentation of GERD in gastroenterology practice [3, 4].

Presently, there are several unmet needs in GERD treatment. Approximately 10–15 % of patients with EE fail to achieve complete healing after 8 weeks of treatment [5]. Moreover, even when the initial healing dose of the PPI is continued, 15–23 % of patients with Los Angeles grades A and B and 24–41 % of those with grades C

R. Fass (✉) · C. Maradey-Romero
Esophageal and Swallowing Center, Division of Gastroenterology and Hepatology, MetroHealth Medical Center, Case Western Reserve University, 2500 MetroHealth Drive, Cleveland, OH, USA
e-mail: ronnie.fass@gmail.com

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Table 6.1 Novel treatment modalities for GERD

Medical	Endoscopic	Surgical
H_2RAs Lavoltidine	*EsophyX* Transoral incisionless fundoplication (*TIF*)	The LES stimulation system (*EndoStim*)
PPIs Tenatoprazole	Medigus ultrasonic surgical endostapler (*MUSE*)	
PPI combinations Vecam Secretol (Omeprazole + lansoprazole) PPI + alginate NMI 826 (nitric-oxide-enhanced PPI)		
P-CABs TAK-438		
Prokinetics 5-HT4 agonist (Reveprexide)		
Pain modulators TRVP1 (AZD1386)		
Bile acid sequestrant IW-3718		

LES lower esophageal sphincter, *PPI* proton pump inhibitor, *H_2RAs* histamine type 2 receptor antagonists

and D relapse within 6 months of initiating maintenance treatment. In addition, up to 40 % of NERD patients remain symptomatic while on standard dose (once daily) of PPI therapy [6]. Treatment of extraesophageal manifestations of GERD has been clinically disappointing [7]. Most of the randomized controlled trials in patients with pharyngeal, laryngeal, or pulmonary symptoms, which are suspected to be GERD related, demonstrate lack of relief or modest benefit with PPI treatment versus placebo. Other unmet needs in GERD include rapid and more effective control of postprandial heartburn, improved control of volume reflux and acid regurgitation, relief of nighttime heartburn symptoms, acid control in Barretts's esophagus (BE) patients, and a more flexible schedule of PPI administration [1].

The goal of the present review is to provide an overview of the new and future drug developments for GERD treatment (Table 6.1).

Histamine Type 2 Receptor Antagonists

H2RAs reduce gastric acid secretion by competitive inhibition of the interaction between histamine and H_2 receptors that are located on the parietal cells. In addition, H_2RAs reduce pepsin and gastric acid volume [8]. Currently, there are four Food and Drug Administration (FDA)-approved H_2RAs in the USA: cimetidine, famatodine, nizatidine, and ranitidine.

The different H_2RAs are considered equivalent in suppressing gastric acid secretion when administered in equipotent doses. The pharmacokinetic and pharmaco-

dynamic differences among the H_2RAs seem to be clinically nonsignificant [9]. Although H_2RAs are effective in controlling basal acid secretion, they have limited efficacy in suppressing postprandial acid secretion. Presently, H_2RAs are used to control symptoms and heal mild to moderate EE (Los Angeles grades A and B) [10]. In addition, several studies have demonstrated that approximately 30% of NERD patients report symptom relief after receiving an H2RA twice daily for 4 weeks [11, 12]. H_2RAs are particularly helpful in relieving postprandial heartburn for up to 12 h [13]. They are also effective in preventing postprandial heartburn if given 30 min before a meal [14]. In addition, H_2RA at bedtime significantly reduced the duration of nocturnal acid breakthrough (NAB) [15].

Nizatidine

Nizatidine is one of the currently available H_2RAs. A recent study evaluated the effect of nizatidine on the rate of transient lower esophageal sphincter relaxations (TLESRs) and the level of esophageal acid exposure. Ten healthy subjects were randomized to receive nizatidine (150 mg) twice a day versus placebo 60 min before a meal for 7 days. Subsequently, patients underwent esophageal manometry and pH testing. Nizatidine significantly increased lower esophageal sphincter (LES) basal pressure as compared with placebo. In addition, nizatidine significantly reduced esophageal acid exposure by decreasing the rate of TLESRs and consequently acid exposure as compared with placebo [16]. The aforementioned effects, in addition to accelerating gastric emptying, are likely due to direct or indirect inhibitory effect of nizatidine on acetylcholinesterase.

Lafutidine

This is a novel second-generation H_2RA. The drug has been primarily used as an antisecretory agent in Japan. In a randomized, double-blind, placebo-controlled study that included 584 subjects with an endoscopic diagnosis of Los Angeles grades A and B EE, patients received lafutidine (20 mg once daily), famotidine (40 mg once daily), or placebo for 8 weeks. The authors demonstrated that lafutidine had an endoscopic healing rate of 71% as compared with 61.4 and 9.7%, in the famotidine and placebo groups, respectively [17]. In another study, 23 patients diagnosed with NERD (two or more heartburn episodes per week, a questionnaire for the diagnosis of reflux esophagitis score of 6 or above, and a negative upper endoscopy) underwent a 24-h pH test at baseline and again after 4 weeks of treatment with lafutidine (10 mg twice daily). The authors demonstrated a significant decrease in the percentage of time that intraesophageal pH was <4 (3.07–1.17%). In addition, the percentage of time that intragastric pH was >3 also increased significantly (26.6–56.5%) [18].

Another multicenter study compared lafutidine with rabeprazole in treating uninvestigated dyspepsia. Subjects were randomized to lafutidine (10 mg) or rabeprazole (20 mg), both once daily for 4 weeks. Both lafutidine and rabeprazole provided a similar rate of symptom relief in patients with heartburn-predominant uninvestigated dyspepsia. The study supports the value of lafutidine as an effective empiric therapy in this subgroup of patients [19].

Lavoltidine (AH234844)

Lavoltidine, also known as loxtidine, is a potent noncompetitive H_2RA. Because of an increased incidence of carcinoid tumors observed in rats and mice after loxtidine treatment, the drug was suspended in 1988. The carcinogenic effect was probably related to the prolonged achlorhydria that was induced by loxtidine. However, it is unlikely that the drug has similar carcinogenic effect on the human gastric mucosa [20]. Since lavoltidine has shown rapid onset of action, high potency, and prolonged duration of effect after a single dose, GlaxoSmithKline conducted two clinical trials with the drug less than a decade ago. One study was a phase 2 pharmacokinetic/pharmacodynamic study which started in 2006. The study compared four different AH234844 (lavoltidine) doses (dose range not available) with esomeprazole (40 mg/day) and ranitidine (300 mg/day) in healthy male subjects [21]. Another phase 1 pharmacodynamic study, which was started in 2007, compared 24-h intragastric pH on days 1, 2, and 7 while subjects were on lavoltidine (40 mg) once daily [22]. Presently, there is no available information about the status of these studies (http://www.gsk-clinicalstudyregister.com/compounds/lavoltidine#ps).

One of the main limitations of H_2RAs is tachyphylaxis that develops quickly, usually within 2 weeks of repeated administration. This pharmacological phenomenon results in a decline in acid suppression that limits the regular use of H2RAs in clinical practice [23, 24]. Thus, it is still unknown if the new H_2RAs have a similar limitation. Furthermore, it will be important to see if the new H_2RAs are more effective in treating GERD patients as compared with the first generation of H_2RAs.

Proton Pump Inhibitors

The introduction of the PPIs into the US market in the early 1990s revolutionized the treatment of acid peptic disorders. This class of drugs is currently considered the best therapeutic option for GERD [25]. The high potency of PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole) is the result of their ability to inhibit the proton pump (H^+, K^+-ATPase), which is the final common pathway of gastric acid secretion. They suppress nocturnal, daytime, and

food-stimulated acid secretion [26]. Currently, PPIs are the most successful antisecretory agents for healing inflammation of the esophageal mucosa and relieving GERD-related symptoms because of their profound and sustained acid inhibition [5, 8]. PPIs have made an important therapeutic impact on advanced EE, GERD complications, and atypical manifestations of GERD. Even in BE, PPIs have made a significant impact on symptoms control, mucosal healing, and esophageal acid exposure.

A recent Cochrane review examined 134 therapeutic trials that included 36,978 subjects with EE and concluded that PPIs demonstrated a better healing effect and faster symptom relief than H_2RAs [27]. The study did not find any major difference in efficacy among the currently available PPIs. However, the effect of PPIs on symptoms differs between patients with NERD and those with EE. The symptomatic therapeutic gain of PPIs over placebo in NERD patients is much lower than that observed in patients with EE [28]. In a systematic review, the therapeutic gain for standard-dose PPI in relieving heartburn symptoms compared with placebo ranged from 30 to 35% for sufficient heartburn control and from 25 to 30% for complete heartburn control. Pooled response rates to PPIs once daily were significantly higher after 4 weeks of treatment for patients with EE compared with NERD patients (56 vs. 37%).

Since the introduction of PPIs into the market, refractory GERD has become the main presentation of GERD in clinical practice. Specifically, approximately 10–15% of patients with EE fail to achieve complete healing after 8 weeks of treatment. This subset of patients usually demonstrates moderate to severe disease (Los Angeles grades C and D) and comprises approximately 25–30% of all EE patients [5]. Moreover, even when continuing the initial healing dose as maintenance treatment for a period of 6 months, 15–23% of patients with Los Angeles grades A or B and 24–41% of those with grades C or D relapse while on treatment. In addition, up to 40% of NERD patients remain symptomatic while on standard dose (once-daily) PPI therapy [6]. Treatment of extraesophageal manifestations of GERD with a PPI has been relatively disappointing, and many trials showed that the drug does no better than placebo in improving or relieving symptoms [7]. Important shortcomings of PPIs include lack of effective control of postprandial and nighttime heartburn as well as limited effect on esophageal acid exposure in BE patients. In addition, PPIs demonstrate a dependence on food consumption for maximal efficacy.

At present, switching to another PPI or doubling the PPI dose has become the most common therapeutic strategy for GERD patients who symptomatically fail to achieve symptom control on PPI with once-daily dosing [3, 8]. According to a recent Cochrane review, doubling the PPI dose is associated with greater healing of EE, with the number needed to treat of 25. However, there is no clear dose–response relationship for heartburn resolution in either EE or NERD [33]. Although doubling the PPI dose has become the standard of care, there is no evidence to support further escalation of the PPI dose beyond PPI twice daily for either symptom control or healing of EE. When doubling the PPI dose, one dose should be given 30–60 min

before breakfast and the other 30–60 min before dinner. The support for splitting the dose originates primarily from physiological studies demonstrating improved control of intragastric pH when one dose is taken in the morning and the other in the evening as compared with both doses being taken before breakfast [29].

Several approaches have been used to improve the acid suppressive effect of PPIs. They include development of enantiomers that undergo slower hepatic metabolism, incorporation of technology that prolongs drug absorption, and combining PPI's with compounds that maximize PPI absorption and thus bioavailability.

Extended-Release PPIs

Tenatoprazole

Tenatoprazole is a novel compound that, unlike other PPIs, is not a benzimidazole molecule. It is characterized by an imidazopyridine backbone with substantially prolonged plasma half-life. Tenatoprazole (40 mg once daily) demonstrated better nighttime acid control than esomeprazole (40 mg once daily) in healthy subjects [30]. Another study found that this drug markedly inhibits intragastric acidity unrelated to dosing time or food intake [31]. S-tenatoprazole-Na, an enantiomer of tenatoprazole, was significantly better in providing gastric acid suppression when compared with esomeprazole (40 mg once daily). Furthermore, it was also demonstrated that higher doses of the drug produced greater acid suppression in a dose–response fashion [32].

AGN 201904-Z (Alevium)

AGN 201904-Z (Alevium) is a prodrug of omeprazole. It is acid stable and therefore requires no enteric coating. This drug has a long plasma half-life due to slow absorption throughout the small intestine. After absorption, the drug is rapidly hydrolyzed in the systemic circulation to omeprazole [33]. A comparison of Alevium (600 mg once daily), with esomeprazole (40 mg once daily) in 24 healthy subjects resulted in significantly greater and more prolonged acid suppression during both daytime and nighttime. Alevium once daily showed a 1.9-fold increase in serum half-life as compared with esomeprazole. After 5 days of treatment, Alevium demonstrated a significantly higher mean 24-h intragastric pH, nocturnal median pH, and percentage of time intragastric pH was greater than 4 as compared with esomeprazole ($P = 0.0001$) [34] (Table 6.2).

Table 6.2 Compounds under development that have been discontinued

Class	Drug	Reason for discontinuation
H_2RAs	Loxtidine	Neuroendocrine tumors in rats
PPIs	AGN201904-Z (Alevium ®)	Poor efficacy
PPI combinations	OX17	Poor efficacy?
P-CABs	Linaprazan (AZD 8065) Soraprazan Revaprazan	Modest or no clinical benefits over PPIs
TLESR reducers	$GABA_B$: Arbaclofen placarbil, Lesogaberan (AZD3335)	Poor efficacy Side effects: diarrhea, nausea, and increased transaminases
	mGluR5 (ADX10059, AZD2066)	Side effects: increased transaminases and hepatic failure
	CB agonist (rimonabant)	Side effects: depression and suicidal tendencies
	CCK/gastrin receptors antagonist (spiroglumide, itriglumide and loxiglumide)	Poor efficacy
Prokinetics	5-HT4 agonist (Tegaserod)	Poor efficacy

TLESR transient lower esophageal sphincter relaxation *PPI* proton pump inhibitor, *H_2RAs* histamine type 2 receptor antagonists, *CCK* cholecystokinin, *$GABA_B$* gamma-aminobutiric acid B, *CB* cannabinoid

PPI Combinations

PPI-VB101 (Vecam)

PPI-VB101 (Vecam) is the coadministration of a PPI with a succinic acid, a food additive that activates proton pumps in the parietal cells. The succinic acid has a pentagastrin-like activity that potentiates activation of proton pumps [35]. The rationale behind this combined therapy is to increase the efficacy of the PPI by maximizing activation of proton pumps. In addition, it may allow administration of PPI without regard to food. In an open-label study, 36 healthy subjects were randomized to receive once-daily Vecam (20 or 40 mg) at bedtime or omeprazole (20 mg) before breakfast. The effect of the different therapeutic arms on intragastric acidity was compared over a 24-h period. Vecam (40 mg) was significantly better in keeping nighttime intragastric pH > 4 as compared with Vecam (20 mg) and omeprazole ($P < 0.0001$). Similarly Vecam (20 mg) showed significantly better control of intragastric pH as compared with omeprazole (20 mg; $P = 0.0069$) [36].

OX17

OX17 is an oral tablet containing a combination of omeprazole and famotidine (doses are unclear) [37]. This combination has shown a 60% increase in total time intragastric pH > 4 as compared with omeprazole alone. Further developments of

this drug have been discontinued [38]. A combination of tenatoprazole and H_2RA has been recently patented (US 20060241136 A1) [39]. However, we are still awaiting studies demonstrating the clinical value of this novel compound as compared with PPI alone.

NMI-826

NMI-826 is a nitric-oxide (NO)-enhanced PPI. The drug has been shown to be more effective than a PPI alone in healing gastric ulcers [40].

Secretol

Secretol is a novel pharmacological compound that combines omeprazole with lansoprazole. Currently, secretol is undergoing a phase II trial that compares its healing rates and symptom control with esomeprazole in subjects with severe EE (www.clinicaltrials.gov NCT01129713). The combined compounds are likely to be niched in certain areas of unmet needs in GERD rather than competing with the currently available PPIs.

PPI-Prokinetics

Rabeprazole Plus Itopride

This compound contains a fixed-dose combination of rabeprazole 20 mg and itopride 150 mg [41, 42]. The efficacy and safety of this drug has been evaluated in patients with functional dyspepsia and NERD [43]. The authors demonstrated that 93% of the patients reported a relief of their symptoms after a 4-week course of therapy. Presently, this formulation is not available in the USA.

Pantoprazole Plus Domperidone

The safety and efficacy of this combination drug composed of pantoprazole 40 mg and domperidone 20 mg (10 mg immediate release form and rest 10 mg in delayed release form tablets) has been evaluated in GERD patients [44]. The authors demonstrated a significant improvement of GERD-related symptoms at week 4 as compared to baseline ($P<0.001$). Currently, this combined drug is not available in the USA.

Potassium-Competitive Acid Blockers (P-CABs)

P-CABs represent a heterogeneous group of drugs that share the same final mechanism of action. This class of drugs inhibits gastric H^+/K^+-ATPase in a K^+competitive but reversible mechanism. Consequently, P-CABs do not require prior proton pump activation to achieve their antisecretory effect. P-CABs exhibit an early onset inhibition of acid secretion due to rapid rise in peak plasma concentration [45]. Given the pharmacokinetic and pharmacodynamic profile of P-CABs, they are likely to be beneficial as an on-demand therapy for symptomatic GERD.

Attempts to develop P-CABs in the past two decades have failed to produce even one compound that reached the market. Comparative trials were unable to demonstrate clinical superiority of P-CABs over currently available PPIs. This is primarily due to common utilization of traditional study designs rather than trials specifically focusing on the unique characteristics of P-CABs. In addition, several P-CABs have been associated with severe adverse effects such as liver toxicity. Thus, despite their promising pharmacokinetics and pharmacodynamics profile, their future in the GERD market remains to be elucidated.

Linaprazan (AZD 8065)

Linaprazan (AZD 8065) demonstrated similar efficacy as esomeprazole in healing and controlling symptoms of GERD patients with EE [46]. However, the drug did not demonstrate any clinical benefits over esomeprazole in symptom control of patients with NERD [47].

Soraprazan

Soraprazan showed an immediate inhibition of acid secretion in in vitro models. In animal models, the drug was found to be superior to esomeprazole in onset of action as well as extent and duration of intragastric $pH > 4$ [48]. Presently, there are no clinical data available for soraprazan.

Revaprazan

Revaprazan was demonstrated to be equivalent to PPIs in acid suppression. In a recent study, the authors compared the bioavailability and tolerability of revaprezan alone to revaprezan plus iotopride. Revaprezan demonstrated bioequivalence to the combination with iotopride without any clinically significant drug-to-drug interaction [49]. Recently, a phase II clinical trial aimed to investigate the safety, tolerability, and

efficacy of revaprazan (YH1885L) in NERD patients has been completed. However, no clinical data are available yet (www.clinicaltrials.gov NCT01750437).

TAK 438

TAK 438 (vonoprazan) demonstrated greater potency and longer lasting inhibitory effect on gastric acid secretion when compared with lansoprazole in animal models [50, 51]. Recently, two randomized, double-blind, placebo-controlled phase I trials were conducted in healthy male volunteers in Japan ($n=60$) and the UK ($n=48$) [52]. TAK 438 given in increasing oral doses (10–40 mg once daily) for 7 days was assessed for safety, tolerability, pharmacokinetics, and pharmacodynamics. The authors demonstrated that on day 7 of treatment with 40 mg once daily of TAK 438, the mean 24-h intragastric pH > 4 was 100 % in the cohort from Japan and 93.2 % in the UK cohort (*P* values not available). Also, TAK 438 (all doses) increased serum concentrations of gastrin, pepsinogen I and II in both studies (*P* values not available). The drug induced some dose-dependent minor adverse events that included, increased serum triglycerides and eosinophil's count, decreased white blood cell-count, nasopharyngitis, headache, abdominal pain, oral herpes, and neck pain [52].

Transient Lower Esophageal Sphincter Relaxation (TLESR) Reducers

TLESR is the main mechanism of gastroesophageal reflux, both acidic and nonacidic, accounting for all reflux episodes in healthy subjects and the majority (55–80 %) of reflux episodes in GERD patients [53]. A wide range of receptors is involved in triggering TLESR including gamma-aminobutiric acid B ($GABA_B$), metabotropic glutamate receptor 5 (mGlucR5), cannabinoid (CB), cholecystokinin (CCK), 5-hydroxytryptamine-4, muscarinic, and opioid [54].

CB Receptor Agonists

Delta-9-tetrahydrocannabinol, a CB1/CB2 receptor agonist, inhibits the rate of TLESRs [55]. A study that evaluated the effect of delta-9-tetrahydrocannabinol on TLESRs in dogs and healthy subjects showed that this compound significantly reduced the number of meal-induced TLESRs. However, the drug also significantly reduced the LES basal pressure. Furthermore, adverse effects such as nausea, vomiting, hypotension, and tachycardia led to premature termination of the study. [56].

Rimonabant is a CB1 receptor antagonist. In a placebo-controlled trial that was conducted in healthy subjects, the drug demonstrated increased LES basal pressure

and decreased rate of TLESRs and postprandial reflux. The drug was withdrawn from further investigation due to psychological side effects such as depression and suicidal tendency [57].

CCK/Gastrin Receptors Antagonist

Gastrin and CCK_2 receptors are identical. Given the physiological importance of gastrin in the stimulation of gastric acid secretion, the development of a selective CCK_2 receptor antagonist offers a potential therapeutic choice for acid-related disorders [48, 58]. Only a few CCK receptor antagonists have been tested in humans, among them spiroglumide, itriglumide, and loxiglumide. Loxiglumide has been shown to inhibit the rate of meal-induced TLESR [58–60]. It is unclear, however, if the effect of loxiglumide is limited to the physiological post-meal increase in TLESRs and reflux episodes, and thus the drug would have no impact on pathological reflux. Itriglumide inhibits gastrin-stimulated acid secretion but might delay mucosal healing; tolerance to the drug may also develop [61].

Other TLESR reducers have been primarily studied as add-on treatments for patients who failed once-daily PPI. However, the development of several novel agents targeting this mechanism has met many obstacles, and thus far none of them has made it to the market [62]. These included the $GABA_B$ agonists arbaclofen placarbil [63, 64], lesogaberan (AZD 3355) [65, 66], mGlucR5 antagonists ADX 10059 [26, 67], and AZD2066 [68].

Prokinetics

Prokinetic agents have been proposed to improve GERD-related symptoms by different potential mechanisms that include improvement in esophageal peristalsis, acceleration of esophageal acid clearance, increase in LES basal pressure, and improved gastric emptying. The clinical benefit of prokinetics as sole treatment for GERD has been modest at best. Moreover, their use has been hampered by many adverse effects.

Mosapride

Mosapride citrate has both 5-HT4 receptor agonist and 5-HT3 receptor antagonist effects. This drug significantly reduced acid reflux and improved GERD-related symptoms primarily as an add-on therapy [69, 70].

Itopride

Itopride is a dopamine (D2) receptor antagonist, which also inhibits acetylcholinesterase. This drug has been shown to improve GERD-related symptoms and reduce esophageal acid exposure in patients with mild EE [71]. Itopride inhibits TLESRs without significantly affecting esophageal peristalsis.

Azithromycin

Azithromycin is a macrolide with motilin agonist properties. The drug also promotes acetylcholine release and stimulates serotonin receptors (5HT3). In a recent study, azithromycin reduced the number of acid reflux events and the size of hiatal hernia as measured by high-resolution manometry. The mean size of the hiatal hernias was larger when reflux episodes were acidic as compared with weakly acidic or nonacidic reflux events. In addition, the acid pocket was more often located below the diaphragm (distal position) [72]. In another study, the effect of azithromycin was evaluated in subjects after lung transplantation (LTx). Subjects receiving the drug demonstrated a significantly lower number of total ($P=0.012$) and acid reflux events ($P=0.0037$) in a 24-h period as well as bile acids levels in bronchoalveolar lavage fluid ($P=0.0106$) [73].

Prucolopride

Prucolopride, a first-in-class dihydrobenzofuran-carboxamide, is a potent selective 5-HT4 receptor agonist with enterokinetic properties. The drug is currently used for chronic constipation. Due to its pharmacodynamic profile, the drug may have a role in GERD patients [74].

Reveprexide

A recent randomized, double-blind, placebo-controlled, parallel-group phase IIb study aimed to evaluate the effect of reveprexide, a 5-HT4 receptor agonist, in 477 patients with GERD who partially responded to PPI treatment [75]. Patients were randomized into four different groups, reveprexide 0.1, 0.5, or 2.0 mg three times a day in addition to their PPI, or placebo plus PPI for 8 weeks. The study demonstrated no difference in percentage of regurgitation-free days among the three reveprexide arms as compared with placebo (0.1 mg, $P=0.128$; 0.5 mg, $P=0.062$; 2.0 mg, $P=0.650$). However, the percentage of heartburn-free day was significantly higher in the reveprexide 0.5-mg group as compared with placebo ($P<0.05$). Occurrence of adverse events was dose dependent, with a rate of approximately 60%

in the reveprexide 2.0-mg group. The most common adverse events include, diarrhea, nausea, headache, abdominal pain, upper respiratory tract infection, back pain, and worsening of pulmonary hypertension [75].

Pumosetrag

Pumosetrag (DDP733) is a partial 5HT3 receptor agonist with gastrointestinal (GI) prokinetic activities. DDP733 increased LES basal pressure in experimental animal models. In addition, DDP733 significantly reduced the rate of reflux events and increased the mean amplitude of distal esophageal contractions without changing the LES basal pressure in healthy human subjects [53, 76].

Pain Modulators

In GERD patients with evidence of esophageal hypersensitivity, such as those with NERD or PPI failure due to nonacidic reflux, pain modulators are likely to play a pivotal therapeutic role [1, 6, 77]. Pain modulators, or visceral analgesics, have been shown to significantly improve symptoms in patients with noncardiac chest pain (NCCP), functional heartburn, and refractory GERD [78]. Non-organ-specific pain modulators such as tricyclic antidepressants (TCAs), trazodone, selective serotonin reuptake inhibitors (SSRIs), and serotonin/norepinephrine reuptake inhibitors (SNRIs) are commonly used in clinical practice to treat functional esophageal disorders [79, 80]. It is believed that these agents confer their visceral analgesic effect by acting at the CNS level and/or peripherally at the sensory afferent level.

AZD1386

AZD1386 is a transient receptor potential vanilloid-1 (TRPV1) antagonist. In a recent randomized, placebo-controlled study that was conducted in 22 healthy male subjects, the authors evaluated the effect of two different doses of AZD1386 (30 and 95 mg). The authors used a multimodal stimulating probe in the esophagus (distension, heat, acid, and electrical stimulation) for drug assessment. AZD1386 (30 and 95 mg) increased esophageal pain thresholds to heat 23 and 28 %, respectively ($P < 0.01$). The drug did not have an effect on perception thresholds for chemical, mechanical, or electrical stimuli [77]. Furthermore, another recent study aimed to investigate the effect of AZD1386 on experimental esophageal pain in NERD patients with partial PPI response reported no analgesic effect on esophageal pain in this patient population [81]. Elevated liver enzymes during drug treatment has been a major concern [82]. In addition, the drug-induced hyperthermia, which could represent a challenge in clinical practice [83].

Rozerem

Rozerem is a melatonin receptor agonist (MT1 and MT2), approved in the USA for the treatment of insomnia [84]. The drug has been studied in GERD patients with nighttime reflux and sleep disturbances. In a study conducted by Jha et al., patients were randomized to receive either rozerem 8 mg or placebo at bedtime for 7 days (www.clinicaltrials.gov NCT01128582) [85]. The authors demonstrated that patients who received rozerem showed a statistically significant decrease in symptom scores, as compared with those who received placebo for daytime and nighttime heartburn (42 vs. 29%, 42 vs. −78%, respectively), 24-h heartburn (42 vs. 3%), and 24-h acid regurgitation (38 vs. −19%; all $P<0.05$). This study was the first to demonstrate that rozerem significantly improved GERD-related symptoms [86].

Pregabalin

Pregabalin is a centrally acting modulator of voltage-sensitive calcium channels. Chua et al. conducted a double-blind, placebo-controlled randomized study in 15 healthy volunteers that assessed the effects of pregabalin on the development of secondary esophageal hypersensitivity [87]. The administration of pregabalin was as follow: 75 mg twice/day for 3 days, then 150 mg twice/day for one day, and finally 150 mg the same day of the study. The authors demonstrated that pregabalin reduced the development of acid-induced hypersensitivity in the proximal esophagus at 30 and 90 min after acid stimulation as compared with placebo. This drug could potentially be used in GERD patients who failed to respond to an adequate anti-reflux therapy.

Mucosal Protectants

Rebamipide is an amino acid derivative of 2-(1*H*)-quinolinone with an anti-inflamatory function and thus may be effective as an esophageal mucosa protectant. A placebo-controlled study in 149 NERD subjects who failed PPI treatment assessed the efficacy of this compound. Unfortunately, the authors were unable to demonstrate a significant effect of rebamipide on subjects' symptoms [88]. In another study, investigators evaluated the effect of combining a PPI with rebamipide on healing esophageal mucosal ulcers that occurred due to endoscopic submucosal dissection (ESD). During the first 2 days after ESD, all subjects received an intravenous dose of omeprazole (20 mg) then switched to either rabeprazole (10 mg) once daily alone or to oral rabeprazole plus rebamipide (100 mg) given three times daily for the following 26 days. It was demonstrated that the number of subjects whose ulcer reached the scar stage 28 days after the ESD was significantly greater in the combination group (68%) as compared with the PPI group (35%; $P=0.011$) [89].

Growth factors, such as epidermal growth factor (EGF) and macrophage colony-stimulating factors (M-CSF), have a key role in mucosal healing. While early studies in animal models were promising, the value of these growth factors in GERD remains to be studied [90].

Bile Acid Sequestrant

IW-3718

IW-3718 (Ironwood, Cambridge, MA) is a novel, gastric retentive formulation of a bile acid sequestrant developed using the proprietary Acuform® drug delivery technology [91]. Recently, a randomized, double-blind, placebo-controlled, multisite, phase IIa study enrolled 93 patients with GERD who partially failed to respond to PPI therapy (www.clinicaltrials.gov NCT02030925). Patients were randomized to receive either 1000 mg of IW-3718 or placebo twice daily for 4 weeks while continued to take their PPI during the study. The exploratory study evaluated a number of GERD-related symptoms rather than specifying a primary end point, and as such was not powered to establish the statistical significance of a particular end point. The percentage of heartburn-free days for IW-3718-treated patients increased by 30.3% in the overall trial population and 34.6% in the bile reflux-positive subgroup (vs. 24.7 and 23.6%, respectively, for the placebo-treated groups). Additionally, 45.7% of the IW-3718-treated patients and 56.3% of the bile reflux-positive subgroup were considered responders (degree of relief of overall GERD symptoms) as compared with 27.7 and 29.4%, respectively, in the placebo-treated groups [91].

Endoscopic Therapy

EsophyX

EsophyX (EndoGastric Solutions, Redmond, WA), which is primarily marketed to surgeons, is used to perform transoral incisionless fundoplication (TIF). The device creates a full-thickness serosa-to-serosa plication and constructs a valve 3–5 cm in length and 200–300° in circumference [92]. TIF increases LES length and resting basal pressure as well as reduces or normalizes intraesophageal pH and cardia circumference. The technique also markedly improves GERD-related symptoms, quality of life, and esophageal inflammation. Most importantly, TIF reduces or completely eliminates PPI consumption by different types of GERD patients, including those with NERD [93, 94]. Long-term follow-up is limited to approximately 3 years, and studies have reported worrisome side effects including esophageal perforation and significant GI bleeding [95]. In addition, many of the therapeutic trials

included small number of participants, lacked comparison with a sham control, and provided limited descriptions of the participants. In one of the largest multicenter trials, which included 86-GERD patients treated with a PPI (most with EE but all with hiatal hernia <2 cm in length), the authors reported the results of a 12-month follow-up [93]. The study demonstrated that after 1 year, 73% of the participants reported 50% improvement in HRQL, 85% discontinued daily PPI use, and 37% normalized esophageal acid exposure.

Most recently, The Randomized EsophyX vs Sham, Placebo-Controlled Transoral Fundoplication (RESPECT) trial, reported about 696 GERD patients who were randomized to either TIF procedure or sham surgery [96]. Two weeks postoperatively, TIF patients were switched to received placebo and sham surgery continued on once- or twice-daily omeprazole 40 mg for 6 months. The authors demonstrated by intention-to-treat analysis, that TIF eliminated troublesome regurgitation in 67% of the patients as compared with 45% of those who were treated with sham surgery and a PPI ($P=0.023$). The mean number of reflux episodes decreased from 135 before TIF to 94 after TIF procedure ($P<0.001$). Mean percent total time pH<4 improved from 9.3 before TIF to 6.4 after the TIF procedure ($P<0.001$). In the sham surgery group, neither the mean number of reflux episodes or the mean percent total time pH<4 were significantly different during a 48-h pH testing off PPIs for 7 days (all $P=$NS). Severe complications were rare.

Medigus Ultrasonic Surgical Endostapler (MUSE)

The transoral endoscopic device (MUSE™, formerly called SRS, Medigus, Omer, Israel) is a novel technique to treat GERD patients, including those with NERD. The MUSE system received FDA clearance in 2014. The MUSE system is used to perform anterior fundoplication using a modified endoscope that incorporates a miniature camera, an ultrasound probe, and stapler at the tip [97]. A recent study compared the safety and efficacy of MUSE system (formerly SRS) with laparoscopic antireflux surgery (LARS) [98]. The authors demonstrated that the procedure times for MUSE and LARS were 47 and 89 min, respectively ($P<0.05$). However, the mean discharge time from the hospital was longer for MUSE 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 MUSE as compared with baseline ($P=0.016$). There was one esophageal perforation in the MUSE group [98].

Recently, Zacherl et al. conducted a multi-center, prospective trial in 66 patients who were diagnosed with GERD (≥2 years documented GERD symptoms, PPI treatment greater than 6 months and abnormal ambulatory esophageal pH monitoring off PPI therapy) and who underwent MUSE procedure with a 6-month follow-up [99]. There was at least 50% reduction in GERD-HRQL total score between baseline (off PPI) and 6-month follow-up scores (9% CI 60–83%) in 72.7% (48/66)

of the patient. The median GERD-HRQL total score significantly improved in 9% (6/66) of patients at 6-month follow-up as compared to baseline scores off PPI treatment ($P<0.001$). The mean % total time with esophageal pH < 4.0 decreased from 10.9 at baseline (off PPI) to 7.3 at 6-month follow-up ($P<0.001$). No significant changes were observed in the esophageal manometry performed at baseline and at 6-month follow-up (all P = NS). There were only two adverse events and neither required further intervention (elevated C-reactive protein and a non-procedure related psychiatric emergency) [99]. The MUSE system is primarily promoted to surgeons and requires further evaluation about its long-term efficacy.

Surgical Therapy

The LES Stimulation System (EndoStim)

Electrical stimulation of the LES using the EndoStim has not yet been approved in the USA. The technique has been shown to increase LES resting pressure in animal models [100–102]. Human studies, however, focused primarily on patients with EE who are on PPI treatment and have low resting LES pressure as well as abnormal 24-h esophageal acid exposure [103, 104]. The authors demonstrated that short-term electrical stimulation of the LES improved LES resting pressure, esophageal acid exposure, GERD-HRQL, and PPI consumption without affecting the amplitude of esophageal peristalsis or LES relaxation. Long-term follow-up of up to 1 year after implanting the EndoStim revealed durability of the original therapeutic effect [105]. Thus far, there are no specific studies in NERD patients using this technique. It is possible that NERD patients with documented abnormal esophageal acid exposure may also benefit from the EndoStim. However, the risk of long-term repeated stimulation of the LES needs to be further evaluated. In addition, comparison with medical or other nonmedical techniques is needed.

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Chapter 7
Minimally Invasive GERD Therapies

Dan E. Azagury and George Triadafilopoulos

Introduction

Studies show that although approximately 30–40 % of patients with gastroesophageal reflux disease (GERD) fail to respond symptomatically to aggressive acid suppressive therapy with proton pump inhibitors (PPI), less than 5 % of them undergo fundoplication, leaving a substantial number of people receiving inadequate treatment for their GERD symptoms [1]. Such reluctance to proceed with surgery is partly due to the fear of possible side effects with fundoplication with or without hernia repair, the reported high rates of surgical failures, and the subsequent need for medical therapy, or repeat surgery [2]. The traditional laparoscopic anti-reflux surgeries (LARS) are listed in Fig. 7.1. Patients who have persistent GERD symptoms despite medical therapy and are not willing to undergo fundoplication fall into what is called the GERD treatment gap (Fig. 7.2). Newer minimally invasive techniques, both endoscopic and laparoscopic, have been introduced to address this gap (Fig. 7.3), and notably they include gastric bypass surgery for the obese patient with GERD [3].

The advantage of these procedures is that they do not dramatically alter the anatomy of the esophagogastric junction (EGJ), esophagus, or stomach, and thus they have a better side-effect profile. By design, these techniques are intended to target patients with mild EGJ defects, and, thus, they should not be considered as alternatives to fundoplication and hernia repair for patients with significant anatomic abnormalities [4]. Table 7.1 outlines the most common reasons to consider minimally invasive GERD therapies.

G. Triadafilopoulos (✉)
Department of Medicine, Stanford University, 300 Pasteur Drive; MC: 5187, Stanford, CA 94305, USA
e-mail: vagt@stanford.edu

D. E. Azagury
Department of Bariatric and Minimally Invasive Surgery, Stanford University School of Medicine, Stanford, CA, USA

M. F. Vaezi (ed.), *Diagnosis and Treatment of Gastroesophageal Reflux Disease,*
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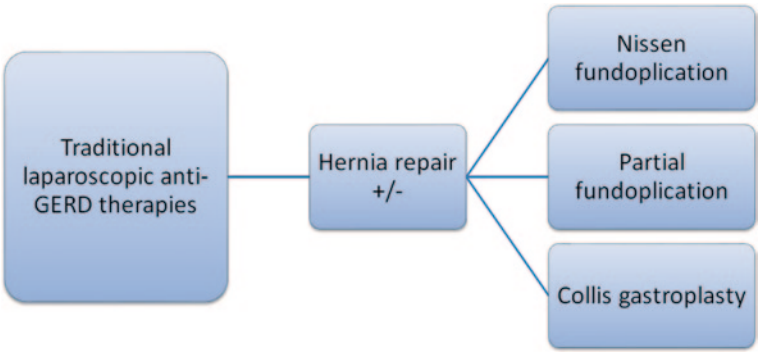

Fig. 7.1 Traditional laparoscopic anti-GERD therapies. *GERD* gastroesophageal reflux disease

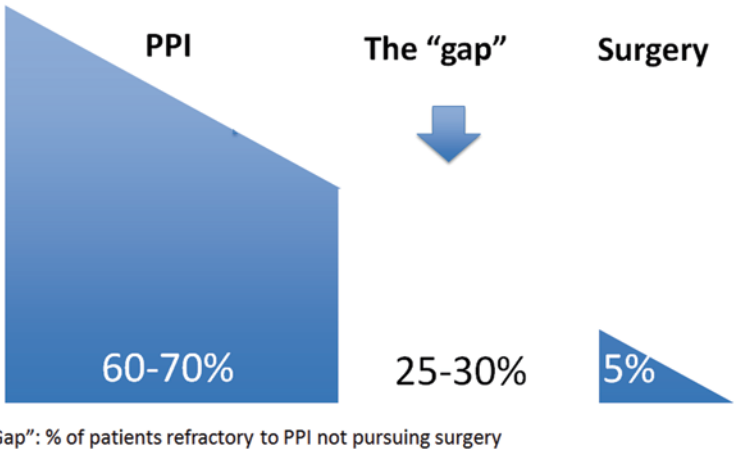

Fig. 7.2 Treatment gap in the management of GERD. *PPI* proton pump inhibitors. (Reprinted from Ref. [9])

Before considering if a minimally invasive GERD therapy is appropriate for a particular patient, it is essential that the diagnosis of GERD is established and other confounding factors have been excluded [5]. Furthermore, there should be confidence that the presenting GERD symptoms are truly reflective of GERD and that the proposed therapy has the potential to eliminate or significantly reduce them. A careful review of the possible determinants of GERD for each patient is essential, since it will help highlight the best strategy (Fig. 7.4) [6]. Unfortunately, various outcome measures have been used to assess the efficacy of minimally invasive GERD therapies, and frequently the lack of efficacy on one or more of these measures is used as a deterring element in the decision-making process. Table 7.2 highlights the most frequent outcome measures used in clinical trials. It is important to note that all of these measures have limitations and that any decision has to be individualized to the particular patient and their expectations. For example, complete normalization of

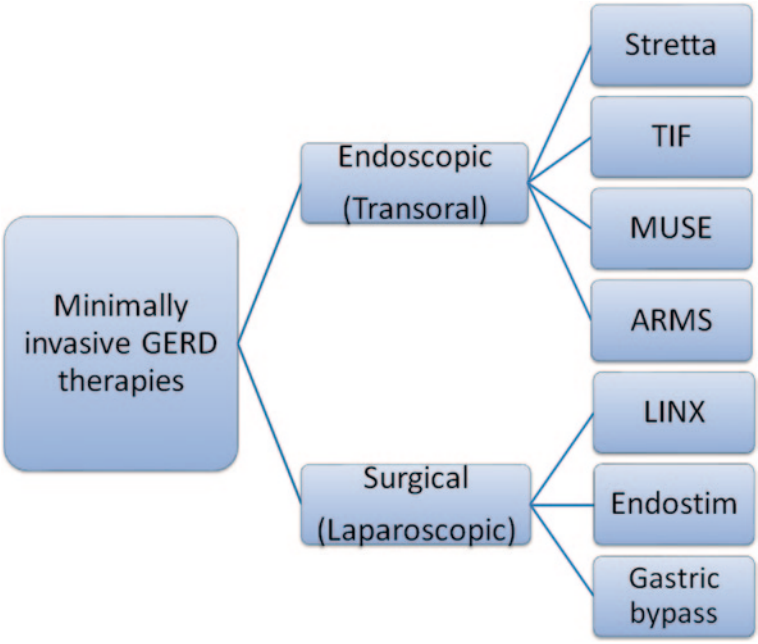

Fig. 7.3 Outline of the various minimally invasive, transoral, and laparoscopic anti-GERD therapies. *GERD* gastroesophageal reflux disease, *TIF* transoral incisionless fundoplication, *MUSE* Medigus Ultrasonic Surgical Endostapler, *ARMS* anti-reflux mucosectomy

Table 7.1 Reasons to consider minimally invasive GERD therapies

Refractory acid reflux and esophagitis despite high-dose PPI
Intolerance to PPI
Inability to comply with daily PPI
Concern about potential PPI-induced long-term adverse effects
Concern about potential short- and long-term adverse effects of surgical fundoplication
Costs of long-term PPI

PPI proton pump inhibitors

esophageal acid exposure time may not be important in a patient who has refractory heartburn despite PPI use, as long as the symptoms improve with the intervention [4]. Similarly, a patient who manages to eliminate volume reflux (regurgitation) but continues to use PPI after a minimally invasive GERD therapy should not be considered a treatment failure. Elimination of troublesome regurgitation and healing of esophagitis are robust clinical end points, but they have only recently been examined in clinical trials [7].

The suitability of a patient for minimally invasive GERD therapy also depends on a careful assessment, both structural and functional, of the EGJ and other factors that could aggravate or precipitate GERD symptoms. Table 7.3 highlights the key determinants of EGJ competence that require expert assessment by endoscopy,

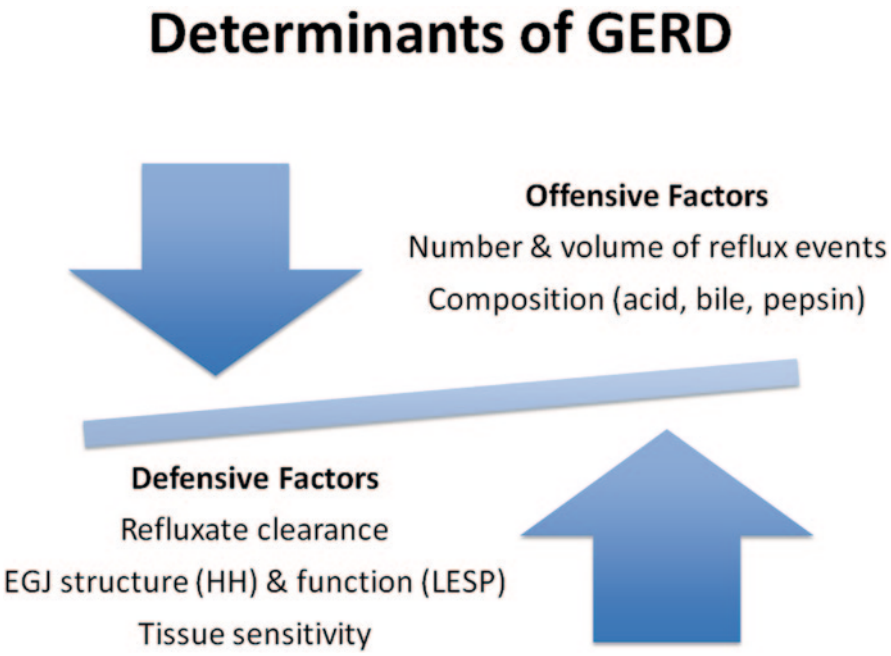

Fig. 7.4 Determinants of GERD that need to be considered prior to an individualized endoscopic or laparoscopic intervention. *EGJ* esophagogastric junction, *HH* hiatal hernia, *LESP* lower esophageal sphincter pressure

Table 7.2 Outcome measures of the efficacy of minimally invasive GERD therapies

Healing of esophagitis
Symptoms (heartburn, regurgitation, etc.)
GERD-related quality of life
PPI use
Esophageal ambulatory pH and impedance testing
Esophageal manometry

PPI proton pump inhibitors, *GERD* gastroesophageal reflux disease

Table 7.3 Determinants of EGJ competence

Intrinsic LES pressure
Intra-abdominal location of the LES
Extrinsic compression of the LES by the crural diaphragm
Integrity of the phreno-esophageal ligament
Preservation of the acute angle of His

LES lower esophageal sphincter

Table 7.4 Essentials of patient assessment

History and physical examination (including BMI)
Prior history of esophagogastric surgery
Endoscopy with biopsies
Endoscopic and radiological assessment of the EGJ
High-resolution manometry (definition of hiatal hernia and peristaltic effectiveness
Esophageal pH/impedance monitoring and symptom association
Gastric emptying

EGJ esophagogastric junction

high-resolution manometry, and barium swallow [8]. Other elements such as the effectiveness of esophageal peristalsis, gastric emptying rate, body mass index (BMI), or prior esophagogastric surgery will also need consideration. The probability of success or failure for each minimally invasive GERD therapy varies significantly, depending on the structural and functional characteristics of an individual patient who has been carefully evaluated and appropriately selected. Clinical trials to date have included a mixed group of patients, resulting in variable and, at times, unsatisfactory results [9]. Table 7.4 outlines the essentials of patient assessment prior to proceeding with anyone of the available minimally invasive endoscopic or surgical techniques.

Figure 7.3 outlines the available minimally invasive GERD therapies that need to be entertained in selected patients. Many of these therapies are at an early stage of their development and utility, and some of them are still not approved in the USA. Their strengths and weaknesses, suitability, and effectiveness need to be balanced against the traditional laparoscopic approaches (with or without hernia repair) or continuation of pharmacologic therapy and lifestyle measures.

Minimally Invasive Endoscopic (Transoral) Therapies

Since the early 2000s, several devices have been developed for the endoscopic treatment of GERD, using approaches such as sewing, transmural fasteners, endoscopic staplers, and thermal treatment using radio-frequency energy. Other devices involving injection (Enteryx, Boston Scientific, Boston, MA, USA) or implantation of foreign materials (Gatekeeper Reflux Repair System, Medtronic, Inc., Minneapolis, MN, USA) at the esophageal junction have been withdrawn from the market. Devices that are currently commercially available for the endoscopic treatment of GERD in the USA include the following: Stretta (Mederi Therapeutics, Greenwich, CT, USA), transoral fundoplication (TF, EndoGastric Solutions, Redmond, WA, USA), and the Medigus Ultrasonic Surgical Endostapler (MUSE™) system (previously known as Supplemental Restraint System (SRS™) system for TF; Medigus, Omer, Israel). Anti-reflux mucosectomy (ARMS) has been recently described, but it is not yet approved for the management of GERD.

Stretta

The Device

Stretta comprises a four-channel radio-frequency (RF) generator and a four-needle balloon–catheter system that delivers pure sine-wave energy (465 kHz, 2–5 W per channel, 80 V maximum at 100–800 Ω). Each needle tip incorporates a thermocouple that automatically adjusts the power output to a desired target temperature of 85 °C in the muscle layer. Temperature is similarly monitored with a thermocouple at each needle base abutting the mucosa, and the power delivery ceases if such mucosal temperature exceeds 50 °C or if impedance exceeds 1000 mΩ. Maintaining tight temperature control prevents mucosal damage, thus preventing stricture formation [10]. The Food and Drug Administration (FDA) originally cleared Stretta for use in 2000 and issued an updated clearance on the RF1 generator in 2011.

The Procedure

An upper gastrointestinal (GI) endoscopy is first performed and the distance from the incisors to the squamocolumnar junction (Z line) is measured. The endoscope is removed, and the RF catheter is passed through the mouth and positioned 1 cm above the Z line according to the distance previously determined. The four needle electrodes are deployed to a preset length of 5.5 mm, and RF delivery is initiated. Additional applications, by rotating and changing the linear position of the catheter, create several rings over a span of 2 cm above and below cardia. The catheter is then removed, and the endoscopy is repeated. Overall, patients receive RF energy at 56 treatment sites over a period of 35 min (Fig. 7.5). Although the exact mechanism of action of Stretta in relieving symptoms of acid reflux is unknown, one potential mechanism is that it decreases the number of transient lower esophageal sphincter relaxations (TLESRs) through a structural rearrangement of the smooth muscle and redistribution of the interstitial cells of Cajal in the smooth muscle of the lower esophageal sphincter (LES) [11].

The Data

Multiple studies, including four randomized clinical trials, have demonstrated the safety and efficacy of Stretta for GERD therapy, and a high rate of symptom control and decrease or elimination of GERD medication use have been consistently achieved. As the endoscopic procedure with the most available data and track record, Stretta appears to be safe, effective, durable, and repeatable, if necessary. Several putative mechanisms could explain Stretta's clinical effectiveness, and they include increased gastric yield pressure, increased thickness of the LES muscle, decreased distensibility of the EGJ without fibrosis, decreased EGJ compliance, and decreased frequency of TLESRs. A recent double-blind sham-controlled study of 22 patients showed that the administration of sildenafil, an esophageal smooth muscle

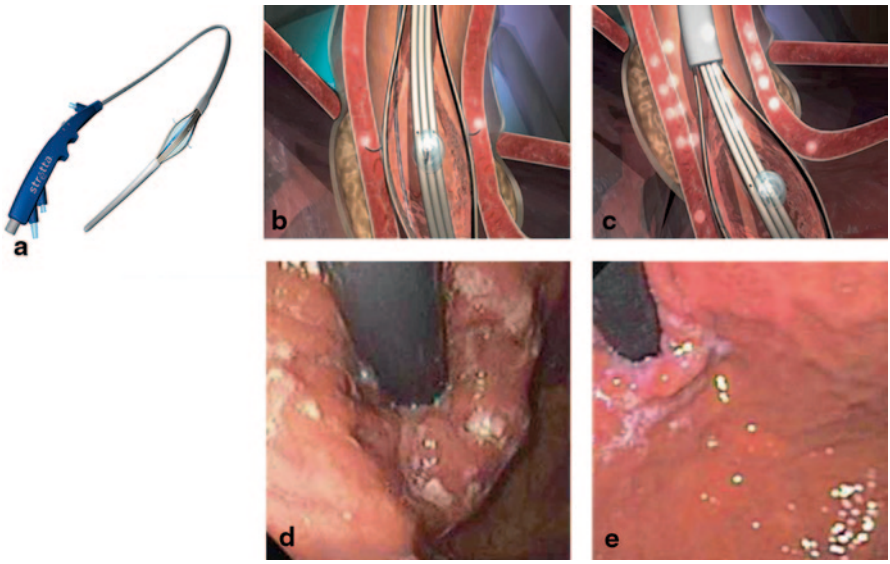

Fig. 7.5 **a** The Stretta catheter. **b**, **c** Diagram of the Stretta procedure depicting the balloon-needle assembly that delivers RF energy to the muscle of the EGJ region (Courtesy of Mederi Inc.). **d** Retroflexed endoscopic image of the cardia immediately after RF energy delivery. **e** Retroflexed endoscopic image of the cardia 3 months after Stretta. (Courtesy of George Triadafilopoulos, MD)

relaxant, normalized the EGJ compliance to pre-Stretta levels, arguing against EGJ fibrosis as an underlying mechanism. Two cohort studies found no adverse effects on vagal function and no significant changes in esophageal motility or swallow-induced LES relaxation pressure arguing against a neurolytic effect. Initial animal studies used porcine and canine models and showed a thickening of the LES, decreased TLESRs, and decreased reflux events [11].

A randomized, sham-controlled trial assigned 64 GERD patients to Stretta or to a sham procedure [12]. At 6 months, active treatment significantly improved patients' heartburn symptoms and quality of life. More active versus sham patients were without daily heartburn symptoms (61 vs. 33 %; $p = 0.05$), and more had a > 50 % improvement in their GERD-health-related quality-of-life (HRQL) scores (61 vs. 30 %; $p = 0.03$). Another randomized prospective trial included 36 patients who were randomized into three groups: single-session Stretta, sham procedure, and single Stretta followed by repeat Stretta if GERD-HRQL was not 75 % improved after 4 months [13]. At 12 months, the mean HRQL scores of those "off" medications, the LES basal pressure, the 24-h pH scores, and the PPI daily dose consumption were significantly improved from baseline in both Stretta groups ($p < 0.01$). Seven patients in the double Stretta treatment group had normalized their HRQL at 12 months compared with two patients in the single-treatment group ($p = 0.035$). Like the other newer techniques, Stretta has not been found useful in patients with hiatal hernias > 3 cm, those with no previous response to PPIs, and those with negative pH or impedance studies.

A recent meta-analysis of 18 studies and 1488 patients concluded that Stretta (1) is very effective in GERD symptom relief, (2) is safe and well tolerated, and (3) significantly reduces acid exposure to the esophagus, but does not consistently normalize pH [14]. On this last point, it is important to note that even PPIs do not normalize pH in up to 50% of symptomatically controlled GERD patients treated with PPIs. Hence, pH normalization is not necessarily an essential clinical end point to be applied to Stretta. In a single-center, long-term (10 years) study, normalization of GERD-related quality of life was achieved in 72% of patients; a 50% or greater reduction in PPI use occurred in 64% of patients (41% eliminating PPIs entirely), and a 60% or greater increase in satisfaction occurred in 54% of patients. Preexisting Barrett's metaplasia regressed in 85% of biopsied patients. Another meta-analysis, however, found that Stretta compared with sham therapy for patients with GERD does not produce significant changes, in physiologic parameters, including time spent at a pH less than 4, LES pressure, ability to stop PPIs, or HRQL [15].

Limitations

Stretta is not to be used in patients with sliding hiatal hernia (>2 cm), severe (>Los Angeles (LA) grade B) esophagitis, or Barrett's esophagus. Data on the procedure's effectiveness and durability have at times produced mixed results. Definitive conclusions have been problematic because of the heterogeneity of measured variables in different studies of variable patient populations.

Summary

With several randomized sham-controlled trials and more than 40 short- and long-term studies, Stretta is a safe, effective, and mature technology and repeatable if necessary [16, 17]. Further, it is the least expensive alternative to medical therapy, and it does not preclude the subsequent use of any other alternative therapy for GERD.

TF

The Device

The device creates molding of tissue and placement of polypropylene suture material in the region of the EGJ. It is composed of a controls handle, a chassis through which the endoscope is inserted and control channels run, side holes on the distal end of the shaft to which external suction can be applied, a tissue mold that pushes tissue against the shaft of the device, a helical screw, which is advanced into tissue to pull tissue, two stylets, which advance from the shaft of the device through the

plicated tissue and then through eyelets in the tissue mold, and a cartridge containing polypropylene H-shaped fasteners [18].

The Procedure

TF is a newer technique devised to perform a partial fundoplication endoscopically (Fig. 7.6). The device retracts the gastric cardia and creates full-thickness serosa-to-serosa plication and valve. In contrast to surgical fundoplication, TF does not involve any abdominal incisions or dissections that could increase the risk for adhesions and complications and is associated with less discomfort and faster recovery. TF has been found to reduce the number of postprandial TLESRs, the number of TLESRs associated with reflux, and EGJ distensibility, leading to a reduction of the number and proximal extent of reflux episodes and improvement of acid exposure [18].

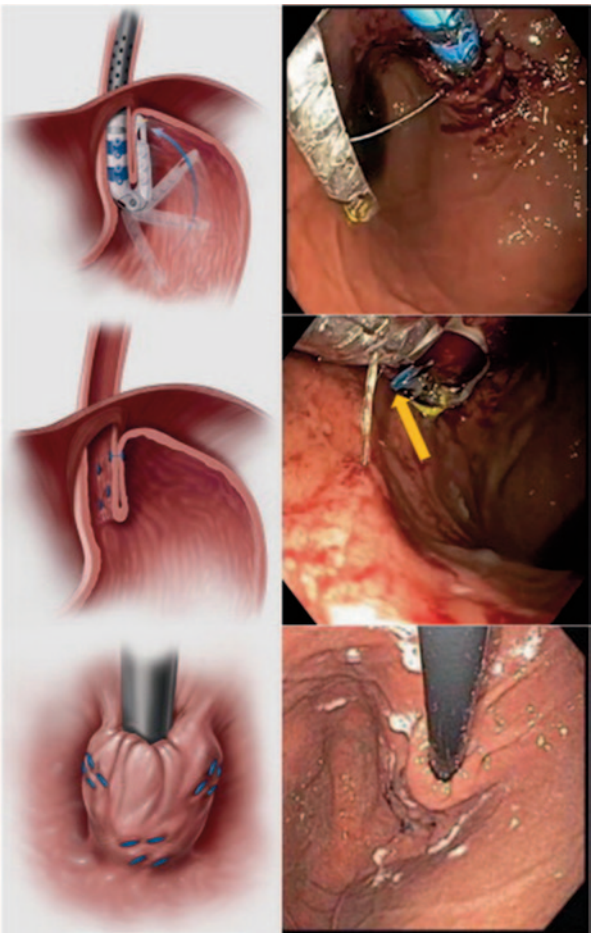

Fig. 7.6 Transoral fundoplication that has created a 3-cm flap valve, 180°–270° in circumference. The valve was created with a minimum of 13 fasteners and was at least 1 cm long at either corner, and 3 cm long in its mid-portion. (Reprinted with permission from [28])

The Data

Several studies have asserted the efficacy and safety of TF. A prospective, sham-controlled trial aimed to determine whether TF would reduce regurgitation more than PPI therapy in patients with GERD without significant (>2 cm) hiatal hernia [19]. Patients were randomly assigned to groups that underwent TF and then received 6 months of placebo ($n=87$), or sham procedure and 6 months of once- or twice-daily omeprazole (controls, $n=42$). Patients were blinded to therapy and reassessed at 2, 12, and 26 weeks. By intention-to-treat analysis, TF eliminated regurgitation in 67% of patients, more than with omeprazole (45%; $p=0.023$). Esophageal acid exposure improved but did not normalize after TF (mean 9.3% before and 6.3% after; $p<0.001$), but not after sham procedure (mean 8.6% before and 8.9% after). Subjects from both groups who completed the protocol had similar reductions in GERD symptom scores. Severe complications were rare (three subjects receiving TF and one receiving the sham procedure).

In patients with incomplete symptom control on high-dose PPI therapy, TF may provide further elimination of symptoms and heal esophagitis [20]. A randomized, multicenter, open-label, crossover study aimed to evaluate if TF could further improve clinical outcomes in partial responders to high-dose PPI therapy and to evaluate the durability of such effect. Patients with GERD and hiatal hernia ≤2 cm were randomized to TF ($n=40$) or high-dose PPI therapy ($n=23$) group. At 6-month follow-up, PPI patients underwent crossover. The investigators then assessed clinical outcomes 6 months post TF in crossover patients, as compared to 6 months of PPI therapy, and 12-month outcomes in patients initially randomized to TF. The primary outcome was symptom control using standard questionnaires. There were 39 analyzable TF patients and 21 crossover patients. In the latter group, TF further improved control of regurgitation and of atypical symptoms achieved after 6 months of PPI. Of 20 patients with GERD symptoms after 6 months of high-dose PPI therapy, 65% (13/20) reported global elimination of troublesome regurgitation and atypical symptoms post TF off PPI; 67% (6/9) reported no significant regurgitation. Esophagitis further healed in 75% (6/8) of patients. Seventy-one percent of crossover patients were off PPI 6 months following TF. In the original TF group, 12-month post-TF, 77% of patients achieved complete symptom control, 82% ceased PPI therapy, 100% healed esophagitis, and 45% normalized esophageal acid exposure.

An open, prospective, multicenter study assessed the 2-year symptom control of TF [21]. Secondary outcomes were PPI use, degree of esophagitis, safety, and changes in esophageal acid exposure. Of the 127 patients who underwent TF, 15% were lost to follow-up; 8 patients underwent revisional surgery but were included, as failures. No serious adverse events were reported. Scores for GERD-related HRQL and regurgitation improved by >50% in 66 and 70% of patients, respectively. Reflux scores normalized in 65% of patients, and daily PPI use decreased from 91 to 29%.

Another open, single-center study assessed the long-term effect of TF on pathological reflux and symptoms in 50 GERD patients who were dependent on PPI

therapy and found that TF achieved lasting elimination of daily dependence on PPI in 75–80% of patients for up to 6 years [22]. In all, 83.7, 79.6, 87.8, and 84.4% of patients stopped or halved the PPI therapy 6, 12, 24, and 36 months after TF. Impedance monitoring indicated significantly fewer total and acid refluxes after treatment ($p=0.01$). Factors predicting good outcomes were pre-procedure Hill's grade I–II, no hiatal hernia or hernia ≤2 cm ($p=0.03$), the absence of ineffective esophageal motility ($p<0.0001$), and the number of fasteners deployed ($p=0.01$). In patients who fail TF, LARS is a feasible and safe option without additional operative morbidity [23].

Limitations

The available data are limited to patients without significant hiatal hernia (<2 cm).

Summary

Transoral incisionless fundoplication (TIF) has emerged as a safe, effective, and durable alternative to GERD patients who do not respond completely to PPI without the adverse event profile associated with LARS.

MUSE™

The Device

The MUSE™ endoscopic stapling system is a recently introduced technique capable of creating an endoscopic partial fundoplication. The device consists of a flexible endoscope, a video camera, an ultrasonic range finder, and a surgical stapler.

The Procedure

The MUSE endoscope is inserted and advanced into the stomach and retroflexed, pulling it back to the correct stapling level above the EGJ. Tissue is then clamped and stapled under ultrasonographic gap finder. The procedure is repeated a few times to form a flap, representing a 180° fundoplication (Fig. 7.7) [24].

The Data

The procedure has shown promise in a preclinical trial, where 12 study animals underwent the procedure, and all of them had a satisfactory partial fundoplication,

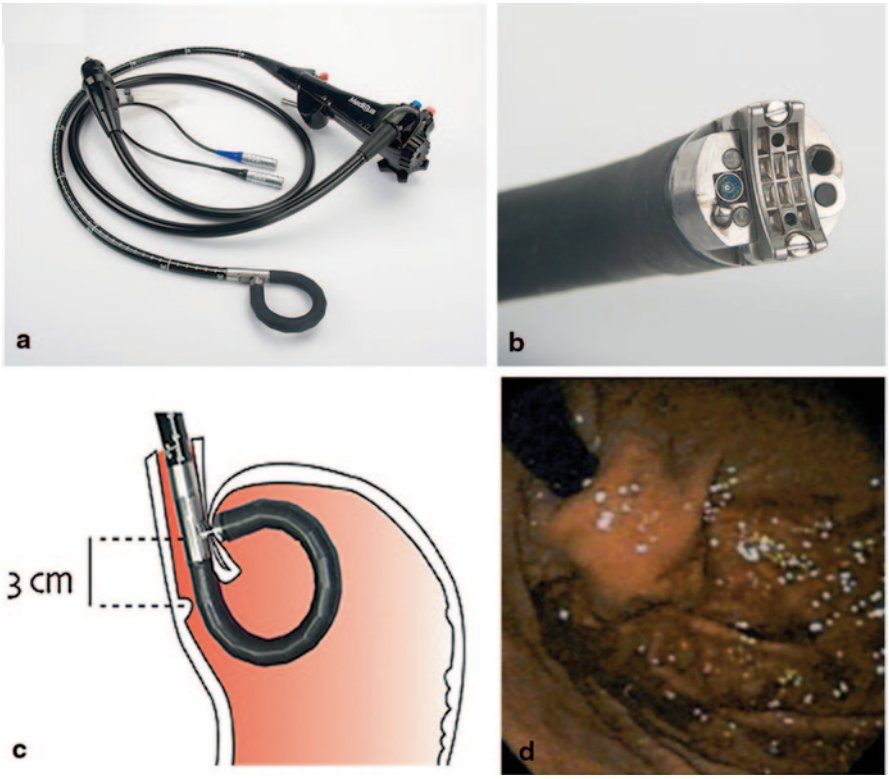

Fig. 7.7 Medigus transoral surgical stapler *(MUSE™)*: **a** Full flexible endostapler, outside diameter *(OD)* 15.5 mm. **b** Distal tip. **c** Positioning of cartridge 3 cm proximal to gastroesophageal junction for stapling. **d** Gastric cardia (retroflexed) view of an effective gastroesophageal flap valve. (Reprinted with permission from Ref. [26])

with no procedure-related complications [25]. One of the first human trials using an earlier version of MUSE was conducted to compare it with LARS. Of 27 non-randomized patients, 11 underwent MUSE and 16 underwent LARS. Over a 6-month follow-up, a decrease in GERD-HRQL scores was achieved in 64 and 87% of patients who had MUSE and LARS, respectively. An esophageal perforation observed in the endoscopic group completely recovered after over-the-scope clipping. Procedure times for MUSE and LARS were 89 and 47 min, respectively ($p < 0.05$). During 6 months mean follow-up, PPI use was similar, and GERD-HRQL scores dropped in both groups.

A multicenter, prospective study evaluated the clinical experiences of 69 patients who received endoscopic anterior fundoplication with a video- and ultrasound-guided transoral surgical stapler [26]. Its initial 6-month data demonstrated safety and efficacy but necessitated procedure and device changes to improve safety, which in turn led to improved results in the later portion of the study. Of the 66 patients who completed follow-up 6 months after the procedure, the GERD-HRQL score

improved by >50% off PPI in 73% of patients and 64.6% were no longer using daily PPI medication. Common adverse events were perioperative chest discomfort and sore throat. Two severe adverse events (empyema and GI bleeding) requiring intervention occurred in the first 24 subjects, but no further esophageal injury was noted in the remaining patients.

Limitations

Larger randomized studies with longer periods of follow-up are required before its clinical use is considered. Continued assessment of durability and safety are ongoing.

Summary

Very early experience with different versions of the device is promising, but inconclusive and randomized trials are needed.

ARMS

The Device

Very recently, Japanese authors have reported the clinical outcomes of two case series in which they used conventional endoscopic polypectomy and dissection tools to perform ARMS [27].

The Procedure

ARMS is performed using endoscopic mucosal resection (EMR) and 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. It is preferably performed in a crescentic fashion along the side of the lesser curve of the stomach, thus preserving a sharp mucosal valve at gastric cardia (Fig. 7.8).

The Data

In one study, GERD symptoms improved significantly after ARMS; the mean heartburn score decreased from 2.7 to 0.3 ($p=0.0011$) and the regurgitation score from 2.5 to 0.3 ($p=0.0022$). Ambulatory 24-h esophageal pH monitoring showed that the

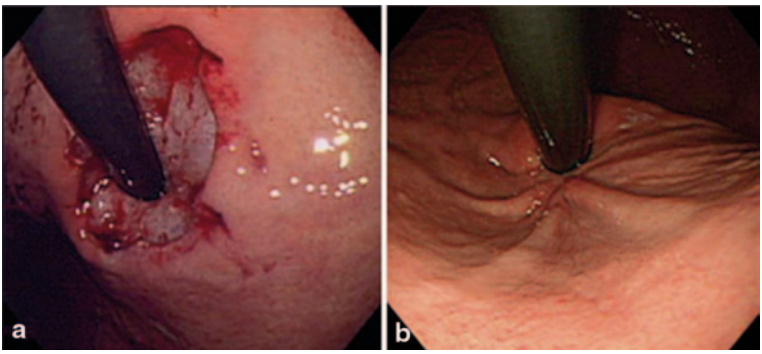

Fig. 7.8 Endoscopic follow-up of circumferential anti-reflux mucosectomy (*ARMS*) (retroflexed views). **a** Immediately after circumferential ARMS. Approximately 2 cm-wide gastric cardia mucosa was circumferentially resected by cap-endoscopic mucosal resection method. **b** Appearance at 3 years revealing a tight gastroesophageal junction with convergence of three gastric folds along the lesser curve of the stomach. (Reprinted with permission from Ref. [28])

fraction of time at pH < 4 improved from 29.1 to 3.1 % ($p = 0.1$) [28]. Fraction time absorbance more than > 0.14 of bile reflux also improved from 52 to 4 % ($p = 0.05$). In two cases of total circumferential resection, repeat balloon dilation was necessary to control distal esophageal stenosis. In all cases, PPI therapy was discontinued.

Limitations

Although these pilot studies showed promising results, larger studies with long-term follow-up will be needed. Dysphagia is a concern.

Summary

The very limited, uncontrolled data from experienced Japanese endoscopists will need to be validated by larger trials.

Minimally Invasive Surgical (Laparoscopic) Therapies

Magnetic Sphincter (LINX)

The Device

The LINX device consists of a necklace of magnetized beads (Torax Medical, Minnesota, USA; Fig. 7.9), and it is placed laparoscopically around the EGJ in order

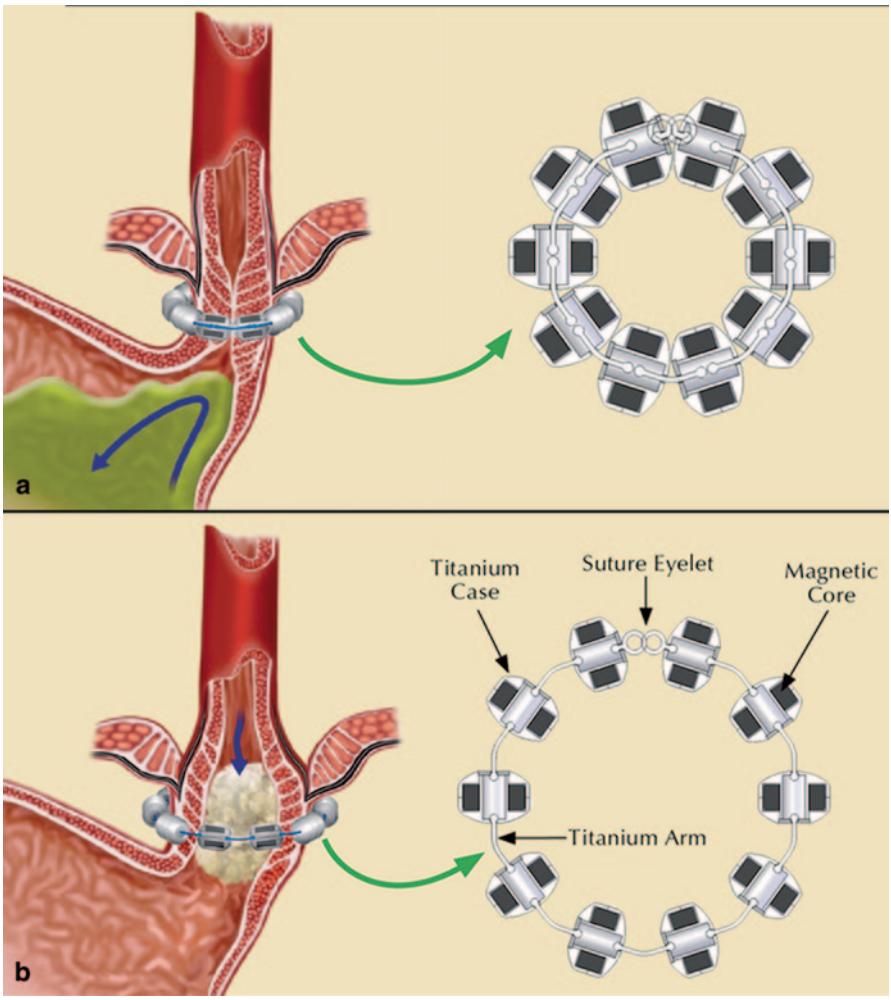

Fig. 7.9 Magnetic device for augmentation of the lower esophageal sphincter. **a** The magnetic device is in the closed position, which helps prevent opening of the lower esophageal sphincter and subsequent reflux. Each magnetic bead rests on adjacent beads to prevent esophageal compression. **b** The device is in the open position, which allows transport of food, belching, and vomiting (Courtesy of TORAX Medical, Inc.)

to mechanically augment the LES function. The device obtained Conformité Européene (CE) mark for Europe in 2008 and the FDA approval for the USA in 2012. The system uses a small expandable ring of linked magnetic beads. The magnetic attractive forces between each bead augment the pressure profile of the LES. At higher intraluminal pressures, the magnetic forces are overcome, allowing functions such as swallowing, belching, or vomiting.

The Procedure

The device is laparoscopically implanted around the distal esophagus, at the level of the EGJ. Dissection is performed along the anterior border of the crura to create a retro-esophageal tunnel. The posterior vagal trunk is dissected off the esophagus as to avoid it being encompassed into the device. A sizing tool similar to the final device is placed through the retro-esophageal window to determine esophageal circumference. The appropriately sized definitive device is then placed in the same fashion, wrapped around the esophagus, and tied.

The Data

The first publications reporting human trials of the LINX device date back to 2008 [29]. The initial study was conducted in Italy and reported 1-year results of 41 patients complaining of heartburn and taking daily PPI. Patients had a BMI between 19 and 38.4 (median 24.5), and exclusion criteria were a sliding hiatal hernia greater than 3 cm, greater than LA grade A esophagitis, or the presence of Barrett's esophagus. After implantation, the GERD-HRQL score decreased from 26.0 to 1.0 ($p<0.005$). At 3 months postoperatively, 89% of patients were off anti-reflux medications, and 79% of patients had a normal 24-h pH test. Interestingly, there was no difference in manometric result before and after implant, with a mean LES tone of 14.1 preoperatively and 19.0 postoperatively ($p=0.19$). All patients preserved the ability to belch. However, mild dysphagia occurred in 17 patients (45%). It resolved in the majority without any treatment but one patient required removal of the device 8 months post-op for persistent dysphagia. A 2-year follow-up of the same cohort was published in 2010 [30], with similar results: 86% of patients were off PPI at 2 years, 90% had normal pH study, and no migration or erosion was reported. No further patient required explant of the device.

In 2012, the FDA panel unanimously voted that the data provided showed safety and efficacy of the device and were therefore approved for use in the USA [31]. The basis for this approval was a 100-patient, multicenter, pivotal trial subsequently published in 2013 [32]. The primary outcome measure was normalization of esophageal acid exposure or a 50% or greater reduction in exposure. At 1 year, 64% of patients achieved >50% reduction or resolution of acid exposure, and 93% achieved a 50% reduction or more of PPI intake. Esophagitis decreased from 40 to 12% at 1 year and 11% at 2 years ($p<0.001$); however, three patients developed de novo esophagitis over the course of the study. Interestingly, 13% of patients were satisfied with their reflux condition with PPI (preoperatively) versus 94% postoperatively. All but two patients maintained their ability to vomit. Dysphagia was reported in 68% of patients postoperatively and 11% at 1 year. Nineteen patients required endoscopic dilation. Early removal of the device (≤3 months) was required in three patients due to severe and persistent dysphagia. Three other patients required late removal (>6 months) due to persistent reflux in one, vomiting in another and chest pain in the last one. The FDA approval did require the company to conduct two post-approval studies to further evaluate long-term

effectiveness and incidence of adverse events: one is an extended 5-year follow-up of the pivotal trial cohort; the second is a 5-year 200-patient multicenter study.

Other studies have now replicated the initial studies with similar findings [33–35]. A recent publication reported the results of the first 1000 cases worldwide by pooling results from published articles, FDA, and manufacturer databases, with a median implant duration of 274 days [36]. Dilation was required in 5.6% of patients, mostly during the first 3 months after implant. There was one intraoperative complication (respiratory arrest), likely non-device related, and readmission rate was 1.3%, mostly due to dysphagia, pain, or nausea and vomiting. The device was removed in 3.4% of patients, mostly due to dysphagia (median 94 days). The first case of erosion was reported in this series: The erosion was endoscopically managed by cutting the link between the exposed magnetic beads. Subsequent endoscopies showed healing of the erosion site, and the device was simply removed laparoscopically 3 months later without complications.

Although there are no randomized controlled trials, the first comparative trial between the LINX system and LARS was recently published [37]. This was a matched case–control study involving 12 patients per group. Patients were matched for age, gender, GERD symptoms, and hiatal hernia size. Operating time was shorter in the LINX group, and symptomatic GERD resolution was similar (75 vs. 83%). While one third of LARS experienced bloating, flatulence, or diarrhea, 83% of LINX patients reported dysphagia versus 58% in the LARS group. However, 50% of LINX patients ultimately required endoscopic dilation (with good results) versus none in the LARS group.

Limitations

Current indications for the LINX system are similar to the inclusion criteria from the pivotal trials which exclude a significant proportion of GERD patients, such as those with Barrett's esophagus or a hiatal hernia >3 cm. Two important questions remain: What will be the long-term risk of erosion from a foreign body around the esophagus, and to what degree will the device be an impediment to the subsequent performance of an MRI? The 5-year data of the initial pivotal trial are forthcoming.

Summary

After more than 1600 cases worldwide, the magnetic sphincter augmentation has so far proven to be both safe and effective for patients who fall in the treatment gap. It provides effective objective and subjective resolution of GERD. Dysphagia is the most common adverse effect of the procedure with a significant portion of patients requiring endoscopic dilatation (with good results thereafter). Erosion rates have so far been very low (1/1000). Contrary to LARS, practically all patients maintain the ability to belch and/or vomit. The procedure does not significantly alter gastric anatomy and can be reversed if necessary.

LES Electrical Stimulation (EndoStim)

The Device

The EndoStim™ LES stimulation system (EndoStim, St. Louis, MO) is an implantable electrical stimulator that delivers electrical energy to the LES (Fig. 7.10). It comprises three components: a bipolar stimulation lead, an implantable pulse generator (IPG), and an external programmer. The stimulation leads are implanted in the LES and secured permanently along with IPG in a subcutaneous pocket. The external programmer allows for wireless interrogation and programming of the IPG. Electrical stimulation is believed to increase the resting pressure and control reflux. The device delivers 30-min sessions of electrical LES stimulation—up to 12 per day—and are scheduled premeal and pre-reflux event based on patient symptoms and baseline 24-h pH recordings. An interesting feature to the device is a sensor to detect upright and supine positions, and the stimulation algorithm can be customized based on patient position in order to address supine/nocturnal reflux [38]. EndoStim is not FDA approved and therefore not available in the USA. It has obtained CE mark in 2012 and is available in Europe. The device is currently evaluated in an ongoing international multicenter trial aiming to recruit 45 patients and an estimated completion date of July 2016 (NCT01574339). A novel potential application and interesting ongoing trial are aiming to evaluate the efficacy of EndoStim on GERD symptoms in patients who have undergone a sleeve gastrectomy (NCT02210975). This study aims to recruit ten patients and should be completed in 2016.

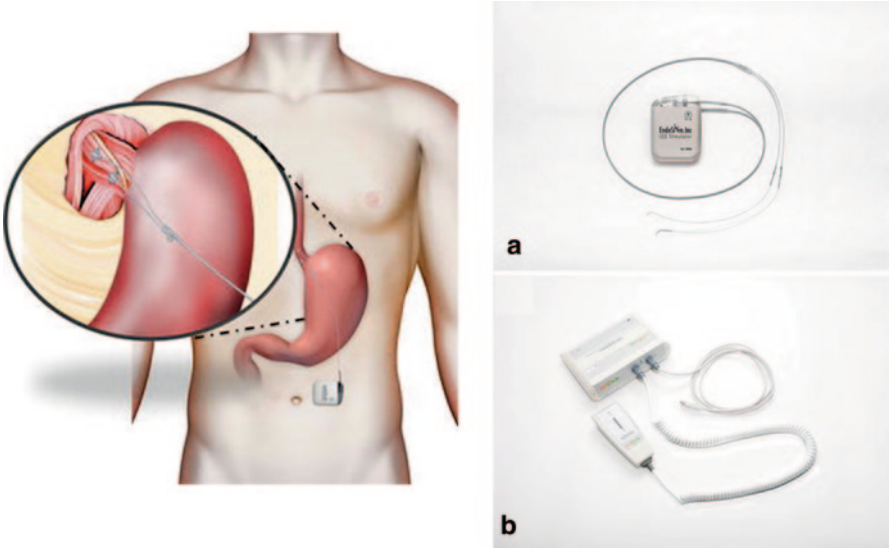

Fig. 7.10 LES neurostimulator. **a** Schematic of the device placement. **b** Stimulator and leads. (With kind permission from Springer Science+Business Media: [41])

The Procedure

The EndoStim is placed laparoscopically, with the two bipolar electrodes sutured 1 cm away from each other, into the anterior portion of the lower esophagus. The Z line is identified endoscopically, and the suture placement is directed by transillumination. Placement of the electrodes is performed under endoscopic visualization. The bifurcated bipolar lead is passed in the esophageal wall using a guiding needle, taking a 15-mm superficial longitudinal bite at the anterior right aspect of the esophagus above the Z line. The electrode is placed in the muscularis propria of the LES. The second electrode is placed in similar fashion in an inline position and approximately 10 mm distal to the first electrode. The IPG is placed in a subcutaneous pocket in the left upper quadrant [38].

The Data

The device's safety and efficacy has been evaluated in a single, open-label trial, involving 24 patients, the results of which were the basis for CE mark approval. This trial has led to three publications of short- (6 months) and long-term results (1 year) and a subgroup analysis evaluating proximal esophageal acid exposure [39–41]. Selection criteria included patients with GERD who were at least partially responsive to PPI therapy, with hiatal hernia ≤ 3 cm. Patients with esophagitis up to LA grade C were included. Manometric selection criteria were also applied and required resting LES end expiratory pressure ≥ 5 mmHg and ≤ 15 mmHg and normal esophageal motility. Median GERD-HRQL score at 6 months was 2.0 (interquartile range (IQR) = 0–5.5) and was significantly better than both baseline on PPI (9.0 (range = 6.0–10.0); $p < 0.001$) and off PPI (23 (21–25); $p < 0.001$) GERD-HRQL. At their 6-month follow-up, 91% (21/23) of the patients were off PPI and had significantly better median GERD-HRQL on LES stimulation compared to their on-PPI GERD-HRQL at baseline (9.0 vs. 2.0; $p < 0.001$). No serious adverse events were reported. At 1 year, 69% of patients showed either normalization or >50% improvement in their distal esophageal pH, and 96% of patients (22/23) were completely off PPI medication. Esophagitis improved by at least one grade in 58% (14/24) of patients at 3 months and 57% (13/23) of patients at 12 months compared with baseline.

One advantage of the device is that electrical stimulation can be tailored to the individual needs using the external programmer. Additional sessions can be added or the timing of existing sessions changed at follow-up to address residual symptoms or residual acid events on pH testing. This however is also time-consuming as seen in the study protocol: pH studies, symptom questionnaire, and device interrogation were performed at 4 weeks, 3 months, 6 months, and 12 months postoperatively. Indeed one patient had the device removed due to "anxiety related to the device and the multiple invasive tests required by the protocol" since the device required multiple adjustments to the electrical stimulation over the 1-year period. However, this also resulted in significantly better results in distal esophageal pH at

12 months (3.3% duration of pH < 4) versus 3 months (6.3% duration of pH < 4) versus baseline (10.1% duration of pH < 4;) $p < 0.001$). Reported adverse event were mostly minor (pain at implantation site, nausea), and one patient had esophageal spasms and underwent a full cardiac workup. No patients reported GI symptoms such as bloating or inability to vomit or belch [42].

In a post hoc analysis of the open-label trial, significant improvement in the outcomes of GERD-HRQL and distal esophageal pH were noted. At baseline, on PPI therapy, 33% of patients reported nocturnal heartburn symptom "bothersome" compared to 0% ($p = 0.04$) at 3 months and 7% ($p = 0.17$) at 6 months. In a more recent study, five patients successfully underwent implantation and all of them had significant increase in LES pressure on all sessions of stimulation, without any adverse event. In another post hoc analysis, the effect of electrical stimulation on proximal esophageal acid exposure measured at 23 cm above the upper border of LES was studied. Total median proximal esophageal acid exposure at baseline was 0.4%, and at 12 months it was 0%. Distal esophageal pH improved from 10.2 to 3.6%. There were no serious adverse events. It was concluded that the device might be useful in treating proximal GERD [41]. LES electrical stimulation also improves sleep quality and work productivity in patients with refractory GERD [43]. In a pilot, short-term trial, endoscopically implanted temporary stimulation leads resulted in a significant increase in LES pressure without affecting patients' swallowing or causing adverse events [44].

Limitations

The EndoStim device has only been evaluated on a small cohort of patients, and it appears that the tailoring of the therapy is time- and resource consuming, as well as somewhat invasive. There are no randomized trials either against other therapies or in on/off settings with the implanted device. Longer-term data will be required to confirm there is no "fading" of the positive effects seen during the first year after implantation. MRI compatibility remains a concern.

Summary

The EndoStim has demonstrated an excellent safety profile in a small patient cohort, while demonstrating effective anti-reflux results. Similarly to the LINX procedure, it is an effective alternative for patients who only partially respond to PPIs. Its lack of any effect of esophageal motility or LES relaxation is an added advantage, especially in patients with poor esophageal motility. It is also reversible, requires minimal disruption of the local anatomy during implantation, and provides symptom relief while maintaining the ability to vomit and belch.

Laparoscopic Roux-en-Y Gastric Bypass

The Device

Conventional laparoscopic surgery equipment is used.

The Procedure

Contrarily to the two previous therapeutic modalities, laparoscopic Roux-en-Y gastric bypass (LRYGB) is neither a device nor new: Open Roux-en-Y gastric bypass (RYGB) was described by Mason and Ito in the 1960s [45], and the effects of RYGB on acid secretion and reflux were studied in the 1970s and 1980s [46], with an emphasis on creating a small proximal pouch [47].

However, with the incidence of obesity dramatically increasing worldwide, and the clear relationship between GERD and obesity [48], the comanagement of these conditions has shed a new light onto LRYGB. Compared to other common bariatric procedures such as adjustable gastric banding or sleeve gastrectomy, LRYGB has a unique impact on GERD. Indeed, beyond the indirect impact via weight loss, RYGB offers a direct and radical elimination of acid reflux. LRYGB includes the creation of a very small (< 20 cc) gastric pouch, along the lesser curve of the proximal stomach. Effectively, this step separates the vast majority of acid producing cells from the distal esophagus, creating a "perfect" anti-reflux configuration. After the small gastric pouch is created, a Roux limb measuring approximately 100–150 cm is brought up and anastomosed to the pouch. A Y reconstruction is performed with a pancreatobiliary limb of at least 40 cm. This configuration therefore not only prevents acid but also bile reflux into the distal esophagus.

The Data

By the current National Institutes of Health (NIH) criteria for bariatric surgery, LRYGB is only performed on patients with a BMI > 35 kg/m^2. Studies have focused on comparing laparoscopic Nissen fundoplication (LNF) and LRYGB for GERD control and studying LRYGB as a "salvage" procedure for obese patients with GERD recurrence after LNF.

In a large study comparing 6100 LNF patients to 21,150 LRYGB patients, the two procedures had a comparable short-term risk profile, with similar length of stay (3 days), mortality (0.05 vs. 0.1 % [NS]), and hospital costs (US$13,100 vs. US$13,200). LRYGB patients had a significantly lower in-hospital complication rate (10 vs. 7 % [$p < 0.05$]) [49].

Effectiveness on GERD has mostly been performed by symptoms questionnaires. A pre- and postoperative study of 152 LRYGB patients with GERD showed a significant decrease in heartburn (87–22 %, $p < 0.001$); water brash (18–7 %,

$p < 0.05$) and wheezing (40–5 %, $p < 0.001$). Postoperatively, the use of PPI and H_2 blockers decreased significantly (44–9 %, $p < 0.001$ and 60–10 %, $p < 0.01$, respectively) [50]. In a similar study of 57 patients, all patients reported improvement or no symptoms of GERD at a mean follow-up of 18 months. GERD-HRQL median score was < 1 (scale, 0–45, 0 = asymptomatic, 45 = worse) [51]. In another study, comparing six LNF to six LRYGB patients, both groups' mean DeMeester scores were normal post-op. Symptoms score improved in a similar fashion in both groups (3.5–0.5 in the LNF group and from 2.2 to 0.2 in the LRYGB group). After surgery, mean LES resting pressures increased more in the LNF group than in the LRYGB group—12.9–35.5 ($p = 0.003$) and 23.6–29.7 ($p = 0.45$)—respectively [52].

An international survey of 92 surgeons showed that 91 % of them felt LRYGB was the best surgical option for morbidly obese patients and 35 % chose to do nothing rather than subject these patients to a fundoplication [53].

Conversion from LNF to LRYGB has been evaluated in small case series. These surgeries are notoriously more complex (as illustrated by an average operative time of 6 h in one study) and complication rates significantly higher than standard LRYGB [54]. GERD symptoms improved significantly in a small series of seven patients with a mean GERD-HRQL score decreasing from 27.9 to 8.4 postoperatively ($p = 0.006$). In a larger recent series of nearly 50 patients, 11 % of patients required reoperation, but 93.3 % were symptom free at the averaged 11-month follow-up [55].

Limitations

LRYGB is essentially limited to morbidly obese patients and carries a higher complication rate than the procedures described above, including severe complications such as anastomotic leaks or thromboembolic events.

Summary

LRYGB is an excellent anti-reflux procedure, and current data support LRYGB as the surgical procedure of choice in morbidly obese patients with GERD.

Conclusion

Exciting new devices and endoscopic as well as laparoscopic techniques have been introduced and are actively and increasingly used in patients with GERD, particularly in those who are not responding to PPI therapy. Table 7.5 highlights these treatment options and synthesizes the data presented above. Endoscopists and surgeons are increasingly called upon to manage such challenging patients with GERD. Figure 7.11 outlines our proposed algorithm on the management of refractory

Table 7.5 Minimally invasive therapies for GERD

Therapy	Key features
Endoscopic (not applicable to those with >2 cm sliding hiatal hernia)	
Stretta	Outpatient, easy, safe, good long-term efficacy, minimal side effects, RCT trials
TF	Outpatient, difficult, safe, limited long-term efficacy, minimal side effects, RCT trials
Medigus	Outpatient, difficult, limited safety and long-term efficacy, and side effects, no RCT trials
ARMS	Outpatient, requires EMR and ESD experience, single-study data, no RCT trials
Laparoscopic (may involve hiatal hernia repair)	
LINX	Short stay, effective, easy, very good safety and efficacy, minimal side effects; foreign body concerns, no RCT trials
EndoStim	Short stay, effective, easy, very good safety and efficacy, minimal side effects; foreign body and battery concerns, no RCT trials
Gastric bypass	Very effective, limited to morbidly obese, long-term nutritional side effects; no RCT trials

RCT randomized controlled trial, *TF* transoral fundoplication, *ARMS* anti-reflux mucosectomy, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

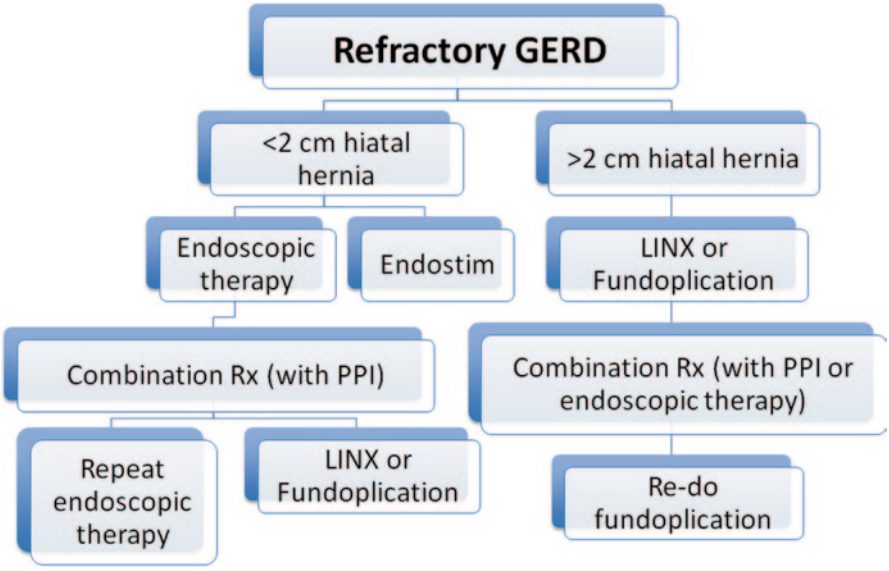

Fig. 7.11 Proposed outline of the management of refractory GERD using minimally invasive, transoral, and/or laparoscopic approaches. Treatment options should be highly individualized, based on patients' history, determinants of GERD and presence of hiatal hernia, desired end points, and physician expertise. For those patients who do not successfully respond to one modality, another approach, single or in combination with others, may be considered. *PPI* proton pump inhibitors

GERD, mostly based on the presence of an underlying sliding hiatal hernia and the degree of symptomatic response to previous interventions. GERD is a chronic disease, and many of its therapies may at some point fail; hence combination strategies may be required over the life span of a particular patient. Accurate clinical assessment of patients in a multidisciplinary milieu and in specialized centers with focused expertise in all minimally invasive techniques is strongly recommended.

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Chapter 8
Role of LES Augmentation for Early Progressive Disease in GERD and Fundoplication for End-Stage Disease in GERD

Stephanie G. Worrell and Tom R. DeMeester

Introduction

Gastroesophageal reflux disease (GERD) is the most common foregut disease in the world and accounts for approximately 75% of all esophageal pathology [1]. The majority of afflicted patients have mild disease and are successfully managed with lifestyle modifications and acid suppression medication [2]. Fortunately, progression to erosive disease occurs in only 13% of patients over 5 years [3]. Unfortunately, progression to Barrett's esophagus occurs in 10% of patients over 5 years [3]. In these patients, the lower esophageal sphincter (LES) progresses from transient to permanent failure. The impetus to identify and counsel patients with progressive disease regarding the need for surgical therapy is critical. This message goes largely unheeded by the gastroenterologist due to their lack of confidence in the durability of a fundoplication and concern over the side effects of the operation. Consequently, the early referral of a patient with symptoms and signs of progressive disease for surgical therapy is resisted. Further, there is widespread concern that not all surgeons are sufficiently experienced in evaluating esophageal patients, many are not knowledgeable enough to select the proper anti-reflux procedure, and some are not sufficiently trained to properly perform the procedure [4, 5]. The advent of sphincter augmentation procedures allows early treatment of patients who have clinical flags of early progressive disease. This will potentially mitigate the risk of the disease progressing to chronic erosive esophagitis, Barrett's esophagus, and esophageal carcinoma.

T. R. DeMeester (✉) · S. G. Worrell
Department of Surgery, Keck Medical Center of University of Southern California, 892 Huntington Garden Drive, San Marino, Los Angeles, CA 91108, USA
e-mail: tom.demeester@med.usc.edu

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Role of LES Augmentation for Early Progressive Disease in GERD

Determining the Status of the LES

The discovery of the lower-esophageal high-pressure zone, or LES as it was late named, led to the realization that almost half of the patients with confirmed GERD by 24-h pH monitoring have a normal LES on a motility study performed off medications, at rest, in the recumbent position, and after an overnight fast [6]. The etiology of reflux in patients with a normal LES is due to dynamic failure of the LES. This consists of transient openings of the LES when challenged by gastric distension or non-pressurized gastric dilation [7, 8]. These events are called transient LES relaxations (TLESRs) and were first described by Dodds in 1982 [9]. Gastric distension occurs with overeating or excessive dry swallowing. Each dry swallow carries with it saliva and the 15 cc of air contained within the pharyngeal space. The swallowed food and air collect in the stomach and if excessive cause pressure-generated gastric distension. Gastric dilation, on the other hand, is due to normal physiologic relaxation of gastric muscle with the ingestion of a meal and is termed adaptive relaxation [10]. Gastric dilation is not associated with an elevation of intragastric pressure.

There are two proposed explanations for the occurrence of TLESRs. One, favored mainly by gastroenterologists, proposes that TLESRs are due to a neuro-mediated reflex initiated by pressurized gastric distension or non-pressurized dilation from gastric adaptive relaxation induced by a meal [11]. These conditions stimulate stretch receptors in the gastric fundus that in turn stimulate vagal afferents that relay the input from the receptors to the medulla. Medullary nuclei then orchestrate the efferent limb of the reflex via the vagal and phrenic nerves to elicit prolonged LES relaxation, crural diaphragm inhibition, and distal esophageal shortening [12].

The second explanation, favored mainly by surgeons, proposes that TLESRs are due to transient shortening of the LES length with the effacement of the LES by pressurized gastric distension or non-pressurized dilation due to meal-induced adaptive relaxation. Normally, in the fasting state and resting recumbent position, the median overall LES length is 3.6 cm and the intra-abdominal length is 2.2 cm [13]. With gastric distension or dilation, the length of the LES shortens as the LES is effaced and taken up by the gastric fundus [8]. When gastric distension or dilation is excessive, the length of the LES shortens to the point where the corresponding pressure of the LES can no longer maintain closure, the LES opens and gastroesophageal reflux occurs [13]. This occurs predominately during the postprandial period [14].

During effacement and shortening, the distal end of the LES is taken up by the fundus and exposed to gastric juice causing inflammation and ulceration of the effaced portion of the distal LES [8]. If the inflammation continues, it can permanently reduce the abdominal length to < 1 cm and limit the ability of the LES to respond to intra-abdominal pressure challenges [15–18]. Similarly, persistence of the

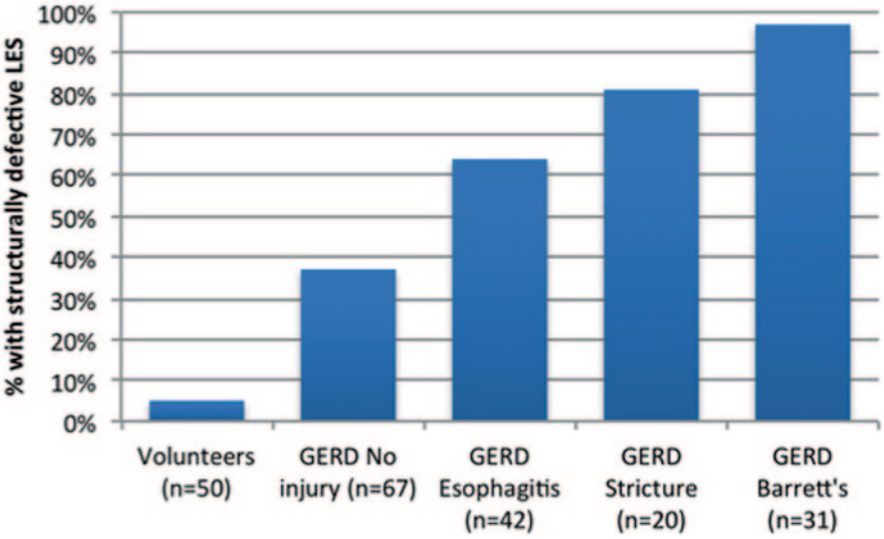

Fig. 8.1 Increase in the incidence of a permanently failed LES in GERD patients with progressive degrees of esophageal injury. *GERD* gastroesophageal reflux disease. (Adapted with permission from Ref. [58])

inflammation can reduce the overall length of the LES to < 2 cm and limit its ability to resist gastric distension or non-pressurized dilation [8, 13]. In both situations, a transient failure of the LES due to gastric distension or dilation has advanced to a permanent failure of the LES due to the loss of abdominal and overall length of the LES. The last component of the LES to go is its pressure due to extensive inflammatory injury. Figure 8.1 shows that the more severe the inflammatory injury to the LES is, the greater the prevalence of a permanently failed LES. Permanent failure of the LES is identified when one or more of the following LES abnormalities are seen on a motility study: an abdominal length of < 1 cm, an overall length < 2 cm, and a resting pressure less than 6 mmHg [6]. When all three components are abnormal, the LES is completely destroyed and will likely require reconstruction with a fundoplication [6, 19].

Figure 8.2 is a schema of the LES based on the median measurements in 50 normal subjects [6]. The median and 5th and 95th percentiles for the LES abdominal length, overall length, and pressure are tabulated along with their point of failure. The most common component to permanently fail is abdominal length, followed by the overall length. The least common permanent failure is a hypotensive LES pressure. Individuals vary in their propensity for transient failure of the LES. Failure from challenges of increased intra-abdominal pressure are dependent on the innate LES abdominal length. Failures from challenges of gastric distension or gastric non-pressurized dilation are dependent on the innate LES overall length.

Performance of a fundoplication on a patient with a normal LES that dynamically fails leads to excessive postprandial symptoms after surgery (Table 8.1) [20]. This occurs because the fundoplication prevents the shortening and opening of the

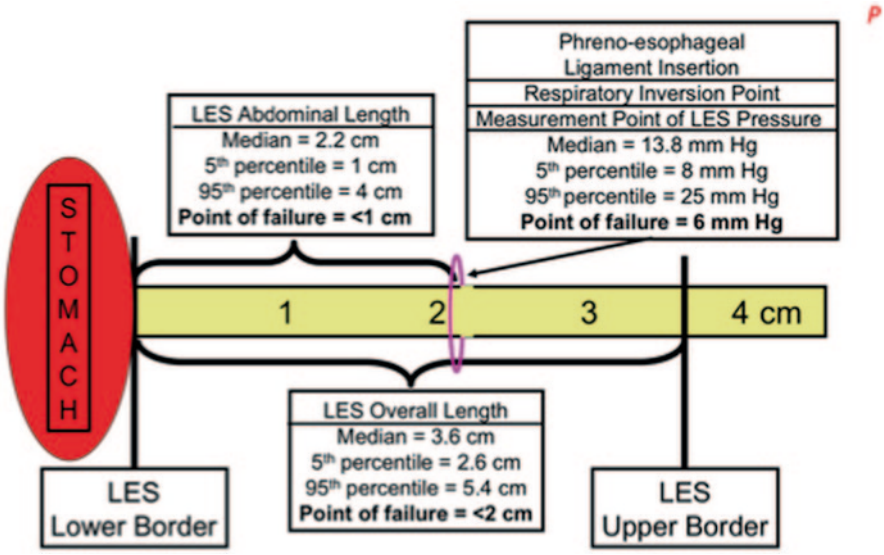

Fig. 8.2 Schema of the components of the LES: pressure, overall length, and abdominal length. The median value for each component and their 5th and 95th percentiles are listed and illustrated. The "point of failure" is the value for a specific component at which esophageal acid exposure becomes abnormally independent from the values of the other components. *LES* lower esophageal sphincter

sphincter to relieve postprandial distension or excessive dilation [21]. As would be expected, these patients complain of bloating, the inability to belch, and social problems associated with increased flatus. These side effects are less frequent and severe when a fundoplication is placed over an LES that has been partially or completely destroyed (see Table 8.1) [20].

The realization of the differences in side effects between a permanently failed LES and an LES that transiently fails has led to the development of surgical procedures specifically designed to prevent transient LES failure and block the progression to permanent failure [22]. The benefit of such procedures is the improvement of LES function with minimal surgical dissection and minimal to no side effects [22]. It is hoped that the effectiveness and gentleness of these procedures will encourage their use earlier in the course of GERD, when the symptoms and signs of progressive disease first appear. It is expected that these procedures will interrupt

Table 8.1 Incidence of side effects post Nissen related to preoperative LES manometrics. (Reprinted with permission from [20])

	Normal LES ($n=43$) (%)	Defective LES ($n=57$) (%)
Symptomatic gas bloat	44	23*
Increased flatus	75	48*

* $p<0.05$

the progression of LES damage, prevent its permanent failure, avoid the complications of end-stage GERD, and eliminate the risk of Barrett's esophagus.

How to Identify the Patient for Sphincter Augmentation

The two primary treatment options for patients with GERD are long-term acid suppressive therapy or surgery. Acid suppression therapy with proton pump inhibitors (PPIs) is the first-line therapy. Medical therapy is focused on reducing the acidity of the gastric juice while accepting that reflux continues to occur unabated [23]. Consequently, 13% of patients will have progression of their disease over 5 years while on acid suppression therapy [3]. Clinical flags of progression are evidence that PPIs are becoming less effective over time. The ineffectiveness of PPIs can be identified by the emergence of incomplete symptom relief, the onset of new symptoms, the need to escalate the dose of PPIs to achieve symptomatic relief, the development of nocturnal symptoms, and the onset of regurgitation and/or extra-esophageal symptoms [3, 18]. The clinical signs of progression are related to the deterioration of the LES and include bipositional reflux on 24-h esophageal pH monitoring, abnormal esophageal acid exposure on both days of a 48-h pH monitoring study, a motility study showing a defective LES, and/or persistent esophagitis despite therapy [3].

Laparoscopic fundoplication has been plagued with well-described side effects, variable outcomes when done by less experienced surgeons and high recurrence rates. Consequently, there is a reluctance for physicians to refer patients with symptoms and signs of progressive disease for surgery early in the course of their progression. Studies on the perception patients have about laparoscopic fundoplication show that 90% are concerned about long-term failure of the procedure, 75% are concerned about the possibility of dysphagia after the procedure, and 41% are concerned about reversing the fundoplication if necessary [25]. Further, patients are concerned about developing new symptoms after fundoplication such as bloating in 31–44% of patients, increased flatus in 47–57% of patients, and the inability to belch or vomit [26–28].

Consequently, it is reasonable that patients with progressive disease become frustrated by the ineffectiveness of the medical therapy and the lack of a dependable and durable surgical solution to their problem that is free of side effects. The specific issues they are anxious about are the persistence of symptoms while on PPI therapy, lifelong dependency on medication, disease progression while on medication, the side effects of medication, and the finality and side effects of a surgical fundoplication. They are asking themselves, what does this mean for me in the long term? The limitations of both medical therapy and laparoscopic fundoplication leaves this group of patients in the equivocal position of either tolerating a lifetime of drug dependence with incomplete symptom relief and the risk of progressive disease or accepting the risk of a surgical procedure that alters gastric anatomy, has significant side effects, and is not easily reversible (Table 8.2). To grasp how significant these factors are is reflected in the number of surgical anti-reflux proce-

Table 8.2 Side effects of the Nissen fundoplication ($n > 100$ with long-term follow-up). (Created with data from [20] (Open series, median follow-up 5 year.); [25] (Lap series, mean follow-up 21 mo.); [26] (Lap series, follow-up 10 year.); [27] (Lap series, follow-up 5 year)

	Open 1986 (1) (%)	Lap 1998 (2) (%)	Lap 2006 (3) (%)	Lap 2011 (4) (%)
Inability to belch	36	20	–	–
Inability to vomit (if tried)	63	25	–	–
Increased flatus	38	47	40	57
Symptomatic gas bloat	15	44	31	40
Persistent dysphagia	3	2	2	11

dures now performed. Currently, fewer than 30,000 fundoplication procedures are performed annually in the USA. This corresponds to less than 1 % of the 20-million medically treated GERD population [29]. Fortunately, there is a new development that can help patients who are frustrated by the ineffectiveness of their medical therapy and the side effects and durability of surgical therapy. The proper evaluation of these patients can identify those who likely have early progressive disease and would benefit from early surgical intervention with new devices that augment the failing LES.

Improved understanding of the LES has led to the development of procedures that augment the sphincter without causing side effects. The procedures are applicable to patients who have earlier evidence of progressive disease manifested by incomplete relief of their symptoms with PPI therapy. On clinical testing, these patients have increased esophageal acid exposure, adequate esophageal body function, and a normal or near-normal LES. As discussed above, such patients have a dynamic failure of the LES due to excessive shortening of its overall length when challenged by gastric distension or non-pressurized dilation. A promising surgical therapy for these patients is the implantation of a new device that focuses on augmenting the function of the existing LES. The anatomy of the hiatus is not altered; unlike a fundoplication, and the procedure does not attempt to improve the exposure of the abdominal length of the LES to the positive environmental pressure of the abdomen. There are three such operations: augmentation of the LES by reducing it's compliance with radio frequency [30], by increasing it's tone and reducing it's compliance with electrical stimulation [31], and preventing it's effacement with a ring of magnetic beads [22]. Of these, the most extensive clinical experience has been with magnetic sphincter augmentation using a device known as the LINX. The LINX remedies dynamic failure of the LES by preventing shortening of its overall length when challenged by gastric distension or non-pressurized dilation [32]. The procedure requires only limited dissection, does not alter the anatomy of the esophageal hiatus, has minimal side effects, and is reversible (Table 8.3). The procedure requires the implantation of a device known as the LINX. It consists of a series of magnetic beads connected to each other by independent wires. It is placed, using a laparoscope, around the esophagus at the gastroesophageal junction (GEJ). Only minimal dissection is done which does not alter the hiatal anatomy, and preserves of the phrenoesophageal ligament. The LINX device can be easily removed

Table 8.3 Side effects following the LINX

	Surgical endoscopy	NEJM	American College Surgery
Follow-up time (months)	48	36	36
Dysphagia (moderate or severe)	0%[a]	0%[a]	0%[b]
Ability to belch	95%	98%	99%
Ability to vomit	95%	98%	99%

Sphincter Augmentation to Prevent Transient Failure of the LES
NEJM New England Journal of Medicine, *GERD* gastroesophageal reflux disease, *HRQL* health-related quality of life
[a] Per adverse reporting event
[b] Per GERD–HRQL score >3

if necessary, thereby preserving the option for a subsequent fundoplication if necessary. More importantly, the LINX device produces little to no persistent side effects and was designed to limit the technical variability that occurs with fundoplication. The goal was to develop a more standardized and gentler anti-reflux procedure that is applicable and acceptable to patients with early progressive disease. The initial studies of the LINX procedure showed improved GERD–HRQL scores in patients who partially respond to PPIs. Five years after the procedure, *85%* of patients no longer required the use of PPIs, *their* median esophageal acid exposure was normalized, the side effects of gas bloat were less than 2%, *the new onset of* persistent dysphagia was *<1%* and 98% maintained the ability to vomit and belch (see Table 8.3) [32, 33]. To date, the LINX device has been implanted in over 1000 patients worldwide, and the outcomes have confirmed its safety and efficacy [32]. It is still uncertain if the LINX device will be effective in patients with a completely destroyed LES. Consequently, at present, patients with more advanced diseases, such as a hiatal hernia >3 cm, endoscopic grade C or D esophagitis, or endoscopic Barrett's esophagus are not considered candidates for sphincter augmentation and should be treated with a traditional surgical fundoplication. Future studies will compare reflux control and side effects with the LINX device to varying degrees of fundoplications. In a propensity-matched case–control series comparing laparoscopic Nissen fundoplication with the LINX in patients with similar disease severity, 1-year outcomes showed similar efficacy in terms of symptom control and PPI use with significantly less gas bloat in the LINX patients [34]. It should be understood that the device is not intended to be a substitute for the Nissen and is intended for use earlier in the disease process in patients with normal or minimal deterioration of their LES to prevent the progression to permanent LES failure and the complication of end-stage GERD. Figure 8.3 is an algorithm for the surgical management of the GERD patient that incorporates the decisions that need to be made in the selection of the correct surgical procedure.

The principles of implanting the LINX device are proper sizing of the device, proper positioning of the device, and constructing, with limited dissection, a tunnel behind the esophagus, between its posterior wall and the posterior vagus nerve. Through this tunnel, the LINX device is passed. The phrenoesophageal ligament

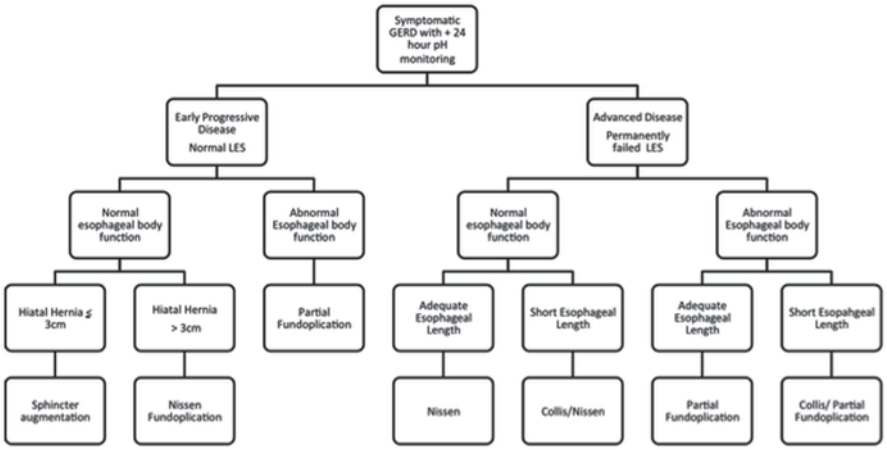

Fig. 8.3 Algorithm of surgical treatment for GERD patients with early progressive disease and a normal or near-normal LES and those with advanced disease and a permanent failed LES

is not dissected and the esophageal hiatus is not explored (Fig. 8.4). Guarding the integrity of the phrenoesophageal ligament during LINX implantation is imperative as the ligament functions to maintain the abdominal length of the LES. This is in contrast to a fundoplication where the hiatus is completely dissected out, and the LES is enveloped with the gastric fundus to provide a conduit to transmit intra-abdominal pressure around the LES. The critical benchmark steps for the LINX procedure are listed in Table 8.4. A detailed description of the implantation of the LINX device has been previously published and is available for reference [33].

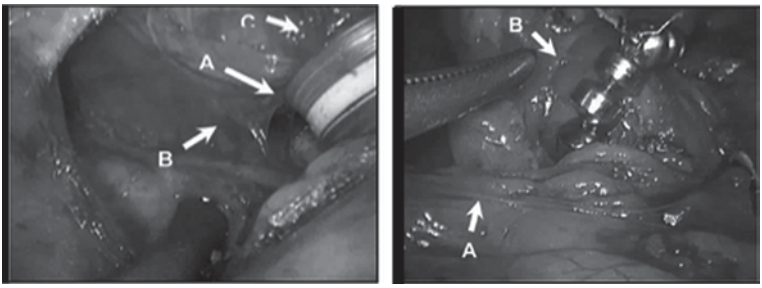

Fig. 8.4 Placement of the LINX device. (*Left*) Surgical dissection for the implantation of the LINX device. **a** Surgically dissected tunnel for the LINX device located between the posterior wall of the esophagus and the posterior vagus nerve. **b** Posterior vagus nerve. **c** Esophagus. (*Right*) LINX device, a bracelet of magnetic beads, in its proper implanted position, that is, encircling the esophagus just above the esophageal-gastric junction. **a** Hepatic branch of the anterior vagus nerve. **b** Insertion of the phreono-esophageal membrane. (Reprinted with permission from [59])

Table 8.4 Critical benchmarks of the LINX

Mobilization of the fundus of the stomach from the diaphragm and surface of the left crus
Open the fascia for 1–2 cm along the inferior–anterior margin of the left crus just above the crural decussation
Initiate the dissection of a tunnel from the left through the fascial incision and posterior to the esophagus for about 1 cm
Open the gastrohepatic ligament above and below the hepatic branch of the anterior vagal nerve
Open the fascia along the inferior–anterior margin of the right crus for 1–2 cm just above the crural decussation
Identify the posterior vagal nerve by slow and gentle dissection while retracting the stomach in an anterior–inferior direction
Dissect a tunnel posterior to the esophagus just above the GEJ and between the posterior vagus nerve and the posterior wall of the esophagus in the patient's right to left direction
Pull a 1/4 in. Penrose drain through the tunnel
If necessary, mobilize the anterior gastroesophageal fat pad inferiorly or trench across the fat pad on the anterior surface of the esophagus above the level of the posterior tunnel
Measure the circumference of the esophagus at the level of the GEJ
Implant the appropriate-sized LINX device through the tunnel and around the esophagus
Endoscope the patient if appropriate to check the position of the LINX device

GEJ gastroesophageal junction

Fundoplication for Permanent Sphincter Failure in End-Stage GERD

How to Identify the Patient for Sphincter Reconstruction

The experience over the past five decades with patients who have received surgical treatment of their reflux disease has shown that those most likely to have a successful outcome have typical symptoms of GERD, a history of a complete or partial symptomatic response to acid suppression medication, and increased esophageal acid exposure on pH monitoring. When all three of these predictors were present, a successful surgical outcome occurred in over 97% of patients [29]. The strongest predictor of outcome is the documentation of increased esophageal acid exposure on pH monitoring. To emphasize this point, the odds of a successful procedure for a patient with typical symptoms that respond to medical therapy, but normal esophageal acid exposure on pH testing, is 16.7 compared to 89.8 if the esophageal acid exposure was abnormal [29].

The best most current randomized study between medical therapy with PPIs and surgical fundoplication is the Long-Term Usage of Esomeprazole vs Surgery for Treatment of Chronic GERD (LOTUS) trial [27]. Efforts were made to standardize the Nissen fundoplication, and 40 surgeons were selected to perform the procedures. The selected surgeons had to have performed over 40 Nissen fundoplications and with a continued rate of 20 fundoplications per year. This was done to avoid inexperienced surgeons from participating in the study. A 6-month run-in period was required to verify the clinical response to esomeprazole at 40 mg per day. This was

Table 8.5 LOTUS trial, symptoms at 5 years

	PPI ($n=192$) (%)	Lap Nissen ($n=180$) (%)	p value
Heartburn	16	8	0.14
Regurgitation	13	2	0.001
Dysphagia	5	11	0.001
Bloating	28	40	0.001
Flatulance	40	57	0.001
Serious adverse events	24	29	>0.05

PPI proton pump inhibitor

done because sustained resolution of reflux symptoms occur in only 70% of GERD patients with esomeprazole therapy. Only those who responded to esomeprazole were randomized into the surgical and medical arms. Partial responders or patients refractory to treatment were excluded [34]. It is likely that the partial or refractory patients had permanent structural failure of their LES, and their inclusion would likely compromise the effectiveness of medical therapy [35]. In the trial, medical failure was defined by the inability to control symptoms after escalation of esomeprazole dose to 40 mg per day for 8 weeks followed by 20 mg twice per day for 8 weeks. Surgical failure was defined by the inability to control symptoms and the requirement for esomeprazole therapy, dysphagia requiring therapy, or any need to reoperate for symptom control. Based on these definitions, 92% of the medical patients and 85% of the surgical patients remained in remission at 5 years ($p=0.048$) [27]. The other end points of the trial are shown in Table 8.5 and illustrate that the downsides of PPI therapy are persistent regurgitation, and the downsides of surgical therapy are dysphagia, bloating, and flatulence.

Anatomical abnormalities associated with GERD, such as a shortened esophagus, an esophageal stricture, or a large sliding hiatus hernia, can significantly impact the complexity and outcome of an anti-reflux procedure. The history of a previously failed anti-reflux procedure is a strong predictor that a subsequent anti-reflux procedure will also fail. The probability of a successful outcome of a second procedure is 80% and a third procedure is 50%. The latter is sufficiently high that many surgeons would consider an esophagectomy for these patients [36–40].

The symptomatic patient who has increased esophageal acid exposure, adequate esophageal body function, and a completely destroyed LES is a candidate for a procedure that reconstructs the LES. This commonly occurs in patients with advanced reflux disease manifest by difficult-to-heal esophagitis, a reflux-induced stricture, or long-length Barrett's esophagus. The operation most applicable for such a patient is a fundoplication as it restores the abdominal length, overall length, and LES pressure and assures that the abdominal length is exposed to variations in intra-abdominal pressure. A full fundoplication has been shown to have an advantage over a more limited degree of fundoplication in its ability to normalize esophageal acid exposure and its robustness in patients with adequate esophageal body function [35, 41]. Choice of the degree of fundoplication is dependent on the amplitude of

esophageal body contractions and the prevalence of peristaltic waveforms [42]. The patient with global contraction amplitudes of <20 mmHg in the distal two thirds of the esophagus and/or less than 50 % peristaltic waveforms is likely to do better with a partial fundoplication. A partial fundoplication tends to have less outflow resistance as suggested by a lower LES pressure and greater degree of LES relaxation [42]. There are multiple randomized trials comparing the outcomes of total fundoplication with lesser degrees of fundoplication. These trials have produced conflicting results. Recently, a meta-analysis has been published that attempts to analyze the effectiveness of an anterior 180° fundoplication versus a complete Nissen fundoplication. The analysis of esophageal acid exposure at 1 year, though not statistically significant, tends to favor the complete Nissen fundoplication, and the reoperation rate at 5 years, though not statistically significant, also tends to favor the complete Nissen fundoplication [43]. Further, the results of a similar randomized trial with 14 years of follow-up showed that an anterior 180° fundoplication had statistically more esophageal acid exposure than the complete Nissen fundoplication (% time pH < 4, 11 vs. 2.8 %, $p = 0.027$), suggesting that the effectiveness of the anterior 180° fundoplication deteriorates with time [44]. These findings make a cogent argument that a complete Nissen fundoplication is likely to be the most effective and robust procedure over time. Further, the proposed benefit of fewer side effects with the partial fundoplication does not hold up over time [43–46].

Critical in evaluating a patient for an anti-reflux procedure is the presence of a short esophagus. This can be implied from a motility tracing that shows an LES with < 1 cm of abdominal length. Clinical flags suggesting a short esophagus are a nonreducing hiatal hernia on upright barium swallow, an esophageal stricture, a long segment of Barrett's esophagus, or a history of a previous anti-reflux procedure [25, 47]. In this situation, the surgical treatment may require increasing the length of the esophagus with a Collis gastroplasty [48]. A fundoplication is placed over the gastroplasty tube. The degree of the fundoplication, complete or partial, is dependent on the motility assessment of the esophageal body [42].

The Technique of Sphincter Reconstruction

The technique for performing a complete fundoplication was described initially by Rudolph Nissen in l956, prior to the discovery of the LES [31, 49]. Time has proven the procedure to be a robust and an effective anti-reflux operation. It was designed to prevent gastroesophageal reflux in a non-physiological way by the construction of an anatomical flap valve. Consequently, its downside is a high prevalence of side effects namely postprandial abdominal distension, the inability to belch or vomit, and a 1–2 % rate of persistent dysphagia. A detailed description of a complete fundoplication performed transabdominally or using a laparoscope has been previously published and is available for reference [25, 50]. More recently, a device has been developed to perform the procedure by the trans-oral approach and is referred to as the TIF procedure [31]. Long-term outcomes and efficacy of this device remain

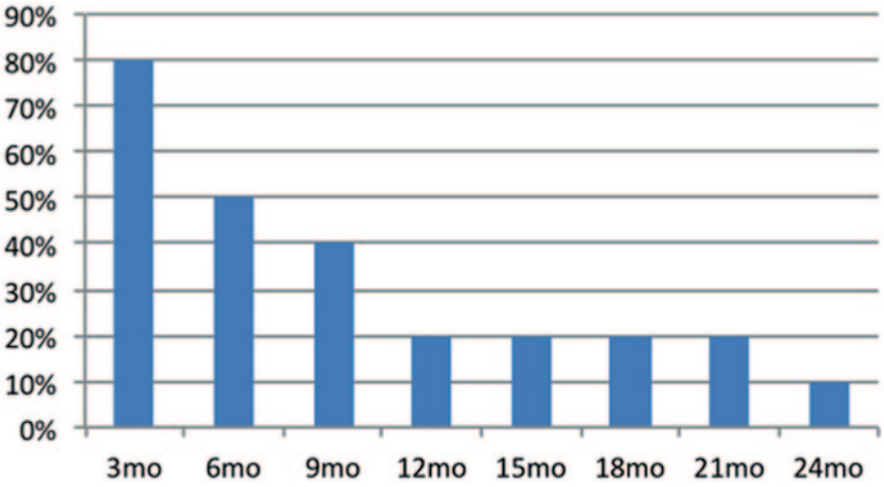

Fig. 8.5 The prevalence (%) of temporary dysphagia after a Nissen fundoplication. Permanent dysphagia occurs in only 2% of patients and is likely due to a technical error. (Adapted with permission from [25])

largely unknown, and there are no comparison studies of the device with laparoscopic fundoplication.

The complete fundoplication has been beleaguered with a 15% late failure rate due to herniation of the repair into the chest or slippage of the fundoplication onto the stomach. Both can lead to recurrent reflux and/or dysphagia [39]. It is thought by most surgeons that a slipped fundoplication is in reality a misplaced fundoplication.

Early postoperative temporary dysphagia is a common occurrence with any antireflux procedure. It usually occurs within 6 weeks of the procedure and is due to tissue edema from manipulation. Up to 80% of patients will experience temporary dysphagia within the first 3 months after surgery, which progressively resolves over 12 months (Fig. 8.5) [25]. Mild intermittent dysphagia may persist in 10% of the patients up to 2 years [25]. Permanent dysphagia occurs in only 2% of patients [51]. It is likely due to a technical error, such as making the fundoplication too tight, too long or twisted, placing the fundoplication in the wrong position, or closing the crura too tightly [52, 53]. Occasionally, persistent dysphagia can be caused by an unabsorbed hematoma within the fundic tissue used to construct the fundoplication.

Outflow resistance is increased in complete fundoplications and less so in partial fundoplications. A postoperative bolus pressure greater than 20 mmHg measured 5 cm above the upper border of the LES is an indication that there is sufficient resistance to interfere with bolus transport and cause persistent dysphagia. Esophageal dilation is usually of minimal sustained benefit. If the dysphagia is sufficiently severe, revision of the fundoplication may be required for relief. It is wise to observe the patient expectantly for 12 months prior to making a decision for reoperation. Reoperation should only be done after a thorough investigation as to the cause of the dysphagia. The type of reoperation is dependent on the status of the esophageal

body motility. The reoperation can be a complete fundoplication if the esophageal body contraction amplitude is globally above 20 mmHg, and the fundoplication is constructed over a 60Fr bougie, lies in place at rest, and the lips can be secured, without tension, over a distance of 1.5–2 cm. If these conditions cannot be met, a partial fundoplication should be performed.

The unfortunate side effects of a complete fundoplication are abdominal bloating, increased flatus, and the inability to belch or vomit (see Table 8.2). As mentioned, these side effects are more common in patients who have a normal LES (see Table 8.1). Increased flatus is more common than bloating and usually is less of a problem by 6 months [54, 55]. There are no effective treatments for the side effects that persist. Dilation or a redo partial fundoplication cannot be depended upon to alleviate these symptoms [56].

When a short esophagus has been identified either preoperatively or intraoperatively, adequate intra-abdominal length must be achieved. The esophagus needs to be lengthened if 2 cm or more of the mobilized distal esophagus do not rest within the abdomen when free of tension. Failure to obtain adequate intra-abdominal esophagus is the leading cause of herniation, slippage, or breakdown of the repair. A total of 20–33 %of patients with inadequate intra-abdominal length and a fundoplication constructed under tension will fail [57]. John Leigh Collis introduced a technique that lengthens the esophagus and is referred to as a gastroplasty procedure [48]. The operation constructs a 4–5-cm gastric tube along the lesser curvature of the stomach in continuity with the esophagus [48]. This lengthens the esophagus by at least 4 cm, but does not move the location of the LES. Although the gastroplasty, by itself, does support the response of the LES to abdominal pressure challenges, the effect is inconsistent. This led to the placement of a partial or complete fundoplication around the gastroplasty tube, to provide a conduit for intra-abdominal pressure to be transmitted and applied to the neoesophagus. This combined technique has provided an acceptable way of dealing with a shortened esophagus. The management of a short esophagus, especially laparoscopically, is problematic for the inexperienced esophageal surgeon, and, as a result, they tend to neglect it or deny its existence.

Conclusion

Over the past five decades, surgical therapy for GERD has gone through an evolution. This evolution was strongly influenced by the identification of the LES and the etiology of reflux in both patients with a dynamic and permanently failed LES. More so now than ever, anti-reflux surgery requires proper patient selection, proper procedure selection, and proper performance of the surgical procedure. Fundoplications are safe, provide substantial symptomatic improvement, and reduce esophageal acid exposure to less than normal levels. However, it alters gastric and hiatal anatomy, which can lead to herniation, slippage, or breakdown of the repair and induces side effects that annoy patients. The fundoplication is too much surgery for

patients with early progressive disease. New surgical procedures have been developed for patients with early progressive disease and a normal or near-normal LES that dynamically fails when challenged by gastric distension or non-pressurized dilation. Of these procedures, the most extensively studied is the LINX device. It is safe, eliminates symptoms, reduces esophageal acid exposure, preserves gastric and hiatal anatomy, and has minimal side effects. The modern approach to antireflux surgery is moving towards utilizing a form of fundoplication for patients with permanently destroyed LESs associated with advanced disease and uncontrolled symptoms. Sphincter augmentation procedures are used for patients who, despite PPI therapy, have symptoms and signs of early progressive disease.

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