PART I
Gastrointestinal disorders

1 CHAPTER 1
Gastroesophageal reflux disease

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Introduction

Gastroesophageal reflux disease (GERD) is a "condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [1]. It is frequently encountered in clinical practice; in 2004, GERD accounted for about 18 million ambulatory care visits or 17% of all digestive disease encounters in the United States of America [2]. Although a variety of symptoms might be associated with GERD, none are pathognomonic. However, in cases presenting with the typical GERD symptoms of heartburn and regurgitation and without "alarm symptoms" of bleeding, dysphagia, or weight loss, it is common practice to treat GERD without investigation.

Definition of GERD

Gastroesophageal reflux (GER) is a physiological event that commonly occurs during and after meals. Such physiological reflux episodes are rapidly cleared by esophageal peristalsis and the residual acidity neutralized by the bicarbonate in swallowed saliva. Physiologic GER is generally asymptomatic [3]. GER becomes pathological when reflux episodes are frequent, occur outside of the postprandial period, and induce typical (heartburn, regurgitation) or atypical symptoms (dysphagia, chest pain, cough, etc.) of sufficient magnitude that they become "troublesome" to the individual. It is difficult to precisely demarcate the transition between physiological GER and GERD based on symptom frequency or intensity, but the "troublesome" threshold was adopted to imply a decrement in quality of life [1]. Having some degree of heartburn is considered normal. Moreover, only a small proportion of patients with GERD seek medical care for the condition [4].

According to the Montreal definition, GERD can also be defined by syndromes characterized by esophageal injury, including reflux esophagitis, Barrett's esophagus, peptic stricture, or adenocarcinoma [1]. This umbrella definition was devised to encompass the broad spectrum of GERD inclusive of both erosive reflux disease (endoscopically defined esophagitis and complications thereof), nonerosive reflux disease (NERD) (patients with troublesome esophageal GERD symptoms, but without esophagitis on endoscopy), and patients with extra-esophageal manifestations of GERD such as laryngitis or cough.

Clinical presentation

The typical symptoms of GERD are heartburn (a burning sensation arising behind the breastbone toward the neck) and regurgitation (experienced as refluxed fluid moving in the chest or a bitter taste in the mouth). However, even these typical symptoms are not specific for GERD as demonstrated by the Diamond study, which evaluated the accuracy of the reflux disease questionnaire (RDQ) for the diagnosis of GERD. The RDQ utilizes six items to score the occurrence and frequency of heartburn, regurgitation, and dyspepsia. In a cohort of 308 patients with troublesome upper gastrointestinal symptoms, the sensitivity and specificity of the RDQ to diagnose GERD were 62% and 67%, respectively, when using the findings from endoscopy and wireless pH-metry as the reference standard [5].

Atypical GERD symptoms can be esophageal or extra-esophageal. Dysphagia is experienced by one-third of GERD patients [6]. This "warning sign" should lead to upper GI endoscopy with esophageal biopsies to evaluate for esophagitis, tumor, stricture, and eosinophilic esophagitis. Chest pain may also be attributed to GERD in up to 50% of patients [7]. However, due to the potential life-threatening nature of cardiac disease, a cardiac evaluation should be prioritized in such patients before accepting an esophageal etiology.

GERD is an etiology of chronic cough and estimates of the prevalence of GERD-associated cough range from 0% to 41% of chronic cough cases [8]. Half of asthma patients have evidence of GERD [9]. A variety of ear nose and throat (ENT) symptoms have been attributed to reflux: dysphonia, globus

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sensation (perception of a lump or fullness in the throat, irrespective of swallowing), throat clearing, sore throat, chronic laryngitis, and laryngospasm. However, controversy persists regarding diagnostic criteria for these "laryngopharyngeal reflux" syndromes, especially between gastroenterologists and ENT physicians [10].

Gastrointestinal symptom scales were recently developed using the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS®) [11]. These scales are intended for use in clinical care and research. Items were determined based on literature searches and administered to patients with gastrointestinal conditions and to the general population. The GER domain items assess: (i) sensations associated with food intake (reflux, regurgitation) or not associated with food intake (lump in the throat); (ii) painful sensations (heartburn, chest pain, throat burn); and (iii) belching, gas (burping), and hiccups. Symptoms occurring during the past seven days are scored.

Epidemiology

Since the criteria used to define GERD in epidemiological studies differ from the Montreal definition, it is difficult to know the actual prevalence of GERD in the general population. However, based on self-reporting of at least weekly heartburn and/or regurgitation estimates of the prevalence of GERD range from 9% to 33% (Table 1.1) [12].

The pitfalls of GERD prevalence estimates were well elucidated by the Diamond study, conducted in primary care practices in Europe and Canada [5]. Three hundred and eight patients with upper GI symptoms underwent a systematic evaluation with endoscopy, esophageal pH monitoring, structured interviews, questionnaires, and a trial of proton pump inhibitor (PPI) medication. Among these patients, 38% were found to have esophagitis, 28% had abnormal esophageal pH-metry, and 49% identified heartburn or regurgitation as their most bothersome symptom. Response to two-week PPI treatment did not clarify these discrepancies. Even though a beneficial PPI response was more frequent in patients with esophagitis (69%) and in patients with normal endoscopy and abnormal esophageal pH-metry (49%), 35% of patients with normal examinations also had symptom improvement [13].

Table 1.1 GERD prevalence worldwide

Geographic location	Estimates of GERD prevalence based on self-reporting heartburn and/or regurgitation
USA	18–28%
Europe	9–26%
South America	23%
Middle East	9–33%
East Asia	3–8%
Australia	12%

Source: Adapted from El-Serag *et al.* 2014 [12].

Major risk factors associated with GERD are age, pregnancy, and obesity. The incidence of GERD increases with age [14]. Half to two-thirds of pregnant women report GERD symptoms [15]. In Western countries, the increased prevalence of GERD has occurred in parallel with increased obesity, evident by an increased prevalence in both obese (body-mass index (BMI) > 30 kg/m^2) and overweight (BMI 25–30 kg/m^2) patients [16].

GERD is also associated with other disease entities including diabetes mellitus [17] and pulmonary disease. Chronic pulmonary diseases and asthma were associated with new GERD diagnoses in a study utilizing the UK General Practice Research Database [14]. Impaired esophageal function is encountered in 80% of scleroderma patients and this frequently leads to GERD symptoms [18]. Esophagitis was observed in 42% of patients with Zollinger–Ellison syndrome, which promotes GERD by increasing the acidity and quantity of gastric acid in the refluxate [19].

Pathophysiology

During physiological reflux, gastric content enters the distal esophagus and is then rapidly cleared by peristalsis. Physiological reflux occurs almost entirely by transient lower esophageal sphincter relaxation (TLESR), which is a complex vago-vagal reflex involving non-deglutitive lower esophageal sphincter (LES) relaxation [20], crural diaphragm inhibition, and distal esophageal shortening. TLESRs are triggered by gastric distension with food, liquid or gas and are the physiological mechanism of belching.

Only a fraction of TLESRs are associated with acid reflux and that fraction is greater in GERD patients than in controls [21]. Another differentiating feature of GERD patients is that reflux can occur by mechanisms other than TLESR. This is especially true in patients with hiatus hernia, a situation in which the LES and the crural diaphragm (CD) are spatially separated. Normally, these elements act in concert as the antireflux barrier at the esophagogastric junction (EGJ), but their spatial separation, be that intermittent or constant, facilitates the occurrence of reflux [22]. Hiatus hernia also predisposes to swallow-induced reflux and strain-induced reflux, especially when associated with a hypotensive LES [23]. Yet another impairment associated with hiatus hernia is of prolonged acid clearance as gastric juice within the hernia refluxes back and forth across the LES with swallows while subjects are in a recumbent posture [23]. Not surprising, hiatus hernia is observed in up to 70% of patients with esophagitis, more so with increasing severity of the esophagitis [24]. Finally, hiatus hernia interacts with the acid pocket, the newly secreted acid that layers on the top of

gastric content in the postprandial period, serving as the reservoir for postprandial acid reflux. With hiatus hernia, the acid pocket is displaced proximally into the hernia compartment, greatly facilitating its access to the distal esophageal mucosa [25].

Although the dominant mechanism of prolonged acid clearance, and consequently prolonged esophageal acid exposure time, in GERD patients is hiatus hernia, clearance is also compromised by weak, or even absent, peristalsis [26]. Peristalsis, primary or secondary, clears the refluxed fluid back to the stomach and ineffective esophageal motility is associated with impaired esophageal clearance [27]. The final step in acid clearance after a reflux event is neutralization of residual acid by swallowed saliva [28]. Hence, hyposalivation, as occurs with many medications, certain collagen vascular diseases, and during sleep can prolong the process of acid clearance and thereby exacerbate the severity of GERD [29, 30].

There is also interplay between the efficacy of gastric emptying and GERD, which is a frequent accompaniment of gastroparesis. However, the relationship is less clear with marginal abnormalities of gastric emptying. In a series of 30 patients referred for both a gastric emptying study and esophageal pH-impedance monitoring, delayed gastric emptying was associated with an increased number of postprandial reflux episodes, but no significant difference in acid esophageal exposure [31]. On the other hand, accelerating gastric emptying with the 5-HT4 receptor agonist prucalopride reportedly decreased esophageal exposure time, but had no effect on the number of reflux episodes in 21 healthy controls [32].

Although the severity of esophagitis correlates with the extent of esophageal acid exposure as determined by pH monitoring studies, the same relationship does not hold for reflux symptom severity. Only 20–40% of patients with GERD symptoms have erosive reflux disease defined by esophageal mucosal breaks [33, 34] and pathological reflux on esophageal pH-metry is reportedly found in only 21–61% of NERD patients [35, 36]. Hence, the determinants of symptom severity are somewhat distinct from those of mucosal erosion. Mucosal injury is facilitated by prolonged exposure to refluxed acid, pepsin, and bile acids. Symptoms, on the other hand, are strongly modulated by sensitivity. Only about 10% of reflux episodes are symptomatic [37], and patients with pathological GERD are more sensitive to acid and esophageal distension than are control subjects [38]. Reflux episodes during which the refluxate reaches the proximal esophagus, which are more common among GERD patients, are also more likely to be symptomatic, and recent physiological data suggest that the proximal esophagus is more sensitive to reflux than is the distal esophagus [39]. Finally, the phenomena of hypersensitivity and hypervigilance are increasingly recognized as major determinants of symptom severity among subsets of NERD patients [40].

Natural history and complications

GERD can present as erosive reflux disease with esophageal mucosal breaks on endoscopy or as NERD, in which case there are symptoms attributable to GERD without endoscopically evident disease. NERD is the dominant form, encountered in about 70% overall [41]. Potential complications of GERD include bleeding, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma. Barrett's esophagus is defined as the replacement of normal squamous esophageal mucosa with columnar epithelium found to contain intestinal metaplasia on histopathology. Barrett's esophagus is the major risk factor for the development of esophageal adenocarcinoma (see Chapter 2).

Only a few studies have examined the natural history of GERD. Both progression from NERD and regression from erosive disease have been observed. Illustrative of this are data from a large multicenter study of 6215 patients conducted in Germany, Austria, and Switzerland reporting progression, regression and stability of GERD within that population [42]. Among 2721 patients who completed the five-year follow up, most remained stable or improved with routine clinical care. Among patients with severe esophagitis at baseline, 61% had NERD at five years. On the other hand, disease progression was observed in 6% of NERD patients, 12% of patients with grade A/B esophagitis, and 19% of patients with grade C/D. In a recent comprehensive review, Savarino reported progression from NERD to erosive disease in 0–30% of patients, progression from mild to severe esophagitis in 10–22%, and progression from erosive disease to Barrett's esophagus in 1–13% [41].

While GERD does not decrease life expectancy [14], it does impair quality of life. In the Kalixanda study, daily symptoms were associated with a greater decrement in quality of life than were less frequent symptoms [43]. Interestingly, esophagitis did not significantly alter quality of life in that study. GERD is also responsible for absenteeism and up to 30% of patients with heartburn reported reduced productivity at work, especially those with nocturnal symptoms [44].

Diagnostic tests

GERD is usually a clinical diagnosis based on a symptom assessment. Testing is reserved for cases in which there are warning signs of complication, atypical symptoms such that the diagnosis is in doubt, an inadequate response to medical treatment, or as a preoperative evaluation to confirm the diagnosis prior to surgical treatment. Hence, the diagnostic approach utilized varies greatly depending on a symptom assessment, an assessment of the risk that complications exist, the history and success of treatment trials, whether or not a potentially morbid therapy is under consideration, and the history of prior testing. As a general rule, the extent of diagnostic testing pursued should be limited to that which

guides management decisions and/or protects the patient from risk.

Symptom assessment and questionnaires

The occurrence of typical heartburn and/or acid regurgitation in a patient without signs of potential complications (dysphagia, odynophagia, weight loss, bleeding, or anemia) is sufficient to diagnose GERD and initiate therapy. Standardized questionnaires have been developed to aid in the clinical diagnosis of GERD. These were devised to facilitate screening patients for GERD in primary care settings and to provide a standardized evaluation. In a recent review, Bolier *et al*. identified 39 questionnaires to assess GERD symptoms, 14 to assess response to treatment, and 18 to assess GERD-related quality of life [45]. The RDQ is the most widely used, consisting of six items that assess the frequency and severity of heartburn, regurgitation, and dyspepsia. Alternatively, the GerdQ questionnaire includes six items (heartburn and regurgitation frequencies, stomach pain, nausea, nocturnal symptoms, and requirement of additional medication) and was also translated in multiple languages. The accuracy of these questionnaires in diagnosing GERD varies with what is being used as the reference standard. If the comparison is with the diagnoses rendered by an experienced clinician [5], the correspondence is very good; if the comparison is to physiological testing and endoscopy, the sensitivity and specificity are only about 65% [46].

PPI trial

The high prevalence of GERD and the impressive therapeutic efficacy of PPIs led some authors to propose using a PPI trial to diagnose GERD. However, as evident from the findings of the Diamond study, responsiveness to PPI therapy, abnormal pH-metry, and symptom-based assessments each detect unique patient populations, which only partially overlap. Illustrative of this, a positive PPI trial was observed in 69% of patients meeting pH-metry and/or endoscopic criteria of GERD in the Diamond study and in 51% of patients not meeting these criteria [13]. Similar findings were reported in a meta-analysis of 15 studies using many variations of the "PPI test." With 24-hour pH-metry as the reference standard, the positive likelihood ratio of the PPI trial for predicting GERD ranged from only 1.63 to 1.87 [47].

The imperfect overlap between patient populations defined by physiologic testing and response to a PPI trial does not negate the practicality and cost-effectiveness of empiric therapy. Fass *et al*. reported that, although a protocol of omeprazole 60 mg daily had relatively poor test characteristics for detecting physiologically defined GERD (sensitivity 80%, specificity of 57%), this protocol saved an average of US $348 per patient with a 64% reduction in the number of upper GI endoscopies and 53% reduction in the use of pH-monitoring [48]. However, empiric PPI therapy also has its limitations. A positive response may be attributable to a placebo effect or the presence of an alternative acid-peptic disorder, while a negative response may occur in truly PPI-refractory GERD. Other considerations are the potential to mask malignancies and to foster inappropriate long-term PPI use, which has clinical and economic implications. In summary, empiric PPI therapy is a simple and cost-effective way to manage typical reflux symptoms in patients without warning signs, but the effectiveness of the therapy does not equate to a diagnosis of GERD.

Upper GI endoscopy

Upper GI endoscopy is the best test for detecting GERD complications and for excluding alternative diagnoses such as malignancy, eosinophilic esophagitis, or peptic ulcer. With respect to establishing a GERD diagnosis, the minimal endoscopic lesion with acceptable inter-observer agreement (kappa 0.4) is a mucosal break, the basis for the Los Angeles classification. Grades A–D of the LA classification are illustrated in Figure 1.1 [49]. The severity of esophageal acid exposure is significantly related to the LA grade of esophagitis, but it is important to note that mild esophagitis (grade A) was found in 5% of asymptomatic controls [34] leading some to question the significance of this finding. Among 280 075 upper GI endoscopies performed between 2000 and 2005 in the Clinical Outcomes Research Initiative (CORI) database, esophagitis was found in 17.3%, esophageal stricture in 9.5%, and Barrett's esophagus in 4.5% [50]. Esophagitis was graded according to the LA classification in fewer than 50% of endoscopies; when documented, esophagitis was grade A or B in 79% of patients.

Upper GI endoscopy might also be useful to detect hiatus hernia. However, estimates of the prevalence of hiatus hernia in the adult population vary enormously from 10% to 80% [51] likely due to subjectivity of diagnostic criteria. In the CORI database, hiatal hernia was observed in 33% of upper GI endoscopies and in 40–45% of patients undergoing endoscopy for reflux symptoms [50]. Thus, even though relevant to a GERD diagnosis, the presence of hiatal hernia is not sufficient to establish that diagnosis.

Histologic examination of distal esophageal mucosal biopsies might increase the diagnostic yield of endoscopy for GERD. Microscopic esophagitis was observed in 65% of NERD patients, but also 15% of controls [52]. Kandulski *et al*. proposed a histological score combining degree of basal cell hyperplasia, presence of papillary elongation, dilated intercellular spaces and inflammation. A score ≥ 5 had a sensitivity of 85% and a specificity of 64% to differentiate NERD from functional heartburn [53].

In summary, endoscopy is an important test to detect complications of GERD and for excluding alternative diagnoses that might explain a patient's symptoms. However, its sensitivity for diagnosing GERD is poor.

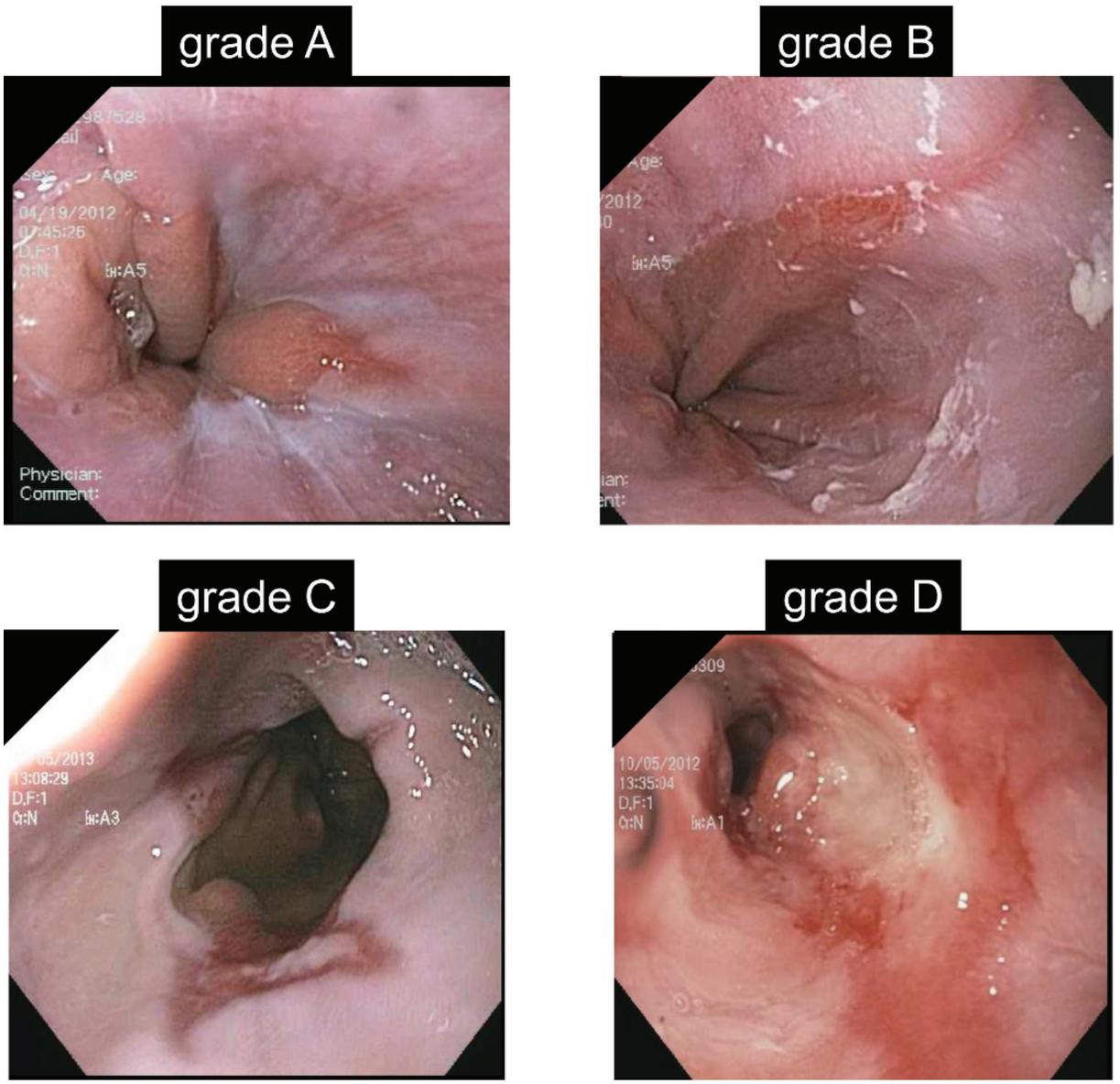

Figure 1.1 Los Angeles Classification. Grade A is defined as one (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds. Grade B is defined as one (or more) mucosal break longer than 5 mm that does not extend between the tops of two mucosal folds. Grade C is defined as one (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference. Grade D is defined as one (or more) mucosal break which involves at least 75% of the esophageal circumference.

Ambulatory GERD testing: pH and pH-impedance monitoring

Ambulatory reflux monitoring can detect pathological reflux in patients without endoscopic esophagitis. Conventional (or wireless) pH-metry detects reflux events on the basis of their acidity, while pH-metry combined with impedance detects all liquid and/or gas reflux. Both methods can be used to correlate reflux events with patient-reported symptoms, albeit in the case of pH-metry this analysis is restricted to acid reflux events.

Ambulatory pH-metry studies are done positioning the pH electrode 5 cm above the proximal margin of the LES or, in

the case of wireless monitoring, 6 cm above the squamocolumnar junction. Esophageal acid exposure is defined as the percentage of the recording time with esophageal pH < 4; the threshold that is most discriminative in differentiating physiological and pathological reflux [54]. Reported upper limits of normal for esophageal acid exposure with catheter-based systems range from 3.9% to 7.2% and for the wireless system from 4.4% to 5.3% [55–57]. The sensitivity and specificity of pH-metry for differentiating control subjects from esophagitis patients are 77–100% and 85–100%, respectively [58–61]. Advantages of wireless pH-metry over catheter-based studies are of improved tolerability and studies that can be prolonged for up to 96 hours, thereby improving the yield for detecting abnormal reflux. Illustrative of this, among 38 patients with normal acid exposure on catheter pH-metry, pathological acid exposure was detected in up to 47% of patients using the wireless technology [62].

Compared to pH-metry, pH-impedance monitoring characterizes reflux not only by its acidity, but also by its gas/liquid content, its direction of flow, and the proximal extent to which it flows into the esophagus. These are all factors potentially relevant to symptom perception, especially in patients taking acid suppressive medication [63]. As with catheter-based pH-metry, the pH-impedance probe is passed transnasally into the esophagus and connected to an external receiver. Combined pH-impedance studies are analyzed both for esophageal acid exposure time and for the number of reflux events, acid or otherwise, with the upper limit of normal reported as ranging from 54 to 75 per 24 hours [64, 65]. When the study is performed withholding PPI therapy there is a nominal increased yield relative to pH-metry alone reported to range from 6% to 11%, attributable to weakly acidic reflux events that correlate with reported symptoms [64]. However, the significance of that increased yield is unclear, given that abnormal acid exposure, but not an abnormal number of reflux episodes, correlates with medical or surgical treatment outcome [66].

Both pH-metry and pH-impedance monitoring are also used to test the relationship between reflux events and patient-reported symptoms. The two most popular indices are the symptom index (SI) and the symptom association probability (SAP). The SI is defined as the percentage of symptom events that occur within two minutes of reflux episodes, irrespective of the number of reflux episodes recorded, with a value of >50% considered positive [67]. A high SI can occur by chance, especially in a patient with numerous reflux episodes. To improve upon this, the SAP is a statistical calculation assessing the probability that the reflux and symptoms co-occur by chance; an SAP >95% is considered significant [68]. However, according to the Rome IV criteria for functional esophageal disorders, the finding of a normal esophageal acid exposure and a positive SI or SAP is now considered reflux hypersensitivity rather than GERD [69]. Consequently, although the SI and SAP may be useful to establish a relationship between reflux events and symptoms, the most relevant outcome of reflux monitoring studies is esophageal acid exposure and the role of symptom indices in patient management is unclear. Similarly, except in unusual circumstances where the pharmacological effectiveness of PPIs is in question, reflux monitoring studies should be done withholding PPI therapy for a week prior to (and during) the study to best address the question "does my patient have pathological GERD?" [54].

Esophageal high-resolution manometry

Esophageal high-resolution manometry (HRM) has no direct role in diagnosing GERD. However HRM can be useful to identify conditions that can facilitate or exacerbate reflux (hiatal hernia, hypotensive EGJ, ineffective esophageal contractions), to identify GERD mechanisms (TLESR, strain), or to diagnose conditions that can mimic GERD (rumination syndrome). Esophageal manometry is also usually performed before pH-metry or pH-impedance monitoring to localize the LES for probe positioning. Finally, manometry is required prior to antireflux surgery to verify the adequacy of peristaltic function and to rule out major motility disorders (achalasia) masquerading as GERD [70].

Barium swallow

Similar to manometry, barium radiography has minimal role in the diagnosis of GERD, but can be useful to identify conditions associated with GERD (hiatal hernia) or anatomical complications that may have bearing on treatment (e.g. short esophagus, stricture, paraesophageal hernia). A recent study reported that barium swallow alone had a sensitivity of 73% to detect hiatal hernia, the same as endoscopy, while HRM had a sensitivity of 92% and a specificity of 93% [71].

Mucosal impedance

Reflux injury to the esophageal mucosa makes it more permeable to ions and small molecules, which in turn alters its resting electrical impedance as can be measured during reflux monitoring studies or with a probe passed through the instrument channel of an endoscope. Recent reports suggest that measurement of esophageal mucosal impedance might be useful to diagnose GERD [72]. An Italian study proposed measuring baseline impedance during the overnight period of 24-hour pH-impedance monitoring studies reporting that a mean nocturnal baseline impedance <2446 Ω was predictive of GERD, defined as PPI-responsive heartburn, with a sensitivity of 98% and a specificity of 79% in a cohort of 120 patients without esophagitis [73]. In another cohort of 52 patients (16 with esophagitis, 19 NERD, and 17 functional heartburn) baseline impedance <2100 Ω had a sensitivity of 78% and a specificity of 71% for GERD [74]. An alternative method to measure baseline esophageal impedance is with a probe passed through the working channel of an endoscope

[75]. Using pH-metry and endoscopy as the reference standard, Ates *et al*. reported that mucosal impedance (<2000 Ω) measured this way had a specificity of 95% and a positive predictive value of 96% for a GERD diagnosis. This device is not yet commercially available and its ultimate place in GERD diagnostics remains to be determined.

Treatment

GERD symptoms are common and impair the quality of life. The aims of treatment are to provide symptom relief sufficient to restore the quality of life, to heal esophagitis, and to prevent complications. Fortunately, complications of GERD are relatively rare and in most cases treatment is rendered based on the symptom profile, without diagnostic testing. Nonetheless, in view of the high prevalence of GERD, the societal costs of the disease including over-the-counter (OTC) medications, prescription medications, and diagnostic testing are very high.

Lifestyle modifications

Although lifestyle modifications are a cornerstone of GERD management, in most cases, their utility is not based on high-level evidence [76]. However, there is broad consensus among physicians that targeted dietary and lifestyle modifications are useful and should be adopted as first-line treatment, especially with mild or infrequent symptoms [77]. Lifestyle modification can be divided into three general categories: (i) avoidance of food that may cause reflux, presumably by relaxing the LES (coffee, alcohol, chocolate, fatty food), (ii) avoidance of acidic foods that may precipitate heartburn by a direct irritant effect on the sensitized esophageal mucosa (citrus, carbonated drinks, spicy foods), and (iii) adopting behaviors that may reduce esophageal acid exposure by reducing the occurrence of reflux and/or enhancing the process of acid clearance (weight loss, smoking cessation, raising the head of the bed, and avoiding recumbency for two to three hours after meals). Clearly, adopting all of these behaviors can be overly restrictive, even to the point of impairing the quality of life beyond that imposed by the symptoms themselves. Consequently, they should be prioritized based on the circumstances of the individual patient and selectively advocated. This is especially true given the generally low level of supporting evidence summarized in Table 1.2 [78].

Obesity and the importance of weight control merit attention in view of the parallel epidemics of obesity and GERD. Weight loss may be beneficial in reducing GERD symptoms and may decrease the requirement for acid suppressive medications, even among normal weight individuals [79, 80]. Although ideally this would be confirmed by more rigorous studies, the general health benefits of avoiding obesity are sufficient to make this recommendation in good conscience with the current evidence.

Table 1.2 Lifestyle modifications for GERD and level of supporting evidence

Recommendation	Level of evidence
Weight loss for overweight and obese patients with esophageal GERD symptoms	Grade B
Elevation of the head of the head of the bed for selected patients who are troubled with heartburn or regurgitation when recumbent	Grade B
Avoiding late meals for individuals troubled by nocturnal heartburn and/or regurgitation	Insufficient
Avoiding specific foods (i.e. coffee, alcohol, chocolate, fatty foods, citrus, carbonated drinks, spicy foods) for individuals in whom specifically identified foods are known triggers of heartburn, regurgitation, or other reflux symptoms (such as cough)	Grade B
Avoiding specific activities altogether, or avoiding eating before embarking on those activities (e.g. running, exercise), that are known triggers of heartburn, regurgitation, or other reflux symptoms (such as cough)	Insufficient
Broadly advocating lifestyle changes for all (as opposed to selected) patients	Insufficient

Grade B indicates a recommendation with fair evidence that it improves important outcomes. "Insufficient" indicates that this is not an evidence-based recommendation because insufficient evidence exists to recommend for or against.

Source: Kahrilas *et al.* 2008 [78]. Reproduced with permission of Elsevier.

Antacids and alginates

Antacids neutralize gastric acid and refluxed acid residing in the esophagus without reducing gastric acid secretion. Consequently, one would anticipate this to be an immediate, albeit short-lived, effect. A meta-analysis of the efficacy of OTC medications in relieving GERD symptoms found a relative benefit of 11% for simple antacids and up to 60% for alginate-antacid combinations compared to placebo [81]. The incremental benefit of alginate-antacid combinations over simple antacid is attributable to the property of alginate wherein it forms an aqueous gel that floats on top of the gastric content and persists in the stomach for three to four hours. This gel colocalizes with the acid pocket, the pool of newly secreted acid that also floats on top of gastric chyme in the postprandial period. The antacid-alginate gel has been shown to eliminate or displace the acid pocket in GERD patients rendering reflux episodes less acidic, presumably by refluxing in lieu of gastric acid [82]. A large randomized controlled trial conducted in 1107 symptomatic GERD patients in China demonstrated that an alginate-antacid combination

(Gaviscon) was superior to placebo in reducing GERD and dyspepsia scores. Over half (52%) of patients in the alginate-antacid group rated their symptoms as at least "moderately better" compared to 39% of the placebo group [83].

Histamine-2 receptor antagonists

Histamine-2 receptor antagonists (H_2RAs) block histamine-stimulated acid secretion and predated PPIs as mainstream therapy for GERD. In a 2007 meta-analysis, two to four weeks of H_2RA therapy was found superior to placebo for adequate heartburn relief [absolute risk reduction 10% (95% confidence interval [CI] 7–13%), number needed to treat (NNT) of 10 (95% CI 7–14)] and to improve heartburn [absolute risk reduction 12% (95% CI 7–17%), NNT of 8 (95% CI 6–14)]. More recently, some authors have proposed adding an H_2RA at nighttime to PPI therapy in patients with refractory nocturnal heartburn, reasoning that this might reduce nocturnal gastric acid breakthrough observed on PPI therapy. However, that effect of H_2RAs exhibits rapid tachyphylaxis [84] and a study comparing four drug regimens (omeprazole 20 mg bid; omeprazole 20 mg bid plus ranitidine 300 mg HS; omeprazole 20 mg QAM and QHS; and omeprazole 20 mg every eight hours), found no difference among regimens in esophageal acid reflux or symptom relief [85]. In summary, H_2RAs are more effective than placebo, but their current indication is limited to patients with mild symptoms needing only on-demand treatment or in patients intolerant of PPI therapy [81].

Proton pump inhibitors

PPIs are potent inhibitors of gastric acid secretion, blocking the final common pathway of acid secretion by covalently binding with gastric H+/K+ ATPase. However, PPIs only bind to the ATPase when in its transmembrane conformation, exposed within the secretory canaliculi and actively secreting hydrogen ion. Consequently, PPIs are more effective when taken before the stimulation of acid secretion and should be taken before a meal [86]. Numerous randomized controlled trials and meta-analyses have reported the superiority of PPI compared to placebo and H_2RAs for healing esophagitis and relieving GERD symptoms. Based on these data, the level of evidence for PPI use in GERD is grade A (strongly recommended based on good evidence that it improves health outcome) [78]. Esophagitis is the best-case scenario for PPI therapy. Standard dose PPI was superior to placebo [risk ratio 0.22 (95% CI 0.15–0.31)] and to H_2RAs [risk ratio 0.51 (0.44–0.59)] in healing esophagitis [87]. With respect to symptoms, a 2013 Cochrane review evaluated the efficacy of short-term PPI treatment for GERD symptoms and NERD, finding PPIs more effective than placebo or H_2RAs (high quality of evidence for PPI vs. placebo and moderate quality of evidence for PPI vs. H_2RA) [88]. Regarding empirical treatment of GERD, the risk ratio for heartburn remission was 0.37 (95% CI 0.32–0.44) for PPI vs. placebo and 0.66 (95% CI 0.60–0.73) for PPI vs. H_2RA. Regarding NERD treatment, the risk ratio was 0.71 (95% CI 0.65–0.78) and 0.78 (95% CI 0.62–0.97), respectively. An interesting 2012 meta-analysis reported that the pooled estimate of complete heartburn relief after four-week PPI therapy was 0.72 (95% CI 0.69–074) in patients with erosive reflux disease and 0.73 (0.69–0.77) in patients with NERD when defined as negative endoscopy and positive pH-metry, while it was only 0.49 (0.44–0.55) in patents with NERD defined only by negative endoscopy and 0.50 (0.43–0.57) in patients treated empirically based on a symptom assessment [89]. Thus, well-defined NERD is an important predictor of response to PPI therapy.

Response to PPI therapy is also dependent on the specific symptom being treated and on whether or not there is additional objective evidence of a GERD diagnosis. For instance, the therapeutic gain of PPI over placebo for heartburn was about 41%, but only 17% for regurgitation [90]. For chest pain, a ≥50% improvement relative to placebo was achieved in 56–85% patients with endoscopic or pH-metry evidence of GERD, but in only 0% to 17% of patients without esophagitis or abnormal pH-metry [91]. When dysphagia was associated with esophagitis, it reportedly resolved in 83% of cases with PPI therapy [92]. Chronic cough is much more challenging. A meta-analysis combining nine studies reported no significant difference in resolution of cough between PPI and placebo (odds ratio [OR] 0.46; 95% CI 0.19–1.15) in Ref. [93]. Most supportive data for treating ENT symptoms with PPIs are in the form of uncontrolled open-label trials, and conflicting results have been reported in small controlled studies [94]. In the largest controlled trial to date, 145 patients with symptoms of chronic posterior laryngitis were randomized to esomeprazole 40 mg bid or placebo for 16 weeks and there was no difference in effectiveness; 15% symptom relief in the esomeprazole group vs. 16% in the placebo group, $p = 0.799$) [95].

PPI dose

Although it may be convenient for providers to view all PPIs as equivalent and interchangeable, there are obvious differences in dosage and substantial pharmacokinetic and pharmacodynamic differences among available products. For example, two products with unique characteristics are dexlansoprazole, formulated to have both an early peak absorption (one to two hours) and a delayed peak absorption (four to five hours) thereby prolonging its acid-inhibitory effect and the non-enteric-coated omeprazole/bicarbonate combination, formulated for immediate bioavailability [96]. Similarly, there is considerable interindividual variation in the degree of acid suppression achieved with a specific PPI regimen. Genetic polymorphism of the cytochrome P450 enzyme (CYP2C19), a major metabolic pathway of PPIs, explains some of this interindividual variability; PPI plasma

levels and the corresponding degree of acid inhibition correlate with their metabolism, potentially affecting dose requirements and clinical efficacy. As an example, a Japanese study using omeprazole to treat *Helicobacter pylori* found that while eradication was achieved in 100% of individuals homozygous for a CYP2C19 mutation (slow omeprazole metabolizers), eradication was achieved in only 60% of heterozygotes (intermediate omeprazole metabolizers), and 29% of patients without the mutation (rapid omeprazole metabolizers) [97].

A practical approach to dealing with the interindividual variability in PPI effectiveness in clinical practice is to increase the PPI dose or switch to another PPI when treatment is unsatisfactory [98]. While this seems reasonable, there is minimal supportive evidence for this approach, other than in the case of high-grade reflux esophagitis. A systematic review of PPI efficacy in severe erosive esophagitis reported that esomeprazole 40 mg had greater healing rates than other PPIs at four weeks [OR 1.84 (95% CI 1.50–2.22)] and eight weeks [OR 1.91 (95% CI 1.13–2.88)] [99]. On the other hand, in the absence of esophagitis, heartburn relief was similar (63%) in patients receiving esopmeprazole 20 or 40 mg [100]. However, Becker *et al*. reported that increasing PPI dosage was more effective in patients with persistent abnormal pH-impedance monitoring on standard PPI therapy than in patients without abnormal studies (91% symptom relief vs. 43%, $p < 0.001$) [57]. Hence, changing the PPI regimen may be effective in patients with severe esophagitis or with a persistently abnormal reflux monitoring study on PPI therapy, but in other circumstances, data in support of this are scarce.

For maintenance therapy, low-dose PPIs and on-demand therapy can be appropriate in up to 80% of patients [101]. In a review, evaluating the efficacy of on-demand therapy in randomized trials treating patients with NERD and mild esophagitis, no significant difference was reported between continuous and on-demand therapy [102]. Current recommendations are to use the lowest dose of PPI sufficient to maintain adequate symptom relief [78]. A step down strategy can be used to achieve this in the majority of patients.

PPI side effects

For short-term use, PPIs are quite safe. Headache and diarrhea are reported in fewer than 5% of patients and are reversible with cessation of therapy. Long-term PPI treatment has raised some safety concerns, most of them related to the profound inhibition of acid secretion and associated hypergastrinemia. PPI use induces hypergastrinemia because gastrin release is modulated by intragastric acidity. A systematic review of 16 studies reported that gastrin levels increased to one to three times the upper limit of normal during long-term PPI therapy associated with an increased prevalence of enterochromaffin-like cell hyperplasia [103]. Enterochromaffin-like cell hyperplasia as well as corpus atrophy were more frequent in *H. pylori* positive patients than in negative ones. No resulting case of gastric adenocarcinoma has been reported.

Idiosyncratic cases of interstitial nephritis and severe hypomagnesemia have been reported with PPI use, although these are quite rare [104, 105]. Apart from that, most reports of PPI side effects come in the form of retrospective epidemiology studies demonstrating weak associations between PPI use and various morbidities (Table 1.3). The earliest and most widely reported of these are the risks of osteopenia and hip fracture. In a meta-analysis, the odds ratio (OR) for hip fracture was 1.25 (95% CI 1.14–1.37) in PPI users compared to nonusers or past users [106]. However, attempts at establishing the causality of this relationship have failed. Comparing PPI users and nonusers, the Canadian Multicenter Osteoporosis Study data set found no significant acceleration of body mineral density loss after 5 and 10 years of PPI use [110].

There is also the potential for drug–drug interactions with PPIs because of shared hepatic metabolism. Historically, this focused on Dilantin, warfarin, and diazepam that share the CYP2C19 pathway with PPIs, but these concerns proved insignificant. More recently, the focus has been on clopidogrel, with observational studies reporting that clopidogrel users taking PPIs have an increased risk of cardiovascular events (hazard/odds ratios 1.25–1.5) [111]. However, the significance of this is debated and a meta-analysis of eight randomized-controlled trials reported no difference in all-cause mortality [OR 0.91 (CI 0.58–1.40)], acute coronary syndrome [OR 0.96 (95% CI 0.88–1.05)], myocardial infarction [OR 1.05 (CI 0.86–1.28)], or cerebrovascular accidents [OR 1.47 (CI 0.66–3.25)] between patients receiving clopidogrel alone or in combination with PPI [108]. On the other hand, another meta-analysis of 12 studies of patients who underwent percutaneous coronary intervention, concomitant therapy with PPI and clopidogrel was associated with a significant increases in myocardial infarction [hazard ratio (HR) = 1.51 (CI 1.40–1.62)], and stroke [HR 1.46 (CI 1.15–1.86)] [112].

Potassium competitive acid blockers

Potassium competitive acid blockers (PCABs) concentrate in the secretory canaliculi of parietal cells and reversibly bind to the active H+/K+ ATPase, thereby achieving nearly complete acid inhibition that persists for a period related to the serum half-life of the drug. The PCAB, vonoprazan 20 mg, which is available in Japan, was compared to lansoprazole 30 mg once daily after breakfast in a non-inferiority randomized trial including 409 patients with erosive esophagitis [113]. After eight weeks of treatment, esophagitis was healed in 99% of patients in the vonoprazan group vs. 96% in the lansoprazole group, confirming non-inferiority ($p < 0.0001$).

Table 1.3 Potential adverse effects reported to be associated with PPI use

Potential adverse effect	Nature of evidence	Risk estimate
Acute interstitial nephritis	Observational, case–control	OR 5.16 (2.21–12.05)
Chronic kidney disease	Observational, population-based cohort	HR 1.50 (1.14–1.96)
Bone fracture	Observational, case–control	OR 2.65 (1.80–3.90)
Hip fracture	Systematic review, meta-analysis	OR 1.25 (1.14–1.37) [106]
Fundic gland polyps	Observational	OR 2.2 (1.3–3.8)
B12 deficiency	Observational, case–control	OR 1.65 (1.58–1.73)
Iron deficiency	Observational, case–control	OR 2.49 (2.35–2.64)
Hypomagnesemia	Observational, population-based cohort	OR 2.00 (1.36–2.93)
Small bowel bacterial overgrowth	Meta-analysis	OR 2.28 (1.23–4.21)
Clostridium difficile infection	Observational cohort study	OR 2.10 (1.20–3.50)
Community-acquired pneumonia	Systematic review, meta-analysis	OR 1.49 (1.16–1.92)
Spontaneous bacterial peritonitis in cirrhotic patients	Systematic review, meta-analysis	OR 2.17 (1.46–2.23)
Hepatic encephalopathy in cirrhotic patients	Observational, case–control	OR 3.01 (1.78–5.10) (dose dependent)
Dementia	Prospective observational cohort	HR 1.44 (1.36–1.52)
Cardiovascular effects	Meta-analysis	RR 1.70 (1.13–2.56) [107]
Myocardial infarction	Observational, data mining	HR 1.16 (1.09–1.24)
Acute coronary syndrome (PPI + clopidogrel vs. clopidogrel alone)	Meta-analysis	OR 0.96 (0.88–1.05) [108]
Cerebrovascular accident (PPI + clopidogrel)	Meta-analysis	OR 1.47 (0.66–3.25) [108]

HR, hazard ratio; OR, odds ratio; RR, risk ratio.

Source: Adapted from Yadlapati and Kahrilas 2017 [109]. https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-017-0804-x. Licensed under CC BY 4.0.

Reflux inhibitors

As TLESRs are a dominant mechanism of GERD and this is a complex neural reflex, inhibiting TLESRs is an attractive target for GERD treatment. Baclofen, a $GABA_B$ agonist inhibits both central and peripheral elements of the vagal pathway for TLESRs [114]. However, while baclofen has been shown to decrease the number of reflux episodes [115], its clinical use is limited by neurologic side effects (somnolence, dizziness, drowsiness) attributable to the drug crossing the blood–brain barrier. Arbaclofen placarbil (R-isomer of baclofen) and lesogabaran (a novel $GABA_B$ agonist) were developed as alternatives to baclofen, but failed to show sufficient additive benefits to a PPI alone when used in combination therapy to warrant further development [116]. Another reflux inhibitor, an mGluR5 inhibitor (ADX10059), was shown to reduce reflux episodes and improve symptoms in GERD patients, but its development was halted due to liver toxicity [117]. Consequently, baclofen remains the only available reflux inhibitor.

Prokinetic drugs

Metoclopramide, an antidopaminergic agent that acts as a 5-HT3 antagonist, a 5-HT4 agonist, and a cholinomimetic, may improve gastric emptying leading some to propose its use in GERD [118]. However, there are no high-quality data supporting its efficacy in GERD and it has serious potential neurological side effects (Parkinsonism, depression, tardive dyskinesia, neuroleptic malignant syndrome, tremor). Hence, practice guidelines recommend against its use in GERD [78]. Newer prokinetics, such as prucalopride (a 5-HT4 agonist) may be of benefit in GERD through the mechanism of accelerated gastric emptying [32], but no high-level data in support of this currently exist. Another 5-HT4 receptor agonist, revexepride, was reported to be no more effective than placebo in two randomized controlled trials enrolling patients partially responsive to PPI therapy [119, 120].

Targeting hypersensitivity

Hypersensitivity is increasingly recognized as an important determinant of refractory GERD symptoms making it an attractive therapeutic target [69]. However, evidence supporting this approach remains scarce. Antidepressants, which may modulate esophageal sensitivity, have been the most studied. In a placebo controlled trial, trazadone was more effective than placebo in patients with esophageal symptoms and contractile abnormalities [121]. In a controlled trial enrolling patients with esophageal hypersensitivity, citalopram was reportedly more effective than placebo in symptom control; 15/39 patients (39%) receiving citalopram 20 mg vs. 24/36 (67%) receiving placebo reported persistent symptoms after six-month treatment ($p = 0.02$) [122]. More

recently, imipramine 25 mg was tested against placebo in 83 patients with esophageal hypersensitivity (normal pH-metry and positive symptom index on pH-impedance monitoring) or functional heartburn (normal pH-metry and negative symptom index) reporting equal relief in both treatment groups (37%, intent-to-treat analysis) [123].

Alternative therapies targeting hypersensitivity or hypervigilance have also been tested. Acupuncture combined with a PPI was associated with better symptom control than double-dose PPI in a series of 30 patients with persistent symptoms on once-daily PPI [124]. A significant decrease of symptom score was observed in the group of patients receiving PPI and acupuncture but not in the PPI alone group. Further, no sham procedure was offered to patients in the PPI group. Hypnotherapy has also been proposed for treating esophageal disorders [125]. Noncardiac chest pain (uninvestigated with respect to GERD) improved in 12/15 patients (80%) treated with hypnotherapy vs. 3/13 (23%) receiving placebo and supportive therapy ($p = 008$) [126]. These studies evaluating alternative therapies are limited by small sample sizes and the absence of sham procedures.

Antireflux surgery

The aims of surgical fundoplication are to anatomically reestablish the competence of the antireflux barrier and to reduce a hiatal hernia, if present [127]. The two most popular surgical procedures are the laparoscopic Nissen (360°) fundoplication and the Toupet (270°) fundoplication. There is broad agreement among experts that patients should have proven reflux disease by endoscopy and/or pH-metry and a relatively normal esophageal motility study prior to undergoing antireflux surgery [128].

Although the relative merits of antireflux surgery and PPI therapy have been hotly debated, high-grade evidence supports the concept that laparoscopic fundoplication is an effective alternative to PPI therapy, particularly for patients with PPI-responsive symptoms and those intolerant of PPI therapy [78]. The best supportive data, the LOTUS trial, was a randomized study comparing expert laparoscopic Nissen fundoplication to esomeprazole in patients with chronic GERD that had responded to PPI therapy. Remission rates at five years slightly favored the esomeprazole group [92% (CI 89–96%)] over the fundoplication group [85% (CI 81–90%), $p = 0.048$]. Interestingly differences were observed with respect to specific symptoms. While heartburn prevalence was similar at five years (16% esomeprazole vs. 8% fundoplication, $p = 0.14$), persistent regurgitation was more frequent in the esomeprazole group (13% vs. 2%, $p < 0.001$) while dysphagia (5% vs. 11%, $p < 0.001$), bloating (28% vs. 40%, $p < 0.001$), and flatulence (40% vs. 57%, $p < 0.001$) more frequent in the fundoplication group. Subsequent analysis suggested that the magnitude of pretreatment esophageal acid exposure did not predict treatment failure [129]. Consequently, these data suggest that the symptom profile (dominant regurgitation), rather than the magnitude of esophageal acid exposure should be the main consideration in choosing fundoplication.

An equally important question regarding antireflux surgery is its success in treating patients who are poorly responsive to PPI therapy, and in this domain data are uncontrolled, limited, and somewhat conflicting. The most consistent predictive factor of success seems to be pathological acid exposure on pH-metry. In a series of patients with persistent symptoms on PPI and pathological acid exposure on pH-metry, Broeders *et al*. observed similar response rate at five years in patients with positive or negative SAP [130]. Similarly, Patel *et al*. observed that abnormal pH-metry, but not SAP, was predictive of improvement in a series of 59 patients who underwent antireflux surgery [66]. Apart from patient selection, it is also apparent that surgical outcomes are very operator dependent. Data from community practice reported up to 30% of patients resume PPI within five years of antireflux surgery [131]. Further, revision antireflux surgery accounts for up to 50% of operations at some referral centers [132].

In summary, the highest-level evidence to recommend fundoplication is for patients with GERD symptoms responding to PPI therapy, particularly if they have persistent troublesome regurgitation. This indication should be balanced with the risk of surgical complications and of side effects (dysphagia, flatulence, inability to belch). In patients with symptoms refractory to PPI, there is currently no high-level evidence to recommend surgery.

Novel surgical and endoscopic procedures

A variety of procedures have been proposed as alternatives to conventional laparoscopic antireflux surgery during the past 20 years. Most had limited efficacy and/or significant adverse events leading to their withdrawal. Currently, there are five procedural therapies available: transoral incisionless fundoplication (EndoGastric Solutions, Redmond, WA), an ultrasound-assisted full thickness plication device (Medigus, Omer, Israel), the Stretta procedure (Mederi Therapeutics Inc., Norwalk, CT), magnetic sphincter augmentation (Torax Medical, Shoreview, NM), and an implantable electrical stimulation device (BV, The Hague, Netherlands). Only two of these have undergone controlled trials, transoral incisionless fundoplication, and the Stretta procedure. Additionally, there is an expanding dataset on the use of magnetic sphincter augmentation that warrants discussion.

The RESPECT trial evaluated transoral incisionless fundoplication + placebo vs. sham procedure + omeprazole 20–40 mg in 129 patients enrolled with troublesome regurgitation despite PPI therapy. Elimination of regurgitation, the primary outcome of the study, was achieved in 67% of

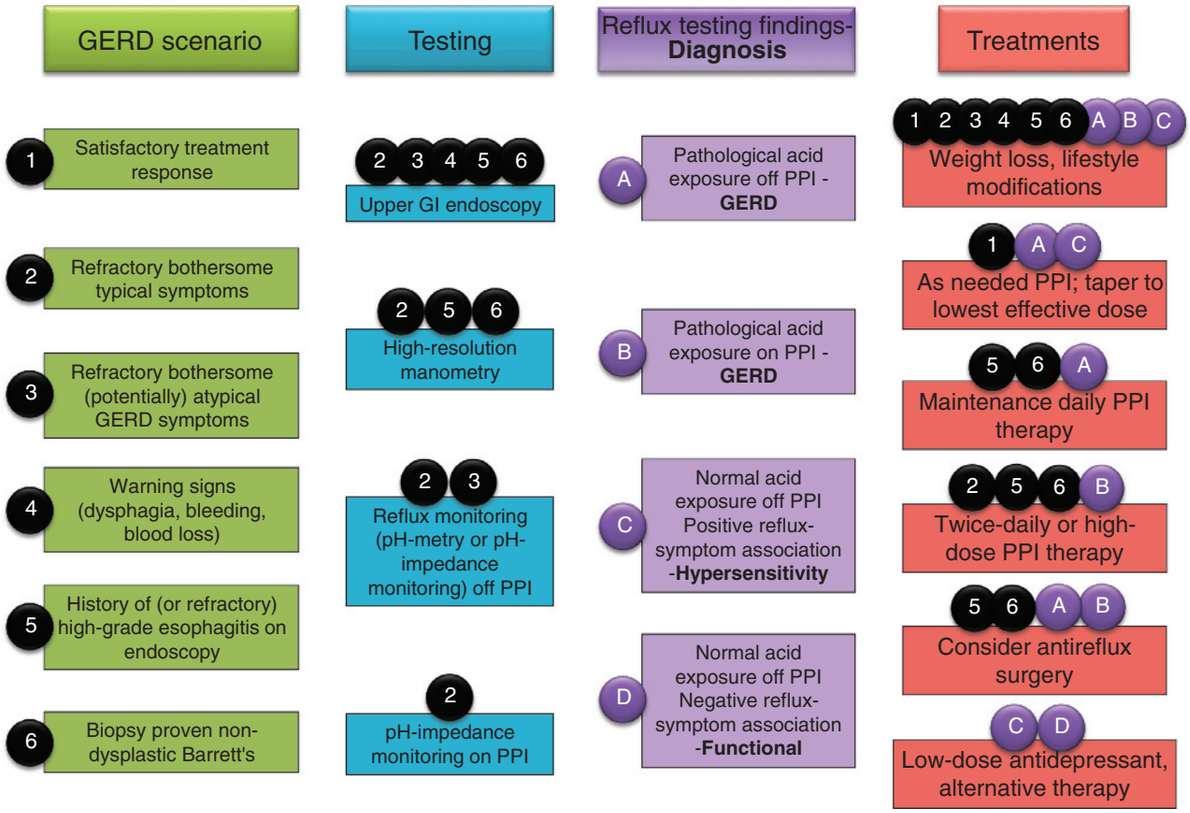

Figure 1.2 A conceptual algorithm on GERD management. Accepting the Montreal definition, there are quite a number of GERD presentations and, consequently, no single branch diagram can ever capture all of the management considerations. In this figure, the 6 major treatment scenarios are indicated in green and numbered. The appropriate clinical testing for each is then indicated in blue. Note that in case 1, with a satisfactory response to empirical treatment and none of conditions 2–6, no testing is requisite. In instances that reflux testing is done, there are four possible outcomes, detailed in purple. Management strategy (peach) then depends on a combination of GERD scenario and reflux test findings as indicated by the letters and numbers attached to each box.

patients in the transoral incisionless fundoplication group vs. 45% in the sham group at six months ($p = 0.023$) [133]. In another randomized trial including patients with objective GERD and symptoms after PPI discontinuation, 59% of patients who underwent TIF were in clinical remission without PPI at six months; the average number of days in remission without PPI was longer in transoral incisionless fundoplication group vs. sham group (197 vs. 107, $p < 0.001$) [134]. Long-term data regarding the efficacy of transoral incisionless fundoplication are lacking. In a randomized trial comparing transoral incisionless fundoplication and PPI, 61% of patients in the TIF group resumed PPI at one year [135] and an observational study demonstrated a decrease in complete response rate over time (51% at one year, 32% at five years) [136].

The Stretta procedure involves applying radiofrequency energy to the LES using a specialized generator and orally passed needle electrode assembly. The purported mechanism of action is to tighten the sphincter, although there are no objective data to confirm that this occurs. A randomized sham-controlled trial reported improved GERD symptoms and quality of life compared with a sham procedure, but did not decrease esophageal acid exposure or medication use at six months [137]. Subsequent physiological studies suggest that the relevant mechanism of action is to reduce esophageal sensitivity [138], presumably by the widely recognized radiofrequency energy effect of neurolysis.

Magnetic sphincter augmentation consists of the surgical implantation of a ring of magnetic beads around the LES. There are no controlled trials of magnetic sphincter augmentation, but a recent five-year outcome study of 85 patients reported that 15% of treated patients were taking PPIs at five years compared to 100% at baseline [139]. Extensive data also demonstrate reduction of esophageal acid exposure on pH-metry with magnetic sphincter augmentation [140]. Device removal because of adverse events, mainly dysphagia, occurs in about 2% of implants.

Conclusion

GERD is very common. The diagnosis is usually established on clinical grounds by symptom assessment when the symptoms are typical, warning signs are absent, and treatment is effective. When investigation is pursued, upper GI endoscopy is the most useful diagnostic test because it evaluates for the major potential morbidities (Barrett's, stricture, cancer) associated with GERD and allows for the exclusion of alternative diagnostic possibilities, However, because it only detects GERD cases associated with esophagitis, its sensitivity for the diagnosis of GERD is quite low. Identification of reflux episodes using pH-metry or pH-impedance monitoring is the accepted reference standard for GERD diagnosis. PPIs are the cornerstone treatment for GERD with high level of evidence. Surgical fundoplication is an effective alternative to PPI treatment in selected patients with typical symptoms responding to PPI therapy. However, given the morbidity associated with surgery and the variability of surgical outcomes as practiced in the community, this should be applied very judiciously. Figure 1.2 is an algorithm of suggested GERD management, recognizing that this is a complex entity and that numerous exceptions to the rules can always be found.

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