Gastroesophageal Reflux Disease in Adults

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Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, nurses, and members of the interprofessional healthcare team involved in the diagnosis, treatment, and care of patients with gastroesophageal reflux disease (GERD).

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Course Objective

The purpose of this course is to provide members of the interprofessional healthcare team with the information necessary to appropriately diagnose, treat, and care for patients with GERD.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the incidence and prevalence of gastroesophageal reflux disease (GERD).
2. Describe the patient, social, and economic impact of GERD.
3. Identify risk factors for GERD.
4. Review the natural history and pathophysiology of GERD.
5. Appropriately categorize GERD according to underlying pathology.
6. Identify signs and symptoms of GERD.
7. Select appropriate diagnostic tests for patients with suspected GERD.
8. Analyze the pharmacologic treatment of GERD.
9. Outline the treatment options for refractory GERD.
10. Describe surgical options for GERD treatment.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is recognized as a complex clinical entity, primarily a motility disorder with impaired lower esophageal sphincter (LES) structure and function playing a central role. However, GERD is widely seen as a simple disorder of acid over-secretion resolved by proton pump inhibitor (PPI) medication. While PPIs are the backbone of clinical management for patients with suspected GERD, many patients remain symptomatic even after initiating treatment. The diverse underlying pathology of GERD symptom presentation requires proper diagnosis to effectively target with therapy. There is also evidence associating long-term PPI therapy with concerning adverse effects. This course will disentangle the conflicting and sometimes confusing clinical guidance and evidence that characterizes the large volume of publications on GERD, empowering primary care clinicians with the clarity and direction to improve the clinical care of these patients.

DEFINITIONS AND DESCRIPTIONS

Acid reflux: Esophageal reflux with pH <4 [1].

Dyspepsia: A condition with epigastric pain that may include epigastric fullness, nausea, vomiting, or heartburn [2].

Eosinophilic esophagitis: An immune-mediated inflammatory disease of the esophageal mucosal layer, mainly caused by GERD [3].

Erosive esophagitis (also referred to as reflux esophagitis or erosive GERD): GERD symptoms with visible esophageal mucosal injury during endoscopy [4].

Esophagitis: Inflammation of the esophageal mucosa, usually associated with symptoms of heartburn, chest pain, or dysphagia (difficulty swallowing) [3].

Functional gastrointestinal disorders (FGIDs): Disorders of gut-brain interaction, with gastrointestinal (GI) symptoms related to any combination of motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut micro-biota, and altered central nervous system (CNS) processing [5]. Rome IV, the 2016 guideline for the diagnosis and management of GERD, eliminated the vague, potentially stigmatizing term "functional" and replaced FGIDs with disorders of gut-brain interaction, but recognized functional is an embedded terminology that will take time to replace [6]. With this terminology introduced in 2016, this course uses functional for consistency with the published literature.

Functional esophageal disorders (FEDs): FGIDs with esophageal symptoms (i.e., chest pain, heartburn, dysphagia) not adequately explained by structural, inflammatory, or motor abnormalities. Also includes reflux hypersensitivity. Treatment markedly differs from GERD [7].

Gastroesophageal reflux disease (GERD): A condition defined by troublesome symptoms, impaired quality of life, and/or mucosal damage or complications resulting from reflux of gastric fluid into the esophagus, oropharynx, and/or respiratory tract [8].

GERD symptoms: Term used to describe heartburn and/or regurgitation symptoms, independent of actual GERD diagnosis.

Heartburn: A rising, burning sensation in the chest or throat.

Non-erosive reflux disease (NERD): GERD symptoms in the absence of visible esophageal mucosal injury during endoscopy; accounts for 70% of the GERD population [4; 8; 9].

Reflux (also referred to as gastroesophageal reflux or GER): An event in which stomach contents leak upward, or reflux, into the esophagus [10].

Regurgitation: Refluxed gastric content reaches the throat or mouth.

Visceral (esophageal) hypersensitivity: Lowered pain threshold and heightened sensitivity to noxious GI stimuli, such as acid reflux [7].

EPIDEMIOLOGY OF GERD

Symptoms suggestive of GERD affect an estimated 30% of Western populations, and the prevalence continues to increase [11]. A comparison of GERD prevalence in different continents showed the highest rates in North America [11]. As noted, the prevalence of NERD in the GERD population is roughly 70% [12].

Among adult residents of Olmsted County, Minnesota (home of the Mayo Clinic), 18.1% had GERD (defined by at least weekly heartburn and/or regurgitation) [13]. Combining these data with results from three other U.S. studies with similar GERD definitions found a prevalence of 18.1% to 27.8% and a sample size-weighted average prevalence of 19.8% [11].

American studies conducted after 1995 show a significantly higher prevalence of GERD than studies conducted before 1995. Among various ethnicities, the incidence of GERD is higher in white individuals, likely related to lifestyle rather than genetic factors [8]. GERD incidence increases with age, especially after 40 years [4].

GERD and functional GI disorders (defined by Rome criteria) frequently co-occur and overlap. In a large study, 83% of patients with irritable bowel syndrome with constipation (IBS-C) had comorbid GERD and/or functional dyspepsia [14].

EXTRAESOPHAGEAL MANIFESTATIONS OF GERD

Extraesophageal manifestations of GERD are typically pulmonary or ear/nose/throat (ENT) and may represent associated symptoms or complications. GERD can be considered a co-factor in the development of asthma, chronic cough, or laryngitis, and GERD-related esophageal disease is associated with chronic bronchitis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasis, and pneumonia [15; 16]. In a study of 6,000 patients with erosive esophagitis or NERD, 30% had extraesophageal manifestations of GERD, including chronic cough (13.3%), laryngeal disorders (10.6%), and asthma (4.5%) [17]. Microaspiration (or "silent" aspiration) of gastric contents is thought to underlie the high prevalence of respiratory disorders in GERD. With multiple irritant and corrosive elements in gastric contents, this effect may be independent of aspirate acidity [18].

Hoarseness and Laryngitis

Hoarseness occurs more frequently in patients with weekly GERD symptoms. Patients with chronic laryngitis often lack typical GERD symptoms of heartburn and regurgitation, but esophageal inflammation is present in 19% to 40%. Abnormal esophageal presence of acidic reflux was found in 55% to 79% of patients with chronic hoarseness and 18% to 70% of those with posterior laryngitis [16; 19; 20; 21].

Chronic Cough

GERD is the third most common cause of chronic cough in adults, after postnasal drip and asthma. The frequency of chronic cough in patients with no, infrequent, or frequent GERD symptoms is 11%, 15%, and 22%, respectively. GERD may be the primary cause in 10% of patients with chronic cough [16; 17; 22].

Non-Cardiac Chest Pain

Non-cardiac chest pain is recurrent chest pain that can be difficult to distinguish from ischemic heart pain, diagnosed after a cardiac cause is excluded. GERD is the most important esophageal cause of non-cardiac chest pain [16]. In a community study, 53% of patients with non-cardiac chest pain experienced heartburn and 58% experienced acid regurgitation. Non-cardiac chest pain was reported by 37% of patients with at least weekly heartburn symptoms, 30.7% with infrequent heartburn (less than weekly), and 7.9% of those without GERD symptoms. Around 50% of patients with non-cardiac chest pain show abnormal esophageal acid exposure [23].

Asthma

GERD is present in 50% to 80% of adults with asthma, and 65% to 77% of adults with asthma report GERD-related symptoms [24]. Roughly 35% of patients with asthma show abnormal esophageal pH [25]. In 341 patients with severe or difficult-to-treat asthma despite standard treatment, 46.3% were diagnosed with GERD at 12- to 15-year follow-up [26]. The prevalence of asthma in patients with GERD increased over five years, from 4.5% to 7.8% [27].

FUNCTIONAL ESOPHAGEAL DISORDERS

Functional Chest Pain

The prevalence of functional chest pain is unknown and is largely inferred from studies of non-cardiac chest pain. Population surveys estimate the lifetime prevalence of functional chest pain at 19% to 33%, but this includes chest pain from GERD, eosinophilic esophagitis, and esophageal motor disorders [23; 28].

Within non-cardiac chest pain cohorts, 50% to 60% have GERD, 15% to 18% have esophageal dysmotility, and 32% to 35% have functional chest pain. The prevalence appears gender-equal but is higher in patients younger than 55 years of age [29].

Functional Heartburn

The prevalence of heartburn is difficult to estimate because its diagnosis is linked to ambulatory reflux testing and PPI response, both of which have limited ability to differentiate from GERD [30]. As many as 21% to 39% of patients with heartburn refractory to PPI undergoing pH-impedance monitoring fulfill the criteria for functional heartburn [31]. Up to 70% of patients with heartburn have normal endoscopy findings and are categorized by the presence or absence of abnormal acid exposure, symptom-reflux association, and PPI response [32]. Functional heartburn is found in roughly 50% of PPI nonresponders and 25% of PPI responders [7; 33].

Reflux Hypersensitivity

The epidemiology of reflux hypersensitivity is unknown but can be inferred from the NERD population. An estimated 37% to 60% of patients with NERD have normal esophageal presence of acidic reflux (measured by ambulatory pH testing) off their PPIs. Less than 10% show acid sensitivity [7; 34; 35]. Reflux hypersensitivity is very common and together with functional heartburn accounts for more than 90% of cases of heartburn refractory to twice-daily PPI. Additionally, it affects primarily young to middle-aged women, commonly overlaps with another FGID, and often is associated with some type of psychological comorbidity [36].

Functional Dysphagia

Functional dysphagia is considered the least prevalent functional esophageal disorder, but the true prevalence is unknown. A population survey of functional disorders estimated that 7% to 8% of dysphagia was unaccounted for by exclusionary criteria, and another study found 0.6% of patients with functional GI disorder complained of frequent dysphagia [7; 37; 38].

GENDER DIFFERENCES IN THE GERD SPECTRUM

Gender differences are found across the GERD spectrum. Differences in GERD symptom expression have been suggested, with women more likely to have heartburn, regurgitation, belching, and extraesophageal symptoms than men [39]. Testing of subjects without reflux symptoms or GERD using ambulatory 24-hour esophageal pH monitoring, which evaluates esophageal acid presence, suggests women experience fewer reflux events, lower total reflux time, and fewer periods with pH <4 [40; 41]. This suggests differences in upper GI response to reflux exposure, with greater sensitivity and symptoms in women despite less noxious acid exposure. However, men are more likely to develop pathologic changes of the esophagus [41]. Women are more likely to have partial response to PPIs, persistent GERD symptoms despite PPI treatment, and a need for PPI dose escalation [14; 42; 43].

PATIENT, SOCIETAL, AND ECONOMIC IMPACT

The frequency and severity of reflux-related symptoms falls on a continuum. Some individuals have occasional, mild heartburn that is not troublesome. Such persons do not meet diagnostic criteria for GERD, and symptoms should be managed with low-intensity, as-needed treatments and lifestyle adjustments [8].

In patients who meet the criteria for GERD, symptoms can impose a serious negative burden on quality of life. Disruptive GERD (more than once weekly symptoms) increases patient time off from work and decreases work productivity. These patients often have sleep impairment and decreases in physical functioning compared with patients with infrequent symptoms. Nocturnal GERD has a greater negative impact on quality of life compared with daytime symptoms. Nocturnal symptoms and sleep disturbances are critical to assess when evaluating the patient with GERD [15]. One nationwide survey of 1,000 adults with heartburn at least once a week found that 79% reported nocturnal heartburn. Of these respondents, 75% reported sleep disruption and 40% reported impaired functioning the next day. In addition, 71% were taking over-the-counter medications, but only 29% rated this approach as effective [16; 44].

Considering the potentially severely deleterious effects on productivity, sleep, and quality of life, GERD criteria were loosened in recognition that once-weekly reflux events can be disruptive in some patients. Even mild symptom severity, when experienced two or more times per week, can be impairing on quality of life [8]. Reflux symptoms in NERD can be as severe as those experienced by patients with esophageal erosion and mucosal damage [45].

Regulatory and treatment guidelines focus on individual upper GI disorders, but clinicians often see patients with overlapping conditions. These patients experience more frequent and more bothersome symptoms, a greater negative impact on work and school activities, and are more likely to seek physician care [14].

GERD accounts for 8.9 million outpatient visits each year, with an estimated annual cost of $24 billion. The annual cost of upper GI endoscopy is estimated at $12.3 billion [46]. PPI therapy is the first-line treatment for GERD and represents a substantial proportion of associated costs [1]. In 2009, more than 119 million prescriptions for PPIs were filled, making this class of medications the third-highest in sales in the United States ($13.6 billion) [47]. Data from the 2007–2011 Medical Expenditure Panel Survey indicated that low-cost PPI expenditures totaled $15.5 billion, compared with $63.4 billion for high-cost PPIs. Use of high-cost PPIs resulted in $47.1 billion in excess expenditure. A total of $6.69 billion was excess in out-of-pocket costs paid by users [48]. These figures do not include the cost burden to patients from over-the-counter purchase of PPIs.

ESOPHAGEAL COMPLICATIONS

GERD results from stomach and bile acid reflux through the LES into the distal esophagus. The stomach is lined by a mucinous columnar epithelium to withstand the acidic environment required for digestion. However, the esophagus is lined by squamous epithelium, which can become inflamed with exposure to the acidic contents of reflux [49].

Left untreated, continued esophageal acid exposure can lead to persistent inflammation (esophagitis), erosive esophagitis, and scarring, fibrosis, or strictures. Barrett esophagus can occur with refractory GERD due to histopathologic changes in the lower esophageal epithelium. Barrett esophagus may develop into a malignant dysplasia and is a risk factor for esophageal adenocarcinoma [50].

ESOPHAGITIS AND EOSINOPHILIC ESOPHAGITIS

Esophagitis is an inflammatory condition of the esophageal mucosa, usually associated with symptoms of heartburn, chest pain, and dysphagia. As noted, the esophageal wall has limited defense against injury from gastric acid, which can induce erosive or nonerosive esophagitis [3; 51].

Erosive esophagitis is esophagitis with more extensive reflux-induced injury, such as inflammation or ulceration [52]. Eosinophilic esophagitis is an immune-mediated inflammatory disease, characterized by eosinophilic infiltration of the esophageal mucosal layer [53]. Eosinophilic esophagitis was first described in the 1970s and became a distinct clinical entity in the early 1990s. GERD is the main cause of eosinophilic esophagitis [3].

Stricture formation is a consequence of untreated erosive esophagitis or eosinophilic esophagitis that develops over time into a diffusely narrow-caliber esophagus. Dominant strictures can potentially cause persistent dysphagia [54]. Length of delay in diagnosis correlates with the presence of fibrostenotic features [55].

BARRETT ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA

Barrett esophagus is a pre-malignant condition whereby the normal esophageal squamous epithelium becomes replaced by metaplastic columnar epithelium. Most cases result from chronic GERD. Barrett esophagus is found in 1.3% to 1.6% of the general population and in 5% to 15% of patients with symptomatic GERD during endoscopy [49].

The main concern with Barrett esophagus is the increased risk for esophageal adenocarcinoma, an outcome with a poor prognosis and high mortality rate [8; 49]. Patients with Barrett esophagus have at least a 20-fold increased risk of developing esophageal adenocarcinoma, but fewer than 4% of patients with Barrett esophagus develop the malignancy [56]. Why Barrett esophagus develops in some patients with GERD and not in others is unclear, but risk factors include male gender, white race, and increased age. Obesity, especially abdominal adiposity, is a strong risk factor for GERD, erosive esophagitis, and Barrett esophagus [49].

Men are more likely to develop pathologic changes of the esophagus, and women have a higher average age (often post-menopause) of esophageal adenocarcinoma onset than men. Beneficial effects of estrogen, including possible anti-inflammatory action and promotion of esophageal epithelial resistance against refluxate, may account for the lower rates and delayed onset in women [41].

STRICTURE

Strictures are advanced forms of esophagitis. Chronic, deep esophageal injury from acid reflux leads to circumferential fibrosis, typically in the mid-to-distal esophagus and visible by endoscopy. Strictures can result in dysphagia to solid meals and vomiting of nondigested foods. As a rule, the presence of esophageal stricture indicates that surgical consultation is needed for the patient [57].

PREDISPOSING AND RISK FACTORS FOR GERD

Predisposing factors for GERD include conditions that weaken the LES (e.g., hiatal hernia, pregnancy), increase pressure on the stomach (e.g., obesity, pregnancy, asthma), or affect transit of food from the stomach to the small intestine (e.g., diabetes, peptic ulcer disease, connective tissue disorders) [49].

OBESITY

Overweight (body mass index [BMI] 25–29.9) and obesity (BMI ≥30) are risk factors for GERD. GERD occurs in up to 70% of obese patients, and symptoms increase with weight gain [16]. Higher BMI and larger waist circumference are associated with the development of GERD complications, including Barrett esophagus [8].

With higher BMI, gastric compression from visceral adiposity increases the separation between the crural diaphragm and the LES, compromising the functional integrity of this antireflux barrier. Obese patients are also likely to have hiatal hernias, which contribute to reflux risk [58].

HIATAL HERNIA

Hiatal hernias are frequently seen in patients with reflux disease. Many patients with hiatal hernias do not have symptomatic reflux, and large hernias (>3 cm) have substantially greater association with GERD than smaller hernias [57; 59].

Large hiatal hernias in patients with GERD are associated with higher amounts of acid reflux and delayed esophageal acid clearance. Large hernias can separate the LES from the crural diaphragm and decrease LES tone, which weakens the gastroesophageal barrier and leads to its functional incompetence. Hiatal hernias are found in 25% of patients with non-erosive GERD, 75% of those with erosive GERD, and more than 90% of patients with Barrett esophagus [4; 60]. Laparoscopic hernia repair should be performed when a large hiatal hernia is present in patients with GERD who remain symptomatic despite twice-daily PPIs [59].

PREGNANCY

GERD symptoms, particularly heartburn, are common during pregnancy. Symptoms can begin in any trimester, with severity increasing throughout the pregnancy. Predictors of heartburn are advanced gestational age, heartburn before pregnancy, and parity, while maternal age is inversely related to heartburn. Race, pre-pregnancy BMI, and weight gain are unrelated to symptom severity. Despite its frequent occurrence in pregnancy, heartburn usually resolves after delivery. The amount of weight gain during pregnancy predicts persistent GERD symptoms one year post-delivery [15].

GERD diagnosis and treatment during pregnancy are based on symptoms; diagnostic testing and ambulatory pH monitoring are generally not required for most patients. In pregnant patients who require testing, upper endoscopy is the test of choice, but it should be reserved for patients whose symptoms are refractory to medical therapy or with suspected complications of GERD. If possible, endoscopy should be delayed until after the first trimester [15].

DIETARY FACTORS

High dietary fat intake is linked to a greater risk of GERD and erosive esophagitis. Carbonated drinks are also a risk factor for heartburn during sleep in patients with GERD. The role of coffee and alcohol as risk factors is unclear; they may increase heartburn in some patients, but the mechanism is unknown. Specific dietary factors will trigger reflux symptoms in some patients, and despite lack of confirmation in randomized controlled trials, these patients should identify and avoid trigger foods or beverages [8]. Excessive, long-term alcohol use has been associated with progression to esophageal malignancy, but this may be independent of an effect of alcohol on GERD. Smoking, like alcohol, is associated with an increased risk of malignancy.

MEDICATIONS

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for anti-inflammatory, analgesic, and antipyretic effects. NSAIDs act by inhibiting cyclooxygenase-1 and -2 (COX-1 and COX-2). COX is an enzyme that converts arachidonic acid to inflammatory mediators (e.g., prostaglandins, thromboxanes). By blocking this conversion, NSAIDs reduce pain and inflammation [61]. However, prostaglandins are important for GI protection and other normal physiologic processes. NSAIDs are associated with adverse GI effects ranging from dyspepsia, heartburn, and abdominal discomfort, to peptic ulcer with life-threatening or fatal complications from upper GI bleeding and perforation. Symptoms are unreliable indicators of upper GI mucosal damage, and risks are similar for short-course and long-term NSAID therapy. NSAIDs are also associated with cardiovascular, hepatic, and renal adverse effects [62].

Combining NSAIDs and selective serotonin reuptake inhibitors (SSRIs) increases the risk of upper GI bleeding greater than either drug alone. NSAIDs with SSRIs can markedly decrease serotonin platelet content, which impairs platelet aggregation in response to injury. This can prolong bleeding time, increase gastric acid secretion, and potentially promote ulcers and perforation. Combining SSRIs and NSAIDs should be avoided, if possible [63; 64; 65; 66].

The recommended approach to mitigate upper GI risk is switching to or initiating the COX-2 inhibitor-dominant NSAID celecoxib and starting a PPI [67]. PPIs can reduce or resolve GERD-like symptoms of heartburn and dyspepsia and are more effective than histamine-2 receptor antagonists (H2RAs). Treatment adherence should be assessed, especially in the elderly [62].

NSAID-induced GI toxicity can also involve non-gastric intestinal ulceration and bleeding. PPIs do not prevent, and may aggravate, intestinal damage by inducing gut dysbiosis. Celecoxib has better intestinal tolerability than other NSAIDs, but this advantage is partially lost by adding a PPI [68; 69; 70]. Given the GI and cardiovascular risk profiles of NSAIDs, the appropriateness of NSAID prescriptions should be assessed. These agents are indicated to control inflammation and pain, rather than pain alone [62].

Other Medications

Increased GERD symptoms are also associated with beta-adrenergic agonists, anticholinergics, nitrates, phosphodiesterase type 5 (PDE5) inhibitors, theophylline, calcium channel blockers, and benzodiazepines [61].

Medication-Induced Esophagitis

Esophageal mucosa damage can be induced by commonly prescribed drugs, but this is underappreciated due in part to sparse attention in the published research. Drug-induced esophagitis is characterized by dysphagia, chest pain, and/or odynophagia. Endoscopic findings of ulcers or erosions are usually confined to the middle third of the esophagus [71]. Antibiotics (e.g., doxycycline, amoxicillin, ciprofloxacin, metronidazole, rifaximin) are the primary cause of drug-induced esophagitis and are potentially more damaging than NSAIDs [3; 72]. Drug-induced esophagitis is a self-limiting side effect that can be resolved by removing the causative agent and providing supportive therapy [73].

COMORBID CONDITIONS

Diabetes, metabolic syndrome, cardiovascular disease, and sleep apnea are seen frequently in patients with GERD. This may be due in part to overweight and obesity, common risk factors for GERD and its comorbidities. GERD is frequently comorbid with functional GI syndromes, such as IBS [8]. The lifetime prevalence of IBS in patients with GERD is 71% [74].

Patients with diabetes are more prone to developing GERD and may present with atypical manifestations. Although there are several proposed mechanisms for the higher prevalence of GERD in patients with diabetes, this complex inter-relationship requires further research [75]. Studies involving treatment options for comorbid disease suggest conflicting drug-drug interactions.

NATURAL HISTORY OF GERD

GERD is a chronic disease. Approximately 70% of patients with GERD experience chronic or relapsing symptoms and require long-term intermittent, on-demand, or continuous acid suppressant therapy, mostly with PPIs, while others may require antireflux surgery [59]. A large longitudinal population study found that among those with GERD at study initiation, GERD persisted for 10 years in 33% [76]. Patients with GERD followed clinically may have more severe and chronic illness than persons with GERD followed in the community. However, in a community study, the rate of chronic, unabated GERD was high and showed a substantial and persistent symptom burden.

Around 10% of patients with NERD may progress to erosive esophagitis and manifest more severe reflux disease. Erosive esophagitis is a major risk factor for Barrett esophagus, and the presence of erosive esophagitis at baseline was associated with a fivefold increased risk of Barrett esophagus at five-year follow-up [77].

The long-term natural history of functional heartburn is incompletely known. Up to 67% of patients with functional heartburn remain symptomatic two years after diagnosis, while symptom intensity and frequency decrease in 20%. This suggests functional heartburn is durable in most patients [7].

PATHOGENESIS AND PATHOPHYSIOLOGY

GERD is widely assumed to arise from acid oversecretion. However, GERD symptoms can result from non-acidic reflux, and the core pathology in GERD involves impaired structure and function of the lower esophagus.

NORMAL STRUCTURE AND FUNCTION

Upper GI

Infrequent or occasional gastroesophageal reflux is normal, particularly after a large meal. The reflux is diluted with saliva, and the esophagus clears the diluted refluxed acid with peristaltic action (a part of esophageal motility). A fully functioning LES, with normal pressure and a normal frequency of transient relaxation episodes, is a crucial physiologic defense against damage from reflux. The LES performs this function with assistance from the diaphragmatic crura, which relies on gastroesophageal junction positioning in the abdomen. This abdominal positioning enables the crura to essentially function as an external sphincter [50].

The crura and LES normally relax during swallowing. Relaxations not initiated by swallowing are termed transient LES relaxations. Transient LES relaxations are also part of normal LES function unrelated to swallowing or peristaltic action, but allow gas to be vented from the stomach (belching) as a normal function. Gastric distention can trigger reflux during transient relaxation and may underlie postprandial reflux [4; 60].

Normal LES function is illustrated by air swallowing when drinking carbonated beverages in the upright position. The ingested air accumulates in the proximal stomach to cause distention. This elicits transient relaxations of the LES, allowing the ingested gas (air) to be vented as a belch. Air swallowing during eating and drinking is normal [78].

To function properly, the LES sustains a higher than normal tone from increased calcium, mediated by excitatory cholinergic neurons. The resting LES has higher intracellular levels of calcium than adjacent esophageal muscle, and decreased LES calcium levels are found in GERD [50].

Persons without GERD have a balance between the aggressive forces associated with injury and irritation of the esophagus and the defensive forces that impede reflux and help clear the refluxate. The primary aggressive forces are reflux causticity and volume burden, and defensive forces are related to the antireflux barrier, clearance mechanisms, and tissue resistance at the cellular level [79].

Gastric Acid Release

In parietal cells that line the stomach wall, proton pumps produce stomach acid by moving hydrogen ions from the parietal cell into the stomach lumen against a concentration gradient. Proton pump release of acid is prompted by signaling from acetylcholine, released by vagal nerve endings; gastrin, a local hormone produced by G cells in the antrum; and histamine, produced by enterochromaffin-like cells in the stomach wall [80]. Gastric acid kills micro-organisms, assists digestion, and facilitates absorption of iron, calcium, and vitamin B12 [81]. It also plays a crucial role in filtering out bacteria and in preventing development of enteric infections [82].

As discussed, PPIs are the foundation of GERD management. They directly inhibit hydrogen ion exchange and acid release prompted by all three stimulatory signaling agents, thus blocking the proton pump. H2RAs only block H2 receptors on the parietal cells, leaving gastrin and acetylcholine as potential signaling stimuli. PPIs are more potent inhibitors of gastric acid secretion than H2RAs [80].

PATHOPHYSIOLOGY

Anti-Reflux Barriers

Reflux occurs when the normal function of antireflux barriers between the stomach and esophagus become impaired. GERD develops when reflux of gastric contents is large or aggressive enough to cause troublesome symptoms and/or complications and adversely affect health-related quality of life [62]. The primary factor in GERD pathogenesis is defective function of the LES and the diaphragmatic crura antireflux barrier [52].

LES incompetence results in frequent transient LES relaxations, defined as LES relaxation occurring in absence of swallowing, lasting longer than 10 seconds, and associated with crural diaphragm inhibition [83]. Frequent or longer-lasting transient LES relaxations result in reflux of gastric fluid through the gastroesophageal junction. Most reflux events (about 90%) occur during transient LES relaxations rather than low resting LES pressure [52; 83]. Mechanisms more likely with hiatal hernia include low gastroesophageal junction pressure, strain, or air swallow-associated reflux [83].

Symptoms develop when offensive factors in reflux make repeated contact with esophageal mucosa [62]. Potential esophageal injury from reflux increases as more elements of esophageal defense break down [84]. With LES compromise, increasing contact with caustic, corrosive reflux elements can induce esophageal mucosal injury and degrade esophageal mucosal defense by impairing mucosal resistance and esophageal clearance of acid and reflux [52]. Other pathogenic factors can include delayed gastric emptying and hiatal hernia [62]. As discussed, pathophysiologic mechanisms of GERD are exaggerated in obese patients [85].

In patients with GERD, reflux markedly increases after meals due to increased transient LES relaxations to accommodate food-induced gastric expansion. Despite the buffering effect of food, the pH of reflux into the distal esophagus is acidic due to a "pocket" of unbuffered gastric acid that accumulates in the proximal stomach after meals and serves as a reservoir for acid reflux [62; 86].

Esophageal Injury

As discussed, GERD causes reflux esophagitis, reflux esophagitis causes Barrett esophagus, and the metaplasia of Barrett esophagus predisposes to esophageal adenocarcinoma. Until recently, the presumed cause of reflux esophagitis was caustic, chemical injury induced by acid and pepsin in reflux. Repeated exposure made the esophageal squamous epithelium permeable to acid, causing epithelial cell death that triggers a proliferative response to repair epithelial injury [87].

Reflux esophagitis is now shown to develop as a cytokine-mediated inflammatory injury. Instead of direct destruction of epithelial cells, acid and bile salts in reflux induce these cells to release pro-inflammatory cytokines. The cytokines initially attract T lymphocytes that trigger the basal cell proliferation characteristic of GERD-induced injury. The inflammatory cells recruit neutrophils to the site of injury, ultimately mediating the epithelial damage [87].

Barrett esophagus develops through metaplasia, a process whereby one type of tissue replaces another type of tissue. Acid and bile reflux damages the squamous mucosa of the distal esophagus. This mucosal damage can heal through regeneration of more squamous epithelium, or through columnar metaplasia, whereby columnar cells replace the damaged squamous cells [87; 88].

Non-acidic elements of reflux (e.g., pepsin, trypsin) also induce esophageal mucosal injury, esophagitis, and GERD. Most patients with NERD show non-acid-reflux-induced alteration in esophageal epithelium. Dilation of spaces between adjacent esophageal epithelial cells is the hallmark feature of microscopic esophagitis and increases penetration of hydrogen ions, pepsin, and bile into esophageal sub-mucosa. Non-acid reflux is mostly alkaline from the presence of duodeno-gastric biliary reflux. Acid and duodeno-gastric biliary reflux act synergistically to induce lesions and increase the risks of Barrett esophagus and esophageal adenocarcinoma [89]. PPIs are very effective at healing inflammation caused by acid reflux but do not suppress duodeno-gastric biliary reflux [87; 88].

GERD Symptom Pain and Discomfort

Most reflux events do not produce GERD symptoms, but symptom-producing events tend to involve lower pH, longer acid clearance time, and higher total acid exposure. In some cases, weekly acidic or non-acidic reflux can also produce symptoms [60; 90].

The relationship between symptom severity and endoscopic findings is non-linear. Severe GERD symptoms can occur with negative endoscopic findings, while endoscopic findings of erosive esophagitis, Barrett esophagus, hemorrhagic esophageal stricture, or esophageal adenocarcinoma can be asymptomatic [60; 91].

In patients with chronic pain or upper GI disorders without obvious pathology on imaging, the symptoms are termed "functional," a reference to the apparent lack of structural pathology (and explanation). Functional pain symptoms are now known to reflect durable abnormalities in peripheral and CNS pain signaling and processing. This also explains functional esophageal symptoms.

Reflux events become bothersome and distressing through complex mechanisms. Proteinase-activated receptor 2 (PAR2) and transient receptor potential vanilloid-1 (TRPV1) are thought to play key roles. Esophageal expression of PAR2 is activated by acid or weakly acidic reflux exposure. PAR2 releases interleukins (IL-8, IL-1b) and other inflammatory cytokines, promoting inflammatory injury in the esophageal mucosa [92; 93]. The sensation of heartburn is generated by visceral sensory neurons within the deep layers of esophageal mucosa [87]. When activated by PAR2, acid, and other inflammatory mediators, visceral sensory neurons upregulate the expression of chemosensitive receptors TRPV1 and acid-sensing ion channel 3 (ASIC3), which release pain mediators that generate heartburn symptoms

HYPERSENSITIVITY, ABNORMAL ACID EXPOSURE, AND REFLUX-RELATED DISORDERS				
Symptom Contributor	**Erosive Esophagitis**	**Non-Erosive Reflux Disease**	**Reflux Hypersensitivity**	**Functional Heartburn**
Acid exposure	++++	+++	++	+
Esophageal hypersensitivity	+	++	+++	++++
Key: ++++, strongly influenced; +, weakly influenced.				
Source: [7]				*Table 1*

[94; 95]. Repeated activation can induce inflammatory and neuroinflammatory effects and promote visceral hypersensitivity [96]. Elevated levels of IL-8 are found in biopsy specimens from patients with GERD and NERD, and high levels of IL-8 in biopsies of patients with NERD predict symptomatic recurrence [97; 98; 99].

Psychologic stress can increase the perception of heartburn and aggravate GERD symptoms [41]. Acute stress can enhance sensitivity to intraesophageal acid perception in patients with reflux esophagitis or NERD, and greater emotional response to stress correlates with increased perceptual response to acid [100; 101]. Previous reports have revealed that low quality of life was severe in patients with extraesophageal symptoms. The quality of life of patients with GERD is also associated with psychologic factors [41; 102; 103].

Functional Esophageal Disorders

Reflux-related esophageal disorders fall on a spectrum, based on interaction between esophageal hypersensitivity and acid exposure and its contribution to reflux symptoms. On one end, symptom contribution from abnormal acid exposure dominates erosive esophagitis; on the other end, contribution from hypersensitivity dominates functional heartburn. Acid exposure and hypersensitivity both contribute to symptoms in reflux hypersensitivity and NERD (***Table 1***) [7].

Patients with functional esophageal disorders present with reflux-related esophageal symptoms (e.g., heartburn, chest pain) not adequately explained by structural, inflammatory, or major motor abnormalities. In these patients, clinical findings typically include [6; 7]:

- Normal endoscopy
- Absence of mechanical obstruction or biopsy-confirmed eosinophilic esophagitis
- Absence of esophageal motor disorder (e.g., achalasia, esophagogastric junction outflow obstruction, distal esophageal spasm)
- Esophageal acid exposure absent or borderline (i.e., pH 4–7)

Structural, motor, or inflammatory abnormality can be present, but a pathologic finding is not sufficient or necessary for diagnosis.

In the context of normal or borderline functional testing, symptom perception is driven by mechanisms that include hypersensitivity from peripheral and/or central sensitization, altered central processing of visceral stimuli, and altered autonomic activity. Altered pain perception with heightened visceral sensitivity and symptom perception and lowered symptom thresholds to chemical, mechanical, or emotional stimuli are consistently shown [1; 104].

Esophageal tissue injury, inflammation, and repetitive mechanical stimuli can all sensitize peripheral afferent nerves. Esophageal hypersensitivity can remain long after resolution of the original insult [7; 105].

Psychologic features are an important aspect of functional esophageal disorders. With recurrent or long-standing states of psychologic stress, centrally mediated processes can alter autonomic nervous system activity and modulate spinal transmission of nociceptive signals. Peripherally, gut mucosa permeability can be altered by mast cell degranulation [106]. These mechanisms contribute to exaggerated perception of physiologic stimuli [7].

SYMPTOMS ASSOCIATED WITH GERD

As noted, the typical symptoms of GERD are heartburn and regurgitation [50; 107]. Heartburn is defined as a burning, retrosternal, rising sensation associated with meals. Clinicians should be aware this definition is often misunderstood by the general population and clarify the nature of symptoms discussed when the term is used. Regurgitation is the effortless appearance of gastric contents in the throat or mouth without associated nausea or retching.

Although heartburn and regurgitation are cardinal features of GERD, they lack sensitivity and specificity in diagnosis. GERD is found in 54% of patients with heartburn-dominant symptoms and 29% with regurgitation-dominant symptoms. This is because heartburn and regurgitation can also be presenting symptoms of a variety of other disorders [1; 62].

In addition to these cardinal symptoms, patients may display atypical symptoms and/or extraesophageal manifestations of GERD, including [8; 50; 79]:

- Gastric
  - Nausea
  - Belching
  - Slow digestion
  - Early satiety
  - Epigastric pain
  - Bloating
- Respiratory
  - Non-cardiac chest pain
  - Chronic cough
  - Asthma
- ENT
  - Laryngopharyngeal reflux
  - Hoarseness
  - Sore throat
  - Otitis media
  - Pharyngeal pain
  - Globus
  - Chronic rhinosinusitis
  - Repetitive throat clearing
- Dental
  - Enamel erosion
  - Other dental manifestations

It should be noted that some of these symptoms and conditions (e.g., chronic cough, dysphonia, asthma, sinusitis, laryngitis, dental erosions) have poor sensitivity and specificity for the diagnosis of GERD and are not recommended for diagnosis [15].

ALARM FEATURES

Alarm features are associated with, but are not specific to, GERD and are symptoms and signs associated with gastric cancer, complicated ulcer disease, or other serious conditions requiring urgent evaluation. They include [8; 50; 107]:

- Recurrent nausea and vomiting
- Dysphagia or odynophagia (painful swallowing)
- Unintentional weight loss
- GI tract bleeding
- Persistent pain
- Evidence of iron deficiency or anemia
- Duration of symptoms longer than five years or less than six months
- Epigastric mass or other abnormalities on physical examination
- Family history of esophageal or gastric adenocarcinoma

DIAGNOSIS OF GERD

Although there is no criterion standard for the diagnosis of GERD, diagnosis is typically based on a combination of frequent reflux events (one or more events per week) with troublesome symptoms, impaired patient quality of life, evaluation of esophageal mucosa, reflux monitoring, and response to therapeutic intervention [15]. Heartburn and regurgitation remain the most sensitive and specific symptoms for GERD, although not as reliable as previously believed [15]. A systematic review found a variable sensitivity of heartburn and regurgitation for erosive esophagitis of 30% to 76%, with the specificity ranging from 62% to 96% [108]. Other presentations considered markers of GERD include dyspepsia and a general gastric discomfort that includes nausea, abdominal pain, and bloating, and non-cardiac chest pain, which can be the presenting symptom after diagnostic workup excludes cardiac causes [15; 50].

The ACG recommends esophageal pH monitoring (Bravo, catheter-based, or combined impedance-pH monitoring) performed off PPIs if the diagnosis of GERD has not been established by a previous pH monitoring study or an endoscopy showing long-segment Barrett esophagus or severe reflux esophagitis (LA grade C or D).

(https://journals.lww.com/ajg/fulltext/2022/01000/acg_clinical_guideline_for_the_diagnosis_and.14.aspx. Last accessed September 9, 2024.)

Level of Evidence/Strength of Recommendation: Low/Conditional

Publications on the GERD diagnostic process increasingly point to the need for a more tailored approach, but the initial empiric PPI trial remains the standard of care.

EMPIRIC PPI TRIAL

Patients presenting with typical symptoms of GERD and no alarm features typically receive a presumptive diagnosis of GERD, confirmed by positive response to an empiric trial of PPI therapy. With a PPI trial, patients are prescribed once-daily PPIs for four to eight weeks. Nonresponders receive dose escalation to twice-daily PPIs for eight weeks. All PPI responders continue PPI therapy. Lack of response to a doubled dose of a PPI demands further objective evaluation [50]. The emphasis on the empiric PPI trial as a diagnostic and therapeutic tool is based on the premise that GERD symptoms and severity are proportional to exposure of esophageal tissue to acidic reflux. By targeting this core pathophysiology, response to PPI acid suppression therapy reliably confirms the diagnosis of GERD [1; 79; 107].

For patients with classic GERD symptoms of heartburn and regurgitation who have no alarm symptoms, the American College of Gastroenterology (ACG) recommends an eight-week trial of empiric PPIs once daily before a meal.

(https://journals.lww.com/ajg/fulltext/2022/01000/acg_clinical_guideline_for_the_diagnosis_and.14.aspx. Last accessed September 9, 2024.)

Level of Evidence/Strength of Recommendation: Moderate/Strong

The empiric PPI trial has advantages of being simple, cost-effective, and, as stated, informative of whether further investigation is required [15; 50; 107]. The clinical approach that emphasizes the empiric PPI trial as a diagnostic and therapeutic tool has been endorsed by professional organizations including the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), the American College of Physicians (ACP), the American Society of Gastrointestinal Endoscopy (ASGE), and the World Gastroenterology Organization [8; 15; 109; 110; 111].

Although empiric PPI trials have clear utility in ease and practicality, over-reliance has come under increasing criticism. This dissent centers on the diverse symptom profile and pathogenesis of reflux presentations that require management guided by symptom presentation and focused diagnostic testing instead of the uniform PPI trial approach [79]. A response to therapy would ideally confirm the diagnosis; however, this method is met with limited specificity (54%) and sensitivity (78%) [15]. A substantial placebo response is shown during empiric PPI trials, and PPI response widely varies by presenting symptom and underlying mechanism. This model has led to 30% to 60% of patients unsatisfied with their treatment, high levels of inappropriate PPI use, and failure to address visceral hypersensitivity, which amplifies symptom perception and complicates patient coping [79; 112; 113].

To better align initial management with disease complexity, updated practice recommendations for GERD were published by the Italian Society of Pharmacology and Italian Association of Hospital Gastroenterologists in 2016 and the AGA in 2017 [62; 79]. In addition, guidelines for dyspepsia by the ACG and the Canadian Association of Gastroenterology (CAG) were updated in 2017, and recommendations for functional esophageal disorders by the Rome Foundation were revised in 2016 [2; 7]. With growing evidence of adverse effects with long-term PPIs, safe PPI prescribing recommendations by the AGA and PPI deprescribing guidelines by the University of Ottawa in Ontario, Canada, were both published in 2017 [67; 114].

As of 2024, clinical guidance for GERD management is conflicting and continues to be in a transition phase. In aggregate, the most useful approach retains the PPI trial while incorporating diagnostic advances that identify underlying causes of GERD symptoms to better inform treatment selection [50].

DIAGNOSTIC WORKUP

As mentioned, patients presenting with heartburn and acid regurgitation (sometimes with non-cardiac chest pain or dysphagia) are considered to have suspected GERD, confirmed by response to an empiric PPI trial. PPI nonresponse does not rule out GERD but prompts diagnostic testing [1]. Typical GERD symptoms can reflect non-GERD conditions with or without abnormal (pathologic) esophageal acid exposure, and GERD can be erosive or non-erosive [52; 115]. With extraesophageal symptoms associated with GERD, reflux is more often a co-factor than an etiology, and these patients should receive proper evaluation for non-GERD causes such as allergic, pulmonary, or ENT disorders [116].

Phenotypic characterization, a key diagnostic concept, means that different underlying pathologies can look similar in symptom expression. The underlying pathologies in GERD-related disorders differ in treatment response, and effective therapeutic targeting hinges on diagnostic findings [59]. Multiple phenotypic characterization is recommended [15]. With this approach, esophageal structure and function are both assessed and diagnosed if abnormal. Endoscopy and biopsy assessment of structure and pH-impedance monitoring plus manometry assessment of function establish the proper diagnosis in most cases [59].

Structural and Histologic Assessment

Upper GI Endoscopy

Endoscopy identifies and documents reflux-related esophageal mucosal damage; the presence and severity of reflux disease complications, such as erosive esophagitis, Barrett esophagus, or peptic ulcers; and anatomic abnormalities, such as hiatal hernia, masses, and strictures [116]. Upper GI endoscopy is the most common initial test in patients with GERD symptoms and PPI nonresponse and is performed urgently in patients with alarm features [1; 117]. This procedure consists of an endoscope being fed down the esophagus into the stomach and duodenum, where a small camera sends video images to a monitor screen for close inspection of the esophageal lining [118].

Endoscopic findings of esophagitis, esophageal erosion, eosinophilic esophagitis, or Barrett esophagus are highly suggestive of chronic esophageal epithelial exposure to reflux [52]. Erosive esophagitis is visually graded during endoscopy using Los Angeles (LA) classification [32].

GERD is diagnosed when endoscopy shows erosive esophagitis, and further testing is usually not needed. However, esophagitis is present in only 33% of patients with GERD symptoms and the absence of esophagitis does not rule out GERD. Patients with negative endoscopy should receive functional assessment [79].

Esophageal Biopsy

Esophageal biopsy specimens allow histologic assessment of esophageal mucosal injury. Biopsies are obtained during endoscopy to confirm or rule out suspicions of eosinophilic esophagitis (suggested by esophageal symptoms) or Barrett esophagus (suggested during endoscopy) [79]. Biopsies can also identify dilated distal intercellular spaces, a possible mechanism of GERD symptoms. Esophageal biopsy is not recommended in suspected GERD with normal endoscopy [79].

Functional Assessment

pH Monitoring

pH monitoring in the distal esophagus measures the extent of acid exposure using either a trans-nasal catheter (24 hours) or wireless, capsule-based pH testing (48 hours) [1; 116; 118; 119]. The capsule-based approach is preferred because it increases detection. Extension of pH monitoring to 96 hours is an option. This increases pathologic findings and diagnostic yield over 24- and 48-hour pH monitoring in more complex patients [120].

Wireless pH monitoring uses a small capsule, endoscopically attached to the esophageal wall, to record and transmit pH data to a receiver worn on the belt. Patients push a button when experiencing symptoms. The capsule detaches and is excreted 7 to 10 days later [118].

pH monitoring measures:

- Acid exposure time (i.e., the percentage of time esophageal pH is <4)
- Number of acid reflux episodes
- Number of episodes lasting longer than five minutes
- Longest reflux episode

Esophageal acid exposure time is the most useful indicator of pathologic acid reflux. Off-PPI testing assesses symptom provocation by acid reflux events; on-PPI testing measures persistent esophageal acid exposure despite PPI acid suppression [52].

In patients with GERD symptoms, NERD is diagnosed with negative endoscopy and pathologic acid reflux. Further testing is performed when endoscopy and pH monitoring are negative.

Esophageal Impedance Monitoring

Non-acid reflux is undetectable by standard pH monitoring but can induce symptoms in patients with GERD or functional esophageal disorders and is common in patients maintained on PPIs [52]. Impedance monitoring is a valuable test in patients with suspected GERD but negative pH testing, atypical or extraesophageal symptoms, or refractory GERD [4].

Esophageal impedance monitoring detects changes in the resistance of electrical current on a catheter placed into the esophagus. Impedance monitoring is usually combined with pH monitoring to record antegrade or retrograde movement of liquid and gas into the esophagus and to identify reflux as acidic, weakly acidic, or weakly alkaline [4]. Acid reflux is defined as a pH <4 in the esophagus; non-acid reflux is pH >4. The latter includes weakly acidic (4 <pH<7) and weakly alkaline (pH ≥7) reflux [1].

High-Resolution Esophageal Manometry

Functional assessment of the LES and the esophageal body is performed by esophageal manometry. High-resolution manometry (HRM) is often used with esophageal impedance; some devices combine both. HRM uses a catheter, inserted transnasally, with closely spaced sensors that measure the intraluminal pressure of the entire esophagus during swallowing [83]. In patients with GERD symptoms or NERD with poor PPI response, HRM identifies altered esophageal motility, impaired LES function, and/or transient LES relaxations to explain symptom persistence [59; 121]. HRM is also valuable in excluding possible underlying esophageal motility disorders [122]. HRM is combined with 48-hour pH testing to assess patients with [1; 79]:

- Persistent esophageal symptoms during PPI therapy to exclude non-GERD causes
- Recurrent symptoms after PPI discontinuation
- Atypical symptoms (e.g., chest pain, asthma) in patients without esophagitis

It should also be conducted before antireflux surgery for diagnostic confirmation. The British Society of Gastroenterology finds HRM superior to standard manometry in terms of reproducibility, speed of performance, and ease of interpretation [119].

Gastric Scintigraphy

Gastroparesis (delayed gastric emptying) is an important contributor to GERD symptoms in many patients. These patients generally have negative endoscopy findings and greater odds of PPI nonresponse. With suspicion of gastroparesis, a four-hour gastric emptying scintigraphy is used [116; 123].

Barium Swallow

Achalasia is an esophageal motility disorder with incomplete LES relaxation, increased LES pressure, and esophageal body aperistalsis, leading to poor clearance and esophageal dilation. Aside from dysphagia to solids and liquids, patients with achalasia may experience heartburn and regurgitation. Barium swallow with HRM can differentiate achalasia and other esophageal motility disorders from GERD [52].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The ACG does not recommend the use of a barium swallow solely as a diagnostic test for GERD.

(https://journals.lww.com/ajg/fulltext/2022/01000/acg_clinical_guideline_for_the_diagnosis_and.14.aspx. Last accessed September 9, 2024.)

Level of Evidence/Strength of Recommendation: Low/Conditional

AMERICAN GASTROENTEROLOGICAL ASSOCIATION RECOMMENDATIONS

The diagnostic process is relatively straightforward until patients with GERD symptoms show negative endoscopic, pH, and impedance findings. At this point, the diagnostic pathway becomes vague, but it is clarified by practice recommendations from the AGA and the Rome Foundation.

The AGA has stated that treatment guidelines emphasizing empiric PPI trials should be rewritten to stress the importance of clinical management guided by symptom presentation, anatomy, and focused diagnostic testing [79]. To this end, the AGA published a novel approach to GERD management in 2017, guided by the four GERD symptom domains identified by the National Institutes of Health and based on patient-reported outcomes [79]:

- Liquid and food sensations (e.g., reflux sensations, regurgitation)
- Painful sensations (e.g., heartburn, chest pain)
- Belching and hiccups (supragastric and gastric belching)
- Head and neck sensations (e.g., ENT and respiratory symptoms)

While GERD diagnosis lacks a criterion standard, the AGA states that focused diagnostic testing based on clinical history and GERD symptom domains can identify the diverse GERD-related phenotypes. This, in turn, best informs the optimal management approach [79].

The AGA stresses the importance of considering hypervigilance, visceral hypersensitivity, and psychosocial distress when patients fail PPIs and diagnostic testing is negative. In any GERD symptom domain, these factors can exacerbate the primary symptoms and adversely impact patients' ability to cope with symptoms [79].

Patients with Food and Liquid Sensation

Primary regurgitation and reflux symptoms (e.g., reflux into throat and mouth, wet burps, choking on liquid or food reflux) may reflect esophageal dysmotility or rumination syndrome. The stepwise diagnostic process outlined by the AGA starts with endoscopy to detect mechanical obstruction, eosinophilic esophagitis, or hiatal hernia [79]. With negative endoscopy, esophageal HRM is used. With meal-related regurgitation or suspected rumination syndrome, postprandial HRM is indicated.

In these patients, PPI response is less than 50%, because symptoms often result from reflux burden/volume instead of reflux acidity [124]. Reflux volume can reflect esophagogastric junction distensibility [52]. With hypotensive gastroesophageal junction or impaired esophageal motility on HRM, the next step is to assess with pH-impedance testing.

With abnormal reflux on PPI, dose-escalation benefit is unlikely and treatment addresses other pathophysiology [79]. With incompetent gastroesophageal junction and/or hiatal hernia, antireflux surgery is indicated to restore antireflux barrier function. Without hiatal hernia or hypotensive gastroesophageal junction, patients may still benefit from antireflux surgery. Transient LES relaxations may drive reflux with normal gastroesophageal junction pressure and anatomy; in these patients, use baclofen for reflux inhibition.

Patients with Painful Sensations

Pain (e.g., chest pain, heartburn, throatburn) is a primary symptom of GERD, and PPI response is often sufficient to guide management [79]. In cases of PPI nonresponse, endoscopy is used to explore alternative diagnoses. With negative endoscopy, pH-impedance testing off-PPI should be done to assess esophageal acid exposure, type of reflux event, and reflux/symptom correlation [79].

With normal impedance testing findings, functional heartburn or chest pain is the likely diagnosis, so HRM should be done to rule out esophageal motility disorders. Patients with positive HRM may have reflux hypersensitivity or refractory GERD (abnormal acid exposure with or without reflux symptom correlation) [7]. With confirmed pathologic acid exposure, pH-impedance testing on-PPI is used to assess PPI-refractory reflux mechanism (e.g., impaired gastric acid suppression, continued reflux, functional overlap) [79; 125]. For patients with functional heartburn/chest pain or reflux hypersensitivity, pain modulators and behavioral therapies are indicated to target visceral hypersensitivity. Patients with reflux hypersensitivity may also require PPIs and baclofen for reflux inhibition.

Patients with Belching Syndromes

Aerophagia is a functional GI disorder of repetitive troublesome belching and abdominal discomfort from excessive air swallowing, also associated with visceral hypersensitivity [78; 116]. Other belching syndromes include [78; 116]:

- Gastric belching (the venting of gas from the stomach)
- Supragastric belching (esophageal air ingestion followed by immediate expulsion before reaching the stomach)
- Rumination syndrome (a behavioral condition with symptoms of postprandial belching and regurgitation often mistaken for GERD)

It is important to distinguish supragastric from gastric belching, because supragastric belches do not originate from the stomach, making transient LES relaxation therapy ineffective.

The first step in assessing these patients is the use of HRM/impedance testing to differentiate belching type, rumination syndrome, or GERD [79; 116; 126; 127]. PPIs may reduce heartburn or chest pain with a transient LES relaxation-mediated belching syndrome. If only belching is present (not other reflux symptoms), PPIs should be discontinued. Patients with supragastric belching or rumination syndrome should be referred to behavioral therapy or a speech pathologist.

If postprandial HRM/impedance is negative for gastric belching, pH-impedance testing is indicated to assess belching pattern and reflux burden [79]. With normal reflux burden and gastric belching, patients may benefit from reflux inhibition with baclofen. Patients with gastric belching and abnormal reflux burden may benefit from the addition of PPIs. Antireflux surgery should be used cautiously in belching syndromes, as the risks of gas bloat and worsening supragastric belching can be substantial.

Patients with Head and Neck Sensations

In the context of presumed GERD, prominent ENT and/or respiratory symptoms are challenging; non-reflux cause is likely. PPI response is comparable to placebo in randomized trials [19]. The extent of symptom association with GERD guides initial management [15; 79]. Without close symptom association, clinicians should focus on non-reflux causes. With closer symptom association, pH-impedance testing off-PPI should be used to guide management decisions. Patients with normal results are unlikely to benefit from PPI dose escalation, but patients with abnormal esophageal acidity may benefit from antireflux procedures, with the caveat that symptoms are more refractory.

FUNCTIONAL ESOPHAGEAL DISORDERS: ROME IV CRITERIA

Functional esophageal disorders are diagnosed and classified using Rome Foundation criteria, which has changed over time to incorporate new scientific evidence. Functional esophageal disorders are highly prevalent in patients with suspected GERD, but their consideration in the GERD diagnostic process is often neglected. It is essential to include these disorders, because treatment is distinct from other GERD-related disorders [5].

Functional esophageal disorders do not progress along a tangible organic natural history, with chronicity reflecting greater pathophysiology and disease burden [7]. All functional esophageal disorders require the following for diagnosis [7; 128]:

- Diagnostic criteria present in the past three months
- Symptom onset at least six months before diagnosis
- Symptom frequency two or more days per week (or one or more days per week for functional chest pain and functional dysphagia)
- Absence of major esophageal motor disorders (e.g., achalasia/gastroesophageal junction outflow obstruction, diffuse esophageal spasm, aperistalsis, hypercontractile peristalsis)

Functional Chest Pain

Functional chest pain is a subtype of non-cardiac chest pain. Initial cardiac evaluation is required in both, because history and physical examination do not reliably differentiate esophageal from cardiac chest pain. Functional chest pain is defined as recurring, unexplained, retrosternal chest pain of presumed esophageal origin, not explained by reflux disease or other mucosal or motor processes and with pain differing from heartburn [7].

Clinical Evaluation and Diagnosis

After exclusion of a cardiac cause, further workup is necessary and is guided by common underlying causes of non-cardiac chest pain and clinical evaluation findings [7; 129]. With high prevalence in GERD, a high-dose PPI trial is used to assess for a possible GERD trigger of chest pain. With PPI nonresponse, pH-impedance testing off-PPI is recommended if suspicion of GERD remains. Endoscopy with biopsy is recommended to rule out eosinophilic esophagitis and Barrett esophagus. HRM may be considered when GERD is ruled out, because major motor disorders are exclusion criteria.

In order to diagnose functional chest pain, all of the following criteria must be present [7; 128]:

- Retrosternal chest pain or discomfort, after cardiac causes are ruled out
- No associated esophageal symptoms, such as heartburn and dysphagia
- No evidence that acid reflux or eosinophilic esophagitis is the cause of symptoms

Functional Heartburn

The definition of functional heartburn has evolved from a NERD-spectrum disorder in Rome III to a stand-alone functional esophageal diagnosis in Rome IV [130]. The current diagnosis emphasizes a lack of conclusive evidence for GERD; the absence of symptom-reflux correlation and PPI nonresponse alert to a possible functional disorder [7].

Clinical Evaluation and Diagnosis

Functional heartburn is diagnosed after careful history identifies heartburn as the dominant symptom and stepwise evaluation is negative for GERD, eosinophilic esophagitis, and esophageal motor disorders. Most patients are identified by PPI nonresponse, a core diagnostic criterion [7; 131]. After nonresponse to PPI trial, endoscopy and esophageal biopsies are used, regardless of esophageal mucosa appearance, to assess for reflux esophagitis, Barrett esophagus, eosinophilic esophagitis, or a nonpeptic inflammatory process. pH-impedance testing is used to identify acidic reflux and symptom/reflux correlation.

Diagnosis of NERD is made when there is evidence of abnormal esophageal acid exposure. When symptoms correlate with weakly acidic/non-acidic reflux events, the diagnosis is reflux hypersensitivity. Functional heartburn is diagnosed with normal esophageal acid and no symptom/reflux correlation. Diagnostic criteria are [7; 128]:

- Burning retrosternal discomfort or pain
- No symptom relief despite optimal PPI therapy
- No evidence that reflux (abnormal acid exposure or symptom/reflux correlation) or eosinophilic esophagitis is the cause of symptoms
- Absence of major esophageal motor disorders (e.g., achalasia, diffuse esophageal spasm)

GERD (proven by endoscopy and pH testing) and PPI nonresponse may reflect [7]:

- True refractory reflux (abnormal acidity during pH-impedance testing on-PPI)
- Overlapping functional heartburn and GERD (normal acid exposure, no symptom/reflux correlation during pH-impedance testing on-PPI)
- Overlapping reflux hypersensitivity and GERD (normal acid exposure, symptom/reflux association during pH-impedance testing on-PPI)

Reflux Hypersensitivity

Reflux hypersensitivity describes heartburn or chest pain symptoms, endoscopy negative for reflux injury, and pH-impedance testing negative for abnormal acid burden but positive for symptom triggering by non-acidic reflux [7].

Clinical Evaluation and Diagnosis

As with functional chest pain and functional heartburn, an empiric PPI trial begins the diagnostic process for reflux hypersensitivity. Partial or poor PPI response points to functional heartburn or reflux hypersensitivity. Endoscopy should be used to rule out esophagitis, Barrett esophagus, and eosinophilic esophagitis [131].

A reflux hypersensitivity diagnosis hinges on sensitivity to reflux events. Acid parameters should be in the normal range on- and off-PPI [132]. Reflux hypersensitivity differs from functional heartburn by significant symptom/non-acidic reflux correlation [7; 35]. The diagnostic criteria are [7; 128]:

- Retrosternal symptoms, including heartburn and chest pain
- Normal endoscopy and no evidence that eosinophilic esophagitis is the cause for symptoms
- Symptoms triggered by reflux events, despite normal acid exposure on pH or pH-impedance testing
- Absence of major esophageal motor disorders (e.g., achalasia, diffuse esophageal spasm)

A PPI response does not exclude this diagnosis.

Globus

Globus describes a persistent or intermittent nonpainful sensation of a lump or a foreign body in the throat. The symptom is commonly episodic, not associated with dysphagia or odynophagia, and frequently improves with eating and swallowing [7].

Clinical Evaluation and Diagnosis

The diagnosis is made primarily by eliciting a compatible clinical history and ruling out an identifiable cause (e.g., structural lesion, GERD, major motor disorder). There must be no dysphagia and no alarm features. Initial evaluation should include physical examination of the neck followed by laryngoscopic examination of the pharynx. After localized structural or inflammatory causes are excluded, the workup may proceed with an empiric trial of PPI therapy for four to eight weeks [7]. If the patient responds, the management shifts to GERD. For non-response to PPI, endoscopy may be considered to identify an alternative cause. Manometry may be helpful to rule out a major motor disorder; however, there are limited data to support a distinct motor pattern associated with globus. Patients not responding to PPI and without an identifiable cause in the oropharynx and esophagus are diagnosed with globus [7]. The diagnostic criteria are [7; 128]:

- Nonpainful, persistent or intermittent sensation of a lump or foreign body in the throat (no structural lesion identified on physical exam, laryngoscopy, or endoscopy)
  - Sensation occurs between meals
  - No dysphagia or odynophagia
  - No gastric inlet patch in proximal esophagus
- No evidence that gastroesophageal reflux or eosinophilic esophagitis is the cause for symptoms
- Absence of major esophageal motor disorders (e.g., achalasia, diffuse esophageal spasm)

Functional Dysphagia

Functional dysphagia is a sensation of abnormal bolus transit through the esophageal body in the absence of structural, mucosal, or motor abnormalities to explain the symptom. Diagnosis requires exclusion of oropharyngeal mechanisms of dysphagia, structural lesions in the tubular esophagus, GERD, eosinophilic esophagitis, and major motor disorders [7].

Clinical Evaluation and Diagnosis

Careful history should be obtained for patients with suspected functional dysphagia to exclude oropharyngeal dysphagia and to detect conditions that mimic or contribute to dysphagia (e.g., globus, xerostomia, odynophagia) [7; 133; 134; 135]. PPI trial and upper endoscopy with biopsy can exclude GERD and eosinophilic esophagitis. Barium contrast using solid boluses is indicated to detect subtle strictures often overlooked on endoscopy and other obstructive processes, such axial hiatal hernias.

In the absence of structural lesions, HRM should be used to exclude major motor disorders. During HRM, multiple rapid swallows, water drinking, or food ingestion can improve detection of obstructive motor mechanisms that explain dysphagia. Borderline or minor motor disorders are compatible with functional dysphagia.

The diagnostic criteria for functional dysphagia are [7; 128]:

- Sense of solid and/or liquid foods sticking, lodging, or passing abnormally through the esophagus
- No evidence that esophageal mucosal or structural abnormality is the cause of symptoms
- No evidence that reflux or eosinophilic esophagitis is the cause of symptoms
- Absence of major esophageal motor disorders (e.g., achalasia, diffuse esophageal spasm)

ESOPHAGEAL DISORDERS

Erosive Esophagitis

Esophageal erosions are observable during endoscopy and visually graded using the LA classification, which provides endoscopic stratification of esophagitis severity [32; 79]:

- Grade A (mild): One or more mucosal breaks ≤5 mm, does not extend between the tops of two mucosal folds
- Grade B (mild): One or more mucosal breaks >5 mm, does not extend between the tops of two mucosal folds
- Grade C (severe): One or more mucosal breaks that are continuous between the tops of two or more mucosal folds but involve less than 75% of the circumference
- Grade D (severe): One or more mucosal breaks that involve ≥75% of the esophageal circumference

Mucosal breaks are areas of slough or erythema with discrete demarcation from adjacent, more normal-looking mucosa. In a validation study, severity of esophageal acid exposure was significantly related to the severity grade of esophagitis. Pretreatment esophagitis grades A through C were significantly related to heartburn severity, PPI treatment outcomes, and risk for symptom relapse off of PPIs [32]. Because there can be significant interobserver variability for mild erosive esophagitis (LA grade A), many experts only consider grades B or higher as objective evidence of GERD [79].

Eosinophilic Esophagitis

Eosinophilic esophagitis is a chronic disorder characterized by an aberrant inflammatory response involving local production of eotaxin-3, a chemokine that attracts eosinophils to the esophageal mucosa. Eosinophils cause local tissue damage and recruit and/or activate other effector cells, such as mast cells, which facilitate esophageal fibrous remodeling [136]. Progressive loss of tissue elasticity from inflammatory cell infiltration can elicit motor abnormalities [3; 137].

Patients with eosinophilic esophagitis that does not respond to PPIs are diagnosed with "true eosinophilic esophagitis;" good PPI response or abnormal acid reflux on pH testing results in a diagnosis of GERD. The term "PPI-responsive eosinophilic esophagitis" was coined for the latter group, despite nearly identical clinical, endoscopic, and histologic features in both groups [136]. GERD is associated with eosinophilic esophagitis and should be ruled out by pH testing [52].

Therapy in patients with PPI-responsive eosinophilic esophagitis can reverse the inflammatory signature, but PPI response as diagnostic exclusion for eosinophilic esophagitis has been controversial [136]. In 2017, the first practice guidelines that eliminated the eosinophilic esophagitis vs. PPI-responsive eosinophilic esophagitis dichotomy were published,

and in 2018, an international consensus conference adopted the updated criteria [138; 139]. In this guideline, diagnostic criteria for eosinophilic esophagitis are organized into three categories [138]:

- Clinical features
  - Symptoms of esophageal dysfunction with dysphagia
  - Food impaction
  - Abdominal pain
  - Nausea
  - Reflux-like symptoms
- Histologic features
  - Esophageal eosinophil-predominant inflammation limited to the esophagus
  - Detection of 15 eosinophils in at least one high-power field
- Other causes ruled out
  - Eosinophilic gastroenteritis
  - Crohn disease
  - Hypereosinophilic syndrome
  - Parasites
  - Drug hypersensitivity
  - Achalasia
  - Vasculitis
  - Connective tissue disorders

Barrett Esophagus

As noted, reflux injury to the esophageal squamous epithelium can lead to Barrett esophagus, a metaplastic process whereby the squamous cells are replaced by columnar epithelium-containing goblet cells [52]. Patients with Barrett esophagus may experience heartburn, regurgitation, or less commonly, dysphagia or a globus sensation, but others remain asymptomatic [49].

The ACG states that Barrett esophagus diagnosis requires endoscopic detection of columnar metaplasia plus biopsy confirmation of metaplasia with goblet cells [140]. In contrast, the British Society of Gastroenterology and the GERD Society Study Committee in Japan state that the presence of goblet cells is not required to diagnose Barrett esophagus, with diagnosis based solely on endoscopic detection of columnar metaplasia [49; 141; 142].

DYSPEPSIA

Dyspepsia is a common GI condition of epigastric pain, and dyspeptic symptoms are common in patients with GERD, especially with frequent reflux-related symptoms [62]. Rome IV minimized the diagnosis of GERD in those with dyspepsia by excluding patients with heartburn and acid regurgitation [143].

This definition is best suited for clinical research, but it is less relevant in clinical practice, because many patients have overlapping GERD and dyspepsia symptoms [2; 144]. To improve relevance in the real-world clinical setting, dyspepsia criteria were jointly updated in 2017 by the ACG/CAG [2]. They are:

- Predominant epigastric pain lasting at least one month
- Associated with any other upper GI symptom (e.g., epigastric fullness, nausea, vomiting, heartburn), but epigastric pain is the primary feature

Functional dyspepsia is dyspepsia in which endoscopy (and other tests, when relevant) has ruled out apparent pathology that explain symptoms [128].

Based on their definition of dyspepsia and functional dyspepsia, recommendations for clinical management were published by ACG/CAG, presented sequentially for patients who fail initial or subsequent therapies [2]. The ACG/CAG states this guideline does not apply to patients with alarm features in the absence of epigastric pain; to patients with epigastric pain that suggests a pancreatic or biliary source; or to patients with other alarm features that require non-endoscopic testing [2].

Patients with dyspepsia who are younger than 60 years of age and without alarm features should be considered for noninvasive testing for *Helicobacter pylori* [145]. If testing is positive, treatment should focus on this infection, which is typically treated with combinations of two to three antibiotics along with a PPI, taken concomitantly or sequentially, for periods ranging from 3 to 14 days [145]. Patients should be asked about previous antibiotic exposure(s) to determine the appropriate *H. Pylori* treatment regimen [145]. The initial course of eradication (i.e., first-line) therapy generally offers the greatest likelihood of treatment success [145].

While clinical practice guidelines recommend a PPI as the agent of choice in *H. pylori* eradication regimens (with H2RAs as potential alternatives), the use of either class of medication may be limited by adverse effects, drug interactions, and tolerability. Vonoprazan, a potassium-competitive acid blocker, may be a safe and effective alternative antisecretory agent for *H. pylori* eradication regimens, as well as other gastrointestinal disorders. Vonoprazan works by competing with potassium on the proton pump to inhibit gastric acid secretion [146]. Vonoprazan received FDA approval in 2023 based on phase III clinical trials that demonstrated the agent to be noninferior to PPIs as a component of *H. pylori* eradication regimens [146].

When patients are *H. pylori*-negative or remain symptomatic after *H. pylori* eradication, PPIs should be prescribed. With nonresponse to PPIs or H. pylori eradication therapy, prokinetic therapy and a tricyclic antidepressant should be offered [2]. With nonresponse to medications, psychologic therapy should be explored.

Endoscopy is not suggested for patients younger than 60 years of age to investigate alarm features or exclude upper GI neoplasia. However, endoscopy is indicated to exclude upper GI neoplasia in patients 60 years of age and older. Motility studies are suggested in selected patients when gastroparesis is strongly suspected.

INITIAL MANAGEMENT OF GERD

The objective of GERD treatment is to control symptoms, heal the esophagus, and prevent recurrent esophagitis or other complications by reducing gastric acidity and decreasing esophageal reflux [50; 57; 147]. The diverse clinical presentation and underlying pathology of GERD has imposed significant challenges in long-term symptomatic management. A patient-centered, individualized approach can optimize patient outcomes across the GERD spectrum, and the following elements are important for clinicians to consider in all patients: a secure and clear diagnosis, early patient engagement, adherence to therapy, and a targeted approach [59].

A secure and differentiated diagnosis is vital, especially in PPI-refractory GERD. Extraesophageal symptoms and their relationship to pathologic acid exposure should be evaluated, because abnormal perception frequently contributes to symptom expression and therapy response.

Early patient engagement is important to help patients' understanding of their GERD symptoms, long-term implications on quality of life, and possible complications of strictures, extraesophageal symptoms, Barrett esophagus, and cancer. This information-sharing empowers patients to take ownership and control of their chronic disease management and minimizes undue fear and anxiety [59; 148].

Clinicians should emphasize the importance of lifelong adherence to dietary and lifestyle measures to prevent relapse or exacerbations, even during long-term PPI or postsurgical remission. Unless such measures are understood and practiced by patients, therapy is likely to fail. Medically or surgically refractory GERD often originates from poor dietary habits and weight gain [59; 149].

Most patients respond well to PPIs, but many can require changes in dose timing, dose doubling, switching to alternative or adjunctive agents, or endoscopic antireflux therapy or antireflux surgery [59]. A tailored, treat-to-target approach that considers long-term safety, tolerability, and patient preference is highly preferable to therapy based on empiricism or cost savings.

LIFESTYLE INTERVENTIONS

Before making pharmacologic recommendations to patients, consider lifestyle modifications that can considerably improve symptoms alone or combined with other strategies. During history-taking and physical examination, note the presence of risk factors for GERD, including agents or physical states that decrease pressure in the LES and increase transient LES relaxations. When these factors are present and modifiable by patient behavior change, they are targets for lifestyle interventions [50].

Most commonly, patients are recommended to avoid foods that decrease LES pressure and to minimize behaviors that predispose to increased esophageal acid exposure [50]. In contrast to the extensive data on acid inhibiting medication in GERD, relatively few studies are published on lifestyle intervention [150]. Lifestyle modifications with the strongest evidence support are weight loss and head-of-bed elevation [50].

Weight Loss

Weight gain and weight loss are associated with an increase and decrease in reflux symptoms, respectively, in both normal and overweight individuals [58]. Weight loss in overweight or obese patients with GERD symptoms is one of the most strongly supported lifestyle modification interventions. Several randomized controlled trials and well-designed observational studies have shown reduced reflux symptoms and esophageal acid exposure with weight loss, with a dose-dependent decreased presence of reflux symptoms following weight reduction [150].

The American Association of Clinical Endocrinologists and American College of Endocrinology recommend all overweight or obese patients with GERD should undergo weight loss, with the goal loss of 10% of body weight or greater. PPI therapy should be administered during dietary and weight-loss interventions [151]. Bariatric and other surgical options for obese patients may be considered.

Head-of-Bed Elevation

The recumbent position is associated with worsening of esophageal pH values and GERD symptoms. Several randomized controlled trials have demonstrated improvement in GERD symptoms and esophageal pH values with head-of-bed elevation. Wood or cement blocks may be placed under the feet of the bed to raise the head end 6 to 10 inches. Wedges can also be inserted between the mattress and box-spring to elevate the body from the waist up and are available at drugstores and medical supply stores. Stacking pillows is ineffective [15; 150]. Some patients may invest in adjustable beds that allow for easy personalization of this elevation. Patients with nocturnal GERD symptoms may find substantial relief from head-of-bed elevation and avoiding meals three hours before bedtime, especially foods with high fat content [50].

Smoking Cessation

Tobacco smoking reduces LES pressure and salivary bicarbonate secretion, which facilitates reflux and decreases acid buffering [150]. However, smoking cessation has shown inconsistent benefits in GERD [15]. A large prospective study of 29,610 participants found smoking cessation was associated with decreased severe reflux symptoms in normal-weight individuals on PPI treatment (versus those who continued daily smoking), but no effect was found in overweight or obese individuals. This was thought to reflect the minimal added contribution from smoking compared with obesity in GERD pathophysiology, with smoking a more important factor in non-obese individuals [152].

Foods and Beverages

Consumption of chocolate and carbonated beverages has been found to decrease LES pressure, but cessation of these agents does not necessarily raise LES pressure, decrease transient relaxations, or improve GERD symptoms [50]. Clinicians routinely recommend patients with GERD avoid coffee and caffeinated beverages, but whether coffee or caffeine itself is a factor in the pathophysiology of GERD is unclear; studies show conflicting results [58].

Protein and dietary fat have shown opposite effects on the LES; protein ingestion increases LES pressure, and fat ingestion decreases LES pressure. Ingestion of total fat, saturated fat, and cholesterol were higher in patients with GERD symptoms than those without symptoms in one study, but this effect only held in patients with BMI >25 [58; 153; 154].

A study examined dietary guideline adherence in 317 patients with GERD and whether adherence was related to reflux symptom severity and frequency. Compared with GERD-free controls, patients with GERD, even with moderate-severe or frequent symptoms, were as likely to consume tomato products and large-portion meals and were significantly more likely to consume soft drinks and tea and eat fried and high-fat foods. The results held when PPI users were excluded. If dietary modification is effective in reducing GERD, the results suggest substantial potential for nondrug interventions for many patients with GERD [155]. BMI was not analyzed separately.

Clinical trials have failed to consistently capture the aggravating effect of the consumption of chocolate, carbonated beverages, alcohol, coffee/caffeine, spicy foods, tomatoes or tomato sauce, citrus, or fatty foods on GERD symptoms. The equivocal findings are partly due to methodology problems [156]. More recent evidence supports the role of certain trigger foods, while population studies endorse decreased reflux symptoms with specific diets [149]. Specific foods or beverages are clearly GERD symptom triggers for some patients. When triggers are identified, their avoidance can bring considerable symptom relief [15].

Interestingly, a comparison of patients with GERD who performed Ramadan fasting and those who did not found significant reductions in GERD symptoms and severity in the fasting group before the end of the month compared with the non-fasting group [157].

Medications

Common medications that facilitate decrease in LES pressure and increase in transient relaxations include beta-adrenergic agonists, anticholinergics, nitrates, PDE-5 inhibitors (e.g., sildenafil, tadalafil), theophylline, calcium channel blockers, and benzodiazepines [50]. As discussed, regular use of NSAIDs is linked to a range of adverse GI effects; concurrent use of NSAIDs and SSRIs further elevates risks of upper GI ulceration and bleeding [114]. In patients prescribed these medications, possible contribution to GERD symptoms should be discussed. It is also worth revisiting if a patient has poor response to acid suppressant medications to determine if therapeutic alternatives are feasible.

NSAIDs should be discontinued whenever possible. If this is not feasible, PPI therapy should be initiated and NSAID dose reduction considered. PPIs are more effective than H2RAs in reducing NSAID-induced upper GI injury [158].

Misoprostol is a prostaglandin analogue also used for gastroprotection during NSAID use and is approved by the U.S. Food and Drug Administration (FDA) for prevention of NSAID-induced ulcer disease. Misoprostol is more effective than H2RAs in preventing NSAID-induced mucosal injury and equally effective as PPI in ulcer prevention with NSAID use. However, GI side effects, especially diarrhea, can limit patient tolerability [158].

ANTACIDS AND HISTAMINE-2 RECEPTOR ANTAGONISTS

GERD is a chronic disease, and proper treatment should be preventive in nature instead of reactive. PPIs are the standard of care, but less potent interventions may be suitable for some patients [50].

Antacids

Antacids are popular for treating occasional mild episodes of reflux and use different combinations of three basic salts—magnesium, calcium, and aluminum—with hydroxide or bicarbonate ions to neutralize gastric acid [10]. Antacids only provide quick, short-acting relief for 30 to 60 minutes, do not promote healing of erosive esophagitis, and only neutralize acid already secreted [84]. The role of antacids in the treatment of GERD is limited to patients with known triggers or breakthrough symptoms not effectively controlled by other medications. If used, antacids should be taken after each meal and at bedtime. Patients should receive education on the differences between occasional indigestion and GERD so they do not try to self-treat and subsequently fail to achieve relief [50].

Histamine-2 Receptor Antagonists

Cimetidine, famotidine, and nizatidine are currently the FDA-approved H2RA agents for the treatment of GERD and are available over the counter. A fourth H2RA, ranitidine, was withdrawn from the U.S. market in 2020 [159]. H2RAs decrease gastric acid secretion in a reversible fashion by blocking the action of histamine on H2 receptors of gastric parietal cells. The inhibition of acid secretion results in an increase in gastric pH and a decrease in pepsin activity [159]. Over-the-counter formulations are available at a dose that is typically half the lowest standard prescription dosage [50].

This class of drugs is uniformly safe and well tolerated. The risk of adverse effects is slightly increased with cimetidine because it interacts with cytochrome P-450, potentially leading to drug-drug interactions [84].

Taken in standard divided doses, H2RAs can achieve symptom relief in some patients with milder or intermittent GERD. However, H2RAs have a dose ceiling; dose escalation above the recommended range does not further improve response. Over-the-counter H2RAs are particularly useful when taken before reflux. The peak potency of antacids and H2RAs is similar, but H2RAs have a much longer duration of action—up to 10 hours [84].

The ACG practice guidelines recommend H2RA use as a maintenance option in patients without erosive disease if patients experience heartburn relief [15]. A main limitation of H2RAs is tachyphylaxis (development of tolerance), often within two weeks of daily use. This pharmacologic phenomenon results in declining acid suppression and limits the regular use of H2RAs in clinical practice [160].

PPI THERAPY

Evidence from a systematic review of publications and practice guidelines addressing safe and appropriate PPI use were synthesized into an expert consensus statement on appropriate indications and treatment durations for PPI therapy (***Table 2***) [161; 162]. The consensus statement reflects current knowledge based on published evidence and real-world clinical use that may not have been available to the FDA when PPI indications were approved.

The initial PPI approved for use in the United States was omeprazole, followed by lansoprazole, rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole. Most are now available in generic forms [159; 163]. Their introduction and widespread use revolutionized the management of acid-related diseases and minimized the role of surgery [164]. By 2015, PPIs ranked in the top 10 national health-related drug expenditures in the United States [162].

PPIs are substituted benzimidazoles and are the most potent inhibitors of gastric acid secretion available. They block the final common pathway of acid secretion in gastric parietal cells by irreversibly binding to and inactivating the proton pump [158]. For gastric secretory activity to be restored, new enzymes need to be resynthesized, a process that normally takes two to five days [84].

INDICATIONS FOR APPROPRIATE PPI THERAPY
FDA-Approved Indications for PPI Therapy
Treatment of GERD Healing of erosive esophagitis Maintenance of healed erosive esophagitis Risk reduction for gastric ulcer associated with NSAIDs *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence in combination with antibiotics Zollinger-Ellison syndrome and other hypersecretory conditions Short-term and maintenance treatment of duodenal ulcer
Long-Term PPI Therapy Appropriate
Barrett esophagus, asymptomatic patients with Barrett esophagus[a] Healing/maintenance of healed Los Angeles grade C or D erosive esophagitis PPI-responsive esophageal eosinophilia Idiopathic (*H. pylori*- and NSAID/aspirin-negative) peptic ulcer disease Zollinger-Ellison syndrome[b] PPI-responsive GERD/NERD[c, d] Patients at risk for ulcer-related bleeding from NSAIDs, for the duration of regular NSAID use[a] Anti-platelet therapy in patients at high-risk for upper GI complications (i.e., age older than 65 years; concomitant use of corticosteroids or anticoagulants; or a history of peptic ulcer disease) Steatorrhea refractory to enzyme replacement therapy in chronic pancreatitis
Short-Term PPI Therapy Appropriate (4 to 12 Weeks)
Healing of Los Angeles grade A or B erosive esophagitis Eosinophilic esophagitis *H. pylori* eradication (combined with antibiotics)[e] Stress ulcer prophylaxis in high-risk patients (e.g., critically ill patients) Functional dyspepsia Treatment and maintenance of peptic ulcer disease Prior to endoscopy for acute upper GI bleeding Following endoscopic treatment of a high-risk ulcer GI bleed
PPI Use Not Appropriate
Corticosteroid users without concomitant NSAID therapy To prevent bleeding from hypertensive gastropathy in patients with cirrhosis Acute pancreatitis Stress ulcer prophylaxis in non-critically ill hospitalized patients not at high-risk for ulcer formation and GI bleeding
PPI Use of Uncertain Benefit
PPI-nonresponsive GERD Extradigestive GERD (e.g., asthma, pseudoangina, dysphoria)
GERD = gastroesophageal reflux disease, GI = gastrointestinal, NERD = non-erosive reflux disease, NSAID = nonsteroidal anti-inflammatory drug. [a]AGA recommendation [b]Requires three to four times the usual dose [c]PPI taper should be attempted to lowest effective dose, on-demand dosing, or intermittent dosing. [d]AGA recommends the dose of long-term PPIs should be periodically re-evaluated so the lowest effective PPI dose can be prescribed to manage the condition. [e]One- to two-week PPI course appropriate
Source: [67; 161; 162] *Table 2*

As discussed, in patients without alarm features, management of GERD usually begins with an empiric PPI trial [165]. An initial trial of once-daily PPIs for at least eight weeks is recommended by the ASGE and the ACG, with four to eight weeks recommended by the ACP [15; 110; 117]. With nonresponse to once-daily PPIs, twice-daily PPI is initiated. Patient response and adherence is assessed after eight weeks before PPI failure/nonresponsiveness is concluded [67; 165]. Some argue that incomplete response to once-daily PPI is sufficient to define PPI failure, but twice-daily dosing achieves adequate symptom control and eliminates residual acid reflux in 20% to 30% of patients with once-daily PPI nonresponse [16; 166; 167].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society for Gastrointestinal Endoscopy suggests that repeat esophagogastroduodenoscopy be performed in patients with severe erosive esophagitis after at least an eight-week course of PPI therapy to exclude underlying Barrett esophagus or dysplasia.

(https://www.asge.org/docs/default-source/education/practice_guidelines/doc-endoscopy_in_the_managment_of_gerd.pdf. Last accessed September 9, 2024.)

Level of Evidence: Low quality

PPI Efficacy

GERD and NERD

Numerous clinical trials have shown PPIs to be superior to H2RAs, antacids, and sucralfate in alleviating GERD symptoms. PPIs result in a significantly faster healing rate of peptic ulcers (12% per week) and heartburn (11.5% per week) compared with H2RAs (6% and 6.4% per week, respectively) [158]. Long-term PPI maintenance is also more effective in preventing recurrence of reflux esophagitis (80% PPIs vs. 49% H2RAs) and esophageal strictures (46% PPIs vs. 30% H2RAs) [67].

A meta-analysis of 98 randomized controlled trials evaluated PPI and H2RA effectiveness after four to eight weeks in adults with GERD. Effectiveness (defined as esophageal healing and GERD symptom relief) and tolerability (defined as discontinuation from ineffectiveness, adverse effects, or nonadherence) was calculated for low- and high-dose daily use; high doses were uniformly more effective [168]. The agent with top-ranked effectiveness was esomeprazole (40 mg/day), followed by rabeprazole (40–50 mg/day) and pantoprazole (80 mg/day). Best tolerability was noted with omeprazole (40 mg/day), then pantoprazole (40 mg/day), lansoprazole (60 mg/day), and the H2RA ranitidine (1,200 mg/day), which, as stated, is no longer marketed in the United States. However, sponsorship bias was detected. Higher PPI outcomes in studies with pharmaceutical company funding may have led to overestimated esophageal healing efficacy [168].

Once-daily PPIs for eight weeks heals reflux esophagitis in more than 80% of patients, and this is further improved by twice-daily dose escalation. Esomeprazole achieves higher short-term healing rates of reflux esophagitis than omeprazole, lansoprazole, and pantoprazole, but this advantage is negligible in less severe esophagitis. PPIs are effective for symptom relief in erosive and non-erosive disease, but efficacy in reducing regurgitation is considerably lower than with heartburn [169; 170].

The belief that PPIs have lower efficacy in NERD was dispelled by a meta-analysis showing that PPI efficacy for NERD was comparable to erosive disease when functional testing using pH-HRM or pH-impedance testing was added to confirm NERD after negative endoscopy findings [62; 171].

GERD practice guidelines and review papers often state that PPIs lack meaningful differences in potency. However, a comparative study of PPI efficacy in intragastric pH control, measured by percentage of time at pH >4 over 24 hours, found relative potencies, compared with omeprazole (1.00; reference), of 0.23 for pantoprazole, 0.90

for lansoprazole, 1.60 for esomeprazole, and 1.82 for rabeprazole [172]. This pharmacodynamic non-equivalence should be considered when prescribing or switching PPIs [62].

Short-term PPIs are generally well-tolerated, with infrequent adverse reactions including flatulence, headache, diarrhea, abdominal pain, and nausea. These reactions are often self-limiting or can be addressed by switching to a different agent [162].

Extraesophageal Manifestations

In contrast to typical symptoms, PPI efficacy in extra-esophageal manifestations of GERD is less clear-cut. PPIs are usually given twice-daily for extended periods, but evidence is not strong enough to allow clear recommendations to be made for patients with only extraesophageal symptoms. Nonetheless, an empiric PPI trial can be the initial approach to diagnose and treat the potential underlying cause of extraesophageal disease [62].

As noted, GERD is the most common and best-studied cause of non-cardiac chest pain, and PPIs are the initial pharmacologic approach in these patients. Patients with non-cardiac chest pain and endoscopic or pH-monitoring evidence of GERD tend to improve, but not resolve, with PPI therapy. In contrast, GERD-negative patients show little or no PPI response. The therapeutic benefit of PPIs in patients with chronic cough is demonstrated, but efficacy in reflux laryngitis is much weaker. Asthma and GERD often coexist, and while asthma medications can trigger GERD, PPIs may improve asthma control [62].

Dyspepsia

Dyspeptic symptoms are common in patients with GERD, especially with frequent reflux-related symptoms. In these patients, PPI therapy improves epigastric pain, belching, bloating, and early satiety, but lacks benefit with nausea and vomiting [173]. PPI efficacy in functional dyspepsia occurs at standard doses, but long-term PPI therapy for functional dyspepsia is not indicated [62].

Dyspeptic symptoms may worsen with PPI therapy or new symptoms (especially postprandial fullness) may emerge from PPI-induced inhibition of gastric motility and delayed gastric emptying. In these cases, patients should be switched to the H2RA nizatidine. In addition to antisecretory activity, this agent displays cholinergic-like activity and accelerated gastric emptying [62; 174].

Optimal Use and Duration

Optimizing PPI Use

To achieve maximum response, it is important that patients receive correct instructions on how to use PPIs. The timing of PPI administration is essential. Patients are usually initiated on once-daily dosing, which must be taken 30 to 60 minutes before the first meal of the day, as the agents are most effective after a prolonged fast (i.e., overnight). Proton pumps are highly active during the postprandial period, and with a plasma half-life of one to two hours, PPIs reach peak concentration at the time of a meal [107; 158]. If increased acid suppression is required, a second dose taken 30 to 60 minutes before the evening meal is more effective than doubling the morning dose [107].

With initial therapy, patients must adhere to daily use. The antisecretory action of PPIs increases with consecutive daily dosing, and full steady-state acid inhibition is achieved after four to five days. Steady-state acid inhibition is lost with non-adherence to daily use [158].

Treatment Duration and Discontinuation

With evidence that links long-term PPI use to potential risks, GERD practice guidelines recommend PPI dose reduction or discontinuation in some patients. In 2017, the AGA recommended that after a three- to six-month treatment course with good PPI response, patients with uncomplicated GERD should attempt to stop or reduce PPIs because patients who cannot reduce PPIs face the likelihood of lifelong PPI use [67]. In these patients, esophageal pH-impedance monitoring distinguishes acid-related disorders from a functional syndrome.

The best candidates for this strategy may be patients with primarily atypical symptoms and those who lack obvious predisposition to GERD from central obesity or large (>3 cm) hiatal hernia.

PPIs can be very difficult to quit, and 75% to 90% of patients with GERD relapse in the initial six months after PPI discontinuation. This is attributed to the chronicity of GERD and NERD and contribution from PPIs, as abrupt cessation may be followed by rebound acid hypersecretion and symptom exacerbation [62; 107; 175].

Before continuing a likely long-term PPI treatment, or for patients already on long-term PPIs, an attempt to stop PPI therapy should be considered. Tapering is more effective as a discontinuation strategy than abrupt withdrawal, patient education, or lifestyle modifications [176]. Weight loss can also be an effective strategy in obese/overweight patients. One study found 54% of patients remaining adherent to a hypocaloric diet were able to stop PPIs, and 32% reduced their PPI dose by 50% [177].

PPIs can induce parietal cell proliferation to promote a hyperacidity state after discontinuation. This rebound hyperacidity can create a dependence on continued PPI use [178]. In a study of 120 healthy volunteers, rebound acid hypersecretion occurred after 8 weeks of PPI treatment, and 44% experienced acid-related symptoms 9 to 12 weeks after discontinuation. The authors concluded patients should taper off PPIs more gradually than is commonly suggested [179]. These results have been replicated in other studies as well [60; 180; 181].

Because relapse frequency and severity are highly variable among patients, long-term PPI maintenance should be individualized based on clinical characteristics of the patient. Strategies include continuous/daily use, intermittent cycles of daily use, and on-demand/symptom-driven therapy. Infrequent reflux symptoms are less likely to be chronic and may respond to a different approach [62].

An alternative approach is a PPI step-down, in which the dose is reduced to determine the minimum needed. This involves a gradual reduction in dose or frequency and may include a goal of switching to "as-needed" therapy. The step-down approach allows patients to implement lifestyle modifications and find the lowest dose they need for adequate symptom control [107]. While full-dose PPIs are superior to half-dose in maintaining remission, step-down dosing with esomeprazole 20 mg maintained a significantly higher proportion of patients with GERD in symptomatic remission than lansoprazole 15 mg or pantoprazole 20 mg [169]. Because PPIs do not correct the underlying esophageal motor abnormalities of GERD, patients may require continuous acid suppression treatment to maintain remission [62].

The AGA guideline for long-term use of PPIs concludes the best current approaches to mitigate potential risks of long-term PPIs are to avoid prescribing when PPIs are not indicated and to reduce their use to the minimum dose when PPIs are indicated [67]. The AGA states most patients with uncomplicated GERD can reduce from twice-daily to once-daily PPI dosing, 33% can successfully transition from PPIs to H2RAs, and 16% are able to transition off all acid suppression. Patients with non-erosive disease who cannot transition off PPIs are usually satisfied with on-demand PPI therapy. Because PPI reduction is often successful in uncomplicated GERD, it is recommended that clinicians periodically re-evaluate patients to ensure they are taking the lowest dose sufficient to manage their condition [67].

Patients with complicated GERD (e.g., erosive disease) are usually unable to successfully reduce PPIs. Patients with good symptom control from daily PPIs who cannot reduce face lifelong PPI therapy. Assessment for an acid-related disorder with esophageal pH-impedance monitoring is recommended. This testing shows a subset of patients with poor correlation between symptoms and acidic reflux events, and strenuous efforts should be made to discontinue or reduce PPIs in these patients [67].

A Canadian guideline was published in 2017 to help clinicians identify when to taper or stop PPI therapy. In adults with upper GI symptoms who have completed a minimum four-week course of PPI treatment with resolution of upper GI symptoms, the following is recommended [114]:

- Decrease the daily dose or stop and change to on-demand (as-needed) use.
- Consider an H2RA as an alternative to PPIs.
- Patients with erosive disease, or who require daily NSAIDs, should continue their regular-dose PPI.

Criteria have also been proposed that may predict greater success halting PPIs in elderly patients living in care facilities. PPI discontinuation outcomes were evaluated in 27 elderly residents (mean age: 80 years) taking a PPI for more than six months who met all of the following criteria: 1) no indication for long-term PPIs; 2) not currently experiencing GI symptoms; 3) no previous PPI discontinuation without success; and 4) no anxiety when medications are discontinued. PPIs were stopped without taper with participants receiving medical monitoring and support. After eight weeks, 70% remained asymptomatic and did not need PPIs to manage GI symptoms [182].

PPI Chemoprevention in Barrett Esophagus

With Barrett esophagus of any mucosal length, long-term PPI use for potential chemopreventive effects against neoplastic transformation is advocated by the ACG and the AGA, but is not recommended by the British Society of Gastroenterology [67; 140; 183]. The evidence supporting this practice is inconsistent. A meta-analysis of observational studies found PPI use associated with a 71% reduction in risk of esophageal adenocarcinoma and/or high-grade dysplasia in Barrett esophagus, but another study concluded standard PPI therapy was unable to normalize esophageal exposure to acid in most patients with Barrett esophagus [184; 185]. Individually tailored maximal acid suppression is needed to control GERD and to achieve any chemopreventive effect in Barrett esophagus [62].

PPI SAFETY CONCERNS

PPI Overuse

Following their introduction and uptake into clinical practice, PPIs became highly successful in managing patients with GERD. However, once PPIs are taken regularly, many patients remain on long-term PPIs often indefinitely, especially the elderly [62]. PPIs are available over the counter and are used indiscriminately for treating conditions without appropriate indication [80]. PPI prescriptions increased from 4.1% in 1999–2000 to 8.6% in 2017–2018. Almost all of the increase occurred among adults 55 years of age and older [186]. An estimated 53% to 69% of PPI prescriptions are written for inappropriate indications—cases in which the benefits of PPI use may not justify the risks [187; 188]. PPIs are often overprescribed, rarely deprescribed, and frequently started inappropriately during a hospital stay, with their use extended to long-term without appropriate medical indication [189].

Use of PPIs appears disproportionate to prescribing guidelines and to the prevalence of acid-related diseases of GERD and NSAID-related gastropathy. Contributing to the continuous increase in PPI use over the last decade is inappropriate prescribing for inappropriate purposes, including prevention of gastroduodenal ulcers in low-risk patients; stress-ulcer prophylaxis in patients receiving corticosteroid therapy or anticoagulant treatment without risk factors for gastroduodenal injury; functional dyspepsia; and mistaken diagnosis of acid-related disorder [164]. The widespread overuse and inappropriate use of PPIs is especially concerning in the elderly, who have greater risk of long-term PPI-related adverse outcomes and drug-drug interactions [62].

Other Safety Concerns

Awareness that PPI use may be associated with adverse effects has increased since they were first approved for marketing. The FDA issued safety warnings for potential increased risk of osteoporosis-related fractures and *Clostridioides difficile* infection associated with PPI therapy in 2010 and 2012, respectively [190]. In 2015, the American Geriatrics Society recommended avoiding PPI use longer

than eight weeks in older adults, due to potential risk of *C. difficile* infection, bone loss, and fractures [191]. Reports also associate PPIs with increased risk of community-acquired pneumonia, vitamin B12 deficiency, dementia, and kidney disease [190].

The association between PPI exposure and increased risk of acute interstitial nephritis, chronic kidney disease, kidney disease progression, end-stage renal disease, and rare but potentially fatal hypomagnesemia is strong [189]. The data linking PPI use with increased risk of *C. difficile* infection are convincing, but the magnitude of risk is very low [158]. The relationship between PPI use and risk of community-acquired pneumonia or cardiovascular events is inconsistent and weak [189]. The duration of PPI therapy that may elevate the risks of some adverse effects is not known [190].

Of note, PPI use and mortality risk were examined in a study of Veterans Affairs healthcare system patients. Among patients newly prescribed PPIs or H2RAs and followed a median 5.71 years, PPI use was associated with a 25% greater risk of death compared with H2RAs [189]. Among new users of PPI therapy, risk of death was associated with greater PPI exposure. Compared with PPI use ≤30 days, the risk of death increased by 31% with 181 to 360 days of exposure and 51% with 361 to 720 days of PPI exposure [189]. Cause of death was not reported in this study, but the authors state the heightened risk of death was likely mediated by adverse events associated with PPI use, including kidney disease, dementia, hypomagnesemia, *C. difficile* infection, and/or osteoporotic fracture [189].

PPIs may also adversely impact microbial biodiversity of the GI tract. The gut microbiome is important in maintaining overall health, and alterations in its biodiversity can promote pathologic conditions. *Streptococcus* spp. are over-represented in biopsies of patients with gastritis and may contribute to the development of peptic ulcer disease. PPI use favors relative streptococcal abundance independent of *H. pylori* status and may explain the persistence of dyspeptic symptoms in patients on PPI therapy. Patients on long-term PPIs also have increased risk of enteric infections. PPI overuse may significantly shift the GI microbiome toward a less healthy state, with significant changes in the microbial composition of gastric and intestinal microbiota [82].

Considering the high prevalence of PPI use, the adverse events associated with PPI use may have public health implications. Given the potential for these risks, limiting the duration and use of PPIs to medically indicated conditions seems warranted [158; 189; 190].

Safety of Over-the-Counter PPIs

PPI safety concerns mostly originate from studies evaluating their prescription use, but over-the-counter use differs in several relevant ways. Patients prescribed PPIs generally take higher doses over longer treatment durations for more severe underlying conditions than over-the-counter users. In contrast, over-the-counter PPIs are generally used for shorter durations at lower dose ranges. A concern with over-the-counter PPI use is that direct consumer access without physician direction may promote inappropriate use. Real-world-use data suggest the opposite; persons using over-the-counter PPIs tend to self-select appropriately based on symptoms and are more likely to take the appropriate or fewer number of doses [192]. When over-the-counter PPI use is consistent with label instructions, a consensus panel of experts concluded that available evidence does not suggest an association with substantial health risks [192].

MANAGEMENT OF GERD IN PATIENTS NONRESPONSIVE TO PPIS

MEDICATION OPTIONS IN PPI-REFRACTORY GERD

If switching to rabeprazole or esomeprazole is ineffective, it is essential to assess for other disorders that may be the cause of persistent symptoms in PPI nonresponders. pH testing and HRM assess bolus clearance, reflux episodes, transient LES relaxations, and the integrity of the antireflux barrier, providing important information for treatment targeting. Excluding functional disorders is critical, as these patients are managed differently from those with pathologic reflux [160].

Pharmacologic options are available to target various mechanisms of PPI-refractory GERD, including transient LES relaxations with reflux, incomplete acid suppression, impaired esophageal clearance, and delayed gastric emptying. Targeting these mechanisms may improve symptoms and eliminate the need for antireflux surgeries [160].

An important criticism of the body of published evidence on non-PPI medications is the pervasive neglect of phenotyping to determine the underlying mechanism of symptom persistence. Without phenotyping, many patients with functional symptoms have been included in these studies, making assessment of efficacy in target populations difficult [79; 160]. The medications discussed in the following sections should be added to PPIs (rather than used alone), because their efficacy alone is less-evaluated and may be poor [1; 193].

H2RAs

H2RAs may improve PPI gastric acid suppression, particularly nocturnal acid breakthrough that occurs in up to 75% of patients on PPIs [160].

Adding famotidine 40 mg before bed improved overall symptoms (72%) and night-time symptoms (74%) in patients taking PPIs [194]. Compared with PPI alone, adding a night-time H2RA for PPI nonresponse significantly reduced nocturnal acid breakthrough (17% vs. 64%) and percent intragastric time pH <4 (18% vs. 31.5%). Esophageal acid exposure (1.9% vs. 3.3%) and positive acid reflux/symptom correlation (0% vs. 10%) were lower but not significantly different [160; 195]. Night-time H2RAs may help suppress nocturnal acid breakthrough, but tachyphylaxis limits their long-term use [160].

Promotility/Prokinetic Agents

Agents with prokinetic properties are proposed as adjunctive medications for PPI nonresponse when delayed gastric emptying is a suspected symptom contributor. Metoclopramide and domperidone are selective dopamine receptor antagonists that may improve esophageal peristalsis, accelerate esophageal acid clearance, increase LES basal pressure, and improve gastric emptying. Other possible agents include revexepride (investigational in the United States), prucalopride, and mosapride [160].

A select group of PPI nonresponders may benefit from adjunctive promotility agents. However, mosapride, the most-studied agent, is not approved in the United States. Domperidone reduced symptom scores better than PPI alone, but is also not approved and carries significant arrythmogenic risks [160]. Metoclopramide is associated with several adverse effects and use in GERD has been limited by safety concerns [196; 197]. In patients with persistent GERD symptoms despite PPI treatment, two randomized controlled trials found revexepride no more effective than placebo in controlling regurgitation and reflux [198; 199]. A small randomized controlled trial of prucalopride in patients with GERD and ineffective esophageal motility suggested this drug may be useful in augmenting peristalsis in these patients [200].

Transient LES Relaxation Inhibitors

Baclofen acts as an agonist of gamma-aminobutyric acid (GABA) type B receptors and is prescribed to decrease transient LES relaxation-related acidic and non-acidic reflux episodes [160]. Baclofen physiologically inhibits transient LES relaxations, and studies measuring baclofen effects with pH-impedance monitoring show significant reductions in postprandial acid- and non-acid-related symptoms in patients with heartburn by reducing transient LES relaxations, increasing LES tone, and decreasing reflux episodes. Studies have also demonstrated that baclofen reduces the number of postprandial and non-acid reflux events, nocturnal reflux activity, and belching episodes [50; 52]. In patients with symptomatic GERD treated with daily omeprazole plus baclofen 10 mg or placebo, baclofen significantly reduced the rates of heartburn (46% vs. 4%) and regurgitation (54% vs. 4%) [201]. Baclofen may be particularly beneficial for patients with abnormally high non- or weakly-acidic reflux events [160]. However, baclofen requires adherence to twice or three times daily dosing, and common side effects include drowsiness, fatigue, and confusion [107].

Mucosal Protective Agents

Especially in patients with NERD, PPI response is often partial or limited and symptom relief requires additional medications. Esophageal mucosal protection from acidic and non-acidic contents is another approach to PPI nonresponse. Some of these agents target the gastric acid pocket in the proximal stomach, a contributor to the pathogenesis of postprandial reflux [202].

Alginates

Alginate is a polysaccharide derived from seaweed that binds water in the acid pocket to form a viscous gel, displacing the acid pocket distally below the diaphragm. Sodium bicarbonate, often added to alginate, is converted to carbon dioxide and forms bubbles trapped within the gel. This changes the gel to a lighter substance that rises to the surface of gastric contents and floats, hence the term "raft-forming agent." Alginates offer a supplemental mechanism of acid suppression [203; 204].

Gaviscon is a common raft-forming alginate formulation. In a randomized controlled trial of 136 patients with persistent reflux symptoms taking once-daily PPIs, adding alginate (10 mL four times/day) for seven days led to significantly greater reductions in reflux score and number of nights with symptoms than placebo [205].

A review of 14 studies in patients with NERD or atypical GERD symptoms found alginate-based therapies more effective in resolving reflux symptoms than placebo or antacids, and somewhat less effective than PPIs or H2RAs [204]. This review evaluated alginate monotherapy, but in practice, alginates are typically added to PPIs. Alginate-antacid formulations show efficacy comparable to single-dose omeprazole in patients with NERD [202].

Mirgeal is an alginate formulation that combines glycyrrhetinic acid and anthocyanosides, both of which have mucosal protective properties. Use in combination with PPIs showed greater reflux symptom control in patients with NERD and poor PPI response compared with alginic acid plus PPI [160].

Sucralfate

Sucralfate is a salt of sucrose sulfate and aluminum hydroxide that creates a physical barrier to block esophageal mucosa exposure to, and diffusion of, hydrochloric acid, pepsin, and bile salts. As an add-on to PPIs, sucralfate can further reduce GERD symptoms and may help induce mucosal healing and reduce recurrent esophagitis during maintenance therapy [202; 206].

Hyaluronic Acid and Chondroitin Sulfate

Hyaluronic acid is involved in several key processes, including cell signaling and wound repair and regeneration. Chondroitin sulfate has possible benefits in inflammatory diseases. Formulations that combine hyaluronic acid and chondroitin sulfate have been introduced and evaluated as treatment of reflux disease [207].

In adults with NERD and poor PPI response, hyaluronic acid/chondroitin sulfate (four times per day) for 14 days led to significantly greater reductions in heartburn and regurgitation symptom intensity than placebo. Onset of effect within 30 minutes was more frequent with hyaluronic acid/chondroitin sulfate than placebo (60% vs. 30%). Complete remission was attained by 50% with hyaluronic acid/chondroitin sulfate and 10% with placebo [207].

A larger randomized controlled trial evaluated improved symptom relief with hyaluronic acid/chondroitin sulfate plus PPI compared with PPI alone in 154 patients with NERD. After two weeks of hyaluronic acid/chondroitin sulfate or placebo, significant reduction in total symptom score (on measures of heartburn, acid regurgitation, retrosternal pain, and acid taste in mouth) was reached by 52.6% with hyaluronic acid/chondroitin sulfate and 32.1% with placebo. The synergistic effect of hyaluronic acid/chondroitin sulfate and PPI treatment suggests mucosal protection added to acid suppression could improve symptom control in patients with NERD [164].

Based on current knowledge, mucosal protective compounds cannot replace PPIs, but show promise in PPI-refractory GERD or NERD in combination with PPIs [160; 202]. The ACG states there is no role for sucralfate or other membrane-protectors, but these agents may represent the only effective medication protection against biliary reflux injury of the esophageal mucosa [15; 89].

Pain Modulators

Compared with healthy subjects, patients with non-cardiac chest pain demonstrate higher pain sensation with esophageal exposure to balloon distension, acid infusion, and electrical and thermal stimulation [208]. In these patients, esophageal hypersensitivity results from sensitization of both peripheral afferent nerves (peripheral sensitization) and spinal dorsal horn neurons (central sensitization). Esophageal hypersensitivity and objective pathology can occur together; around 30% of patients with non-cardiac chest pain have abnormal esophageal findings on HRM [209].

Most PPI-refractory patients have NERD or functional symptoms, making treatment with pain modulators a reasonable option. Antidepressants are the most-studied medications for this indication and include tricyclic antidepressants (e.g., imipramine, nortriptyline), SSRIs (e.g., sertraline), serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), and trazodone. Doses used are lower than in depression, and randomized controlled trials have found them effective in reducing esophageal pain, especially in patients with esophageal hypersensitivity [210]. Antidepressants act by modulating the esophagus-brain axis. Patients with NERD and painful heartburn received functional magnetic resonance imaging (off-PPI) after 21 days of nortriptyline or placebo. Acid-induced activation in prefrontal cortex, caudate, insula, cingulate, and hippocampus brain areas were significantly reduced with nortriptyline compared with placebo [211].

A systematic review of 15 randomized controlled trials found that, compared to baseline, antidepressants increased esophageal pain thresholds 7% to 37%, reduced functional chest pain 18% to 67%, and reduced heartburn in patients with GERD 23% to 61%. Antidepressants modulate esophageal sensation, reduce functional chest pain, and may benefit a subgroup with GERD [212]. In these patients, PPI therapy can (and should) be discontinued when ineffective. The clinical relevance of distinguishing functional heartburn from esophageal hypersensitivity is unclear [213].

In patients with non-cardiac chest pain, chest pain was reduced by 50% to 63% with venlafaxine, sertraline, or imipramine, compared with 1% to 15% in those randomized to placebo. This improvement was independent of effects on depression. Side effects are the main drawback with antidepressant therapy for esophageal hypersensitivity and can adversely impact their tolerability and lead to discontinuation. Antidepressant study drop-out rates as high as 53% have been reported in this population, highlighting the need for safer, more tolerable drugs [1; 214].

Novel Agents

Vonoprazan

A novel potassium-competitive acid blocker, vonoprazan, has demonstrated more potent and sustained acid suppressive effects than the PPIs lansoprazole, esomeprazole, and rabeprazole [160]. The metabolism of vonoprazan is not impacted by genetic polymorphisms of CYP2C19, which impair the efficacy of some PPIs. Vonoprazan was comparable to lansoprazole for the treatment of erosive esophagitis and overall shows more favorable pharmacodynamic and pharmacogenetic properties compared to PPIs. As stated, vonoprazan received FDA approval in 2023 based on phase III clinical trials that demonstrated it to be noninferior to PPIs as a component of *H. pylori* eradication regimens [146].

Melatonin

Melatonin is an important signaling molecule in gut motility and gut-liver communication, and the esophageal mucosa possesses large numbers of melatonin-binding sites [60]. Exogenous melatonin is thought to control GERD symptoms by stimulating production of nitric oxide and prostaglandin E2, inhibiting gastric acid secretion, reducing inflammatory cytokines, and preventing acid/pepsin-induced esophagitis. Melatonin is not conventional therapy but may represent an alternative for patients lacking benefit from PPIs [50].

Clinical trials in GERD are limited, but published results suggest improvements in heartburn, epigastric pain, and LES function [50]. Ramelteon is a melatonin (MT) receptor agonist with high affinity for MT1 and MT2 receptors, essentially a pharmaceutical version of melatonin that is FDA-approved for insomnia [159]. Ramelteon is considerably more expensive than melatonin but is produced under quality control not found with melatonin supplements, because the quality and purity of supplements are unregulated in the United States. In one study, patients with frequent heartburn and/or regurgitation and chronic insomnia received ramelteon 8 mg or placebo before bed for four weeks. Ramelteon led to significant decreases in symptom scores (vs. placebo) for daytime heartburn, nighttime heartburn, 24-hour heartburn, and 24-hour acid regurgitation. Insomnia severity scores were significantly reduced with ramelteon compared with placebo. Ramelteon also led to improvements in sleep efficiency and sleep latency. No significant adverse events were observed [215].

OPTIMIZING PPI ADHERENCE

Up to 40% of patients report persistent GERD symptoms despite PPI therapy [160]. An important cause of PPI failure is treatment non-adherence, with inadequate dosing or poor timing [52].

Treatment adherence should be assessed to determine true PPI nonresponse, because PPIs are often taken inappropriately; 27% of patients with GERD dose their PPI correctly and only 12% dose optimally [216]. There is poor understanding of PPI pharmacokinetics, with nearly 70% of primary care physicians and 20% of gastroenterologists incorrectly instructing patients about when to take doses [217].

PPI failure can result from taking PPIs incorrectly. As noted, gastric acid production is stimulated by food, and PPIs inactivate proton pumps only during acid production. Thus, PPI effectiveness is lost by failure to dose 30 to 60 minutes before a meal. Patients may take PPIs at bedtime for night-time symptoms, which is far less effective than before meals. Taking PPIs infrequently or as-needed, before stable efficacy is achieved, significantly reduces their benefit [1].

SWITCHING TO ANOTHER PPI

Another reason for PPI failure is variation in PPI metabolism. PPIs are primarily metabolized by the hepatic cytochrome (CY) P450 enzymatic system. CYP2C19 and CYP3A4 are the most important isoenzymes in metabolic degradation of PPIs. CYP2C19 polymorphisms (genetic variations) are common and influence the rate of serum clearance and elimination of metabolized drugs. Patient genotypes include extensive metabolizers (normal) and rapid/ultra-rapid metabolizers [52].

Omeprazole is extensively metabolized by CYP2C19. Rapid/ultra-rapid metabolizers show lower serum levels of omeprazole, reduced efficacy from rapid drug clearance, and lower rates of endoscopic healing, remission, and GERD symptom response with CYP2C19-dependent PPIs [1]. Measuring a patient's PPI metabolizer genotype is expensive, but switching to a CYP2C19-independent PPI (rabeprazole or esomeprazole) is a simple, conservative measure that may be useful in patients with incomplete acid suppression from other PPIs [160].

REFRACTORY HEARTBURN AND NOCTURNAL HEARTBURN

PPIs tend to be more effective in postprandial reflux control during the daytime than in night-time heartburn [218]. PPI-refractory heartburn is more common in NERD than erosive disease. Once-daily PPIs may control symptoms, but nocturnal intragastric acidity often remains elevated enough to produce nocturnal acid breakthrough in these patients [219]. In patients with persistent nocturnal acid breakthrough despite twice-daily PPIs, adding an H2RA at bedtime may control nocturnal acid breakthrough and associated esophageal acidification, but development of tolerance to the H2RA is likely [62].

PPI PARTIAL RESPONDERS

PPI partial responders are patients with some improvement in GERD symptoms but a significant remaining symptom burden despite optimized PPIs. Assessment of this patient population suggests functional GI disorders are common [79].

ANTIREFLUX SURGERY

Antireflux surgery was introduced when acid reflux was the presumed cause of GERD. Refinements in antireflux surgery and the introduction of minimally invasive options may eliminate or markedly reduce GERD symptoms by structurally restoring anatomic failure of the LES antireflux barrier—the primary underlying pathology [89].

Outcomes after any surgical management of refractory GERD are highly dependent on adherence to strict surgical indications and appropriate patient and procedure selection [220]. Guidelines for patient-procedure matching have been established (***Table 3***).

LAPAROSCOPIC FUNDOPLICATION

Fundoplication was introduced in 1955 and subsequently modified to laparoscopic fundoplication in 1991 by Dr. Rudolph Nissen, hence the term Nissen fundoplication surgery (NFS) [167]. NFS is also referred to as laparoscopic antireflux surgery or laparoscopic Nissen fundoplication. It is considered the criterion-standard antireflux surgery approach [15; 59; 221].

With NFS, the gastric fundus is used as a wrap to tightly augment the LES in order to reduce reflux episodes [107]. While effective at preventing reflux, this technique also prevents the normal venting of swallowed air (belching) and reduces normal reflux episodes, which can result in side effects of gas bloating syndrome, flatulence, inability to belch or vomit, and dysphagia [15; 57].

PATIENT-PROCEDURE MATCHING FOR INDIVIDUALS WITH REFRACTORY GERD	
Patient Characteristics	**Indicated Surgical Procedure**
Symptomatic GERD despite twice-daily PPIs	Laparoscopic hernia repair plus magnetic sphincter augmentation (LINX) for hernias <2 cm Laparoscopic hernia repair plus Nissen fundoplication surgery (NFS) for hernias >3 cm Postoperatively, follow patients to ensure lifestyle and dietary adherence, minimize disease recurrence, and detect treatment failure
Incomplete PPI response, ongoing regurgitation, and patient wish for an endoscopic option	Offer transoral incisionless fundoplication (TIF)
Refractory patients with ineffective esophageal motility	TIF or a modified (Toupet) fundoplication to avoid postoperative dysphagia
Patients with good symptom control who want to discontinue PPIs	LINX or NFS
Obese patients (BMI >35) with GERD	Bariatric surgery, with Roux-en-Y bypass preferred over adjustable gastric banding or sleeve gastrectomy
Source: [52; 59]	*Table 3*

Appropriate patient selection is essential for a positive outcome with this procedure, and the strongest predictors include abnormal acidic pH, symptoms of heartburn and regurgitation, and positive PPI trial [15; 222]. In practice, many common indications for NFS (e.g., PPI-refractory GERD symptoms/esophagitis, GERD medication intolerance, desire to discontinue PPIs, large hiatal hernia, PPI non-adherence) deviate from positive outcome predictors [8; 15]. PPI nonresponse is considered a predictor of unfavorable NFS outcomes but remains the most common indication [167]. Antireflux surgery does not lead to significant regression of Barrett esophagus or reduce the risk of esophageal adenocarcinoma [107].

Patients with GERD symptoms who are considered for NFS are recommended to undergo diagnostic confirmation beforehand. pH monitoring rules out functional heartburn, while HRM and barium swallow rule out other possible diagnoses [217].

In GERD with PPI nonresponse, NFS remains the most-studied treatment with the largest data on outcomes after 10 years. NFS can provide symptomatic and physiologic relief of acid reflux, including in patients with NERD and those without symptom/reflux event correlations [167; 223].

Unfortunately, efficacy wanes with time. Ten years after NFS, nearly 35% of patients experience recurrent heartburn and 30% experience regurgitation. Resumption of PPI use increases from 8.8% at 1 year to 18.2% at 10 years, and 9.6% of patients require surgical re-intervention within 10 years [224; 225; 226]. One study concluded as many as 50% patients who underwent NFS resumed PPI use 10 to 15 years post-surgery [227]. Only a minority of patients with GERD are offered a surgical option, mainly due to concerns over potential side effects, variable success rates, and the extreme alteration of gastric anatomy with NFS [221]. The potentially significant side-effect profile of NFS can negatively impact patient quality of life, and this has contributed to the declining popularity of this procedure, with fewer than 20,000 patients undergoing NFS annually. Clinicians may be wary of fundoplication due to significant side effects of dysphagia, gas-bloat syndrome, and inability to vomit [228; 229]. In typical patients with GERD and good symptom control using PPIs, some experts have concluded there appears to be no net benefit over PPI therapy to warrant the use of NFS [230; 231; 232].

MAGNETIC SPHINCTER AUGMENTATION

Magnetic sphincter augmentation (MSA), transoral incisionless fundoplication (TIF), and radiofrequency energy delivery (RFED) are emerging as alternatives to NFS. As with NFS, patient selection remains crucial.

MSA was designed to obviate many of the issues experienced with NFS. The LINX Reflux Management System is a flexible, expandable MSA device laparoscopically placed around the external gastroesophageal junction. The device augments LES function to prevent reflux into the esophagus, while allowing normal LES opening during swallowing, belching, and vomiting often prevented with fundoplication [233]. The LINX is FDA-approved for patients diagnosed with GERD, defined by abnormal pH testing, who continue having chronic GERD symptoms despite maximum PPI therapy [234].

The body of published evidence demonstrates that MSA is an effective alternative to NFS [167]. Compared with NFS, five-year MSA outcomes showed comparable esophageal acid exposure, heartburn, regurgitation, PPI use, quality-of-life scores, and dysphagia, and lower rates of bloating and inability to belch or vomit [167; 230]. MSA has the other advantages of being a less extensive surgical procedure, requiring minimally invasive removal, and less inter-surgeon variability with a standardized device. MSA is not indicated for patients with severe erosive disease, motility disorders, or large hiatal hernia (>3 cm) [167]. Negative predictors of excellent/good outcome with MSA include BMI >35, structurally defective LES, and elevated LES residual pressure [235].

TRANSORAL INCISIONLESS FUNDOPLICATION

TIF and the Medigus endoscopic stapling procedure avoid the risks of laparoscopic fundoplication by creating endoscopic fundoplications to correct anatomical defects of the LES. EsophyX, the only FDA-approved TIF, uses a 270-degree anterior wrap fundoplication. These procedures are limited to patients with normal anatomy, because hiatal hernia repair cannot be performed [58; 167; 230].

In PPI-responsive patients, TIF shows good long-term results up to six years, with lasting symptom relief, decreased reflux on pH-impedance monitoring, and reduced esophageal acid exposure. PPI use is slightly higher in TIF than with NFS or MSA, and symptom remission is lower than with NFS [58]. The longest follow-up in PPI nonresponsive patients is 22 months [167; 230]. In a meta-analysis that compared TIF to NFS, TIF was found to have the highest probability of increasing patients' health-related quality of life, whereas NFS had the highest probability of increasing percent time at pH <4. NFS also had the highest probability of increasing LES pressure. Although TIF is a minimally invasive procedure, the reviewers concluded that it could not be recommended as a long-term alternative to PPI or NFS treatment of GERD [236].

The ACG suggests consideration of transoral incisionless fundoplication (TIF) for patients with troublesome regurgitation or heartburn who do not wish to undergo antireflux surgery and who do not have severe reflux esophagitis (LA grade C or D) or hiatal hernias >2 cm.

(https://journals.lww.com/ajg/fulltext/2022/01000/acg_clinical_guideline_for_the_diagnosis_and.14.aspx. Last accessed September 9, 2024.)

Level of Evidence/Strength of Recommendation: Low/Conditional

RADIOFREQUENCY ENERGY DELIVERY

RFED to the LES via the Stretta system was introduced in 2000 as a minimally invasive endoscopic treatment for PPI-nonresponsive GERD [230]. Stretta delivers radiofrequency energy to a broad region of the LES, on the premise that postprocedure ablation scarring and fibrosis will increase LES tone. A systematic review evaluating the efficacy of Stretta in GERD found no difference between Stretta, sham treatment, or PPIs in time spent at pH <4, LES pressure, PPI cessation, or health-related quality of life [237]. Use of RFED has limited evidence support; MSA and TIF are better minimally invasive alternatives [167].

BARIATRIC SURGERY IN PATIENTS WITH GERD AND OBESITY

As discussed, obesity plays a major role in the development of GERD, and treating obesity is an important step in the treatment of GERD. While many studies show comparable outcomes with NFS across weight groups, other surgical options are recommended for obese patients with GERD [15; 52]. For patients with moderate obesity (BMI 35–40), LNF shows good symptom control and moderate weight loss. For patients with BMI >40, bariatric surgery with gastric bypass is preferred [58; 238].

Roux-en-Y gastric bypass (RYGB) remains the favored bariatric approach due to its benefit in GERD and long-term weight loss. Performed laparoscopically, RYGB involves creation of a small gastric pouch connected directly to the small intestine to bypass a major portion of the mid/distal stomach and duodenum [52]. A comparative study found laparoscopic RYGB as safe as fundoplication for morbidly obese patients. In-hospital complications were significantly lower in the bypass group, while the mean length of hospitalization, mortality, and treatment costs were comparable [239].

Bariatric surgery options are broadening for obese patients with GERD, including laparoscopic adjustable gastric banding (LAGB) and laparoscopic sleeve gastrectomy. However, there are growing concerns about side effects induced by these techniques. LAGB is associated with high rates of reoperation or conversion to more definitive bariatric surgery, band erosion, and motor dysfunction of the esophagus, stomach, and small bowel in obese patients with GERD, and is not recommended [16; 58; 240]. Sleeve gastrectomy is considered an effective weight-loss surgery but is consistently associated with new-onset reflux in non-GERD populations and worsening GERD symptoms when reflux is already present, and is not recommended in patients with GERD and obesity as a first-line option [15; 58]. The results of one study suggest that implementing a comprehensive protocol of foregut evaluation could objectively assess which procedure would best suit each individual patient [240].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving demographics in the United States, interaction with patients for whom English is not a native language is inevitable. It is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures is being provided, the use of an interpreter should be considered.

CONCLUSION

GERD is a far more complex clinical entity than is often appreciated, with impaired lower esophageal structure and function, not gastric acid over-secretion, the core pathology. Advances in characterizing GERD also show a diverse underlying pathology of symptom presentations and point to the need for a more tailored approach to diagnosis. PPI acid-suppressant medication is the backbone of GERD management, and an empiric PPI trial is a reasonable starting point for most patients. Patients who remain symptomatic require a diagnostic workup to identify the underlying cause of symptom persistence for effective therapeutic targeting. The importance of patient adherence with PPI therapy cannot be overstated. A range of medications and antireflux procedures are available for PPI-refractory patients.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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Evidence-Based Practice Recommendations Citations

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