

## Overview of Pathophysiology and Treatment in Gastro-Esophageal Reflux Disease

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### Abstract

GERD (gastro-esophageal reflux disease) is a common condition caused by reflux of stomach or duodenal contents proximally, more commonly into the lower esophagus; to cause symptoms of heartburn, nausea and lower chest pain. GERD is one of the most common gastrointestinal ailments worldwide; affecting the lives of millions worldwide. GERD is associated with older age, male gender, smoking, alcohol consumption, and hiatal hernia. Obesity is also known to be a risk factor for significant GERD.

Complications like esophagitis, stricture, and Barrett esophagus occur in over 50% of untreated individuals and long-standing reflux leading to Barrettes esophagus is a risk factor for development of esophageal adenocarcinoma.

Typically, GER is a malfunction of the lower esophageal sphincter, or the diaphragmatic component of the sphincter mechanism or relative alteration of the length of the abdominal esophagus. The resulting TLESR (transient lower esophageal sphincter relaxations); esophageal hypomotility resulting in lower clearance efficacy, and the quality of the refluxate determine the nature and severity of esophageal mucosal injury.

Determining the degree of injury and the mechanism of injury through upper GI endoscopy, 24-h esophageal pH monitoring; lower esophageal sphincter manometry; detecting the degree of bile reflux and the quantitative acid pocket in the distal esophagus help in the clinical management of GERD. The treatment of GER is often accomplished medically alone; but where indicated surgical treatment through anti-reflux surgery seems to be superior to medical management alone over many years. Patients merit treatment on an individualized basis and treatment needs to be adjusted according to clinical scenario, patient age, symptoms and the presence and absence of complication and structural abnormalities.

**Keywords:** GERD; Reflux; Barretts; Esophagitis; Hiatus Hernia; Manometry; Bile Reflux

### Introduction

Gastroesophageal reflux disease (GERD) is a chronic condition that arises from a backflow of gastroduodenal contents to the esophagus or duodenum to stomach, causing a variable range of symptoms and signs, which may be associated or not with tissue injury and almost always quality of life impairment. GERD is one of the most common gastrointestinal ailments worldwide; up to 40% of the US population report oesophageal symptoms intermittently and 10 - 20% have at least weekly symptoms. About 20 - 22% population in South Asia suffer from GERD.

The prevalence of GERD was found to be 22.2% in southern India and was more common among older subjects and men [1].

Typical GERD symptoms consist of heartburn with reflux, nausea, epigastric or lower sternal discomfort, and clinical diagnosis is made on the basis of typical symptoms, supported by symptom relief after PPI therapy [2]. Symptoms suggesting complications (for example, dysphagia, weight loss, anemia); atypical presentations (chest pain, laryngeal symptoms, respiratory symptoms or aspiration) and lack of response to empiric therapy prompt further evaluation with an upper GI endoscopy [3]. The clinical picture is generally characterized by heartburn and regurgitation, considered typical symptoms. Heartburn usually presents like a burning sensation on retrosternal portion that radiates from the sternal manubrium to the base of the neck, can reach the throat and/or acid regurgitation or sour brash. Stress is widely recognized as a negative factor for heartburn, most likely for an amplifying effect of the symptom instead of gastroesophageal reflux increase [4].

Some patients report dyspepsia associated symptoms like postprandial bloating or discomfort, gastric fullness, belching and nausea or the desire to vomit. If the patient presents to the doctor with typical symptoms at least two times per week in a four to eight weeks period or more, a diagnosis of GERD is more likely.

Previous studies have reported positive associations between GERD and older age, male gender, smoking, alcohol consumption, and hiatal hernia [5]. Obesity is also known to be a risk factor for significant GERD. Further evidences have demonstrated that abdominal obesity, which is the core component of metabolic syndrome, may be a stronger predictor of GERD than obesity [6,7]. A retrospective case-control study in China found a high waist-hip ratio, hyperglycemia, hypertriglyceridemia, and metabolic syndrome were risk factors for reflux and GERD, and that HDL-C was associated with a reduced risk of GERD and reflux esophagitis in men [8].

### Anatomy and physiology

The esophagus is a muscular tube that originates from endoderm (gut), 25 - 28 cm long, approximately 2 cm in diameter, located between lower border of laryngopharynx and cardia of stomach. The gastroesophageal junction corresponds to xiphoid process of sternum. Five cm of esophagus is in the neck, and it descends over superior mediastinum and posterior mediastinum approximately 17 - 18 cm, continues for 1 - 1.5 cm in diaphragm, ending with 2 - 3 cm of esophagus in abdomen [9]. Sex, age, physical condition, and gender affect the length of esophagus. A newborn's esophagus is 18 cm long, and it begins and ends one or two vertebra higher than in adult. Esophagus lengthens to 22 cm long by age 3 years and to 27 cm by age 10 years [10].

The gastroesophageal junction is a complex valve composed of a smooth muscle element (LES) and a diaphragmatic element. These normally supplement each other to maintain competence in a static condition and during dynamic stresses associated with increased intra-abdominal pressure or swallowing. These sphincteric components also interact with each other pathophysiologically [11]. During swallowing, large hernias impair the process of esophageal emptying, thereby prolonging acid clearance. The susceptibility to stress reflux inherent during periods of diminished LES pressure is also dramatically increased by disabling the diaphragmatic sphincter. These functional impairments of the gastroesophageal junction associated with hiatus hernia lead to increased esophageal acid exposure and offer one explanation for the chronicity of reflux disease. The gastroesophageal region is subjected to a double conflict in functional terms. One is a dynamic conflict between two organs in terms of movement-the diaphragm with respiratory movements and the esophagus with peristaltic movements secondary to swallowing. This mobility implies the existence of a gliding mechanism between the esophagus and the crura of the diaphragm. The other is a conflict of pressure. The region of the cardia is in a frontier zone between the positive pressure of the abdominal cavity and the negative pressure of the thoracic cavity. This gradient of abdomino-thoracic pressure tends to cause an ascent of gastric fluid toward the esophagus and an ascent of the cardia through the diaphragmatic orifice.

The discovery of a zone of high pressure at the lower part of the esophagus reflected the presence of a true physiologic lower esophageal sphincter; (LES) that regulates precisely and predominantly the function of this region. Anatomists have been interested in describing the structures supporting the cardia in the abdomen, and Surgeons have promoted techniques based on the principle of construction of a valve that will have the role of an extrinsic sphincter around the esophagus.

The distal thoracic esophagus is located on the left side of midline. As the thoracic esophagus enters the abdomen through the esophageal opening, i.e. hiatus in the diaphragm, it becomes the abdominal esophagus. The hiatus is formed principally by the right crus of the diaphragm, which forms a sling around the esophagus with the right and left pillars, so that the esophagus narrows when the diaphragm contracts. The actual contribution the diaphragm provides in maintaining an adequate length of intra-abdominal esophagus is not clearly understood; however, careful identification and approximation of the pillars during surgical treatment is crucial for preventing recurrence of reflux disease.

At this level, the phreno-esophageal membrane, which is the reflection of the sub-diaphragmatic fascia onto the transversalis fascia of the anterior abdominal wall, also encircles the esophagus. The oesophago-gastric (O-G junction) junction lies in the abdomen and forms the angle of his between the long axis of the esophagus and the greater curvature of the stomach. The acute angle and the length of abdominal esophagus both contribute to the normal closure of the esophagus when intra-gastric and intra-abdominal pressures are high.

The lower esophageal sphincter i.e. the distal esophageal high-pressure zone (HPZ)-is the distal most segment of the esophagus (3 - 5 cm in adults) and can be anywhere from 2 - 5 cm in length. Maintenance of an adequate intra-abdominal HPZ is crucial in preventing GERD [12]. This HPZ does not correspond to any visible anatomic structure. It is a zone created by a complex architecture of smooth muscle fibers, and it is typically identified during manometry.

Usually, GERD is caused by a malfunction of one or more of these anatomic features.

### Clinical findings

Gastroesophageal reflux disease (GERD) is associated with a set of typical (esophageal) symptoms, including heartburn, regurgitation, and dysphagia. GERD can also cause atypical (extra-esophageal) symptoms, such as coughing, chest pain, and wheezing. Patients with GERD may also experience symptoms suggesting complications like esophagitis, stricture, and Barrett esophagus. Approximately 50% of patients with gastric reflux develop esophagitis.

Coughing and/or wheezing are respiratory symptoms resulting from the aspiration of gastric contents into the tracheobronchial tree or from the vagal reflex arc producing bronchoconstriction. Approximately 50% of patients who have GERD-induced asthma do not experience heartburn. Hoarseness results from irritation of the vocal cords by gastric refluxate and is often experienced by patients in the morning.

Reflux is the most common cause of non-cardiac chest pain, accounting for approximately 50% of cases. Patients can present to the emergency department with pain resembling a myocardial infarction. Reflux should be ruled out (using esophageal manometry and 24-hour pH testing if necessary) once a cardiac cause for the chest pain has been excluded. Alternatively, a therapeutic trial of a high-dose proton pump inhibitor (PPI) can be tried.

Additional atypical symptoms from abnormal reflux include damage to the lungs (e.g. pneumonia, asthma, idiopathic pulmonary fibrosis), vocal cords (e.g. laryngitis, cancer), ear (e.g. otitis media), and teeth (e.g. enamel decay).

### Mechanisms

- 1. Ineffective esophago-gastric junction (EGJ) barrier:** Hiatus hernia and transient lower esophageal sphincter relaxation (TLESR) are the commonest abnormalities seen in patients with GERD. Excessive reflux during TLESRs is the most common EGJ event seen in patients with GERD [13]. High-resolution manometry (HRM) criteria for TLESRs include profound EGJ relaxation of > 10s in the absence of swallowing [14], with inhibition of crural diaphragm contraction. TLESRs are not routinely evaluated on oesophageal manometry and are often missed of routine evaluation. The intrinsic LES can independently have a low resting tone, with values < 5 mmHg during the end expiratory phase being considered abnormal [15]. In the presence of a hiatus hernia, the resting tone of the intrinsic LES is typically hypotensive, with oesophageal reflux burden higher than with either weaker LES or with defective inspiratory crural diaphragm augmentation.
- 2. Oesophageal hypomotility:** When a reflux episode occurs, the refluxate is cleared rapidly by esophageal peristalsis. The spectrum of hypomotility consists of fragmented peristalsis, ineffective oesophageal motility and absent contractility, with increased prevalence of abnormal oesophageal bolus clearance [16].
- 3. Refluxate quality:** Delayed gastric emptying and acid hyper-secretory states, such as in gastrin-secreting tumours (gastrinomas), contribute to oesophageal reflux burden. Acid and other components of the refluxate (pepsin, bile acid) can participate in mucosal damage and in complications including Barrett metaplasia [17].

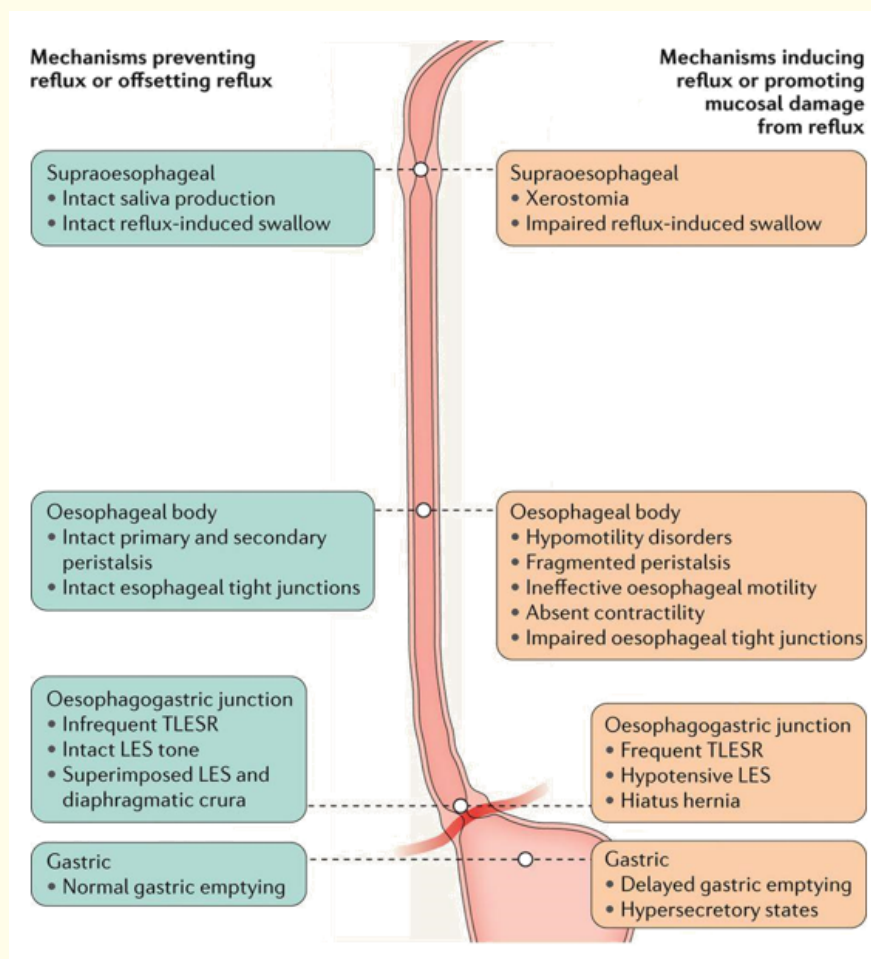


Figure 1

### Work-up and investigation

Mandatory studies include upper GI endoscopy (UGIE) and manometry.

**Endoscopy:** Endoscopy can help confirm the diagnosis of reflux by demonstrating complications of reflux (esophagitis, strictures, Barrett esophagus) and can help in evaluating the anatomy (e.g. hiatal hernia, masses, strictures). Although UGIE is frequently performed to help diagnose GERD, it is not the most cost-effective diagnostic study, because esophagitis is absent in half the patients with GERD.

**Esophageal manometry:** Defines the function of the LES and the esophageal body (peristalsis). Manometry identifies the strength of peristalsis, the timing and duration of TLESRs and esophageal clearance. Indications for esophageal manometry and prolonged pH monitoring include the following:

- Persistence of symptoms while taking adequate PPI therapy.
- Recurrence of symptoms after discontinuation of acid-reducing medications.
- Investigation of atypical symptoms, such as chest pain or asthma, in patients without esophagitis.
- Confirmation of the diagnosis in preparation for anti-reflux surgery.

**Ambulatory 24-hour pH monitoring:** Is the gold standard in establishing a diagnosis of GERD, with a sensitivity of 96% and a specificity of 95% [18]. It quantifies the gastroesophageal reflux and allows a correlation between the symptoms of reflux and the episodes of reflux. However, patients with endoscopically confirmed esophagitis do not need pH monitoring to establish a diagnosis of GERD. But, there are concerns about sensitivity, highlighted by the observation that as many as 23% of patients with endoscopically detected oesophagitis may demonstrate values that fall within the normal range [19].

The problems of pH monitoring are multifactorial in origin; i.e. reduced patient physical and dietary activity during the recording period owing to nasal and pharyngeal irritation of the pH catheter, day-to-day variability in acid exposure, and problems of appropriate pH electrode positioning in the oesophagus. Reflux of bile, pancreatic enzyme and non-acidic gastric contents are events that are not detected by conventional pH monitoring. Variability in intrinsic host susceptibility to both visceral sensation and mucosal injury in response to reflux events would also affect the sensitivity and specificity of pH monitoring. Issues of patient discomfort leading to limitation in dietary and physical activity during conventional ambulatory pH monitoring have been reported in recent studies. Catheter displacement, either by physiological causes or by improper placement of the probe, may lead to potential problems with test accuracy with conventional 24-h pH monitoring.

### **Bilitec: how important is bile reflux in GERD pathogenesis?**

Duodenogastro-oesophageal reflux (DGER) or bile reflux in GERD pathology has been the subject of numerous investigations and has re-emerged as a topic of recent studies. DGER is currently best detected using the Bilitec 2000 recorder (Medtronic, Inc.), which spectrophotometrically detects bilirubin in DGER. In one study in 1996, Vaezi, *et al.* found that as the severity of disease increased, the prevalence of mixed bile and acid reflux also increased, occurring in 50% of patients with NERD (non-erosive reflux disease), 79% of patients with EE (erosive esophagitis), 89% of patients with uncomplicated BE (Barrett's esophagus) and 100% of patients with complicated BE [20]. DGER occurs more often in patients with esophagitis and Barrett's, and that the reflux of acid parallels duodeno-gastric reflux. Overall, DGER alone is an infrequent cause of GERD [20] and treatment with common proton pump inhibitors has been shown to decrease not only acid reflux, but DGER as well. DGER in the absence of acid reflux has also been shown to produce symptoms; yet symptoms are more often related to acid reflux than to bile reflux [21]. Bile reflux may play a role in patients who continue to remain symptomatic while taking PPI therapy and that the reduction of pathological DGER may reduce PPI-refractory symptoms in patients with normalized esophageal acid exposure [22].

**Bravo capsule pH monitoring system:** The Bravo capsule is affixed to the trans-nasal mucosa, it avoids the issues surrounding proximal or distal catheter displacement. The absence of the trans-nasal catheter also improves patient tolerability and compliance with normal physical and dietary activities. It allows for a 48 hour prolonged pH monitoring and therefore improves diagnostic accuracy [15]. Dual pH monitoring showed that oesophageal refluxate after meals was often more acidic than contents in the body of the stomach. This layer post-prandial is significantly more acidic compared with the contents of the rest of the stomach (median pH = 1.6 vs. pH = 4.7) and extends from the gastric cardia 1.8 cm into the distal oesophagus. This acid pocket may explain the prevalence of oesophageal erosions as well as intestinal metaplasia in this area [23].

**Imaging:** Chest x-rays may demonstrate a large hiatal hernia, but contrast or double contrast x-rays have a better diagnostic yield. Single-contrast techniques are more sensitive for structural defects such as hiatal hernias and strictures or esophageal rings [24].

**Gastroesophageal reflux scintigraphy:** Is much more commonly used in infants and children due to the noninvasive nature of the study and relatively low radiation dose. In infants and children, the study is often performed with labeled milk. In addition to evaluating the degree of reflux, pulmonary aspiration can be detected by imaging over the lungs.

**Intraluminal esophageal electrical impedance:** (EEI) a newer test, is useful for detecting both acid reflux and nonacid reflux by measuring retrograde flow in the esophagus. EEI monitoring may help improve the accuracy of the symptom intensity in GERD, because it detects all episodes of reflux regardless of acid content.

### Treatment

Approximately 80% of patients have a recurrent but non-progressive form of GERD that is controlled with medications alone. Identifying the 20% of patients who have a progressive form of the disease is important, because they may develop severe complications, such as strictures or Barrett esophagus and predisposing to malignant change and adenocarcinoma of the GE junction. For patients who develop complications, surgical treatment should be considered at an earlier stage to avoid the sequelae of the disease that can have serious consequences.

Lifestyle modification, including modification of diet and exercise patterns help in a majority of patients [18]. Lifestyle modifications include losing weight (if overweight); avoiding alcohol, chocolate, citrus juice, and tomato-based products, peppermint, coffee, and possibly the onion family; avoiding large meals, avoiding lying down 3 hours after a meal and elevating the head of the bed by 8 inches.

### Pharmacotherapy

Antacids, H<sub>2</sub> receptor antagonists and proton pump inhibitors (PPI) are the drugs used for symptom relief in GERD. Antacids are useful for mild symptoms and rapid relief in severe symptoms. They should be taken after each meal and at bedtime.

**H<sub>2</sub> receptor antagonists:** Are effective for healing only mild esophagitis in 70 - 80% of patients with GERD and for providing maintenance therapy to prevent relapse. Tachyphylaxis has been observed, suggesting that pharmacologic tolerance can reduce the long-term efficacy of these drugs.

**PPIs:** Have few adverse effects and are well tolerated in long-term use. But, PPIs can interfere with calcium homeostasis and aggravate cardiac conduction defects. In clinical trials, the most commonly reported adverse reactions to rabeprazole were sore throat, flatulence, infection, and constipation in adults, and abdominal pain, diarrhea, and headache in adolescents [25]. PPIs were superior to H<sub>2</sub> receptor antagonists for the resolution of GERD symptoms at 4 weeks and healing of esophagitis at 8 weeks [26].

**Prokinetics:** Prokinetics like Metoclopramide, Levosulpiride and Domperidone augment gastric emptying, avert retention and reflux of acid or food and relieve symptoms of dyspepsia. Another class of prokinetics are serotonergic agents (e.g. cisapride, mosapride). Domperidone and Levosulpiride have both antiemetic and prokinetic properties since they antagonize dopamine receptors in the central nervous system as well as in the gastrointestinal tract where dopamine apply compelling inhibitory effects on motility [27]. Prokinetics are reported to be considerably superior to placebo (relative risk reduction, 40%). Levosulpiride, Domperidone and Metoclopramide are all effective in improving dyspeptic symptoms. However, the overall dyspeptic symptom relief rates are significantly higher in the Levosulpiride and more consistent [28].

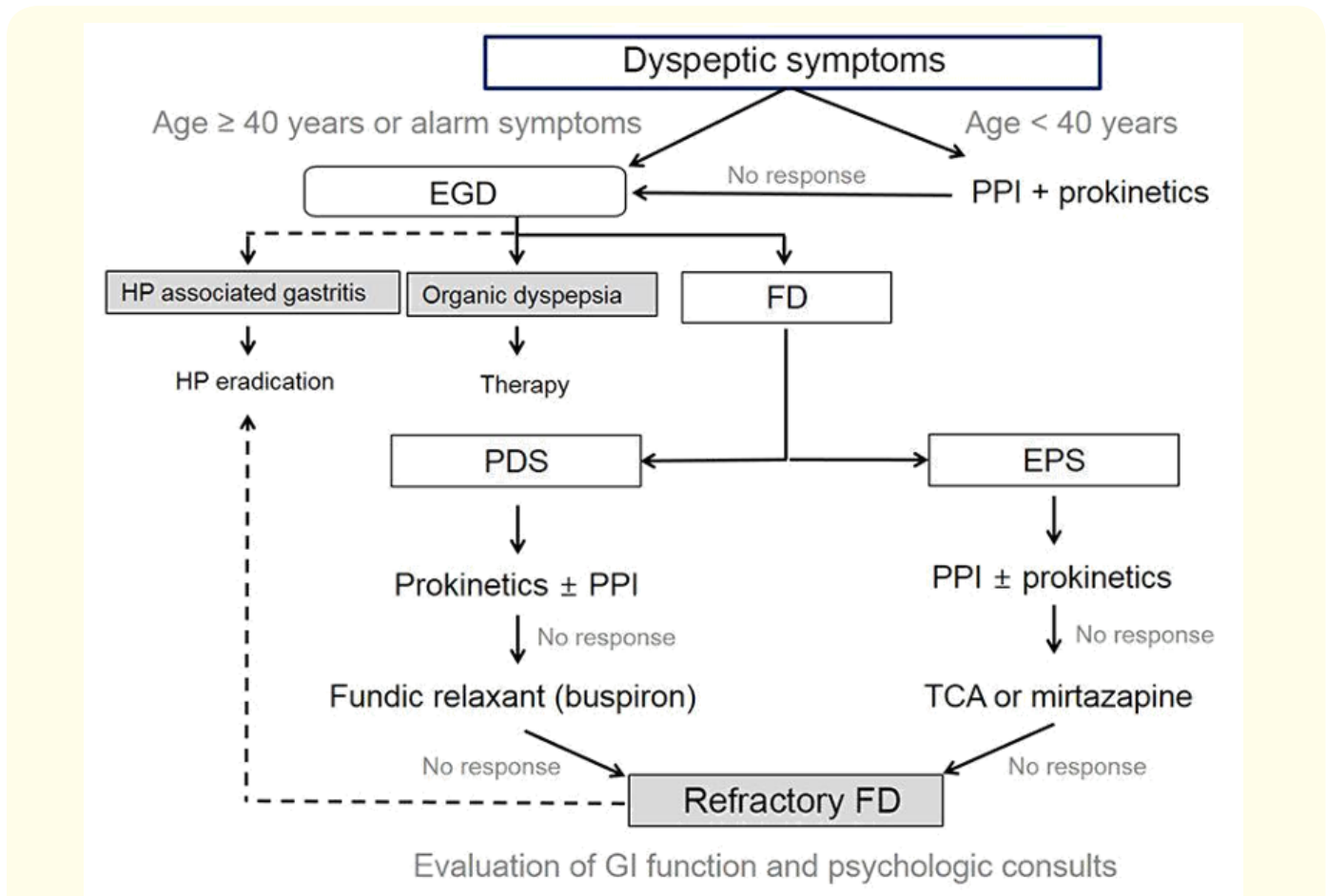
### Surgical therapy

Currently accepted indications for surgical treatment of GERD include the following:

- Patients with symptoms that are not completely controlled by PPI therapy.
- Patients with well-controlled GERD who desire definitive, one-time treatment.
- The presence of Barrett esophagus is an indication for surgery (whether acid suppression improves the outcome or prevents the progression of Barrett esophagus remains unknown, but most authorities recommend complete acid suppression in patients with histologically proven Barrett esophagus).
- The presence of extraesophageal manifestations of GERD may indicate the need for surgery; respiratory manifestations (e.g. cough, wheezing, aspiration); throat manifestations (e.g. hoarseness, sore throat, otitis media); and dental manifestations (e.g. enamel erosion).
- Young patients.
- Poor patient compliance with regard to medications.
- Postmenopausal women with osteoporosis-relative contraindication to long term PPI. Patients with cardiac conduction defects - adverse effects of medication related.
- Cost of medical therapy.

Several randomized clinical trials have challenged the benefits of surgery as compared to PPIs, whereas many found that more than half the operated patients were back on PPIs 10y after surgery [29,30].

Anvari, *et al.* reestablished surgery as the criterion standard in treating GERD and showed that, at 1 year, the outcome and the symptom control in the surgical group was better than that in the medical group [31]. Long-term results of laparoscopic anti-reflux surgery have shown that, at 10 years, 90% of patients are symptom free and only a minority still take PPIs [32]. Long-term follow-up results from a multicenter, randomized trial showed that, relative to pharmacotherapy, fundoplication maintained better symptomatic relief in the management of gastroesophageal reflux disease without evidence of long-term postsurgical adverse symptoms [33].



**Figure 2:** Algorithm for functional dyspepsia/GERD. [EGD: Esophagogastroduodenoscopy; PPI: Proton Pump Inhibitor; HP: Helicobacter pylori; FD: Functional Dyspepsia; PDS: Postprandial Distress Syndrome; EPS: Epigastric Pain Syndrome; TCA: Tricyclic Antidepressant; GI: Gastrointestinal].

### Practice guideline for surgical treatment of gastroesophageal reflux disease [34]:

1. Anti-reflux surgery is recommended to patients with GERD for its symptomatic relief, ability to increase quality of life, superior long-term outcomes, and cost-effectiveness.
2. Anti-reflux surgery could be considered for a substantial proportion of patients showing an inadequate response to PPI therapy. Thorough examinations for the differential diagnosis and careful patient selection should be performed in those patients prior to the anti-reflux surgery.
3. Anti-reflux surgery is recommended for gastroesophageal reflux patients with extraesophageal manifestations.
4. Partial fundoplication and total fundoplication are comparably effective at treating GERD.
5. Fundoplication in addition to PEH (para-esophageal hernia) repair is recommended to decrease the risk of postoperative gastroesophageal reflux and esophagitis.

### Conclusion

The management of reflux disease can be complex, involving multiple avenues of trial and error, from lifestyle modifications to medication therapy. PPI therapy can be successful for some, but often does not provide complete resolution of symptoms. Long-term PPI therapy may run the risk for serious side effects and needless expense. The brain-gut connection may be important in explaining non-PPI responders. Given that the goal of treatment is managing symptoms, patient-physician communication is important. A disparity between patients and providers regarding GERD management can also impact patient satisfaction. This necessitates understanding and validating a patient's perspectives and values pertaining to his or her illness and choices.

Understanding mechanisms of pathological acid reflux in terms of abnormalities of oesophageal and oesophagogastric junction structure and function, including the acid pocket will help us in understanding GERD better. Clarification as to whether pathological acid reflux is the cause of abnormal oesophageal motor function, or if reflux is the consequence of abnormal motor function in GERD is still a matter of debate. The importance of oesophageal sensitivity as a mechanism for GERD symptom reporting and a potential target for treatment is something that will need delving into.

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