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GERD – Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) is defined by its cardinal symptoms (recurrent and troublesome heartburn and regurgitation) or by its specific complications (esophagitis, peptic strictures, and Barrett´s esophagus). Barrett´s esophagus is a columnar metaplasia replacing parts of the native squamous cell epithelium that can progress to esophageal adenocarcinoma. GERD can be a serious problem and should not be confused with less severe disease such as gastritis or the very common symptoms of dyspepsia or regurgitation that occur in almost all individuals without any underlying gastrointestinal pathology. GERD is caused by gastric contents' reaching the esophagus. Except for causing esophageal symptoms or complications, gastric juices can also reach more proximally (ie, into the pharynx, mouth, larynx, and airways) and cause or worsen various extraesophageal symptoms and conditions such as hoarseness, wheezing, cough, and asthma. Established risk factors for developing GERD include increased body mass index, tobacco smoking, and genetic predisposition, whereas infection with the gastric bacterium Helicobacter pylori can decrease this risk. The prevalence of GERD is high and increasing, with greater rates in high-income countries (15%-25%) than in most low- and middle-income countries (<10%).

Pathophysiology

GERD involves dysfunction in the esophagogastric junction barrier, including loss of effective lower esophageal sphincter function, allowing increased regurgitation of acidic gastric contents into the esophagus. Transient lower esophageal sphincter relaxation is a normal physiologic response to gastric distention that facilitates belching but can contribute to GERD if the relaxations are frequent and prolonged. A sliding hiatal hernia (i.e. in which a portion of the proximal stomach has herniated through the diaphragm and is located in the thoracic cavity) is a common anatomic configuration that facilitates reflux by increasing the angulation between the gastroesophageal junction and the gastric fundus, reducing the valve function.

Occurrence

The prevalence of GERD is age dependent. Nearly 50% of newborn infants regurgitate or vomit daily, but this resolves spontaneously in 90% of children by aged 1 year. After that, the prevalence of GERD again increases with age, and by adolescence, its prevalence approaches that of adults. In adults, the prevalence further increases with older age, and according to some trials is a prevalence among individuals younger than 50 years 14% and among those aged 50 years or older 17.3%.

Etiology

Increasing body mass index from normal to obese is associated with increased risk of developing GERD. Prevalence of GERD of 22.1% among obese individuals compared with 14.2% among nonobese ones. Increased intra-abdominal pressure, a higher prevalence of hiatal hernia, higher gradient of abdominal to thoracic pressure, increased levels of estrogen, and increased production of bile and pancreatic enzymes may contribute to the association between obesity and GERD. An association between tobacco smoking and GERD is also well documented. Tobacco can prolong acid clearance time of the esophagus and reduce the pressure in the lower esophageal sphincter. The third well-established risk factor is genetic predisposition. Infection with H pylori may prevent GERD by causing atrophy of the gastric mucosa, which can decrease the acid production of the parietal cells. Alcohol consumption and dietary factors (fatty, sour, spicy food, tomatoes, chocolate, mint, coffee) might precipitate episodes of like symptoms in individuals with known GERD by increasing the acidity, but these exposures have not been associated with the development of GERD.

Clinical Presentation

The cardinal symptoms of GERD are heartburn and acid regurgitation, but chest pain is also common. Less common symptoms, often denoted as atypical, include dysphagia, bleeding, chronic cough, asthma, chronic laryngitis, hoarseness, teeth erosions, belching, and bloating. Patients with GERD symptoms combined with warning symptoms of malignancy such as progressive dysphagia, involuntary weight loss, or bleeding should undergo upper gastrointestinal endoscopy. Patients who do not respond to an empirical medical treatment trial with a proton pump inhibitor (PPI) of standard dose once daily should also be considered for endoscopy. Endoscopy can reveal malignancy, complications of GERD (eg, erosive esophagitis, esophageal strictures, Barrett´s esophagus), and other explanations for the symptoms.

Assessment and Diagnosis

Proposed clinical management algorithm for patients with suspected GERD is shown below. A thorough medical history can help determine the differential diagnoses for patients presenting with GERD-like symptoms. Symptoms resembling GERD are common and are not always caused by it. It is important to make careful differential diagnosis, especially in patients with a history of chest pain. In patients with typical heartburn and acid regurgitation, a presumptive diagnosis of GERD can be made and a trial treatment with a PPI initiated. Endoscopy, esophageal manometry, and esophageal pH monitoring are indicated if the patient does not respond to empirical PPI treatment and the diagnosis of GERD remains likely but needs to be further investigated to rule out other possible causes for the symptoms.

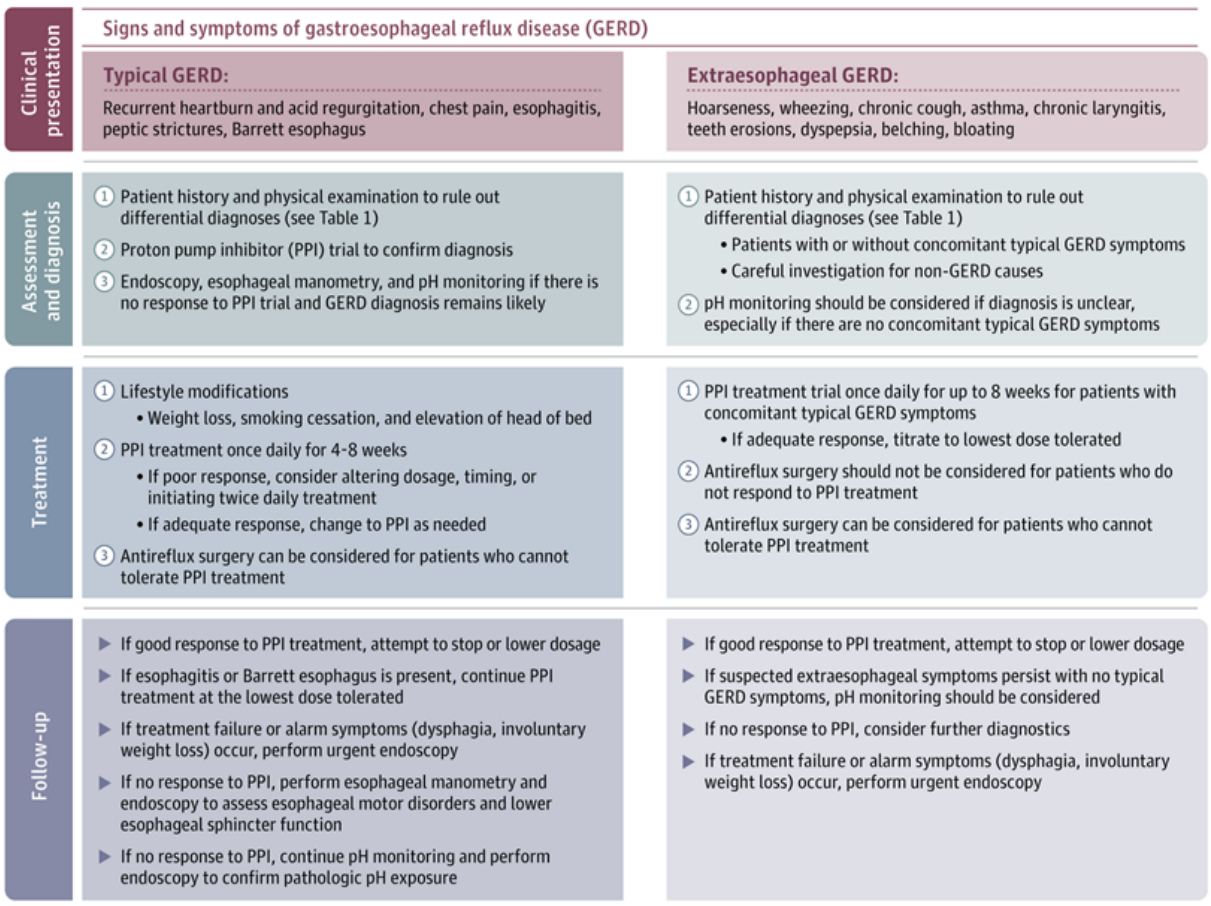


Table 1. Differential Diagnoses to Be Considered in the Evaluation of a Patient With Suspected Gastroesophageal Reflux Disease

Differential diagnosis	Main symptoms	Main diagnostic tool
Coronary heart disease	Chest pain, particularly when triggered by effort	ECG, blood tests such as for troponin level, exercise stress test with ECG
Gastrointestinal malignancy	Eating difficulties, weight loss, vomiting	Endoscopy
Peptic ulcer disease	Epigastric pain, nausea, vomiting	Endoscopy
Biliary tract disease	Abdominal pain, jaundice	Ultrasonography, blood tests
Eosinophilic esophagitis	Swallowing difficulties with hooking, reflux symptoms	Endoscopy
Achalasia or other upper gastrointestinal motility disorders	Swallowing difficulties, vomiting of undigested food	Esophageal manometry

Abbreviation: ECG, electrocardiography.

Consequences of GERD

Esophagitis

The most common complication of GERD is esophagitis, an inflammation of the mucosa of the distal esophagus that causes erosions and occurs in 18% to 25% of patients with GERD symptoms. Erosive reflux esophagitis can be associated with typical symptoms of GERD, but may also be asymptomatic. Esophagitis is detected at endoscopy and graded according to the Los Angeles classification. Patients with esophagitis should be treated with long-term PPIs because discontinuation often leads to recurrence, but once clinically effective, the dose should be titrated to the lowest daily one tolerated.

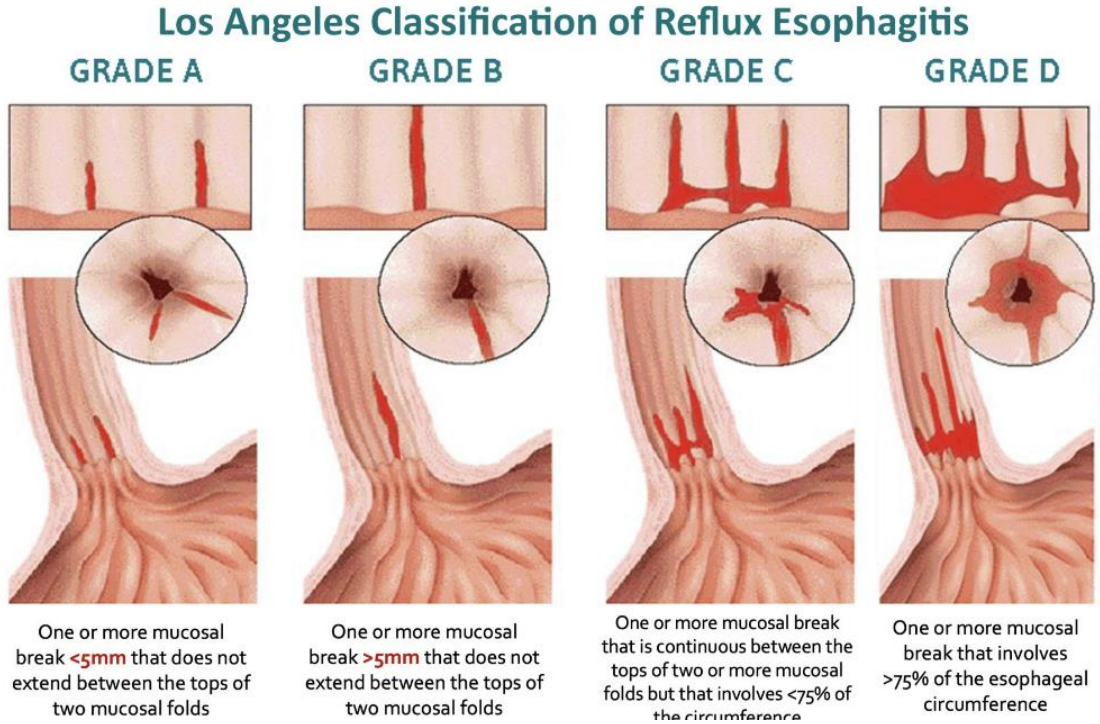
Stricture

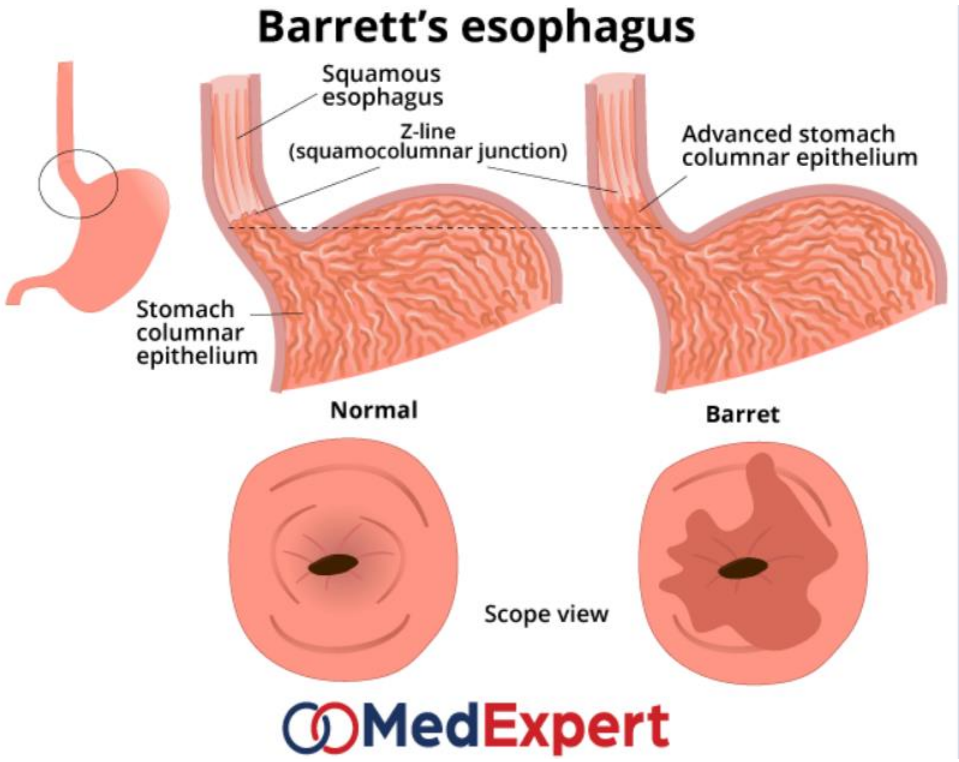
Peptic esophageal strictures can occur if the acidic exposure to the esophagus results in fibrotic scarring. The incidence of peptic strictures is 7% to 23% in untreated patients with erosive esophagitis. Patients with esophageal stricture often present with dysphagia. The treatment includes continuous long-term PPI therapy, combined with endoscopic balloon dilatation, which might need to be repeated and which successfully resolves esophageal strictures in more than 80% of patients.

Barrett´s Esophagus

Barrett´s esophagus represents the end result of metaplastic conversion of normal squamous epithelium of the esophagus to columnar epithelium. BE presents on endoscopy as characteristic salmon-pink colored extensions (or “tongues”) of mucosa that grow into the esophagus above the esophageal gastric junction. BE is the precursor lesion to esophageal adenocarcinoma. A meta-analysis of 42 studies and 26 521 individuals with GERD found a pooled prevalence of Barrett´s esophagus in 7.2%, including 13.9% with dysplasia, with more than 80% of patients having low-grade dysplasia. The absolute risk of esophageal adenocarcinoma is low in nondysplastic Barrett´s esophagus, but considerably higher in the

presence of dysplasia. Main risk factors for tumor progression are older age, male sex, tobacco smoking, longer segment of the Barrett´s mucosa, and central obesity. Patients with Barrett´s esophagus should be treated with continuous PPI treatment. For patients with high-grade dysplasia and in some cases low-grade dysplasia, endoscopic removal of Barrett´s t mucosa is the recommended treatment.





Esophageal Adenocarcinoma

GERD is, through development of Barrett´s esophagus, associated with esophageal adenocarcinoma. The incidence of esophageal adenocarcinoma has increased rapidly during the last 4 decades, particularly in Western countries, with a global incidence rate of 1.1 cases per 100 000 person-years among men and 0.3 per 100 000 person-years among women, and less than 20% of patients survive for 5 years. The primary risk factors for esophageal adenocarcinoma include GERD, male sex, advancing age, white race, obesity and tobacco use. Patients with long-standing reflux symptoms, nocturnal symptoms or more frequent symptoms are at higher risk.

Risk factors of esophageal squamous cell carcinoma (SCC) are slightly different. The primary risk factors for developing esophageal SCC include black and Asiatic race, smoking, alcohol, genetic factors, consummation of tea, mate and coffee (depending of amount consumed and temperature).

Treatment

Lifestyle Changes

Lifestyle changes can reduce GERD symptoms, primarily weight loss in obese patients and tobacco smoking cessation in smokers. In the presence of nocturnal GERD, particularly regurgitation, elevation of the head of the bed and avoiding late meals (at least 2 hours before sleeping) are recommended. Exclusion of food specific items (alcohol, spicy, sour and fatty food, chocolate, mint, coffee) is recommended, whereas alkaline water and a Mediterranean diet can be beneficial.

Medication

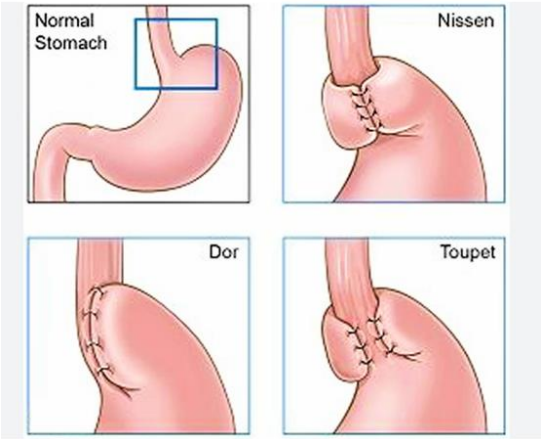
PPI use is the most effective pharmacologic treatment of GERD symptoms and healing of erosive esophagitis. PPIs irreversibly inhibit hydrogen-potassium ATPase in the parietal cells of the stomach, reducing the acidity of the gastric contents, and usually alleviate GERD symptoms. PPI is one of the most commonly prescribed medications, used by an estimated 7% to 9% of all adults. Current clinical guidelines support an initial trial treatment period of once-daily PPI of standard dose for 4 weeks in patients with typical GERD symptoms and a treatment period of 8 weeks for healing of endoscopy-verified erosive esophagitis. If this treatment is successful, the patient should receive PPI of the lowest effective maintenance dose, provided that continued medication is considered necessary for a longer period. Patients with typical GERD symptoms can often begin receiving on-demand or intermittent PPI treatment, whereas those with known esophagitis or Barrett´s esophagus should continue once-daily PPI even in the absence of symptoms because of the risk of recurrence of esophagitis or tumor progression, respectively.

An alternative to PPI as maintenance therapy for GERD is histamine2 receptor antagonists, the GERD medication of choice before the introduction of PPIs. Histamine2 receptor antagonists block the histamine receptors in the parietal cells of the stomach, thereby reducing the production of acid and often offering reasonable symptom control. Another medical treatment option is antacids (e.g. magnesium hydroxide), which neutralize stomach acidity.

Surgery

The most commonly performed surgical procedure for GERD is laparoscopic partial or total fundoplication, which enhances the esophagogastric junction’s ability to prevent reflux into the esophagus. Fundoplication may be considered in select patients with low surgical risks and objectively confirmed GERD. According to some trials comparing the PPI with laparoscopic fundoplication is

remission similar in the medication group and surgery group but patients complained about worse symptoms of acid regurgitation in the medication group compared with the surgery group. Recurrent GERD-like symptoms after GERD surgery can be caused by the patient's not having a proper indication for the initial antireflux surgery, an incomplete preoperative evaluation, or inadequate surgical technique.



Types of fundoplication.

Endoscopic methods to remove Barrett´s esophagus

Endoscopic resection of visible lesions if any, followed by ablation of the rest of the BE epithelium is the current standard of care for management of BE with confirmed dysplasia. Amongst the ablation modalities, photodynamic therapy, argon plasma coagulation, cryotherapy and radiofrequency ablation (RFA) have been developed. RFA is the most widely used modality currently. The underlying principle behind the ablation therapies is that under conditions of maximal acid suppression, injury to BE mucosa leads to regeneration of normal squamous mucosa.

Another endoscopic approach used for the eradication of BE involves resection techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The advantage of ESD over EMR lies in its ability to resect lesions en bloc that are larger than 15 mm.

Management of esophageal carcinoma

Endoscopic resection methods with complete excision of a mucosal carcinoma is recommended for superficially invasive adenocarcinoma. The resection can be performed as an endoscopic mucosal resection or as an endoscopic submucosal dissection.

Invasion into the submucosa, especially the deep submucosa, is associated with an increased rate of lymph node involvement, making endoscopic therapy a suboptimal approach in the good surgical candidate. For patients with T1b tumors (submucosal invasion), esophagectomy may be employed as a sole therapeutic modality. For patients with locally advanced disease without distant metastases, the most common treatment is neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy in patients who are candidates for surgery. For those with distant metastatic disease, definitive CRT is often used. In patients with local advanced disease, as well as those with distant metastases, endoscopic therapy (balloon dilatation or metallic stent insertion) can offer significant palliation of dysphagia and improve oral intake.

Peptic ulcer disease

The peptic ulcer disease (PUD) mechanism results from an imbalance between gastric mucosal protective and destructive factors. Risk factors predisposing to the development of PUD are Helicobacter pylori infection, non-steroidal anti-inflammatory drugs (NSAID) use, first-degree relative with PUD, lower socioeconomic status, African American/Hispanic ethnicity.

With peptic ulcers, there is usually a defect in the mucosa that extends to the muscularis mucosa. Once the protective superficial mucosal layer is damaged, the inner layers are susceptible to acidity. Further, the ability of the mucosal cells to secrete bicarbonate is compromised.

H. pylori is a gram-negative bacillus that is found within the gastric epithelial cells. This bacterium is responsible for 90% of duodenal ulcers and 70% to 90% of gastric ulcers. H. pylori infection is more prevalent among those with lower socioeconomic status and is commonly acquired during childhood. H. pylori is known to colonize the gastric mucosa and causes inflammation. The H. pylori also impairs the secretion of bicarbonate, promoting the development of acidity and gastric metaplasia.

NSAID use is the second most common cause of PUD after H. pylori infection. The secretion of prostaglandin normally protects the gastric mucosa. NSAIDs block prostaglandin synthesis by inhibiting the COX-1 enzyme, resulting in decreased gastric mucus and bicarbonate production and a decrease in mucosal blood flow.

Apart from NSAIDs, corticosteroids, bisphosphonates, potassium chloride, and fluorouracil have been implicated in the etiology of PUD.

Smoking also appears to play a role in duodenal ulcers, but the correlation is not linear. Alcohol can irritate the gastric mucosa and induce acidity.

Signs and symptoms of peptic ulcer disease may vary depending upon the location of the disease and age. Gastric and duodenal ulcers can be differentiated from the timing of their symptoms in relation to meals. Nocturnal pain is common with duodenal ulcers. Common signs and symptoms include epigastric abdominal pain, bloating, abdominal fullness, nausea and vomiting, weight loss/weight gain, gastrointestinal bleeding signs (hematemesis, melena).

Antisecretory drugs used for peptic ulcer disease (PUD) include PPI and H2-receptor antagonists.

Testing for H.pylori is recommended for every patient with a peptic ulcer. If the test is positive, triple eradication therapy is indicated. The recommended first-line therapy includes a PPI taken twice daily, combined with the antibiotics amoxicillin and clarithromycin. In cases where this therapy is ineffective, a different triple therapy regimen is recommended, consisting of a PPI taken twice daily, along with amoxicillin and metronidazole.

Resources

- Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal Reflux Disease: A Review. *JAMA.* 2020;324(24):2536–2547. doi:10.1001/jama.2020.21360
- Singh T, Sanaka MR, Thota PN. Endoscopic therapy for Barrett's esophagus and early esophageal cancer: Where do we go from here? World J Gastrointest Endosc. 2018 Sep 16;10(9):165-174. doi: 10.4253/wjge.v10.i9.165. PMID: 30283599; PMCID: PMC6162248.
- Rubenstein JH, Shaheen NJ. Epidemiology, Diagnosis, and Management of Esophageal Adenocarcinoma. Gastroenterology. 2015 Aug;149(2):302-17.e1. doi: 10.1053/j.gastro.2015.04.053. Epub 2015 May 7. PMID: 25957861; PMCID: PMC4516638.

- Kamada T, Satoh K, Itoh T, Ito M, Iwamoto J, Okimoto T, Kanno T, Sugimoto M, Chiba T, Nomura S, Mieda M, Hiraishi H, Yoshino J, Takagi A, Watanabe S, Koike K. Evidence-based clinical practice guidelines for peptic ulcer disease 2020. J Gastroenterol. 2021 Apr;56(4):303-322. doi: 10.1007/s00535-021-01769-0. Epub 2021 Feb 23. PMID: 33620586; PMCID: PMC8005399.
- https://www.grepmed.com/images/13202/egd-losangeles-esophagitis-diagnosis-grading
- https://healthjade.com/fundoplication/