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Chapter 31
ESOPHAGEAL DISEASES

31.1. GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is a disorder related to inflammatory changes in the distal esophagus and/or presenting with typical symptoms caused by regularly repeated gastric and/or duodenal contents regurgitation into the esophagus.

GERD (as defined by the Russian Association of Gastroenterology) is a chronic recurrent condition caused by a violation of motor-evacuation function of the gastroesophageal area organs and presenting with regular regurgitation of gastric and duodenal contents into the esophagus that results in clinical symptoms affecting quality of life and disrupting distal esophageal mucosa, with further development of dystrophic changes in stratified non-squamous epithelium, catarrhal or erosive-ulcerative esophagitis (reflux esophagitis), and in some patients — columnar epithelial metaplasia.

Epidemiology

The true prevalence of GERD is unknown due to the great variability of clinical symptoms — from episodic heartburn to vivid signs of complicated reflux esophagitis. The true prevalence of GERD is significantly higher than published statistics, that is explained by difficulties in the application of diagnostic techniques. Moreover, less than 1/3 GERD patients seek doctor's advice.

GERD is one of the most common gastrointestinal (GI) disorders. Symptoms of GERD are revealed in 20–50% of adults, and endoscopic signs are found in more than 7–10% of those studied among the population. Esophagitis develops in 45–80% of GERD patients. The prevalence of Barrett's esophagus (BE) among those with esophagitis is close to 8% (ranging from 5 to 30%).

Classification

According to the International Classification of Diseases, 10th ed., GERD with esophagitis (reflux esophagitis) (K21.0) and GERD without esophagitis (K21.9) are differentiated.

In clinical practice, another terminology is commonly used:

- endoscopy-negative reflux disease, or non-erosive reflux disease;
- endoscopy-positive reflux disease, or reflux esophagitis.

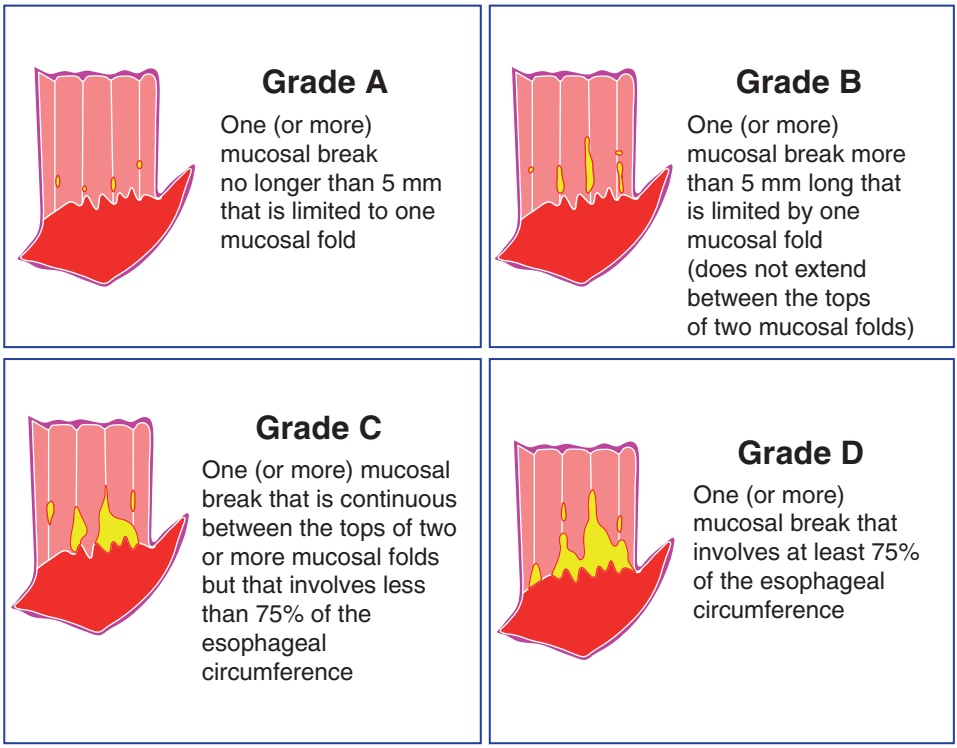

Fig 31.1. Grades of reflux esophagitis

To describe reflux esophagitis in detail, a classification following the 10th World Congress of Gastroenterology (Los Angeles, 1994 (Table 31.1; Fig. 31.1) is recommended.

Table 31.1. Grades of reflux esophagitis

Grade (severity)	Feature
A	One (or more) mucosal break no longer than 5 mm that is limited to one mucosal fold
B	One (or more) mucosal break more than 5 mm long that is limited by one mucosal fold (does not extend between the tops of two mucosal folds)
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but that involves less than 75% of the esophageal circumference
D	One (or more) mucosal break that involves at least 75% of the esophageal circumference

Complications of GERD include peptic strictures, esophageal bleeding, BE.

Approximately 60% of patients are diagnosed with non-erosive reflux disease, 30% are found to have reflux esophagitis, and 5% develop complications. Bleeding occurs in 2% of patients with erosive and ulcerative esophageal lesions, and peptic esophageal strictures develop in 2–20% of GERD patients. The most dangerous complications

of GERD include BE, since it poses an increased risk of esophageal adenocarcinoma development; its incidence has increased by 3–3.5 times over the past 20 years. Some authors report that GERD also contributes to laryngeal cancer.

Etiology and Pathogenesis

The factors causing GERD development include the following:

- decreased anti-reflux barrier function (gastric cardiac closing mechanisms);
- decreased esophageal clearance;
- impaired resistance of esophageal mucosa to damaging factors;
- increased hydrochloric acid and pepsin production in stomach, bile regurgitation into the stomach.

Since gastric pressure is always higher than thoracic pressure, a specific mechanism exists that prevents the reflux of gastric contents — the so-called cardiac closing mechanisms. Normally, reflux is rare and short-term (< 5 min). This is a physiological process observed after eating and characterized by the absence of clinical symptoms and a short duration of episodes, it may occur during sleep. The normal pH in the lower third of the esophagus is 6.0.

Esophageal reflux is considered pathological if the time during that the esophagus pH reaches 4.0 or less is 1 hour per day or the total number of gastroesophageal refluxes during the day exceeds 50, they develop both during the day and night.

The mechanisms supporting viable gastroesophageal junction functioning (cardiac closing mechanisms) include the following:

- lower esophageal sphincter (LES);
- phrenoesophageal ligament;
- mucous rosette;
- acute angle of His that forms the Gubarev's fold;
- intra-abdominal LES location;
- circular muscle fibers of gastric cardia.

Lower Esophageal Sphincter

The condition of LES plays a key role in functioning of the closing mechanism. At rest, it is closed in a healthy individual. Normally, transient relaxation lasts 5–30 seconds and contributes to removal of excess air swallowed while eating from the stomach. In GERD patients, these spontaneous episodes of LES relaxation are frequent and prolonged. The reasons for this are impaired esophageal motility, fast and plentiful eating accompanied by swallowing a large amount of air.

LES tone is reduced by:

- caffeine-containing foods (chocolate, coffee, tea, Coca-Cola), citrus fruits, tomatoes, alcohol, nicotine, and fats;
- some medicinal products (MPs): anticholinergics, sedatives, and hypnotics, β-blockers, nitrates, slow calcium channel blockers, theophylline, and other medications;
- vagus nerve damage [vagal neuropathy in diabetes mellitus (DM), after vagotomy].

LES pressure decrease is caused by the effects of a number of gastrointestinal hormones: glucagon, somatostatin, cholecystokinin, secretin, vasoactive intestinal peptide, enkephalins.

The decrease in antireflux barrier function may occur in three ways:

- primary decrease in LES pressure;
- increased number of its transient relaxation episodes;
- complete or partial sphincter destruction, for instance, in the presence of hiatus hernia, scleroderma, as a result of surgery or pneumatic cardiac dilatation.

Angle of His

This is the angle of the lateral esophageal wall transition into the greater curvature of the stomach, whereas its other lateral wall steeply transits into the lesser gastric curvature. Under the effects of gastric air bladder and intragastric pressure, the folds of the gastric mucosa forming the angle of His are tightly pressed against the right wall (Gubarev's fold) preventing gastric contents from leaking upward into the esophagus.

Clearance Reduction

The esophagus has an effective mechanism for eliminating pH acidic shifts, the so-called esophageal clearance. In 50% of GERD patients, esophageal clearance is decreased. In this case, the following esophageal clearance types are affected: chemical — due to decreased neutralizing effect of salivary bicarbonates and esophageal mucus; volumetric — due to secondary peristalsis inhibition and decreased tone of esophageal walls in its thoracic portion. Esophageal peristalsis plays a crucial role in maintaining normal esophageal clearance.

The immediate cause of reflux esophagitis is prolonged exposure of esophageal mucosa to gastric or duodenal contents.

Esophageal Mucosal Resistance

It is provided by pre-epithelial, epithelial and postepithelial factors.

- Pre-epithelial factor: a protective layer of mucus and active bicarbonate secretion. Epithelial damage is initiated when hydrogen ions and pepsin or bile acids penetrate this barrier.
- Epithelial factor: structural features and functions of cellular membranes, intercellular junctions, intra- and intercellular transport that create an optimal pH level.
- Postepithelial factor: blood supply to esophageal mucosa providing adequate trophism and optimal acid-base balance.

From the pathophysiological point of view, GERD is an acid-dependent condition developing in the presence of initial motor dysfunction of the upper gastrointestinal tract.

Clinical Picture

A specific feature of GERD is a lack of relationship between clinical symptom severity (heartburn, pain, regurgitation) and the degree of esophageal mucosal

changes. The disease symptoms preclude differentiating between non-erosive reflux disease and reflux esophagitis.

All symptoms can be combined into two groups:

- esophageal (heartburn; sour, bitter or food belching; regurgitation; dysphagia; odynophagia; retrosternal pain);
- extraesophageal (cough, asthma attacks, shortness of breath; hoarseness; dry throat, excessive salivation; caries; signs of anemia).

The leading symptom in the clinical picture is heartburn, belching with acidic contents that occurs when leaning forward and during nighttime. The second most common manifestation of this disease is retrosternal pain. Less commonly, are dysphagia, regurgitation, and odynophagia (painful swallowing) are observed.

Esophageal Symptoms

Heartburn

Heartburn is a specific burning or heat sensation of varying severity that is localized behind the sternum (in the lower third of the esophagus) or in the epigastric region. It is observed in 83% of GERD patients. It is caused by prolonged exposure of esophageal mucosa to gastric contents. The severity of heartburn does not correlate with that of esophagitis. Its increase is typical for diet violations, intake of carbonated beverages, alcohol, for physical exertion, bending forward, and in the horizontal position.

Belching and Food Regurgitation

52% of patients complain of regurgitation. As a rule, it becomes more severe after a meal, after consuming carbonated beverages. Food regurgitation observed in some patients occurs as a result of physical exertion and body position contributing to regurgitation. Belching and regurgitation are typical for a disorder with severely impaired esophageal motor function.

Dysphagia and Odynophagia

Dysphagia and odynophagia are observed in 19% of GERD patients. A characteristic feature of those symptoms is their intermittent nature. The basis of these symptoms is hypermotor esophageal dyskinesia that disrupts its peristalsis. Odynophagia (painful passage of food through the esophagus), as a rule, is indicative of erosive and ulcerative mucosal lesions. Persistent dysphagia and a simultaneous decrease in heartburn evidence the development of esophageal strictures. Rapidly progressing dysphagia and weight loss may indicate the development of adenocarcinoma.

Retrosternal Pain

The pain spreads to the interscapular region, neck, lower jaw, left half of the chest, and can mimic angina pectoris. When differentiating the origin of pain, it is important to establish what provokes and what relieves it. Esophageal pain is associated with food intake, specific body position, and is relieved by the intake of alkaline mineral water and antacids. Pain is stopped by nitrates, but, unlike angina pectoris, is not associated with physical exertion. The cause of the pain is hypermotor esophageal dyskinesia (secondary esophageal spasm).

Extraesophageal Symptoms

Extra-esophageal manifestations are divided into bronchopulmonary, otorhinolaryngological, and dental manifestations (the so-called GERD mimics).

Bronchopulmonary signs and symptoms include cough, recurrent bronchitis and pneumonia, asthma, and pulmonary fibrosis. Numerous studies have shown an increased risk of asthma, as well as its severity in GERD patients. In 30–90% of patients with asthma, gastroesophageal reflux is identified that contributes to the more severe asthma course. In the presence of GERD, the development of bronchial obstruction is due to microaspiration and vago-vagal reflex.

Otolaryngological mimic of GERD presents with an itchy throat, voice hoarseness or loss, and a rough barking cough. The development of ulcers and granulomas of the vocal cords, stenosis of the compartments distal to the glottis has been described. Laryngitis, chronic rhinitis, recurrent otitis media, otalgia are common and may be due to gastroesophageal reflux.

Dental manifestations are primarily characterized by tooth damage due to the exposure of tooth enamel to aggressive gastric juice (development of dental erosion, caries), as well as by fetor oris, periodontitis, stomatitis, gingivitis, etc.

Diagnosis

Principal methods used for GERD diagnostics:

- X-ray examination;
- endoscopic examination;
- histological examination;
- daily monitoring of esophageal pH;
- esophageal motor function study.

X-ray examination. Esophageal X-ray examination reveals ingress of contrast medium from the stomach into the esophagus, hiatal hernia; signs of esophagitis (folds thickening, motility disorders, uneven outlines of esophagus), esophageal erosions, ulcers, and strictures are detected.

Endoscopic examination plays a significant role in the diagnosis, the assessment of esophagitis severity and generalization, and helps to highlight complications. Endoscopy reveals hyperemia and looseness of esophageal mucosa typical of catarrhal esophagitis, erosive lesions and ulcers characteristic of erosive esophagitis, and the exudate, fibrin, or signs of bleeding are present. To assess mucosal changes in GERD, the Savary–Miller classification based on the grade of endoscopic changes severity and the presence of GERD complications, as well as the Los Angeles classification (see above) based on the disease generalization estimates, are used.

The classification of Savary–Miller includes 4 reflux esophagitis stages:

- Stage I — separate non-merging erosions and/or erythema of the distal esophagus;
- Stage II — confluent lesions, not covering the entire surface of esophageal mucosa;
- Stage III — inflammatory and erosive changes, confluent and covering the entire esophagus circumference;

- Stage IV — similar to the previous stage, but with complications, i.e. constriction preventing the passage of endoscope, ulcers, and BP development.

Chromoendoscopy. Chromoendoscopy identifies meta- and dysplastic epithelial changes by applying agents staining healthy and affected tissues in different ways, to the mucous membrane. In addition, it is possible to observe the prolapse of gastric mucosa into the esophageal lumen, especially evident when vomiting, and true esophageal shortening with gastroesophageal junction located above the diaphragm. Assessment of the cardiac closing mechanisms is challenging since it can be opened in response to the endoscope introduction or air inflation.

Histological examination of biopsy material of esophageal mucosa is applied to rule out BP, esophageal adenocarcinoma, and eosinophilic esophagitis. Histological examination reveals epithelial thinning and atrophy, connective tissue proliferation (sclerosis), dystrophic, necrotic, acute and chronic inflammatory changes of different severity. Metaplasia of non-keratinized stratified squamous cell epithelium of esophagus leading to the growth of columnar epithelium of cardiac or fundal type gastric mucosa. If metaplasia leads to the appearance of differentiated small-intestinal columnar epithelium, there is a risk of developing esophageal adenocarcinoma. The differentiated epithelium is incomplete small-intestinal metaplasia of glandular epithelium with the presence of goblet cells. The morphological substrate of GERD is considered to be widening and edema of intercellular spaces, especially in the basal epithelial layer, that is clearly defined using electron microscopic examination. The appearance of differentiated epithelium representing incomplete small-intestinal metaplasia of glandular epithelium sharply increases the risk of esophageal adenocarcinoma development.

24-hour esophageal pH-metry is the most informative diagnostic technique in GERD, especially in non-erosive reflux disease, and it allows defining the frequency, duration, and severity of refluxes. As compared to other methods [X-ray examination, esophagogastroduodenoscopy (EGD), LES tonometry] 24-hour pH-metry is characterized by high sensitivity in the detection of gastroesophageal reflux (88–95%). The information obtained makes it possible to accurately determine the duration of esophageal mucosa exposure to hydrochloric acid, to evaluate the effectiveness of esophageal clearance, to match the occurrence of refluxes with clinical symptoms, to examine the gastric acid-producing function throughout the day, aids in adjusting medical therapy and control its efficacy on an individual basis.

To diagnose GERD, the pH-metry results are estimated by the overall duration of pH <4.0, the total number of refluxes per day, the number of refluxes lasting >5 min, and by the longest duration of reflux.

pH impedansometry. Impedansometry in conjunction with pH monitoring allows revealing acidic as well as slightly acidic, alkaline and gas reflux. The main indications for impedansometry are refractory GERD, atypical forms and extraesophageal GERD manifestations, antisecretory therapy efficacy evaluation without discontinuing the drug for surgical GERD treatment.

Esophageal scintigraphy. To assess esophageal clearance, radioactive technetium isotope is used. The retention of ingested isotope in the esophagus for more than 10 minutes indicates a delay in esophageal clearance. 24-hour pH and esophageal clearance measurement reveal reflux before the development of esophagitis.

Manometry. This method allows exploring esophageal motor function and revealing a decrease in basal LES pressure <10 mm Hg in GERD, as well as the increased number of transient relaxations and decreased amplitude of peristaltic esophageal wall contractions. Recently, the technique of high-resolution manometry that provides higher sensitivity is gaining wide recognition.

In GERD, high-pressure manometry reveals decreases in LES pressure, increased number of transient LES relaxations, the presence of hiatal hernia, measures quantitative characteristics of overall peristaltic esophageal wall activity, identifies esophagospasm, atypical cases of cardiac achalasia (CA), and helps to diagnose supragastric burping and rumination syndromes. This test allows determining the position of LES to perform pH-metry. It is considered necessary for making a decision on GERD surgical treatment. When analyzing the results of high-resolution manometry, the Chicago classification of esophageal motility disorders is used.

Other Diagnostic Techniques

- Electrocardiography (ECG) to differentiate with cardiovascular pathology.
- Prior to probe studies, it is necessary to run blood tests for human immunodeficiency virus (HIV), hepatitis, and syphilis.
- For differential diagnosis of GERD extraesophageal manifestations, consultations of pulmonologist, cardiologist, otorhinolaryngologist, and dentist are indicated.
- Therapeutic test with one of proton pump inhibitors (PPIs), alginate test. For example, the disappearance of disease manifestations including extraesophageal symptoms in 1–3 days after starting Rabeprasole 20 mg may suggest the presence of GERD.
- Functional tests revealing gastroesophageal reflux (Bernstein's, Stepanenko's) define the relationship between the present clinical symptoms (retrosternal pain, heartburn) and esophageal mucosa hypersensitivity to acid.
- Bilirubin level monitoring is used to diagnose duodenogastroesophageal reflux. This method correlates well with gastric level of bile acids.
- Endoscopic ultrasound examination of esophagus serves as a major diagnostic modality for tumors with endophytic growth.
- Special endoscopic diagnostic techniques (high-definition endoscopy, magnifying endoscopy, narrow-band imaging endoscopy — with cospectral mapping, confocal endomicroscopy) during targeted biopsy provide a more accurate identification of metaplasia foci in the esophageal epithelium.

For diagnosing GERD in highly specialized tertiary care institutions, such methods as impedance measurement of esophageal mucosa, determination of pepsin level in saliva, and impedance planimetry can be used.

Complications

The risk factors of complications include frequent and persistent symptoms, severe stage of erosive esophagitis, and the presence of hiatal hernia. The complications of GERD include esophageal ulcers, hemorrhages, strictures, and BP development.

Esophageal peptic ulcers. These ulcers are observed in 2–7% of GERD patients, in 15% of them the ulcers are complicated with perforation, more commonly into mediastinum.

Hemorrhages. Acute and chronic bleeding of various grades is observed in almost every patient with peptic esophageal ulcers, with severe bleeding being reported in 1/2 of them.

Strictures. This disorder is observed in approximately 10% of GERD patients: esophageal stenosis confers a more persistent character to the disease (dysphagia progresses, general condition deteriorates, and body weight decreases). The clinical presentation of stenosis (dysphagia) develops if esophageal lumen is narrowed down to 2 cm.

BP (see Section 31.2 "Barrett's esophagus").

Treatment

The selection of treatment modality depends on the features of GERD course and its causative factor. Pharmacological or surgical treatment of GERD can be elected.

General Recommendations

The patient is recommended to follow a certain lifestyle and diet.

- Avoid physical exertion that may increase intraabdominal pressure:
  - refrain from wearing tight clothing and belts, corsets;
  - do not lift weights more than 8–10 kg (with both hands); avoid physical exercises associated with abdominal press overstraining.
- Dietary considerations:
  - avoid heavy meals; no late meals (dinner should be no later than 2–3 hours before bedtime). After a meal, avoid leaning forward and do not lie down. At the same time, the number of meals should not be increased: 3–4 meals/day regimen should be followed, and consuming so-called "snacks" should be avoided. Recommendations for frequent split meals are insubstantiated;
  - limit consumption of foodstuffs reducing LES pressure and irritating the esophageal mucosa, i.e. fat-rich foods (whole milk, cream, pies, cakes, goose, duck, pork, lamb, fat beef), alcohol, caffeine-containing beverages (coffee, Coca-Cola, strong tea, chocolate), citrus fruits, tomatoes, onions, garlic, fried dishes.
- Avoid DPs causing reflux (sedatives and tranquilizers, slow calcium channel blockers, beta-blockers, theophylline, prostaglandins, nitrates).
- Sleep with the headboard raised.
- Quit from smoking.
- Bring the body weight to norm.

Pharmacological Treatment

Treatment duration. The key principles of GERD treatment presume the use of PPIs and long-term basic (no less than 4–8 weeks) and supportive (no less than 6–12 months) therapy.

Drug therapy includes the administration of prokinetics, antacids, alginates, and antisecretory agents.

Prokinetics. These agents increase LES tone, enhance esophageal peristalsis and improve esophageal clearance. Prokinetics include metoclopramide and domperidone (10 mg 3–4 times a day, 30 min before meal). However, it is preferable to prescribe Itopride 50 mg 3 times a day before meal, since it is considered the safest among prokinetics. Together with PPIs, prokinetics are used in the complex GERD therapy.

Antacids are effective in the presence of moderate and infrequent symptoms. They have a cytoprotective effect and neutralize hydrochloric acid in gastric juice. In rare cases of heartburn not associated with esophagitis, they can be used as a monotherapy, and are included in the complex therapy of GERD. Usually drugs are prescribed 3 times a day, 1.5–2 hours after meal, and at night. The most convenient formulation are gels. Each pain and heartburn attack should be alleviated, since these symptoms indicate progressive mucosal damage to esophagus.

Alginates. Drugs containing sodium alginate have proven efficacy in the treatment of reflux esophagitis. This compound forms a foamy antacid suspension floating on the surface of gastric contents, and provides a therapeutic effect if regurgitated to the esophagus in case of gastroesophageal reflux. Alginates reduce the number of both acidic and slightly alkaline refluxes, and also have a cytoprotective and sorption effect. They are dosed at 10 ml 3–4 times a day, 30–40 minutes after meal, and once before bed till relief of persistent symptoms, and then in on-demand mode.

H_2receptors blockers. In reflux esophagitis, ranitidine and famotidine reducing the gastric reflux acidity are widely used, aiding alleviation of inflammatory and erosive-ulcerative process in esophageal mucosa. However, the typical doses of H_2-histamine receptor blockers administered to patients with erosive reflux esophagitis are often not quite effective.

Proton pump inhibitors (PPIs). Currently, the drugs of choice are considered to be H^+/K^+ adenosine triphosphatase (ATPase) blockers that provide a pronounced and prolonged suppression of hydrochloric acid gastric secretion by inhibiting the proton pump. The following PPIs are administered: Omeprasole (20 mg BID), Lansoprasole (30 mg SID), Pantoprasole (40 mg SID), Rabeprasole (20 mg SID), Esomeprasole (40 mg SID) Dexlansoprasole (60 mg SID). PPIs are the most potent antisecretory DPs; they are particularly effective in peptic erosive-ulcerative esophagitis, providing scarring of affected areas in 90–96% of cases after 4–5 weeks of therapy.

Surgical Treatment

The surgical management is considered in case of a long-term and/or ineffective drug therapy, and in the presence of complications (esophageal strictures, recurrent hemorrhages, BP). Particularly commonly surgical treatment is indicated in a combination of GERD with hiatal hernia.

Prognosis

In non-erosive reflux disease and mild reflux esophagitis, the prognosis is favorable in most cases. The prognosis worsens with a long disease history combined with frequent and long-term relapses, and in complicated GERD forms, especially those with BP development, due to an increased risk of esophageal adenocarcinoma.