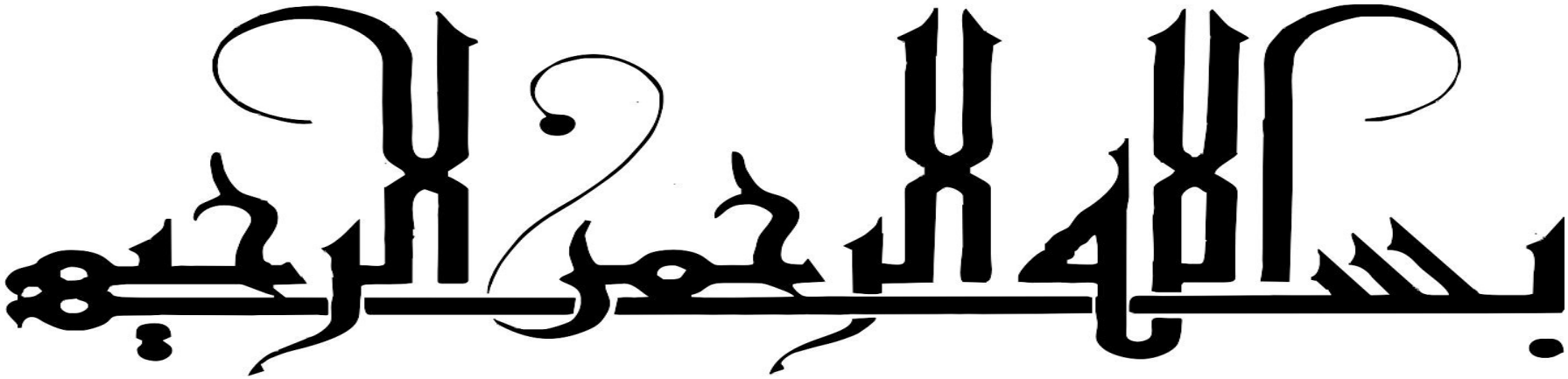


دکتر شاهین شهبازی

دانشیار بیماریهای گوارش

Physiologic reflux

- **Physiologic reflux** episodes typically occur postprandially, are short-lived, asymptomatic, and rarely occur during sleep.
- **Pathologic reflux** is associated with symptoms or mucosal injury and often occurs nocturnally.

MECHANISMS OF GASTROESOPHAGEAL REFLUX DISEASE

- — (GERD) reflects an imbalance between injurious and defensive factors (esophageal acid clearance, mucosal integrity)

Gastroesophageal junction incompetence

- Transient lower esophageal sphincter relaxations (TLESRs)
- A hypotensive lower esophageal sphincter (LES)
- Anatomic disruption of the gastroesophageal junction, often associated with a hiatal hernia

- **Transient lower esophageal sphincter relaxations** — Transient lower TLESR is part of the physiological mechanism of belching. TLESR is an active, vagally mediated reflex allowing air to escape from the stomach A primary determinant of reflux disease is an increased proportion of TLESRs that are associated with acid reflux rather than gas venting alone .

- **Hypotensive lower esophageal sphincter** — Only a minority of individuals with GERD have a grossly hypotensive LES (<10 mmHg)
- smoking, and specific foods and medications , Strain-induced reflux

- **Anatomic disruption of the gastroesophageal junction** — Laxity in the LES-crural diaphragm attachment, and increased intra-abdominal pressure can result in mechanical impairment of the EGJ. Patients with hiatus hernia also have progressive disruption of the diaphragmatic sphincter.

Characteristics of the refluxate

The degree of mucosal damage is more significant if :

- the refluxate pH is less than two
- Pepsin, bile acids, trypsin, and food hyperosmolality increase the susceptibility of the esophageal mucosa to acid injury

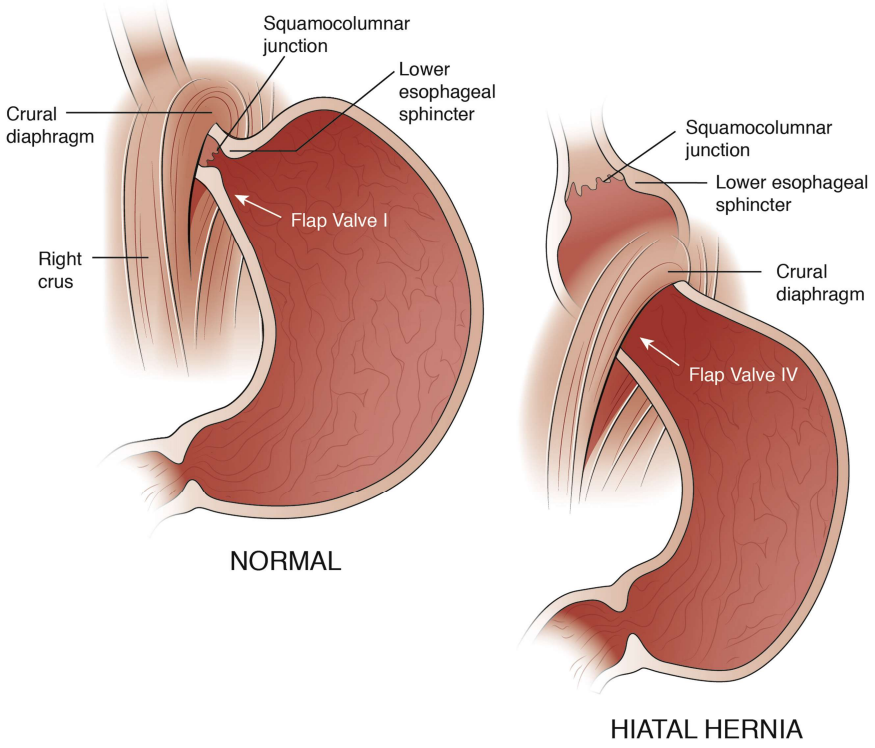
- **Impaired esophageal acid clearance**

Peristalsis clears gastric fluid from the esophagus,

whereas the swallowing of saliva (pH of 7.8 to 8.0) neutralizes any remaining acid.

- Ineffective esophageal motility – Ineffective esophageal motility can be manifest as either failed or hypotensive peristaltic contractions

- **Re-reflux** –Re-reflux from the hernia during swallowing peristalsis-induced esophageal shortening.


Squamocolumnar junction
Lower esophageal sphincter
Crural diaphragm
Flap Valve I
Right crus
NORMAL
Squamocolumnar junction
Lower esophageal sphincter
Crural diaphragm
Flap Valve IV
HIATAL HERNIA

Diminished salivary function —

- 7 ml of saliva will neutralize 1 ml of 0.1 N HCl,
- Diminished salivation during sleep,
- Cigarette smokers Chronic xerostomia

Impaired defense against epithelial injury — Age and nutritional status

- Epithelial tight junctions –"tight" epithelium, tight junctions and the lipid-rich matrix in the intercellular space

Hydrogen ion extrusion –

- a Na+/H+ exchanger; and a sodium dependent Cl-/HCO3- exchanger
  Thus, blood flow is the main post-epithelial defense,

Esophageal hypersensitivity —

- normal esophageal acid exposure ,enhanced sensory perception of physiological reflux (visceral hyperalgesia)

Hiatus hernia —

- The severity of reflux esophagitis correlates with the size of hiatus hernia
- impairment of the crural diaphragmatic component of the EGJ

Obesity-

- a significant correlation of body mass index and waist circumference with intragastric pressure and the gastroesophageal pressure gradient

Pregnancy and exogenous estrogen

Diet and medications —

- Specific foods ,smoking, and several drugs can cause reflux by inducing LES hypotension.

UNCLEAR ROLE OF HELICOBACTER PYLORI

Manifestations

- **Erosive esophagitis** — Erosive esophagitis is characterized by endoscopically visible breaks in the distal esophageal mucosa with or without troublesome symptoms of GERD.
- **Nonerosive reflux disease** — Nonerosive reflux disease or endoscopy negative reflux disease is characterized by the presence of troublesome symptoms of GERD without visible esophageal mucosal injury.

Classic symptoms of gastroesophageal reflux disease (GERD) are heartburn (pyrosis) and regurgitation.

Complications —

- Complications from GERD can arise even in patients who lack typical esophageal symptoms.
- These complications may be esophageal (eg, Barrett's esophagus, esophageal stricture, esophageal adenocarcinoma) or extra-esophageal (eg, chronic laryngitis, exacerbation of asthma).

DIAGNOSIS

Patients with classic symptoms —

- The diagnosis of gastroesophageal reflux disease (GERD) can often be based on clinical symptoms alone in patients with classic symptoms such as heartburn and/or regurgitation

Patients without classic symptoms —

- Other disorders need to be excluded before attributing the symptoms to GERD.

Upper gastrointestinal endoscopy

Indications —

- evaluate alarm features or abnormal imaging
- Barrett’s esophagus in patients with risk factors.

- Upper endoscopy is not required to make a diagnosis of GERD.

Alarm features

- New onset of dyspepsia in patient ≥60 years
- Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
- Iron deficiency anemia
- Anorexia
- Unexplained weight loss
- Dysphagia
- Odynophagia
- Persistent vomiting
- Gastrointestinal cancer in a first-degree relative

Risk factors for Barrett's esophagus

- Duration of GERD of at least 5 to 10 years
- Age 50 years or older
- Male sex
- White race
- Hiatal hernia
- Obesity
- Nocturnal reflux
- Tobacco use (past or current)
- First-degree relative with Barrett's esophagus and/or adenocarcinoma

SCREENING PATIENTS FOR BARRETT'S ESOPHAGUS

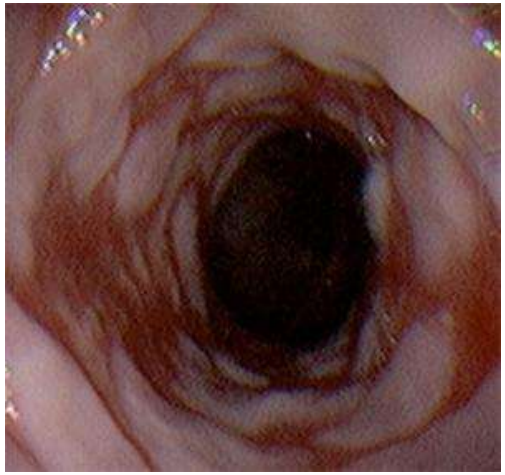
Whom to screen

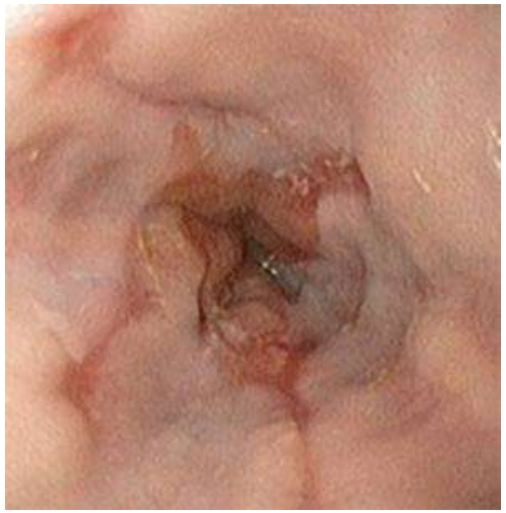
- hiatal hernia
- age ≥50
- male sex
- chronic gastroesophageal reflux disease (GERD)
- White individuals
- central obesity
- cigarette smoking
- confirmed history of Barrett's esophagus or esophageal adenocarcinoma in a first-degree relative
- In patients with erosive esophagitis found on the initial examination, we perform repeat endoscopy after a three-month course of acid suppression to exclude the presence of Barrett's esophagus.

ulcerations seen in peptic esophagitis are usually irregularly shaped or linear, multiple, and are in the distal esophagus.

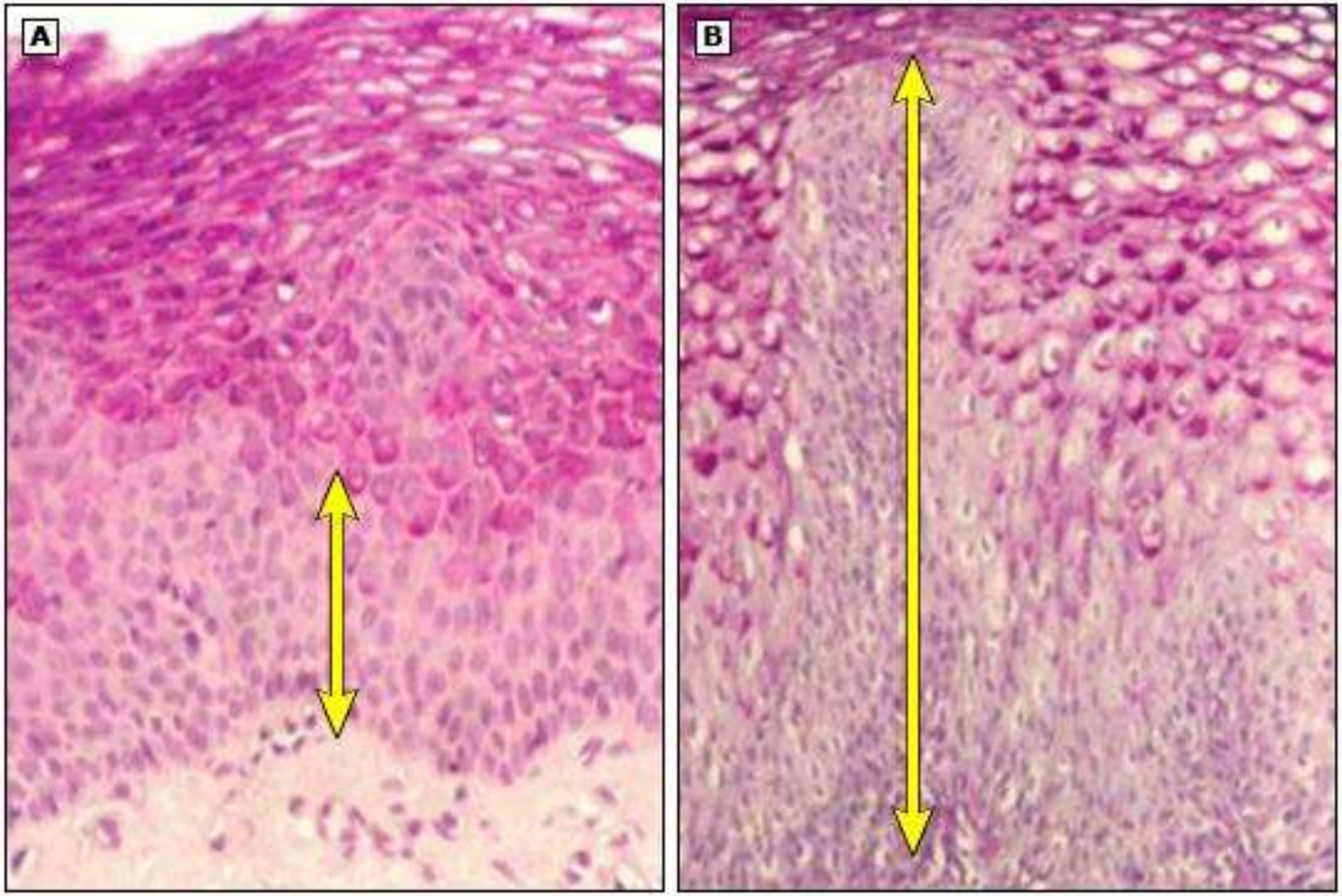
Los Angeles classification –

- -Grade A – One or more mucosal breaks each ≤5 mm in length
- -Grade B – At least one mucosal break >5 mm long, but not continuous between the tops of adjacent mucosal folds
- -Grade C – At least one mucosal break that is continuous between the tops of adjacent mucosal folds, but which is not circumferential
- Grade D – Mucosal break that involves at least three-fourths of the luminal circumference





Histology — Approximately two-thirds of patients with symptoms of GERD and no visible endoscopic findings

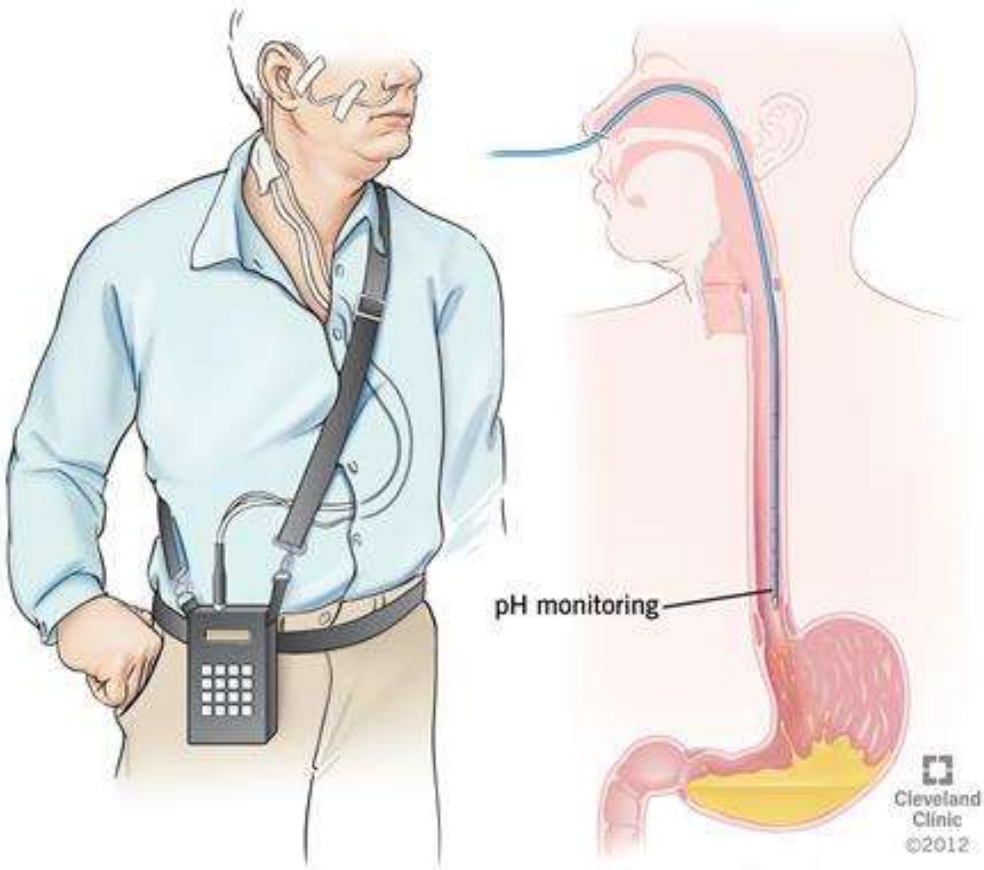

A
B

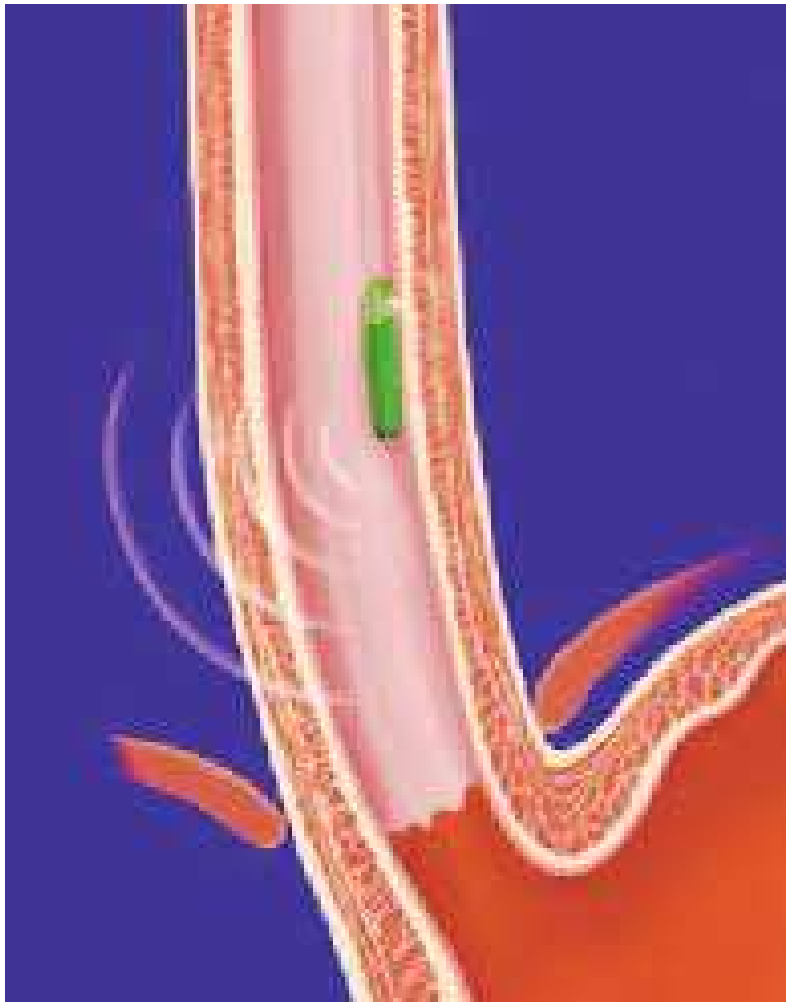
Esophageal manometry —

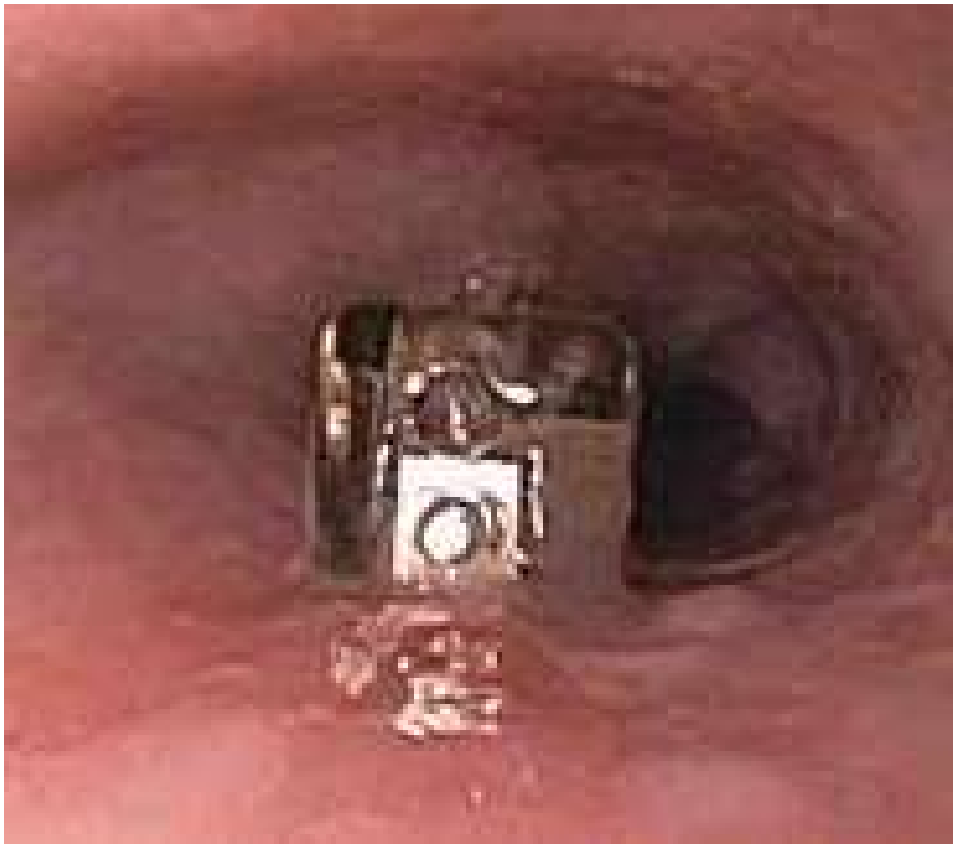
- chest pain and/or dysphagia and a normal upper endoscopy,
- ambulatory pH probes are placed correctly but cannot diagnose GERD.
- evaluate peristaltic function before antireflux surgery for GERD

Ambulatory esophageal pH monitoring

- Ambulatory pH monitoring is also used to confirm the diagnosis of GERD in those with persistent symptoms (whether typical or atypical, particularly if a trial of twice-daily PPI has failed) or to monitor the adequacy of treatment in those with continued symptoms
- Ambulatory pH monitoring can be performed with either a transnasally placed catheter or a wireless, capsule-shaped device that is affixed to the distal esophageal mucosa .


pH monitoring
Cleveland Clinic
©2012

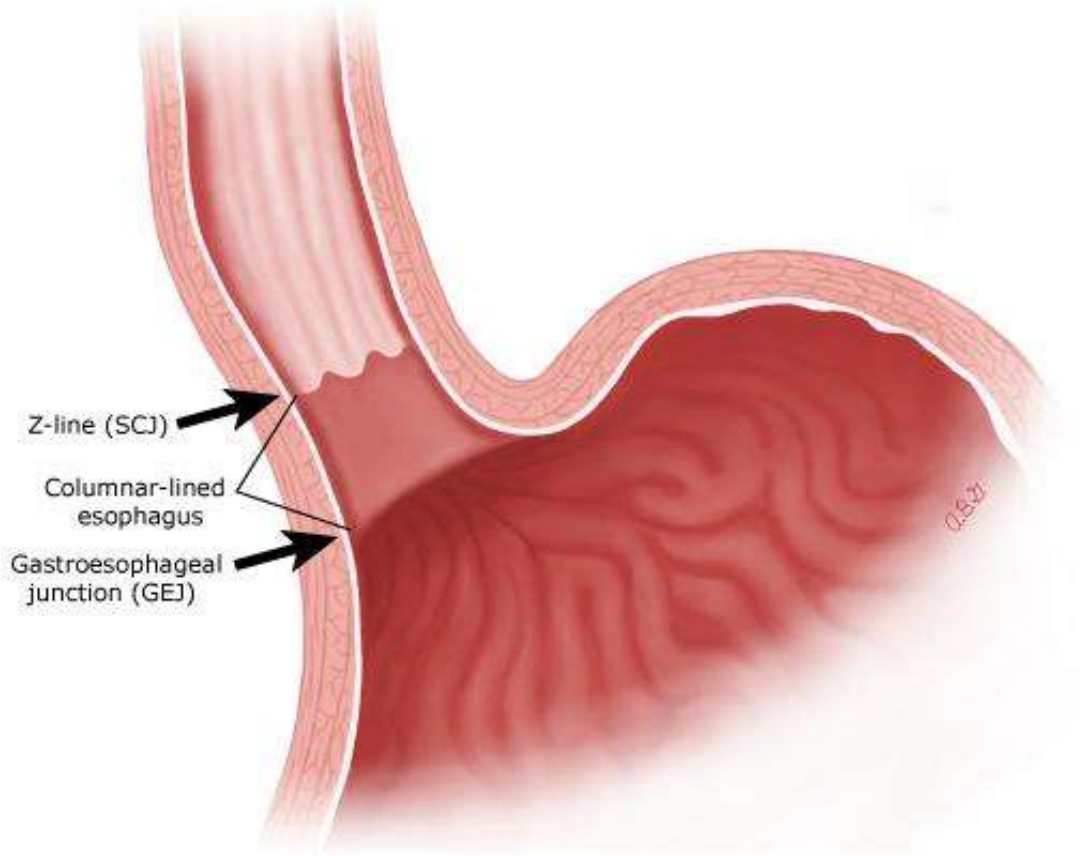


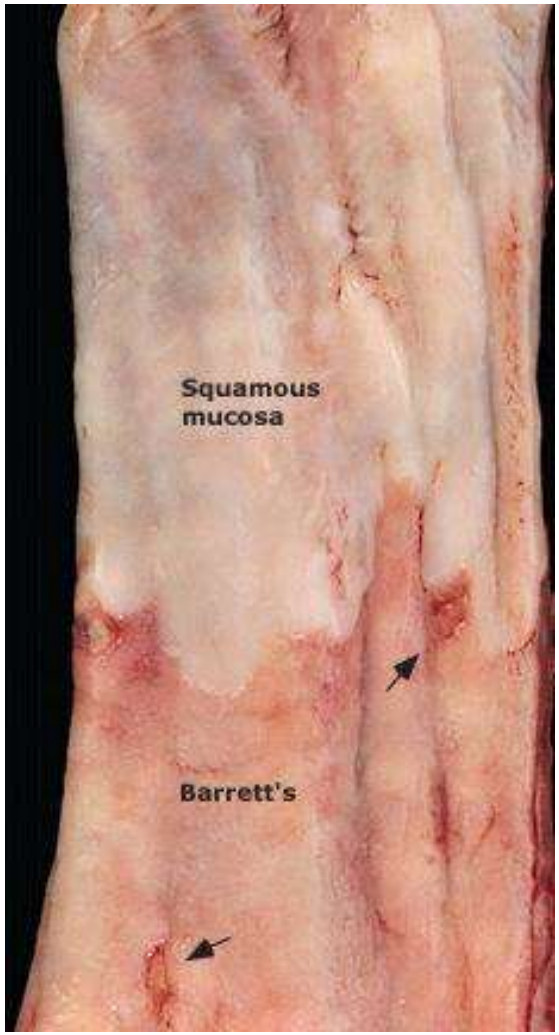


- Reflux hypersensitivity have normal acid exposure but a positive symptom association with acid or weakly acid reflux.
- Functional heartburn have normal acid exposure and a negative symptom reflux association.
- Functional dyspepsia have heartburn in one third of cases, but early satiety and postprandial fullness are the predominant symptoms.

Complications

- **Erosive esophagitis**
- **Barrett's esophagus** Barrett's esophagus should be suspected when the squamocolumnar junction is located ≥1 cm proximal to the gastroesophageal junction (GEJ)
- **Esophageal stricture** Patients may have solid food dysphagia and episodic food impaction.


Z-line (SCJ)
Columnar-lined esophagus
Gastroesophageal junction (GEJ)


Squamous
mucosa
Barrett's

- **EXTRAESOPHAGEAL COMPLICATIONS** —
- **Asthma** — increased vagal tone, heightened bronchial reactivity, and microaspiration of gastric contents into the upper airway.
- **Otolaryngologic complications** — Otolaryngologic complications of GERD can result from laryngopharyngeal reflux (LPR) in which the reflux of gastric contents results in contact injury to the pharyngeal and laryngeal

Chronic laryngitis —

Laryngeal and tracheal stenosis —

Other complications — Other chronic complications of GERD include chronic cough, dental erosions, chronic sinusitis, and recurrent pneumonitis

Management

- is based on the :
- Frequency and severity of symptoms and the presence of erosive esophagitis or Barrett's esophagus on upper endoscopy, if previously performed.
- We suggest lifestyle and dietary modification in all patients with GERD

- mild and intermittent symptoms (fewer than two episodes per week) and no evidence of erosive esophagitis, we suggest step-up therapy for GERD.

step-up

- lifestyle and dietary modification and, as needed, low-dose histamine 2 receptor antagonists (H2RAs) We suggest concomitant antacids and/or sodium alginate as needed if symptoms occur less than once a week.

- For patients with continued symptoms despite these measures, we increase the dose of H2RAs to standard dose, twice daily for a minimum of two weeks.
- if symptoms of GERD persist, we discontinue H2RAs and initiate once-daily proton pump inhibitors (PPIs) at a low dose and then increase to standard doses if required .We make incremental changes in therapy at four to eight-week intervals.
- Once symptoms are controlled, treatment should be continued for at least eight weeks.

Medication	Low dose (adult, oral)	Standard dose (adult, oral)
Histamine 2 receptor antagonists*		
Famotidine	10 mg twice daily[¶]	20 mg twice daily[Δ]
Nizatidine	75 mg twice daily[¶]	150 mg twice daily
Cimetidine	200 mg twice daily[¶]	400 mg twice daily[Δ]
Proton pump inhibitors		
Omeprazole	10 mg daily[◇]	20 mg daily[¶]
Lansoprazole	15 mg daily[¶]	30 mg daily
Esomeprazole	10 mg daily[◇]	20 mg daily[¶]
Pantoprazole	20 mg daily[¶]	40 mg daily
Dexlansoprazole	Not available	30 mg daily
Rabeprazole	10 mg daily[◇]	20 mg daily

step-down

- Erosive esophagitis, frequent symptoms (two or more episodes per week), and/or severe symptoms that impair quality
- standard-dose PPI once daily for eight weeks in addition to lifestyle and dietary modification .

Lifestyle and dietary modification

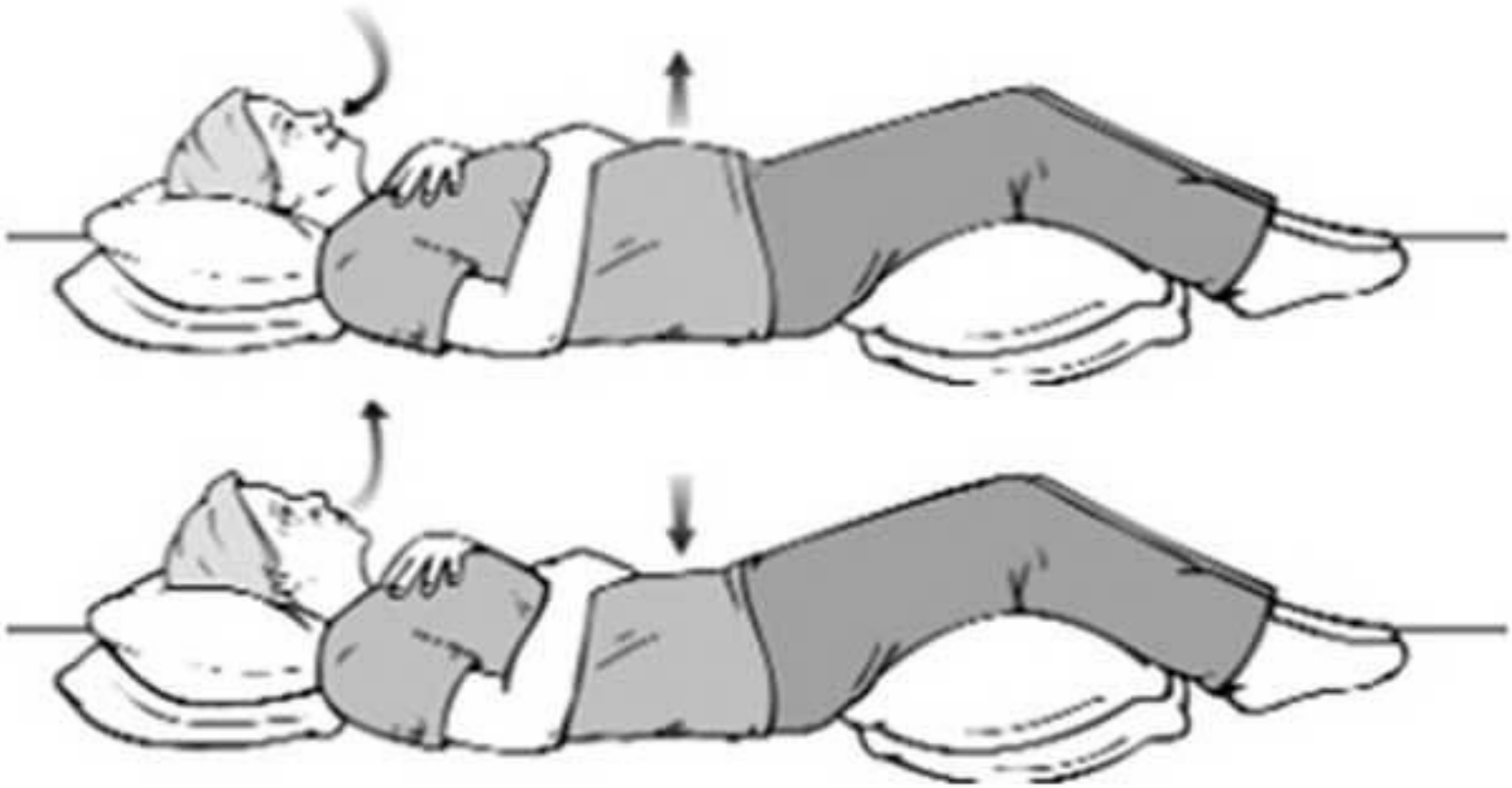
- —only weight loss and elevation of the head end of the bed improved esophageal pH-metry and/or GERD symptoms.

- Elevation of the head of the bed in individuals with nocturnal or laryngeal symptoms (eg, cough, hoarseness, throat clearing).
- This can be achieved either by putting six- to eight-inch blocks under the legs at the head of the bed or a Styrofoam wedge under the mattress.
- refraining from assuming a supine position after meals and avoidance of meals two to three hours before bedtime.

- elective elimination of dietary triggers (caffeine, chocolate, spicy foods, food with high fat content, carbonated beverages, and peppermint) in patients who note correlation with GERD symptoms and an improvement in symptoms with elimination.

Avoidance of tight-fitting garments

- chewing gum
- Avoidance of tobacco and alcohol
- Abdominal breathing exercises



Antacids

- —not prevent GERD,
- relief of mild GERD symptoms
- magnesium trisilicate, aluminum hydroxide, or calcium carbonate, و relief of heartburn within five minutes, but have a short duration of effect of 30 to 60 minutes.

Surface agents and alginates —

- **Sucralfate** (aluminum sucrose sulfate), a surface agent, adheres to the mucosal surface, promotes healing, and protects from peptic injury وshort duration of action the use of sucralfate is limited to the management of **GERD in pregnancy**
- **Sodium alginate** is a polysaccharide derived from seaweed that forms a viscous gum that floats within the stomach and neutralizes the postprandial acid pocket in the proximal stomach

Histamine 2 receptor antagonist —

- development of tachyphylaxis within two to six weeks of initiation of H2RAs limits their use in the management of GERD
- action of 4 to 10 hours
- H2RAs have limited efficacy in patients with erosive esophagitis. are ineffective in patients with severe esophagitis

Proton pump inhibitors —

- patients who fail twice-daily H2RA therapy and in patients with erosive esophagitis and/or frequent (two or more episodes per week) or severe symptoms of GERD that impair quality of life.
- irreversibly binding to and inhibiting the hydrogen-potassium (H-K) ATPase pump.

- Limitations of PPIs include a higher cost as compared with H2RAs, and potential side effects.

Repeat endoscopy for severe erosive esophagitis —

- Patients with severe erosive esophagitis (Los Angeles classification Grade C and D) on initial endoscopy should undergo a follow-up endoscopy after a two-month course of PPI therapy to assess healing and rule out Barrett's esophagus.

PPI refractory symptoms —

- Patients who fail to respond to once-daily proton pump inhibitors (PPI) therapy are considered to have refractory GERD.

severe esophagitis or Barrett's esophagus —

- Patients with severe erosive esophagitis or Barrett's esophagus require maintenance acid suppression with a PPI at standard dose as they are likely to have recurrent symptoms and complications if acid suppression is decreased or discontinued

Patients without severe erosive esophagitis and Barrett's esophagus —

- PPIs should be prescribed at the lowest dose and for the shortest duration appropriate to the condition being treated
- In patients on PPIs for longer than six months, we taper the PPI dose before discontinuing it and use H2RAs for mild or intermittent symptoms.
- We discontinue acid suppression completely in all asymptomatic patients.

Recurrent symptoms —

- Approximately two-thirds relapse when acid suppression is discontinued.
- should be managed with acid suppressive therapy with the medication and dose used to previously control symptoms .If necessary for symptom control, therapy may be stepped up to medications of increasing potency as with initial therapy

- In patients with recurrent symptoms ≥3 months after discontinuing acid suppression, we use repeated eight-week courses of acid suppressive therapy.

- In patients with recurrent symptoms <3 months of discontinuing acid suppression who have not previously undergone an upper endoscopy, we perform an upper endoscopy to rule out other etiologies and complications of GERD.

Indications for referral —

- who fail to respond to once daily PPI therapy (refractory GERD), and patients who cannot tolerate long-term PPIs or want to discontinue therapy.

No role for empiric eradication of H. pylori —

- It is uncertain whether chronic acid suppression with PPIs increases the risk for atrophic gastritis in patients with H. pylori. Therefore, routine screening for H. pylori infection and empiric eradication of H. pylori are not recommended in patients with GERD .

PREGNANCY AND LACTATION

- — Initial management of gastroesophageal reflux disease (GERD) in pregnancy consists of lifestyle and dietary modification (eg, elevation of the head end of the bed, avoidance of dietary triggers). In patients with persistent symptoms, pharmacologic therapy should begin with antacids followed by sucralfate.
- In patients who fail to respond, similar to nonpregnant patients, histamine 2 receptor antagonists (H2RAs) and then proton pump inhibitors (PPIs) should be used to control symptoms (table 1). (See 'Mild and intermittent symptoms' above.)

- Most antacids are considered safe in pregnancy and are compatible with breastfeeding .However, antacids containing sodium bicarbonate and magnesium trisilicate should be avoided in pregnancy.
- **Sucralfate** is likely safe during pregnancy and lactation because it is poorly absorbed .
- In patients who continue to have symptoms of GERD despite antacids, we suggest sucralfate (1 g orally three times daily) .While all H2RAs appear to be safe in pregnancy, in patients with continued GERD symptoms on sucralfate, we suggest cimetidine as it has the most safety data available . Cimetidine is concentrated in breast milk, but is compatible with breastfeeding

- Omeprazole and pantoprazole are secreted in low concentrations in breast milk .
- omeprazole, lansoprazole, or pantoprazole rather than other PPIs, as they have been more widely used in pregnancy.

- Upper endoscopy should be performed during pregnancy only if there is a strong indication (eg, significant gastrointestinal bleeding). When possible, endoscopy should be postponed until the second trimester

Refractory GERD

- lack of satisfactory symptomatic response to PPI once a day should be considered a failure of PPI therapy.
- Most patients with GERD who do not respond to a PPI have either nonerosive reflux (NERD) or functional heartburn.
- insufficient suppression of gastric acid.

Residual acid reflux —

- the incidence in patients on twice daily therapy is low .
- acid pocket, likely has a limited role in refractory GERD by causing re-reflux of gastric acid.

Functional heartburn —

- According to the Rome IV criteria, a diagnosis of functional heartburn requires all of the following criteria :

●Burning retrosternal discomfort or pain

●Absence of symptom relief despite optimal antisecretory therapy

●Absence of evidence that gastroesophageal reflux (abnormal acid exposure and symptom reflux association) or eosinophilic esophagitis are the cause of symptoms

●Absence of major esophageal motor disorders (achalasia/esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis)

- Increased esophageal sensitivity to chemical, mechanical, and electrical stimuli in this patient population has not been consistently demonstrated
- Psychological co-morbidities may provide an explanation for functional heartburn .Patients with poor correlation of symptoms with acid reflux events display a high level of anxiety
- In population-based studies, anxiety and depression have been also been demonstrated to increase GERD-related symptoms

Alarm features — Alarm features that may be suggestive of a gastrointestinal malignancy include

- New onset dyspepsia in patient ≥60 years
- Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
- Iron deficiency anemia
- Anorexia
- Unexplained weight loss
- Dysphagia
- Odynophagia
- Persistent vomiting
- Gastrointestinal cancer in a first-degree relative

Patients with alarm features

Early upper endoscopy —

- (within two weeks) should be performed for the evaluation of new alarm features
- Upper endoscopy should not be delayed pending a trial of empiric therapy in patients with alarm symptoms.

Normal upper endoscopy

- additional evaluation may be required based on symptoms (eg, abdominal imaging in patients with concurrent weight loss).
- If this evaluation is normal and symptoms of GERD persist, patients should be managed similarly to patients without alarm features.

Patients without alarm features

General measures —

- compliance with PPI therapy should be reinforced. Patients should be instructed to take a PPI 30 minutes before a meal.
- Lifestyle and dietary modification include avoidance of identified dietary triggers, weight loss for patients who are overweight or have had recent weight gain, elevation of the head of the bed in individuals with nocturnal symptoms, refraining from assuming a supine position after meals and avoidance of meals two to three hours before bedtime.

Optimize PPI therapy —

In patients with reflux symptoms despite standard dose once daily PPI (eg, omeprazole 40 mg once daily), options include splitting the dose (eg, omeprazole 20 mg twice daily), doubling the PPI dose (eg, omeprazole 40 mg twice daily), or switching to another PPI (eg, lansoprazole 30 mg once daily).

Anti-reflux procedures

- **Anti-reflux surgery** –
- Antireflux surgery is reserved for patients who require high doses of PPIs to control symptoms, for persistent proven GERD symptoms or esophageal mucosal damage despite maximal medical therapy, and when there is significant structural disruption at the esophagogastric junction (eg, hiatus hernia).

Endoscopic procedures –

- The two main endoscopic approaches for treating GERD include application of controlled radiofrequency energy to the lower esophageal sphincter region (Stretta procedure) and transoral incisionless fundoplication .
- Both techniques have demonstrated a decrease in PPI requirement in patients with GERD. However, their long-term efficacy has not been established.

Reflux hypersensitivity or functional heartburn

- — Patients should be reassured regarding the benign nature of these conditions.
- We usually begin with nortriptyline 25 mg, citalopram 20 mg, or fluoxetine 20 mg.