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Gastroesophageal Reflux Disease

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Clinical Vignette

A 50-year-old man with a history of hypertension and hyperlipidemia presents with a 4-month history of chest discomfort. He describes the discomfort as a burning and occasionally a pressure sensation in the mid-sternal area. The discomfort often occurs 45 minutes after eating a meal and lasts for about 3 hours, gradually improving thereafter. He occasionally awakens in the morning with a sore throat, cough, and bitter taste in his mouth. He has tried over-the-counter ranitidine, with only minimal relief. He was recently seen in the emergency department for an episode of severe chest pain. A cardiac work-up, including an electrocardiogram, cardiac enzymes, and a stress echocardiogram, was negative. Physical examination reveals a well-built, well-nourished man in no apparent distress. The blood pressure is 137/84 mmHg, pulse rate 72 per minute, respiratory rate 14 per minute, and body mass index 30. The physical examination is otherwise unremarkable.

General

- Gastroesophageal reflux disease (GERD) is defined as symptoms or tissue damage caused by the reflux of gastric contents into the esophagus.
- GERD is a common disorder, affecting almost half of the US population, with varying severity. Some 40% of the US population experiences reflux symptoms about once per month, 20% complain of symptoms once per week, and 7–10% report daily symptoms.
- GERD affects 10–20% of western populations. It is less common in Asian and African countries.
- It is estimated that GERD costs the US nearly $2 billion each week in lost productivity.

Sitaraman and Friedman's Essentials of Gastroenterology, Second Edition.
Edited by Shanthi Srinivasan and Lawrence S. Friedman.

The most common symptoms of GERD are heartburn and regurgitation. GERD is the most common cause of noncardiac chest pain.

Risk Factors

- Advancing age (>65 years)
- Obesity
- Genetic factors
- Alcohol use
- Pregnancy
- Smoking

Spectrum of GERD

- The clinical spectrum of GERD ranges from nonerosive reflux disease (NERD) to erosive esophagitis (Figure 1.1). NERD is defined as symptoms of acid reflux without evidence of esophageal damage, such as mucosal erosions or breaks on esophagogastroduodenoscopy (EGD) in patients who are not on acid-suppressive therapy.
- A small proportion of patients will develop metaplasia of the squamous esophageal epithelium to columnar epithelium (Barrett's esophagus). Barrett's esophagus is a risk factor for adenocarcinoma.
- Some patients who present with heartburn have 'functional' heartburn. This is defined as a burning retrosternal discomfort in the absence of

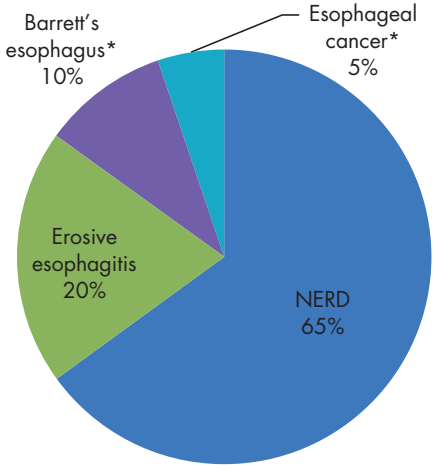

Figure 1.1 Clinical spectrum of GERD. (*May be associated with erosive esophagitis; NERD, nonerosive esophageal reflux disease.)

gastroesophageal reflux or an esophageal motor disorder. Ambulatory pH testing may be useful to differentiate NERD from functional heartburn.

Pathophysiology

- Transient lower esophageal sphincter relaxations (TLESRs):
  - The etiology of GERD is multifactorial; however, 'aberrant' TLESRs are the major pathophysiologic factors in many patients with GERD.
  - A TLESR is defined as relaxation of the lower esophageal sphincter in response to gastric distension. In healthy persons, TLESRs occur in the absence of a swallow, last 10–30 seconds, and result in physiologic gastroesophageal reflux.
  - TLESRs are regulated by the neurotransmitter γ-aminobutyric acid (GABA) acting on GABA type B receptors located in the peripheral nervous system, as well as in the brainstem.
  - In many cases, GERD is thought to be caused by an increased number or a prolonged duration of TLESRs.
- Gastric factors:
  - Increased gastric acid production as well as delayed gastric emptying with distention may trigger TLESRs.
- Diminished esophageal clearance:
  - Poor esophageal clearance due to defects in primary or secondary esophageal peristalsis allows prolonged exposure of the esophageal mucosa to acid.
- Diet and medications:
  - Dietary factors such as acidic foods, caffeine, alcohol, peppermint, and chocolate may reduce lower esophageal sphincter (LES) tone or increase gastric acid production.
  - Medications such as calcium channel blockers, hormones (e.g., progesterone, cholecystokinins, secretin), beta-adrenergic agonists (albuterol), nitrates, and barbiturates can decrease LES tone, thereby predisposing to gastroesophageal reflux.
  - Smoking has also been associated with a predisposition to gastroesophageal reflux.
- Hiatal hernia:
  - A hiatal hernia usually occurs when there is a defect in the diaphragmatic hiatus that allows the proximal stomach to herniate above the diaphragm and into the thorax. It is unclear how this predisposes to gastroesophageal reflux. The barrier function of the LES to prevent the reflux of gastric contents into the esophagus is thought to be disrupted. Large hiatal hernias also lead to increased acid dwell times in the distal esophagus.

Clinical Features

- Thorough history-taking detailing the onset and duration of symptoms and the association of symptoms with meals and diet should be conducted. 'Alarm symptoms' such as vomiting, gastrointestinal bleeding, weight loss, dysphagia, early satiety, and symptoms of cardiac disease should be elicited.
- Patients may present with typical (classic) or atypical symptoms.
- Typical symptoms:
  - **Heartburn** is described as a burning sensation in the substernal area that may radiate to the neck and/or back.
  - **Regurgitation** is the feeling of stomach contents traveling retrograde from the stomach up to the chest and often into the mouth.
  - **Dysphagia** (difficulty swallowing) is reported in about 30% of patients with GERD, even in the absence of esophageal inflammation or a stricture.
  - Less common symptoms associated with GERD include water brash, burping, hiccups, nausea, and vomiting. Water brash is the sudden appearance of a sour or salty fluid in the mouth, and represents secretions from the salivary glands in response to acid reflux. Odynophagia (painful swallowing) occurs when there is severe esophagitis.
  - The sensitivity of typical symptoms for detecting GERD is poor.
- Atypical symptoms:
  - Patients may present with chest pain, chronic cough, difficult-to-treat asthma, and laryngeal symptoms such as hoarseness, throat clearing, or throat pain.
  - Patients with atypical symptoms are less likely than patients with typical symptoms to have endoscopic evidence of esophagitis or Barrett's esophagus. They also have a less predictable response to therapy. Ambulatory esophageal pH testing (see later) is not as sensitive for diagnosing GERD in patients with atypical symptoms as it is in patients with typical symptoms.
- In uncomplicated GERD, physical findings are minimal or absent.

GERD as the etiology of chest pain should be pursued only after potentially life-threatening cardiac etiologies have been excluded.

Diagnosis

Trial of Proton Pump Inhibitor (PPI) Therapy

- A PPI trial is the simplest approach for diagnosing GERD and evaluating symptom response to treatment.

- A 30-day trial of a PPI (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, dexlansoprazole) once daily (taken 1 hour before breakfast) is recommended. If the patient has GERD, symptoms will usually improve within 1–2 weeks.
- The pooled sensitivity of a PPI trial for diagnosing GERD is 78% with a specificity of 54% when compared with 24-hour pH testing.

A PPI trial is recommended as the initial diagnostic and therapeutic intervention in patients with uncomplicated GERD. In patients who fail a PPI trial, additional testing is recommended.

Barium Swallow

- This is a radiographic test that can detect reflux of barium contrast into the esophagus after the patient drinks the contrast solution (see Chapter 27).
- A barium swallow can evaluate other potential mechanical causes for the symptoms (e.g., stricture, neoplasm); however, the test lacks sensitivity (20–30%) to assess mucosal damage. Therefore, barium swallow studies should not be used to diagnose GERD.

Upper Endoscopy

- Upper endoscopy (esophagogastroduodenoscopy, EGD) allows direct visualization of the esophageal mucosa.
- The test has a high sensitivity (90–95%) for diagnosing GERD, but the specificity is only 50%.
- The spectrum of findings on upper endoscopy in persons with GERD includes normal mucosa and esophageal inflammation characterized by erythema, erosions, mucosal breaks, bleeding, and ulceration of the esophageal mucosa.
- Upper endoscopy is recommended for all patients with alarm symptoms such as weight loss, dysphagia, hematemesis, and bleeding.
- Upper endoscopy is used to detect complications of GERD such as stricture or Barrett's esophagus and other upper gastrointestinal disorders (e.g., peptic ulcer).
- Los Angeles classification of erosive esophagitis:
  - grade A: greater than 1 mucosal break, ≤5 mm long;
  - grade B: greater than 1 mucosal break, >5 mm long;
  - grade C: greater than 1 mucosal break, bridging tops of folds but <75% of the circumference of the esophagus;
  - grade D: greater than 1 mucosal break, bridging tops of folds ≥75% of the circumference of the esophagus;
  - Most patients have mild (LA grade A–B) esophagitis.

Endoscopic mucosal biopsies should be obtained in all patients with dysphagia to exclude eosinophilic esophagitis (see Chapter 2).

Ambulatory Esophageal pH Testing

- If an upper endoscopy is normal in a patient with GERD symptoms, esophageal pH testing should be performed next.
- pH monitoring is the 'gold standard' for detecting acid reflux and correlation of reflux with the patient's symptoms.
- A pressure catheter is inserted transnasally and advanced to 5 cm above the manometrically determined LES. The catheter is attached to a data logger that records pH values of the distal esophagus for 24 hours. The patient records his/her meals, position (upright/supine), and symptoms. The patient returns the data logger, and the pH data are downloaded onto a computer that transforms the data into a 24-hour tracing.
- The sensitivity of pH monitoring ranges from 79–96%, with a specificity of 85–100%, in patients with typical symptoms of gastroesophageal reflux.
- A wireless ambulatory pH capsule (Bravo) placed endoscopically allows for 48 hours of pH data recording. The sensitivity of this technique is greater than that of conventional pH monitoring.
- Ambulatory esophageal reflux monitoring should be performed before consideration of endoscopic or surgical therapy in patients with NERD. It is also part of the evaluation of patients refractory to PPI therapy, and should additionally be used in situations when the diagnosis of GERD is questionable.
- Many patients (25–60%) with noncardiac chest pain will have an abnormal ambulatory pH study result.
- Clinical indications for pH monitoring include:
  - refractory gastroesophageal reflux symptoms;
  - atypical symptoms;
  - typical symptoms and a normal upper endoscopy;
  - preoperatively before a fundoplication;
  - follow up of antireflux therapy (see later).
- The most sensitive parameter used to determine pathologic acid reflux includes the percentage of time the pH remains <4 and the correlation with symptoms. A pH <4 suggests that active pepsin may be a part of the refluxate, leading to erosion of the esophageal mucosa and symptoms.
- Some patients continue to have reflux symptoms despite documentation of a negative 24-hour pH test. Weakly acidic (pH = 4–7) as well as nonacidic (pH >7) reflux can produce reflux symptoms. **Multichannel impedance testing** combined with pH testing can be used to assess acidic, weakly acidic, and nonacidic reflux and the relationship of reflux events to symptom events.

Complications

Esophageal Stricture

- The frequency of esophageal strictures (also called peptic strictures) in patients with GERD is 0.1%.
- Esophageal strictures are generally smooth, scarred, circumferential narrowings usually in the distal esophagus (see Chapter 2).
- Patients typically present with progressive dysphagia for solids that usually is not associated with weight loss, as occurs with malignant strictures (see Chapter 2).
- Esophageal peptic strictures are treated with per-endoscopic dilation. Dysphagia improves once the esophageal luminal diameter reaches 15 mm or above.

Barrett's Esophagus

- Prolonged esophageal acid exposure can result in damage to the esophageal mucosa, leading to metaplasia of the squamous epithelium of the distal mucosa to specialized columnar mucosa with goblet cells; this is referred to as **intestinal metaplasia**.
- The diagnosis of GERD is associated with a 10–15% risk of Barrett's esophagus.
- In some persons, intestinal metaplasia may progress to dysplasia and esophageal adenocarcinoma. The risk of progression to adenocarcinoma is estimated to be 0.5–1.0% per year.
- The frequency of Barrett's esophagus is highest in Caucasian men over 50 years of age.
- The diagnosis of Barrett's esophagus is suspected on upper endoscopy by the detection of salmon-colored mucosa extending above the gastroesophageal junction (Z-line) (Figure 1.2). The diagnosis is confirmed by histologic examination (see Chapter 28).
- Endoscopic surveillance should utilize high-resolution/high-definition white-light endoscopy.
- Virtually all patients with Barrett's esophagus are treated with a PPI once daily, indefinitely.
- For Barrett's esophagus patients without dysplasia, endoscopic surveillance should take place at intervals of 3–5 years.
- Endoscopic ablative therapies should not be performed routinely in patients with nondysplastic Barrett's esophagus because of their low risk of progression to esophageal adenocarcinoma.
- In patients with dysplasia, radiofrequency ablation (RFA) is currently the preferred endoscopic ablative therapy, with the goal of removing all neoplasia and Barrett's mucosa. RFA is used to perform circumferential and then focal ablation of dysplasia.

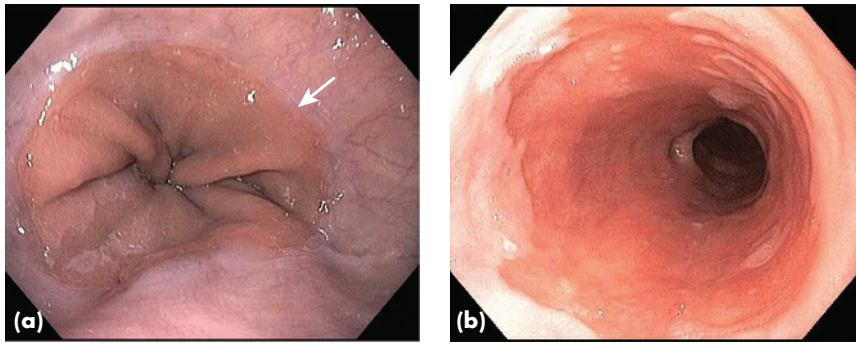

Figure 1.2 Endoscopic images of the normal esophagus and complications of GERD. (a) Normal esophagus showing the squamocolumnar junction (arrow); (b) Barrett's esophagus: intestinal metaplasia is seen as salmon-colored mucosa that extends above the gastroesophageal junction.

- Cryotherapy is a newer method of treating dysplasia, in which liquid nitrogen or carbon dioxide is applied under endoscopic visualization. Studies suggest it eradicates dysplasia in 85–90% of patients.
- Photodynamic therapy uses a photosensitizing agent and laser light to cause cytotoxicity in Barrett's mucosa. It is not used as often as RFA and cryotherapy.
- Endoscopic resection is a technique in which the excision of a large segment of mucosa down to the submucosa is performed. It can be combined with other ablative therapies to eradicate Barrett's esophagus
- After complete elimination of intestinal metaplasia, endoscopic surveillance should be continued to detect recurrent metaplasia or dysplasia.

Treatment

Treatment of GERD depends on the severity of symptoms. Therapy includes lifestyle modification, medication, surgery, or a combination of these.

Lifestyle Modifications

- In patients with mild and infrequent symptoms, lifestyle modifications can decrease the frequency and severity of symptoms, and are considered first-line therapy.
- Recommended changes include weight loss, avoidance of late-night meals, elevation of the head of the bed to at least a 30° angle in an attempt to minimize acid reflux, the avoidance of spicy and greasy foods, acidic foods (such as tomato-based products, and citrus juices), cessation of smoking, and a reduction in alcohol consumption and caffeinated products such as chocolate and carbonated beverages.

- Weight loss and elevation of the head of the bed seem to be the most beneficial lifestyle interventions.

Antacids

- Antacids neutralize gastric acid, thereby raising the pH above 4 and decreasing reflux symptoms.
- The onset of action is approximately 5 minutes after ingestion, and the effect lasts for 90 minutes.
- Over-the-counter antacids and alginates have been found to be helpful in patients with mild, infrequent symptoms of GERD.
- Side effects include diarrhea with magnesium-containing products, and constipation with aluminum-containing formulations.

Histamine H2 Receptor Antagonists (H2RAs)

- H2RAs block histamine H2 receptors on parietal cells of the stomach, thereby inhibiting histamine binding to the cell and decreasing gastric acid production.
- They have a rapid onset of action with a duration of effect from 6–10 hours.
- The healing rate for esophagitis is 50% compared with 24% for placebo.
- These drugs are effective in patients with mild, infrequent symptoms of GERD.

PPIs

- PPIs bind covalently and irreversibly with the hydrogen/potassium adenosine triphosphatase (H+/K + -ATPase) pump on the apical surface of parietal cells in the stomach.
- PPI therapy is the mainstay of treatment for moderate to severe GERD and is used as maintenance therapy.
- Usually, once-a-day dosing is effective. PPIs have been shown to maintain intragastric pH above 4 for 15–21 hours. Occasionally, twice-daily dosing is necessary for patients with severe symptoms or those with erosive esophagitis.
- PPIs have been shown to be superior to H2RAs in healing esophagitis at 8 weeks (83–96% for PPIs versus 50% for H2RAs).
- Reasons for a failure to respond to a PPI include poor adherence, inadequate acid suppression with breakthrough acid secretion, weakly acidic reflux as the cause of symptoms, duodenogastroesophageal reflux, delayed gastric emptying, and functional heartburn.
- The most common side effects of PPIs include diarrhea, headache, and abdominal pain. Chronic PPI use has been associated with a slightly increased susceptibility to enteric infections, including *Clostridium difficile* colitis, small intestinal bacterial overgrowth, electrolyte abnormalities, hip fractures, chronic kidney disease, and dementia, although conclusive evidence for most of these complications is lacking.

- Although there may be slight differences among the various PPIs with respect to potency, the choice of PPI is best made on the basis of prescription plan coverage and a history of adverse side effects.

Additional Medications

- Prokinetic agents such as metoclopramide, a dopamine antagonist, may be effective as an adjunct to PPIs in persons with delayed gastric emptying. Prokinetic agents have no effect in improving esophageal clearance. Side effects include tremors, Parkinson-like symptoms, and tardive dyskinesia. The US Food and Drug Administration (FDA) has not approved metoclopramide for GERD.
- Two GABA-B agonists, baclofen and lesogaberan, have been studied in the treatment of GERD in patients who have not responded to PPIs. They act by inhibiting TLESRs and reflux episodes. Side effects include drowsiness, nausea, and an increased risk of seizures. Neither drug is approved by the FDA for the treatment of GERD.

Endoscopic Therapy

- Endoscopic approaches to the treatment of GERD are considered experimental and are not recommended for its routine treatment.
- The goals of endoscopic therapy are to reduce reflux, alter neural response to acid, and improve symptoms.
- Endoscopic approaches include the delivery of radiofrequency energy to the gastroesophageal junction, the injection of bulking agents in the LES, and the implantation of a prosthetic device into the LES.
- Following such therapy, patients often must continue acid-suppression therapy because of persistent, although often less severe, symptoms.
- Endoscopic gastroplication is a technique in which sutures are placed immediately below the LES to strengthen the LES and reduce reflux. This method has been shown to improve symptoms and quality of life.

Surgical Therapy

- Antireflux surgery corrects the mechanical factors that contribute to GERD. The most common surgical procedure performed is the Nissen fundoplication. The technique involves a 360° wrap of the upper portion of the stomach (fundus) around the distal esophagus to enhance the integrity of the LES (see Chapter 4). This prevents gastric contents from flowing in a retrograde manner into the esophagus, thereby reducing GERD symptoms and allowing the esophageal mucosa to heal. In a patient with a hiatal hernia, the hernia is reduced back into the abdomen during surgery.
- A partial wrap (Toupet fundoplication) is performed in patients who have poor esophageal motility.

- These procedures are most often done laparoscopically to reduce the length of hospital stay and operative morbidity.
- Surgery does not appear to reduce the rate of progression of Barrett's esophagus to adenocarcinoma.
- Surgery is as effective as PPIs in controlling symptoms in the short term (5 years).
- Common adverse effects of a fundoplication include dysphagia (20%) due to too tight a wrap at the LES, and so-called 'gas–bloat syndrome' due to difficulty in expelling air from the stomach. Half of all patients who undergo fundoplication still require acid-suppression medication.
- Surgical fundoplication is a good alternative to PPI treatment in patients who:
  - respond to PPI therapy but want a more permanent treatment or do not tolerate PPIs;
  - respond to PPIs in terms of a decrease in heartburn but continue to have regurgitation;
  - develop recurrent complications of GERD such as a stricture or respiratory complications.

An algorithm for the management of GERD is shown in Figure 1.3.

Pearls

- GERD is a common chronic gastrointestinal disorder. Most patients have mild or moderate symptoms that respond to lifestyle modifications and antacid therapy. However, some patients have severe daily, as well as night-time, symptoms that can significantly reduce their quality of life.
- In patients with typical symptoms (heartburn and regurgitation), a PPI is the mainstay of therapy.
- In patients with atypical or refractory symptoms, ambulatory pH testing and, in some cases, impedance testing are helpful in determining whether the symptoms are truly related to gastroesophageal reflux.
- Early recognition of GERD can result in a reduction in both symptoms and complications of GERD and an improved quality of life.
- GERD can lead to Barrett's esophagus, which can occasionally progress to esophageal adenocarcinoma. Therefore, early diagnosis and treatment of GERD are key.
- There are various methods of treating GERD and its complications.
- Surgical treatment is appropriate in patients who do not wish to be on long-term medical therapy or who continue to have complications of GERD.

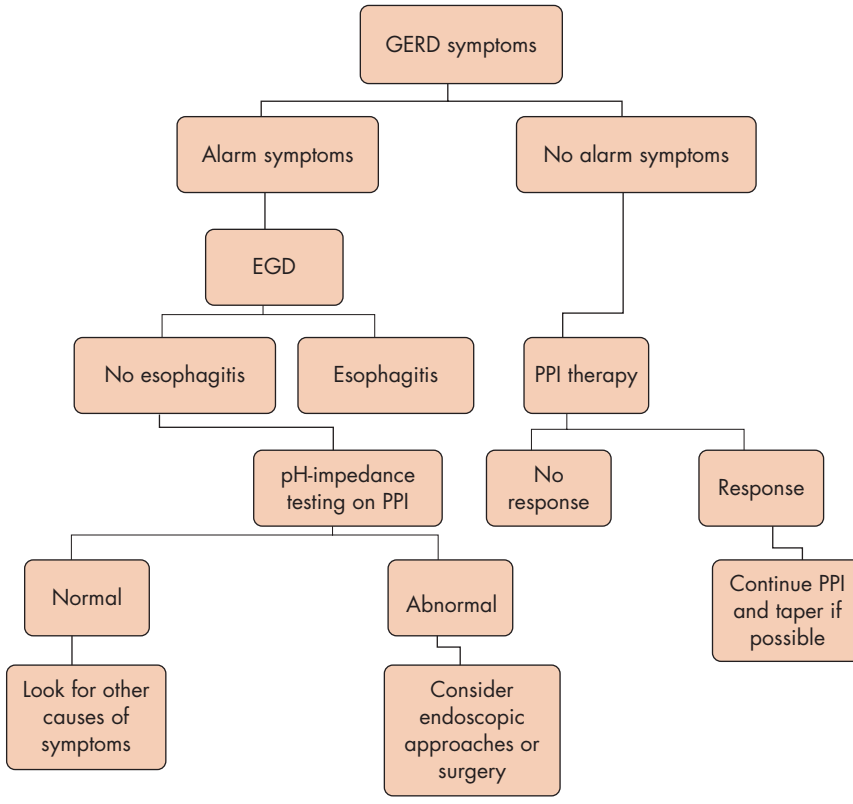

Figure 1.3 Algorithm for the management of GERD. EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

Questions

Questions 1 and 2 relate to the clinical vignette discussed at the beginning of this chapter.

1 Which of the following management strategies would you recommend for this patient?
- **A** Schedule an EGD.
- **B** Continue ranitidine as needed.
- **C** Start a PPI.
- **D** Order a barium swallow.
- **E** Order a 24-hour pH study.

2 Six months later, the patient reports intermittent difficulty swallowing solid food such as bread or rice. He denies odynophagia, weight loss, vomiting, or other symptoms. Which of the following is the most likely cause of dysphagia?

A Achalasia.
B Benign esophageal stricture.
C Esophageal cancer.
D Barrett's esophagus.
E Hiatal hernia.

3 Which of the following is considered to be the major pathophysiologic factor in GERD?

A Hiatal hernia.
B Smoking.
C Poor esophageal motility.
D TLESRs.
E Obesity.

4 Long-standing GERD is a risk factor for which of the following?

A Squamous cell cancer of the esophagus.
B Adenocarcinoma of the esophagus.
C Peptic ulcer disease.
D Gastric adenocarcinoma.
E Achalasia.

5 Surgical fundoplication for GERD has been shown to result in which of the following?

A Greater improvement in symptoms of GERD compared with therapy with a PPI.
B Greater improvement in symptoms of GERD in patients with persistent regurgitation despite therapy with a PPI.
C Improvement in esophageal clearance.
D Reduction in the frequency of adenocarcinoma in patients with Barrett's esophagus.
E Reduction in gastric acid production.

6 Which of the following does NOT reduce the symptoms of GERD?

A Weight loss.
B Avoidance of caffeine.
C Alcohol cessation.
D Gluten-free diet.
E Tobacco cessation.

7 Which of the following medications does NOT provide symptomatic improvement in GERD?
A GABA-B agonists.
B PPIs.
C Benzodiazepines.
D H2RAs.
E Antacids.

Answers

1 C
The patient presents with symptoms of GERD, including heartburn, chest discomfort, a sore throat, and a bitter taste in the mouth. GERD may cause chest pain that can be indistinguishable from ischemic cardiac pain, and the first priority often is to rule out heart disease as the etiology. In this patient, a cardiac work-up was negative. An upper endoscopy may be a reasonable choice if the patient is >50 years of age (the risks of Barrett's esophagus and adenocarcinoma increase with age), has alarm symptoms such as unintentional weight loss, gastrointestinal bleeding, vomiting, or dysphagia, or does not respond to a trial of a PPI. The most cost-effective diagnostic test for GERD in a younger person is a trial of a PPI. A barium swallow is not sensitive to diagnose GERD. A 24-hour pH study may be obtained if the patient does not respond to a trial of a PPI.

2 B
The most common complication of GERD is a benign esophageal stricture, which occurs in 0.1% of patients with GERD. Esophageal cancer (adenocarcinoma) is a possibility in a patient with long-standing GERD, but is less likely in the absence of alarm symptoms. Patients with Barrett's esophagus are often asymptomatic or have typical symptoms of GERD. A hiatal hernia contributes to GERD but generally does not cause dysphagia. Achalasia is a motility disorder of the esophagus that presents with progressive dysphagia for both solids and liquids.

3 D
The etiology of GERD is multifactorial; smoking, poor esophageal motility, obesity, and hiatal hernia may contribute to GERD. TLESRs are the major etiologic factors in most patients with GERD.

4 B

5 B
Surgical fundoplication (wrapping or plicating of the stomach around the esophagus) is as effective as PPI therapy in controlling symptoms in the short

term (5 years). It is a good alternative to PPI treatment in patients who have persistent regurgitation or develop complications of GERD, such as a benign stricture or respiratory complications. Surgical fundoplication does not decrease the rate of progression of Barrett's esophagus to adenocarcinoma and does not affect gastric acid secretion.

6 D

All of the approaches listed have been shown to improve GERD symptoms except for a gluten-free diet. Gluten intake has not been shown to have any effect on GERD.

7 C

Benzodiazepines have not been shown to alleviate GERD symptoms. GABA-B agonists, PPIs, H2RAs, and antacids have all been shown to provide symptomatic improvement in GERD.

Further Reading

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Weblinks

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