Gastroesophageal Reflux Disease

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1. Diagnosis

Consider GERD in patients with a history of troublesome symptoms or complications resulting from the reflux of gastric contents.

1.1 Look for troublesome heartburn and regurgitation as symptoms of the typical reflux syndrome.

Recommendations

- Understand that heartburn is a burning sensation in the retrosternal area.
- Understand that regurgitation is the perceived flow of refluxed gastric contents into the mouth or hypopharynx.
- Ask specifically if heartburn and/or regurgitation:
  - Occur most often after meals, especially fatty meals
  - Are aggravated by recumbency, bending, or physical exertion
  - Are relieved by antacids
- Ask about the presence and frequency of nighttime heartburn:
  - Does heartburn awaken the patient from sleep?
  - Does nighttime heartburn disturb sleep?
- Ask about warning symptoms including dysphagia, odynophagia, bleeding, anemia, early satiety, choking, coughing, weight loss, and frequent vomiting which may suggest more serious diagnoses such as peptic stricture, ulceration, or cancer.
- Ask about induction of GERD symptoms by physical exercise.
- Do not diagnose GERD in patients who do not consider their symptoms troublesome.
- See figure Approach to the Treatment in the Primary Care Setting.

Evidence

- Definitions of GERD and its related syndromes were derived by expert consensus (1).
- Typical symptoms are sufficient to make the diagnosis in uncomplicated cases (2).
- When the principal symptoms of heartburn (pyrosis) (89% specificity, 81% positive predictive value) and regurgitation (95% specificity, 57% positive predictive value) occur together, a physician can diagnose GERD with >90% accuracy (3; 4).
- Approximately 20% of the U.S. population report heartburn at least weekly, and 40% have symptoms at least monthly (5; 6).
- Two national telephone surveys conducted to assess the prevalence and impact of nocturnal symptoms in patients with GERD found that nocturnal heartburn occurs in a majority of adults with GERD and negatively affects their health-related quality of life (7; 8).
- Studies have shown increased esophageal acid exposure during intense exercise (9).
- Two reviews discuss the severity of nocturnal GERD and the associated increased risk for esophageal and respiratory complications (10; 11).

Rationale

- Patients with classic symptoms rarely require a confirmatory test, given the positive predictive value of these symptoms; symptom resolution frequently is used as the clinical endpoint.
- Prevalence of nighttime heartburn is high among patients with GERD.
• Sleep-related nighttime reflux is associated with more severe esophageal damage.

Comments
• Due to the high prevalence of symptoms, ordering diagnostic tests for all patients with symptoms would incur enormous costs.
• The actual frequency of sleep-related gastroesophageal reflux among patients with nighttime heartburn is not known, but subjective reports of nighttime heartburn are associated with more severe daytime symptoms, and patients with nighttime symptoms report that those symptoms are more bothersome than daytime symptoms (7; 12).
• Some reflux is physiologic; therefore, patients should not be diagnosed as having GERD by virtue of merely reporting symptoms without those symptoms being troublesome.

1.2 Always consider a cardiac source of symptoms if chest pain is present.

Recommendations
• Exclude CAD in patients with chest pain suspected to be due to GERD, or in patients with chest pain in addition to symptoms of GERD.
• See table Differential Diagnosis of GERD.

Evidence
• Symptoms are unreliable in differentiating GERD from a cardiac source of chest pain (13).
• Eleven percent of patients with GERD as the cause of chest pain do not have classic symptoms of heartburn or regurgitation (14).
• Up to 50% of patients with cardiac pain may have classic esophageal symptoms of heartburn and regurgitation (15).
• A population-based cohort study with nested case-control analysis using the UK General Practice Research Database studied 3028 adults with new chest pain without history of ischemic heart disease. Over a period of 1 year, these patients were more likely than controls to receive a diagnosis of ischemic heart disease (HR = 18.2 [CI, 11.6 to 28.6]) (16).
• GERD is present in approximately 50% of unexplained chest pain cases after CAD has been excluded (14).

Rationale
• The morbidity and mortality of CAD far exceeds that of GERD.

Comments
• In patients without classic symptoms of GERD, 24-hour esophageal pH monitoring may be helpful in identifying gastroesophageal reflux as the cause of unexplained chest pain (17; 18).

1.3 Consider a diagnosis of GERD in patients with non-cardiac chest pain.

Recommendations
• Once a cardiac cause has been ruled out, investigate patients with non-cardiac chest pain in the same manner as patients with typical reflux symptoms.

Evidence
• A retrospective review of esophageal manometry results in 140 patients with non-cardiac chest pain found that hypotensive lower esophageal sphincter was found in 61%, while ‘nutcracker esophagus’ and non-specific esophageal motility disorders were diagnosed in only 10% (19).
• A 2005 meta-analysis of six placebo-controlled studies evaluated the accuracy of PPI testing in the diagnosis of GERD in patients with non-cardiac chest pain. In these studies, GERD was confirmed with either 24-hour esophageal pH monitoring or endoscopy. The PPI test had a higher
discriminative power (diagnostic OR, 19.35 [CI, 8.54 to 43.84] compared with 0.61 [CI, 0.20 to 1.86] in the placebo group) (20).

**Rationale**
- Non-cardiac chest pain is common.
- Reflux chest pain may be indistinguishable from ischemic chest pain.
- Reflux chest pain may not be accompanied by heartburn or regurgitation.
- Although esophageal motor disorders may also cause non-cardiac chest pain, GERD is a more frequent cause.

**Comments**
- Esophageal motility disorders should be suspected more strongly when dysphagia is present in association with non-cardiac chest pain.

**1.4 Diagnose GERD in patients with defined esophageal injury.**

**Recommendations**
- Diagnose GERD in patients with reflux esophagitis, reflux stricture, Barrett's esophagus, or esophageal adenocarcinoma, all of which are considered defining complications.
- Suspect stricture in patients with GERD who complain of troublesome dysphagia.
- Note that dysphagia is considered a warning or alarm symptom that needs immediate evaluation as it may be due to stricture.

**Evidence**
- In one study, 37% of GERD patients had dysphagia; 83% reported improved dysphagia with PPI treatment (21).
- Reflux stricture develops in less than 5% of patients with GERD (22).
- The risk for esophageal adenocarcinoma is increased in patients with GERD (OR, 7.7) (23).

**Rationale**
- Although less than half of patients with GERD have esophagitis seen at endoscopy, its presence is indicative of GERD.
- Reflux stricture, Barrett's esophagus, and adenocarcinoma are thought to arise as a consequence of esophagitis in susceptible patients.

**Comments**
- Heartburn intensity and frequency do not accurately predict severity of mucosal injury or development of other complications.
- Dysphagia is common in GERD but not always troublesome, and not always indicative of stricture.
- The overall lifetime risk for adenocarcinoma remains low (less than 1%).

**1.5 Ask about extra-esophageal manifestations, including pulmonary and otolaryngological symptoms.**

**Recommendations**
- Ask specifically about atypical or extra-esophageal symptoms that may be associated with other disease processes, including:
  - Wheezing
  - Shortness of breath
  - Chronic cough
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- Chronic hoarseness
- Unexplained chest pain
- Globus, choking
- Halitosis
- Sore throat
- Dental erosions

**Evidence**

- Extra-esophageal symptoms are common in patients (24).
- GERD has been associated with a spectrum of bronchopulmonary and otolaryngological disorders (25; 26).
- Reflux symptoms are reported in up to 77% of asthmatic patients, and 32% to 82% of asthmatic patients have abnormal pH studies (27; 28; 29).
- GERD is a primary etiologic factor in 10% to 20% of patients with chronic cough, up to 80% with chronic hoarseness, and in 15% to 50% with globus sensation (30).
- Up to 80% of patients have at least one extra-esophageal symptom (6).
- A randomized, controlled study of 770 asthmatics showed improved peak expiratory flow with twice-daily PPI use only in those with nocturnal pulmonary and GERD symptoms (31).
- Two randomized, controlled studies of fundoplication surgery led to improvement in asthma in patients who also had objective evidence of GERD (32; 33).

**Rationale**

- GERD may cause extra-esophageal disease via supra-esophageal reflux or vagal reflexes, resulting in bronchial hypersensitivity.

**Comments**

- Although these conditions are associated, establishing a definitive causal relationship between GERD and extra-esophageal conditions has been difficult. GERD may be one of many causes for these conditions.
- These manifestations rarely occur in the absence of concomitant typical reflux symptoms.
- Randomized, controlled studies of GERD treatment for improvement of chronic cough or laryngitis have failed to show a complete treatment response, although observational and uncontrolled trials have shown a benefit.
- Other conditions, including pharyngitis, sinusitis, idiopathic pulmonary fibrosis, and recurrent otitis media, have been proposed as associated with GERD, although evidence is less robust.

### 1.6 Perform a focused physical exam to look for complications or extra-esophageal manifestations.

**Recommendations**

- Look for warning or alarm findings, including weight loss or evidence of gastrointestinal bleeding such as hemoccult-positive stools, which may be due to serious disease or complications (e.g., ulcerations or cancer).
- On physical exam, look for pulmonary or oropharyngeal manifestations, especially when warning or extra-esophageal symptoms (e.g., wheezing, pharyngitis, dental erosions) occur.

**Evidence**

- The diagnosis can be made reliably by history alone (3; 34).

**Rationale**
A physical exam, although rarely remarkable, is recommended for patients with uncomplicated GERD.

Comments
- No studies have examined the effect of physical exam on the diagnosis or treatment. The physical exam is usually normal even in the presence of severe, extra-esophageal, or complicated disease.

1.7 Consider a response to an empirical trial of acid suppression in a patient with classic symptoms to be a sufficiently diagnostic ‘laboratory test.’

Recommendations
- Make the diagnosis in patients with symptoms of heartburn or regurgitation who respond to an empirical course of high-dose acid suppression with double-dose PPIs (e.g., omeprazole, 20 to 40 mg bid) for 1 week or standard-dose PPIs for 2 weeks, reserving further studies for atypical or persistent cases or patients with warning or alarm symptoms or signs.
- See table Laboratory and Other Studies for GERD.
- See table Drug Treatment for GERD.

Evidence
- The sensitivity of empirical high-dose acid suppression for erosive esophagitis is 80% (35).
- The sensitivity for empirical high-dose acid suppression with PPIs is 83% for non-erosive GERD (36).
- In one study, the sensitivity and specificity for empirical high-dose acid suppression was 75% and 55%, respectively (37).

Rationale
- Relief of classic symptoms with high-dose acid suppression is sufficiently sensitive and specific for diagnosis.

Comments
- The high-dose empirical acid suppression in these studies consisted of omeprazole, 20 to 40 mg bid, for 1 week.
- In another study, 14 days of omeprazole, 40 mg/day, had the same diagnostic accuracy as pH testing (38).

1.8 Consider upper endoscopy of the esophagus in specific subsets of patients.

Recommendations
- Obtain upper GI endoscopy:
  - In patients with alarm symptoms suggestive of GERD complications (including dysphagia, bleeding, anemia, weight loss, and recurrent vomiting)
  - To rule out Barrett's esophagus in patients at increased risk for this condition (see recommendations on consulting with a gastroenterologist for endoscopy when the risk for Barrett's esophagus is increased)
  - In patients with typical GERD symptoms that persist despite a therapeutic trial of 4 to 8 weeks of twice-daily PPI therapy
  - In patients with severe erosive esophagitis after a 2-month course of PPI therapy to assess healing and rule out Barrett's esophagus
  - Defer upper endoscopy for diagnosis if the patient responds to empirical therapy.
  - Do not order screening endoscopy for the general population with GERD.
- See table Laboratory and Other Studies for GERD.
Evidence

- In 2012, the Clinical Guidelines Committee of the American College of Physicians provided best practice advice on when an upper endoscopy is indicated in patients with GERD (39).
- The specificity of endoscopy for esophagitis is 90% to 100% (34).
- The sensitivity of endoscopy is 30% to 50% (34).
- The combination of typical symptoms and endoscopic evidence of reflux is 97% specific for the diagnosis when supported by pH testing (34).
- The diagnostic accuracy of radiography is poor when compared with endoscopy for mild (25%) and moderate (80%) esophagitis (40).
- Approximately 50% to 70% of patients with classic symptoms have negative endoscopic results. In rare patients, endoscopic esophagitis is not caused by reflux but rather by infection, pill-induced injury, or radiation. There is little value for histologic evaluation of normal-appearing squamous mucosa to detect pathologic acid reflux (41).
- In 1999, the American College of Gastroenterology established guidelines for the diagnosis and treatment of GERD (2).
- The above recommendations on the diagnosis and treatment of GERD are drawn from the Practice Parameters Committee of the American College of Gastroenterology (2).

Rationale

- Endoscopic confirmation of Barrett's esophagus allows initiation of a surveillance program.
- GERD complications such as peptic stricture, ulceration, Barrett's esophagus, and adenocarcinoma of the esophagus require immediate diagnosis for proper management.

Comments

- The absence of erosive esophagitis on endoscopy does not preclude GERD as a cause of a patient's symptoms and does not preclude treatment of GERD in patients who are symptomatic.

1.9 Recognize that ambulatory pH monitoring is the most effective test to establish the presence of gastric acid reflux.

Recommendations

- Obtain ambulatory pH monitoring in patients with symptoms refractory to empirical therapy with PPIs or who have persistent extra-esophageal symptoms while on PPI therapy.
- See table Laboratory and Other Studies for GERD.

Evidence

- Endoscopy is normal in 50% to 70% of patients with typical symptoms and in >50% of patients with extra-esophageal manifestations (42; 43; 44).
- Ambulatory pH monitoring is the most effective test to determine if increased reflux is present in patients with extra-esophageal manifestations (24; 45) or in those with esophagitis resistant to treatment (46).
- Ambulatory pH monitoring is an imperfect 'gold standard' because up to 25% of patients with documented esophagitis may have normal acid exposure on pH monitoring (47).

Rationale

- Many patients with typical and atypical symptoms who have increased esophageal acid exposure do not have esophagitis confirmed by endoscopy.

Comments
Despite limitations, ambulatory pH monitoring remains the best diagnostic test to measure the actual amount of time reflux is present in a given patient, and to correlate symptoms with reflux events. The determination of whether to obtain upper endoscopy or ambulatory pH monitoring in the diagnostic evaluation depends on the clinical information desired. Endoscopy is the appropriate test for the presence of mucosal damage, and pH monitoring is the appropriate test for the presence of pathological gastroesophageal reflux.

The use of the pH test has been limited to assessment of therapeutic failure in patients with classic GERD symptoms or patients with atypical extra-esophageal manifestations of GERD who continue to experience symptoms while on once- or twice-daily PPI therapy.

Esophageal pH studies can be accomplished by applying a wireless pH sensor to the esophageal mucosa during endoscopy. These studies allow the convenience of easy pH placement during sedation, and data can be more easily collected for up to 48 hours, which increases the sensitivity of the test. Endoscopic placement limits the utility of this method.

Nonacid (volume) reflux may be responsible for ongoing symptoms in some GERD patients whose acid is already suppressed or who have seen no benefit from acid suppression.

Consider combined impedance-pH testing in patients with persistent symptoms despite an adequate medical trial, or for monitoring patients while on therapy.

Intraluminal impedance studies can be useful in determining the extent to which persistent symptoms on treatment or atypical symptoms can be attributable to non-acidic reflux (48; 49).

1.10 Recognize that the use of barium radiography is limited.

Recommendations
- Do not use barium radiography in the routine diagnosis.
- Note that barium swallow is the most sensitive test for detecting esophageal strictures and, thus, may be useful in the evaluation of patients with dysphagia.
- See table Laboratory and Other Studies for GERD.

Evidence
- Reflux of barium during radiographic exam is positive only 25% to 75% of the time in patients and is falsely positive in up to 20% of controls (2; 50).
- The accuracy of radiography is inferior to endoscopy in the diagnosis of esophagitis (40).
- Reflux of barium and hiatal hernia shown on radiographic exam have poor sensitivity and specificity compared with pH testing (51).
- One study found that by combining a test to provoke reflux with a double-contrast technique to measure the internal diameter of the cardiac esophagus, barium radiology becomes a sensitive screening test for reflux (52).

Rationale
- Reflux of barium, hiatal hernia, and esophagitis detected on barium radiography have poor sensitivity and specificity when compared with endoscopy or ambulatory pH monitoring.

1.11 Recognize that esophageal manometry has a limited role in the diagnosis.

Recommendations
- Use esophageal manometry only to facilitate placement of ambulatory pH probes and to evaluate esophageal function before antireflux surgery.
- See table Laboratory and Other Studies for GERD.
Evidence
• Manometrically determined impaired peristalsis, LES hypotension, decreased LES length, and/or an increased number of transient LES relaxations are associated; however, manometric findings have no demonstrable influence on diagnosis, staging, or drug treatment (17).
• Low LES pressure has low sensitivity (58%) and specificity (84%) for abnormal acid exposure (53).
• Manometry has been used to identify the LES to allow accurate placement of pH probes (54).
• Esophageal manometry may be important in the preoperative evaluation before antireflux surgery. Surgeons may alter the surgical approach in patients with manometrically determined peristaltic dysfunction (55; 56).

Rationale
• There are no specific manometric findings sensitive and specific for the clinical diagnosis.

Comments
• Multichannel intraluminal impedance determines the composition of the refluxate by assessing electrical conductivity and pH with an integrated pH sensor. Use of this technique is limited to research protocols.

1.12 Consider alternative esophageal, upper-GI, or biliary disease in patients with atypical presentations.

Recommendations
• In patients with atypical symptoms (e.g., dysphagia/odynophagia, chest pain, dyspepsia) or who have not responded to empirical therapy, consider the following disease processes:
  • Infectious esophagitis
  • Pill esophagitis
  • Esophageal motility disorders
  • Esophageal cancer
  • Non-ulcer dyspepsia
  • Peptic ulcer disease
  • Biliary tract disease
  • Consider doing an esophageal motility study to rule out esophageal motility disorders such as hypertensive esophageal contractions or other esophageal dysmotilities as a potential cause of atypical symptoms.
  • See table Differential Diagnosis of GERD.

Evidence
• Dysphagia and/or odynophagia are unusual symptoms of uncomplicated GERD (57).
• Esophageal motility disorders can be associated with atypical symptoms of chest pain, globus, and dysphagia (18; 19).

Rationale
• The differential diagnosis is limited in patients with typical symptoms of heartburn and regurgitation.
• Symptoms of dysphagia and/or chest pain have been noted in patients with hypertensive esophageal contractions, i.e., the ‘nutcracker esophagus’ or other esophageal motility disorders which may be associated with GERD.

Comments
• Up to 50% of patients with dyspepsia report symptoms of GERD (58).
• Although patients with atypical symptoms of GERD may have esophageal motility disorders, the sensitivity and specificity of motility findings are not particularly useful in identifying a definitive cause of the symptom. The best approach is to attempt to treat the underlying motility disorder to determine whether treatment resolves the particular symptom of interest.
2. Consultation

Consider consultation with a gastroenterologist when there is diagnostic uncertainty, therapeutic failure, or suspicion of complicated disease. Consider consultation for management of refractory, complicated, or extra-esophageal manifestations of GERD; when Barrett's esophagus is suspected; or when surgical therapy is contemplated.\[BC\]

2.1 Consider consultation with a gastroenterologist or other appropriate specialist when there is diagnostic uncertainty or therapeutic failure.\[B\]

Recommendations

- Consider the following indications for consultation:
  - Lack of response to an empirical trial of acid suppression with standard-dose PPIs for 4 to 8 weeks
  - Pulmonary or otolaryngological symptoms, including wheezing, shortness of breath, chronic cough, chronic hoarseness, unexplained chest pain, globus, choking, halitosis, or sore throat, which have not responded to an empirical therapy of at least double-dose PPIs for a period of 2 to 3 months

Evidence

- Only 43% of patients with ear, nose, and throat manifestations complain of heartburn (\[60\]).
- Evaluation of atypical or extra-esophageal manifestations may require an empirical trial of acid suppression with PPIs (\[61; 62\]).
- Treatment with PPIs results in 90% to 100% effectiveness rates (\[63; 64\]).
- Treatment of extra-esophageal symptoms such as laryngitis, cough, etc., is associated with variable and unpredictable symptom relief (\[65\]).

Rationale

- Patients with pulmonary or otolaryngological symptoms may not have typical symptoms (e.g., heartburn, regurgitation) associated with their extra-esophageal manifestations. Patients who do not respond to acid-suppression therapy may not have GERD as the cause of their symptoms.

Comments

- In all patients treated with PPIs it should be emphasized, and verified in non-responders, that the drug is taken approximately 30 minutes before a meal. Absorption and blood levels are markedly diminished without meal-stimulated activation of proton pumps in the gastric parietal cell.
- An 8-week trial of a high-dose (twice-daily) PPI, followed by pH testing in non-responders, has been advocated by some experts to fully rule out excessive acid exposure as a cause of possible extra-esophageal syndromes.

2.2 Consider consultation with a gastroenterologist for diagnosis when complicated disease is suspected.\[BC\]

Recommendations

- Consider referral for diagnostic endoscopy for patients who develop warning symptoms, including:
  - Dysphagia or odynophagia
  - Bleeding
  - Weight loss
  - Anemia
Evidence

- Early satiety
- Choking (acid causing coughing, shortness of breath, or hoarseness)
- Anorexia
- Frequent vomiting

Rationale

- Patients with warning symptoms may have developed a complication such as cancer, stricture, or ulceration. Endoscopy is the most effective modality to diagnose and treat complications.

Comments

- In patients with dysphagia, an esophageal motility study may be helpful in identifying patients who may have an underlying motility disorder such as achalasia or esophageal spasm.
- When complicated disease or Barrett’s esophagus is not suspected, there is no proven benefit of periodic or routine endoscopy to assess for disease progression in patients with chronic GERD.

2.3 Consider consultation with a gastroenterologist for endoscopy when the risk for Barrett's esophagus is increased.

Recommendations

- Consider obtaining a screening endoscopy to exclude Barrett's esophagus in patients with longstanding GERD who have multiple risk factors for adenocarcinoma.
- Order upper endoscopy to detect Barrett's esophagus or adenocarcinoma in men aged more than 50 years with GERD symptoms for more than 5 years and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated BMI, tobacco use, and intra-abdominal distribution of fat).
- Do not order screening endoscopy in the general population with GERD.
- Note that the diagnosis of Barrett's esophagus requires the presence of specialized intestinal metaplasia in endoscopic biopsy samples taken from abnormal-appearing mucosa in the tubular esophagus.

Evidence

- In 2012, the Clinical Guidelines Committee of the American College of Physicians provided best practice advice on when an upper endoscopy is indicated in patients with GERD (39).
- The American Gastroenterological Association recommends screening for Barrett's esophagus in patients with multiple risk factors for esophageal adenocarcinoma (71).
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- The American College of Gastroenterology notes that screening for Barrett's esophagus remains controversial (72).
- The risk for Barrett's esophagus developing in patients with symptoms lasting more than 5 years was 5 times that of patients with symptoms lasting less than 1 year (73).
- Other studies have shown an increased risk for Barrett's esophagus and esophageal adenocarcinoma in white men aged over 50 years (74).
- Symptom severity is unreliable in patients with Barrett's esophagus because they have decreased acid sensitivity (75).
- The risk for adenocarcinoma developing from Barrett's esophagus is 30 to 40 times that of the general population. The incidence of adenocarcinoma developing from Barrett's esophagus is approximately 0.12% to 1.0% per year (76; 77).
- The incidence of the esophageal adenocarcinoma and gastric cardia is rising rapidly in the Western world (78).
- Two retrospective studies (19 patients and 17 patients) found that endoscopic surveillance of patients with Barrett's esophagus detects carcinoma at an early stage and can improve long-term survival rates (79; 80).
- An autopsy study from Olmsted County in Minnesota showed that the incidence of Barrett's esophagus was 20 times the incidence of patients seeking medical care for reflux symptoms (81).

**Rationale**

- Clinical severity of symptoms alone is unreliable in distinguishing patients with Barrett's esophagus from those with GERD only.
- The risk for Barrett's esophagus and adenocarcinoma is increased in patients with chronic symptoms (lasting more than 5 to 10 years), white race, age over 50, hiatal hernia, and elevated BMI. The severity of symptoms is unreliable when trying to differentiate patients with and without Barrett's esophagus.

**Comments**

- The diagnosis of Barrett's esophagus is made when intestinal metaplasia is seen in endoscopic biopsy samples taken from columnar-appearing mucosa in the tubular esophagus.
- Clinicians should understand that a recommendation to screen even higher-risk patients for Barrett's esophagus is based on expert opinion, and has not been shown to reduce mortality from esophageal adenocarcinoma.

### 2.4 Consider referring patients to a gastroenterologist when symptoms are refractory to PPI therapy.

**Recommendations**

- Refer patients who are refractory to PPI therapy to a gastroenterologist for further management.
- Consider using the PPI Acid Suppression Symptom (PASS) test to identify patients on PPI therapy with persistent symptoms who may benefit from a change in therapy.

**Evidence**

- Patients who do not respond to standard-dose PPI therapy may benefit from doubling the dose (145).
- Medical therapy with PPIs once daily produces esophageal inflammation remission rates of up to 94% (146).
• The PASS test is an easy-to-use, validated patient questionnaire whereby an affirmative answer to any of the following five questions identifies a patient with persistent symptoms (147):
  • Are you still experiencing stomach symptoms?
  • Are you using OTC medications in addition to PPIs for control of symptoms?
  • Is your sleep affected by stomach symptoms?
  • Are your eating or drinking habits affected by stomach symptoms?
  • Are your stomach symptoms interfering with your daily activities?
• Endoscopy-oriented treatment was found to be less cost-effective than empiric PPI use for patients with suspected GERD (148).
• Some refractory patients may have non-acidic reflux (149).
• Drug therapy may be directed by the endoscopic appearance of the esophagus (150).

Rationale
• Most patients’ symptoms are controlled with PPI therapy; symptoms that do not respond to PPI therapy may not be caused by GERD.

Comments
• Esophageal manometry generally is indicated only before antireflux surgery.
• Impedance reflux monitoring studies can identify the presence and symptom correlation for both acidic and non-acidic reflux (48; 49).

2.5 Consider referring patients to a gastroenterologist for management of complications.C

Recommendations
• Refer patients who have warning symptoms after appropriate medical management, because they may have developed a complication.

Evidence
• Expert opinion recommends further diagnostic evaluation if warning symptoms are present (4).
• Esophageal strictures can be medically well managed with the addition of endoscopic dilation (151).
• Treatment with PPIs has been shown to decrease the need for stricture dilation (117).
• Peptic strictures develop in 2% to 10% of patients (67).
• Although dysphagia may be a symptom of a stricture or cancer, non-obstructive causes (e.g., peristaltic dysfunction, erosive esophagitis) may occur in patients (68) or hypertensive or spastic esophageal motility disorders (69).

Rationale
• Patients sometimes develop complications, such as cancer, stricture, or ulceration.

2.6 Consider referring patients to a subspecialist to exclude extra-esophageal manifestations of GERD.C

Recommendations
• Consider referral to cardiology, pulmonary, and/or otolaryngological consultants, depending on the extra-esophageal manifestation or if other causes of the symptoms are likely.

Evidence
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- Seventy-eight percent of patients with unexplained chest pain due to GERD responded to high-dose acid suppression with omeprazole, which was more cost effective than other diagnostic testing (61).
- Twenty-seven percent of patients with asthma and GERD needed more than 20 mg/day of omeprazole to normalize esophageal acid exposure. In addition, symptoms continued to improve for the duration of the 3-month trial (152).
- A review of data from patients with refractory reflux esophagitis who were undergoing maintenance therapy with more than 20 mg/day for a range of 1.4 to 11.2 years, found that omeprazole therapy is effective and safe for the control of reflux esophagitis (153).
- These patients may or may not have the classic symptoms (heartburn and regurgitation) and are often best diagnosed with an empirical trial of high-dose acid suppression or ambulatory pH testing (154).

Rationale

- Patients with extra-esophageal manifestations may not have the classic esophageal symptoms and often require higher doses of acid suppression and longer therapeutic trials than do patients with heartburn and regurgitation.

Comments

- Highly selected patients with extra-esophageal symptoms refractory to high-dose acid suppression may respond to antireflux surgery (155).

2.7 Consider referring patients to a gastroenterologist for management of Barrett's esophagus.

Recommendations

- Ensure that patients with Barrett's esophagus are followed by a gastroenterologist, because Barrett's esophagus requires surveillance via endoscopy and biopsy to check for the presence and grade of dysplasia.
- Note that estimates of the risk for adenocarcinoma in patients with Barrett's esophagus show a lower absolute risk than previously shown, although the risk is still increased compared with patients without Barrett's esophagus.
- Recognize that Barrett's esophagus with evidence of dysplasia mandates close follow-up with a gastroenterologist, requiring accelerated surveillance and possible intervention.
- See figure Proposed Surveillance and Management Algorithm for Patients with Barrett's Esophagus Based on Grade of Dysplasia Detected by Endoscopic Biopsy.
- See module Barrett's Esophagus.

Evidence

- Barrett's esophagus is present in 10% to 15% of patients (156).
- Studies have shown somewhat variable increased risk for malignancy in patients with Barrett's esophagus, from an 11-fold relative risk (77) to a 30- to 125-fold greater risk (76).
- The incidence of adenocarcinoma developing from Barrett's esophagus previously reported at approximately 0.5% to 1.0% per year (76) has been reported in another cohort study of over 11,000 patients with Barrett's esophagus to be 0.12% per year (77).
- The incidence of esophageal adenocarcinoma is rising rapidly in the Western world (157).
- The interval for surveillance is determined by the presence and grade of dysplasia on pathologic biopsy sample, generally every 3 to 5 years in the absence of dysplasia (74).
• Decision analysis modeling shows that screening 50-year-old men for Barrett's esophagus with endoscopy is cost effective (158).

Rationale
• Barrett's esophagus is a pre-malignant lesion with increased risk for developing esophageal adenocarcinoma. Regular surveillance is recommended with the hope that it can allow earlier detection of adenocarcinoma with improved survival.

Comments
• The management of Barrett's esophagus is complex and requires knowledge of the latest endoscopic and medical management techniques, such as endoscopic ablation, and possible surgical management in patients who develop adenocarcinoma.
• See also Follow-up with patients in whom Barrett's esophagus has been detected.

2.8 Consider referring patients with GERD to a gastroenterologist and surgeon when contemplating surgical therapy.66

Recommendations
• Although the indications for surgery are controversial in GERD, consider surgery as an option for patients with well-documented disease who require chronic PPI maintenance therapy but showed satisfactory relief of symptoms who:
  • Are aged less than 50 years
  • Consider chronic medication a financial burden
  • Are non-compliant with drug therapy
  • Prefer a single surgical intervention to long-term drug treatment
  • Experience prominent symptoms of regurgitation, even with medical control of heartburn symptoms
  • Carry out careful preoperative evaluation before surgery, including documentation of GERD and esophageal manometry.

Evidence
• Antireflux surgery has been shown to be superior to H2RAs and prokinetics for long-term maintenance (159).
• A 2010 Cochrane review identified four studies that compared medical management with laparoscopic fundoplication surgery. The analysis found evidence that laparoscopic fundoplication surgery was more effective than medical therapy at 1 year follow-up. However, the surgery had some risks (160).
• Antireflux surgery is as effective as acid suppression with PPIs for maintenance at 5-year follow-up (135).
• Careful preoperative evaluation results in a change in the type of surgical therapy in up to 10% of cases referred for surgical management (161).
• The long-term durability of antireflux surgery is defined inadequately, but initial studies have shown durability for as long as 20 years (162). However, in a follow-up study conducted 11 to 13 years post-antireflux surgery, approximately 60% of the patients were back on medical therapy (134). Laparoscopic antireflux surgery seems to be equal in effectiveness to open surgery, with much decreased morbidity (163). Surgical experience also has been shown to be important in outcome of laparoscopic fundoplication (164).
• Eighteen percent of patients with low-grade dysplasia and 28% of patients with high-grade dysplasia develop esophageal adenocarcinoma, depending on the length of follow-up (165).
• Comorbid carcinoma is present in up to 41% of patients with high-grade dysplasia (166).
• Given the relatively high morbidity of surgical esophagectomy, evaluation for development of neoplasia should be performed in medically fit patients (165).

• The development of novel ablative and resection techniques may make more patients eligible for surveillance. These include photodynamic therapy, argon plasma coagulation, multipolar electrocautery, or endoscopic mucosal resection (167; 168).

Rationale
• Patients with dysplasia are at high risk for coincident carcinoma or progression to carcinoma. Esophageal adenocarcinoma is curable only in early stages with surgical resection.

• GERD is a chronic, relapsing condition requiring prolonged maintenance therapy in most cases. Both medical and surgical treatments have been shown to be equally efficacious for maintenance. Careful preoperative evaluation is essential to prevent postoperative complications. However, caution is warranted before antireflux surgery in patients who do not respond to medical management because the symptoms may not be due to GERD, in which case consultation with a gastroenterologist is important.
3. Hospitalization

Hospitalize only patients who require surgical procedures or have an acute complication. [AB]

3.1 Hospitalize patients who require fundoplication. [AB]

Recommendations
- Hospitalize patients who are undergoing fundoplication (antireflux surgery) only after careful preoperative evaluation by a gastroenterologist.
- See information on surgical antireflux therapy and referring patients to a gastroenterologist and surgeon.

Evidence
- See information on surgical antireflux therapy and referring patients to a gastroenterologist and surgeon.

Rationale
- Fundoplication may be selected by patients to control symptoms.

3.2 Hospitalize patients who present with acute complications of GERD that may require intervention or additional testing. [BC]

Recommendations
- Hospitalize patients with food impaction or severe dysphagia with poor hydration from peptic stricture.
- Hospitalize patients with active upper GI bleeding if etiologies other than erosive esophagitis are possible.

Evidence
- Esophagitis accounts for 3% to 12% of acute upper GI bleeding (82).

Rationale
- Patients with a narrow peptic (reflux-induced) stricture may occasionally require hospitalization for management of food impaction or relief of severe dysphagia leading to malnutrition or dehydration.
- Patients with erosive esophagitis may present with hematemesis or melena that is initially indistinguishable from other more dangerous causes of upper GI bleeding.
4. Therapy

Counsel all patients about lifestyle modifications. Recognize that the goal of drug therapy is elimination of symptoms, healing of esophagitis, prevention of complications, and maintenance of remission. 

4.1 Advise modifications in activities and habits that may be effective in treatment as appropriate.

Recommendations

- Urge patients to:
  - Elevate the head of the bed while sleeping
  - Avoid recumbency for 3 hours after meals
  - Sleep in the left lateral decubitus position
  - Stop smoking
  - Avoid alcohol
- Tailor these recommendations to individual patients as appropriate.

Evidence

- Studies have indicated that the following lifestyle modifications decrease distal acid exposure:
  - Elevation of the head of the bed (83; 84)
  - Decreased fat intake (85)
  - Smoking cessation (86)
  - Sleeping in the left lateral position (87)
  - Avoiding recumbency 3 hours after meals. In a trial of 32 patients with typical reflux symptoms, those randomized to a meal at 2 hours before bedtime showed significantly more esophageal acid exposure by pH probe compared with those randomized to a meal 6 hours before bedtime (88).
- Although these modifications have been shown to decrease esophageal acid exposure, the true efficacy of these modifications in patients has not been rigorously tested in clinical trials (89).

Rationale

- Lifestyle modifications help decrease symptoms of reflux.

Comments

- Lifestyle modifications have never been rigorously tested in a controlled clinical trial. Their benefits are modest at best, and they should generally be used as an adjunct to medical therapy.
- These lifestyle changes should be tailored to each patient and need not be broadly recommended to every patient with GERD.

4.2 Consider dietary modifications in the management of GERD.

Recommendations

- Urge patients to avoid large, fatty meals and foods and beverages that promote esophageal reflux (e.g., chocolate, peppermint, onions, garlic, alcohol, coffee).

Evidence

- Chocolate, carminatives, carbonated beverages, and alcohol decrease LES pressure (40). Citrus juices and tomato products also may provoke heartburn (90).
- Raw onions are associated with an increase in postprandial acid exposure (91).
• Although the efficacy of these maneuvers has not been tested directly in clinical trials, most experts assume that the 20% to 30% placebo-response rate seen in studies is due to lifestyle changes and dietary modifications; therefore, patient education on these factors is recommended (89).

Rationale
• Certain foods decrease LES pressure, delay gastric emptying, or provoke reflux symptoms.

Comments
• Lifestyle modifications have never been rigorously tested in a controlled clinical trial. Their benefits are modest at best, and they should generally be used as an adjunct to medical therapy.
• These lifestyle changes should be tailored to each patient and need not be broadly recommended to every patient with GERD.

4.3 Recommend weight loss for overweight or obese patients with esophageal GERD symptoms.\[i\]

Recommendations
• Counsel overweight and obese patients to reduce their BMI in order to improve GERD symptoms, especially if prior weight gain correlated with worsened symptoms.

Evidence
• A dose-dependent relationship between increasing BMI and reflux symptoms as well as pH-measured reflux events has been shown (92; 93; 94).
• One study of 34 overweight and obese patients reported improved GERD symptoms after weight loss (95).
• The Nurses’ Health Study showed an association between weight and reflux symptoms over time (92).
• A randomized, controlled study failed to show improvement in GERD symptoms in 20 obese patients who lost weight (96).

Rationale
• Obesity is purported to facilitate reflux by an altered intra-abdominal pressure, altered esophagogastric junction anatomy, and increased frequency of transient LES relaxations.

Comments
• Although not borne out in randomized, controlled trials, this otherwise healthy intervention should be considered, especially in overweight or obese patients whose symptoms worsened with weight gain.

4.4 Consider how medications may cause reflux in patients.\[i\]

Recommendations
• Review all current medications in patients and specifically consider modifying drugs that decrease LES pressure (e.g., theophylline, nitrates, anticholinergic agents, calcium-channel blockers, alpha-adrenergic antagonists, prostaglandins, diazepam).

Evidence
• Theophylline, nitrates, anticholinergic agents, calcium-channel blockers, alpha-adrenergic antagonists, prostaglandins, and sedatives may decrease LES pressure (4).
• Medications that may reduce LES baseline pressure have been associated with increased risk for adenocarcinoma of the esophagus (97).

Rationale
Gastroesophageal Reflux Disease

- Certain medications may increase reflux by decreasing LES pressure or decreasing esophageal acid clearance.

4.5 Apply the same non-drug measures in patients with esophageal strictures as those used in patients with uncomplicated GERD.  

**Recommendations**

- Avoid medications that may cause pill esophagitis in patients with strictures.
- In patients with esophageal strictures, suggest that patients chew their food well and have ill-fitting dentures or poor dentition corrected.
- Tell patients that liquid medications or small tablets may be better tolerated until more definitive therapy is instituted.
- See information on modifying lifestyle, diet, weight, and medication.  

**Evidence**

- NSAIDs, alendronate, potassium preparations, quinidine, iron supplements, and multiple antibiotics have been implicated in pill-induced esophagitis (98).

**Rationale**

- Pills may lodge proximal to strictures and result in complications, including esophagitis, ulcers, and recurrent or refractory strictures.

4.6 Consider antacids and OTC acid suppressants, in addition to lifestyle modifications, as appropriate initial patient-directed therapy.  

**Recommendations**

- Consider as-needed non-prescription treatments, such as antacids and OTC H2RA drugs, for the treatment of mild or intermittent symptoms.
- Consider a 14-day course of OTC omeprazole for more frequent symptoms (2 or more days of symptoms per week).
- Include lifestyle, diet, weight, and drug modifications.
- See table Drug Treatment for GERD.  

**Evidence**

- Experts assume that the 20% to 30% placebo-response rate seen in some studies is due to lifestyle changes and that patient education for these factors is reasonable (89).
- Two long-term trials reported that effective symptom relief occurs in 20% of patients using OTC agents (99; 100).

**Rationale**

- Many patients with mild GERD have adequate relief of symptoms with antacids and OTC acid suppressants.

**Comments**

- The true efficacy of lifestyle modifications and OTC medications vs. no intervention has not been tested rigorously outside the context of trials for other drugs.
- OTC H2RAs may be useful when taken before an activity that predictably produces reflux symptoms (for example, exercise or a large meal).

4.7 Provide initial therapy with an H2RA.  

**Recommendations**
• Give an H₂RA in divided doses for uncomplicated GERD.
• Consider a step-up approach by initiating therapy with standard-dose H₂RA and switch to a once-daily PPI if symptoms persist or are not fully controlled.
• See table Drug Treatment for GERD.
• See figure Step-up vs. Step-down Therapy.

Evidence
• Standard-dose H₂RA provides symptom relief in 50% to 60% of patients and heals endoscopic esophagitis in 48% (40).
• Higher doses of an H₂RA (usually double the standard) increase healing and symptom-resolution rates (101).
• All H₂RAs are equally efficacious when given in equipotent doses (102).

Rationale
• An H₂RA at standard or higher doses provides adequate symptom relief in most patients with mild to moderate GERD.

Comments
• H₂RAs are less effective than PPIs for acute treatment of severe or erosive esophagitis and are ineffective for long-term maintenance for these conditions.
• Tolerance to H₂RAs may develop quickly in patients taking these medications on a regular basis, limiting their efficacy.
• Adding an H₂RA at bedtime in patients in whom a once- or twice-daily PPI was ineffective may have limited therapeutic efficacy due to tolerance development.

4.8 Use a PPI to suppress acid in patients requiring drug therapy, beginning with once-daily dosing.

Recommendations
• Give a once-daily dose of a PPI, and consider doubling the PPI dose in patients who continue to be symptomatic.
• Note that PPIs provide rapid symptomatic relief and healing of esophagitis in the highest percentage of patients.
• Note that there is no consensus on whether step-down therapy or step-up therapy should be used in the initial treatment.
• Note that the approach of using either step-up or step-down therapy should be left to the individual practitioner in consultation with the patient.
• Note that twice-daily PPI dosing is a reasonable strategy in these situations:
  • During diagnostic trials of non-cardiac chest pain
  • During the empiric treatment of suspected extra-esophageal GERD syndromes
  • In patients with a partial response to standard daily dosing
  • In patients with concomitant dysmotility
  • In patients with Barrett’s esophagus
• Note that there is no clear evidence that ‘add-on’ nighttime H₂RA use results in greater control of nocturnal acid exposure or symptoms.
• See table Drug Treatment for GERD.
• See table Relative Efficacies of Antireflux Therapies.


- See figure [Step-up vs. Step-down Therapy](image).

**Evidence**

- A 2005 [guideline](image) from the American College of Gastroenterology for the diagnosis and treatment of GERD stated that twice-daily dosing of PPI is a reasonable strategy during diagnostic trials of non-cardiac chest pain, during the empiric treatment of suspected extra-esophageal GERD syndromes, in patients with a partial response to standard daily dosing, in patients with concomitant dysmotility, and in patients with Barrett's esophagus (72).

- A 2011 Cochrane review of medical treatments for the short-term therapy of GERD included 134 studies with nearly 36,000 participants. PPI therapy (RR, 0.22 [CI, 0.15 to 0.31]) and H2RA (RR, 0.74 [CI, 0.66 to 0.84]) were superior to placebo for the healing of esophagitis. PPI therapy was superior to H2RA therapy (RR, 0.51 [CI, 0.44 to 0.59]) for the healing of esophagitis. Prokinetic therapy was not superior to placebo (103).

- Standard-dose PPIs result in symptom relief in 83% of patients and healing of esophagitis in up to 90% of patients (104).

- Endoscopically determined severe esophagitis is much more likely to heal with daily PPI (89%) vs. weekend PPI therapy (32%) or twice-daily H2RA therapy (25%) (107).

- Efficacy and cost-effectiveness models have not shown superiority of step-up or step-down approach; however, a significant percentage of patients may be able to step down from PPI therapy (108).

- A Veterans Administration study of 71 'PPI-dependent' subjects showed that 42% could be managed with H2RAs, a prokinetic, or alternative agents, and that 15% could be taken off medications entirely (108).

**Rationale**

- PPIs heal esophagitis and resolve symptoms more frequently and rapidly than do other agents, either alone or in combination. However, neither the step-up nor the step-down approach has been shown to be convincingly superior to the other in management.

**Comments**

- The step-down approach starts with once- or twice-daily PPI therapy and decreases to the least potent acid suppression therapy that controls symptoms.

- The step-up approach initiates therapy with standard or even OTC doses of an H2RA and titrates up to the most potent acid suppression therapy that controls symptoms.

- Note that high- or double-dose PPI use, although recommended by expert opinion, has only minimal evidence of benefit, especially for patients with non-erosive disease.

- There is limited evidence to support the benefit of using one PPI over another. Clinicians may switch to a particular formulation based on prescription coverage or to avoid side effects.

**4.9 Provide continuous maintenance PPI therapy if needed to control symptoms using the lowest effective dose.**

**Recommendations**

- Recognize that an estimated 20% of patients need only intermittent therapy with OTC medications and lifestyle modifications.

- **High-value care:** Titrate long-term acid suppression therapy to the lowest effective dose for symptom control.
• Consider a trial without medications to see if symptoms recur in patients with mild to moderate disease.

• Note that standard or even higher doses of H₂RAs are not appropriate maintenance therapy.

• Use chronic PPI therapy as maintenance therapy for most patients with more severe GERD.

• See table Drug Treatment for GERD.

Evidence

• A 2007 systematic review of 17 randomized, controlled studies found that on-demand therapy with a PPI is effective for patients with non-erosive, mild, or uninvestigated reflux disease but not in patients with severe (erosive) disease (109).

• Patients with more severe esophagitis seen on endoscopy are more likely to have a relapse (110).

• Reflux symptoms disappear in a minority of patients (111).

• Fifty percent to 80% of patients with erosive esophagitis or non-erosive GERD have recurrence after 6 to 12 months of follow-up, regardless of the agent used to achieve healing or symptom control (112; 113).

• Patients who have disease controlled with PPIs often have relapses with standard-dose or even higher-dose H₂RAs or prokinetics (114; 115).

Rationale

• Effective maintenance therapy should keep the patient's symptoms under control and prevent complications. Most patients with symptomatic GERD require maintenance therapy.

Comments

• On-demand or intermittent PPI therapy may be applicable to a subset of patients with non-erosive GERD. In the on-demand approach, patients determine the time and duration of PPI consumption. In the intermittent approach, the duration of PPI consumption is predetermined by a physician (usually 1 to 2 weeks).

• Maintenance therapy for treatment of suspected extra-esophageal syndromes (asthma, laryngitis, cough) has not been shown to be effective. However, statistical improvements in certain measurements have been shown (for example, higher mean morning peak expiratory flow rate in asthmatics taking PPIs) (116).

• Nighttime 'add-on' H₂RA therapy has not been consistently shown to improve symptoms in patients who have not responded to twice-daily PPI therapy.

4.10 Treat patients with GERD and known peptic strictures with standard-dose PPI therapy.

Recommendations

• Use continual therapy with a standard-dose PPI in patients with GERD and known peptic strictures.

• See table Drug Treatment for GERD.

Evidence

• A randomized trial compared omeprazole to ranitidine in 34 patients with dyspepsia and gastric strictures. Treatment with a PPI resulted in significantly fewer repeat dilations (30% vs. 43%) and better symptom relief (117).

• Acid suppression with an H₂RA does not decrease the recurrence rate of peptic strictures (118).

• Two percent to 10% of patients develop peptic esophageal strictures (67).
• Potent acid suppression decreases the recurrence of this complication.

### 4.11 Maintain acid suppression in all patients who have Barrett's esophagus.

**Recommendations**
- In patients with GERD and Barrett's esophagus, treat with a PPI to control symptoms.
- Because GERD may be an insidious process, begin a trial of PPI therapy in even relatively asymptomatic patients to determine if there is retrospective recognition of symptoms.
- Note that no other specific drug therapy for Barrett's esophagus exists.
- See table [Drug Treatment for GERD](https://www.acponline.org/Education/ModuleDetail.aspx?moduleid=3657).

**Evidence**
- Barrett's esophagus does not seem to regress with medical or surgical therapy (63).
- Even high-dose PPI therapy that normalizes esophageal acid exposure does not result in a reversal of Barrett's esophagus or in a decreased Barrett's mucosa length (119).
- Chronic use of PPIs in patients with Barrett's esophagus may decrease neoplastic progression (120).
- Control of symptoms may require higher-than-usual doses of PPIs, because patients with Barrett's esophagus often have greater esophageal acid exposure (121).
- Occasionally, islands of squamous mucosa develop in patients with Barrett's esophagus treated with PPIs, but the clinical significance of this change is unknown (122).

**Rationale**
- Although acid suppression does not lead to regression of Barrett's esophagus, it may play a role in retarding progression.

### 4.12 Do not use promotility agents as monotherapy for patients with GERD.

**Recommendations**
- Do not use promotility agents instead of acid-suppressing agents as the mainstay of therapy.
- Recognize, however, that promotility agents show some efficacy for improvement of GERD.
- See table [Drug Treatment for GERD](https://www.acponline.org/Education/ModuleDetail.aspx?moduleid=3657).

**Evidence**
- Tegaserod has been shown to decrease esophageal acid exposure only when used in combination with other agents (123).

**Rationale**
- Motility, including esophageal clearance, LES tone, and gastric emptying, may play a role in GERD.
- The efficacy of promotility agents is limited by side effect profiles and drug availability.

**Comments**
- Cisapride and domperidone have been shown to improve GERD symptoms but are not available in the U.S.
- Baclofen has been shown to decrease the number of reflux episodes by suppressing transient LES relaxations, but has a significant side-effect profile (124).
4.13 **Recognize that acid inhibition with PPI therapy carries potential risks, although their long-term use is strongly justified when clinically indicated.**

### Recommendations

- Continue long-term PPI use for accepted indications, with acknowledgement of risk for adverse events.
- See the table [Drug Treatment for GERD](https://www.acponline.org) for details of potential risks of PPI use.

### Evidence

- In a 2002 cohort study in a Montreal hospital, *C. difficile* diarrhea developed in 81 (6.8%) of the 1187 patients who received antibiotics while in the hospital. In a multivariate analysis, *C. difficile* diarrhea was significantly associated with use of PPIs (OR, 2.1 [CI, 1.2 to 3.5]) (125).
- In a 2007 systematic review of 12 papers evaluating 2948 patients with *C. difficile*, those patients infected with *C. difficile* had increased PPI use (OR, 1.96 [CI, 1.28 to 3.00]) (126).
- In a nested case-control study involving 364,683 patients in a primary care database in the Netherlands, the adjusted relative risk for pneumonia among persons currently using PPIs compared with those who stopped using PPIs was 1.89 (CI, 1.36 to 2.62) (126).
- In a 2011 meta-analysis of eight observational studies, the overall risk for pneumonia was higher among patients using PPIs (OR, 1.27 [CI, 1.11 to 1.46]) (127).
- A nested case-control study using the General Practice Research Database in the UK identified 13,556 cases of hip fracture. PPI use for longer than 1 year in patients aged over 50 years was associated with an increased risk for hip fracture (OR, 1.44 [CI, 1.30 to 1.59]) (128).
- A 2011 meta-analysis of 11 observational case-control or cohort studies found that the risk for hip fracture was increased modestly among individuals taking PPIs (RR, 1.30 [CI, 1.19 to 1.43]) (129). A similar 2011 meta-analysis found a comparable risk for hip fracture, but no significant increase in risk for hip fracture in long-term PPI users compared with short-duration users (130).
- A cohort study of 840,968 live births, which included 5082 babies exposed to PPIs between 4 weeks before conception and the end of the first trimester, showed no increased risk for major birth defects (131).
- Interaction between PPIs and clopidogrel has been noted in vitro (132), and initial concerns about this potential drug interaction were raised by the FDA (FDA drug safety communication 11/17/2009). However, a 2012 meta-analysis of the existing literature identified two randomized clinical studies which did not show an increased risk for adverse outcomes for patients treated with clopidogrel and PPIs (133).

### Rationale

- Decreased stomach acid may lead to hypo- or achlorhydria, which reduces bactericidal ability and may affect absorption of some substances.
- PPI use may result in hypergastrinemia, which has a trophic effect on certain cells.
- Idiopathic side effects, drug-drug interactions, and teratogenicity concerns exist for PPIs as they do for other drug classes. The increasingly frequent use of these agents magnifies such concerns.

### Comments

- Case reports of poor absorption of vitamin B₁₂, iron, and magnesium in PPI users have been described.
- Routine testing for bone density or *H. pylori* is not recommended for chronic PPI users, nor is routine calcium, iron, or other vitamin supplementation. However, calcium, iron, or other vitamin supplementation may be considered on a case-by-case basis.
• Gastric fundic gland polyps are more common in PPI users.
• No increase in carcinoid tumors or H. pylori-associated metaplasia or cancer has been observed in humans using PPIs.

4.14 Consider surgical antireflux therapy in select patients. [A3]

Recommendations
• Consider antireflux surgery in patients who showed an excellent response to PPI therapy and who are not interested in long-term medical therapy due to concerns about taking daily medication or cost.
• Note that Barrett’s esophagus alone is not an indication for surgical therapy.
• See information on fundoplication

Evidence
• Antireflux surgery was shown to have equal outcomes compared with medical therapy with H2RAs and prokinetics at 10-year follow-up, but 62% of surgical groups used antireflux medications regularly (134).
• Antireflux surgery is as effective as acid suppression with PPIs for maintenance at 5-year follow-up, but costs for surgical therapy are higher (135; 136).
• Antireflux surgery has not been shown to prevent progression to dysplasia or esophageal adenocarcinoma in patients with Barrett’s esophagus (137; 138).
• The best clinical predictive factor for a successful outcome after antireflux surgery is age less than 50 years and typical symptoms that completely respond to PPI therapy (139).
• Atypical and extra-esophageal symptoms are less likely to be reliably improved by antireflux surgery, especially in the absence of concomitant typical symptoms (140).

Rationale
• Data show that surgical therapy is at least as efficacious as medical therapy for maintenance treatment.

Comments
• Carefully consider all options before choosing surgical therapy for patients who have not responded significantly to medical therapy, because their symptoms may not be caused by GERD.
• Ambulatory pH and esophageal manometry testing are typically performed before surgery.
• Post-surgical side effects such as gas-bloat syndrome, increased flatulence, diarrhea, and dysphagia may be long-lasting.
• Greater experience and higher case volume of the operating surgeon have been associated with better outcomes and fewer complications.

4.15 Consider endoscopic antireflux therapy in select patients, in or outside of clinical trials. [B-C]

Recommendations
• Consider radiofrequency ablation of the LES, injection of materials into the LES, or endoscopic sewing devices for control of reflux in specific, informed patients with typical symptoms responsive to PPI therapy.

Evidence
• Systematic reviews of radiofrequency ablation of the LES (141), endoscopic sewing devices (142), and injection of materials into the LES (143) failed to show clear indications for them but acknowledged their role in clinical trials and in case-by-case situations.

Rationale
• Endoscopic techniques have been developed to minimize the invasiveness of antireflux procedures.
5. Patient Counseling

Educate patients about etiology, need for long-term therapy, and possible complications.

5.1 Educate patients about the time course of GERD and the need for treatment.

Recommendations
- Advise patients that GERD is a chronic condition usually requiring ongoing maintenance therapy with PPIs to prevent complications.
- Urge patients to:
  - Elevate the head while sleeping
  - Avoid recumbency for 3 hours after meals
  - Sleep in the left lateral decubitus position
  - Stop smoking
  - Avoid alcohol
  - Avoid large, fatty meals and foods and beverages that increase esophageal reflux (e.g., chocolate, peppermint, onions, garlic, coffee, alcohol)
- Inform patients that GERD is rarely cured and that without ongoing treatment symptoms and complications may return.

Evidence
- Marked improvement in symptoms is noted with acid suppression and usually is followed by a rapid return of symptoms if medications are discontinued (144).
- Acid suppression with PPIs decreases the recurrence of peptic strictures (117).
- Barrett’s esophagus does not seem to regress with medical or surgical therapy (63).
- Studies have indicated that the following lifestyle modifications decrease distal acid exposure:
  - Elevation of the head of the bed (83; 84)
  - Decreased fat intake (85)
  - Smoking cessation (86)
  - Sleeping in the left lateral position (87)
  - Avoiding recumbency 3 hours after meals (88)
- Although these modifications have been shown to decrease esophageal acid exposure, their true efficacy in patients has not been tested. However, patient education regarding these factors is reasonable (89).
- Chocolate, carminatives, and alcohol decrease LES pressure (40). Citrus juices, tomato products, and colas may provoke reflux.

Rationale
- Lifestyle modification and acid suppression provide symptom control and decrease the incidence of complications.
- Certain foods decrease LES pressure and/or provoke reflux symptoms.

5.2 Educate patients about complications and the need to report ongoing or new symptoms.

Recommendations
• Counsel patients to look for these warning symptoms and to report them if they occur:
  • Dysphagia or odynophagia
  • Bleeding
  • Weight loss
  • Early satiety
  • Choking (acid that causes coughing, shortness of breath, or hoarseness)
  • Chest pain
  • Frequent vomiting
• Advise patients with long-term, uncontrolled reflux symptoms of the need for endoscopy to look for Barrett's esophagus and the need for periodic surveillance (by endoscopy plus biopsies) once Barrett's esophagus has developed.

Evidence
• Dysphagia is the most common presenting symptom in patients with benign esophageal strictures. The major differential diagnosis of progressive solid-food dysphagia is benign esophageal stricture vs. esophageal cancer (67).
• It is not possible to determine which patients have Barrett's esophagus based on the severity of symptoms. Patients with Barrett's esophagus typically do not present with warning symptoms unless another complication has developed (75).

Rationale
• The presence of warning symptoms suggests the presence of complications (e.g., strictures, ulceration, esophageal cancer).
6. Follow-up

Provide follow-up to monitor for complications, to screen for Barrett's esophagus (when appropriate), and to ensure that medical maintenance therapy controls symptoms in the most cost-effective manner.

6.1 Consider either the step-up or step-down method for initial treatment and follow-up.

Recommendations
- Begin step-up therapy with a standard-dose H₂RA and titrate upward to symptom control.
- Begin step-down therapy with standard PPI therapy and then titrate downward to a standard-dose H₂RA if it controls symptoms.
- See figure Step-up vs. Step-down Therapy.

Evidence
- There are no randomized, controlled trials that have compared these regimens. Neither approach has shown superiority in decision analyses (169; 170).

Rationale
- Both methods may result in cost-effective management depending on the individual patient.

Comments
- In one study, up to 58% of patients were able to step down from PPI therapy (108).

6.2 Monitor patients for symptoms that suggest the development of complicated disease.

Recommendations
- Ask patients about warning symptoms, such as:
  - Dysphagia or odynophagia
  - Bleeding
  - Weight loss/anorexia
  - Early satiety
  - Choking/coughing
  - Frequent vomiting
- If warning symptoms are present, refer patients to a gastroenterologist for further management.

Evidence
- Expert opinion recommends further diagnostic evaluation if warning symptoms are present (4).
- Peptic strictures develop in 2% to 10% of patients (67).
- The risk for esophageal adenocarcinoma, which usually presents with dysphagia and weight loss, is increased 43 times in patients with longstanding severe GERD (23).

Rationale
- Patients with warning symptoms may have developed a complication, such as cancer, stricture, or ulceration.

Comments
• Although dysphagia may be a warning symptom of complicated disease, non-obstructive causes (e.g., including esophageal inflammation or peristaltic dysfunction) may be present in patients.

6.3 Follow-up with patients to ensure that surveillance endoscopies are performed after Barrett's esophagus has been detected. 📊

**Recommendations**

- Ensure surveillance endoscopy with biopsy every 3 to 5 years (or more often, depending on the grade of dysplasia on biopsy) to detect neoplastic transformation once Barrett's esophagus has been diagnosed.
- Recognize that diagnosis of high-grade dysplasia requires repeat endoscopy to exclude concomitant cancer and document high-grade dysplasia by an expert pathologist.
- See figure [Proposed Surveillance and Management Algorithm for Patients with Barrett's Esophagus Based on Grade of Dysplasia Detected by Endoscopic Biopsy](#).

**Evidence**

- The risk for adenocarcinoma developing in Barrett's esophagus is 30- to 40-fold greater than in the general population (76).
- The incidence of adenocarcinoma developing from Barrett's esophagus is 0.12% to 0.5% annually rather than the 1% thought previously (76; 77; 171).
- The incidence of the adenocarcinoma of the esophagus and gastroesophageal junction is rapidly rising in the Western world (77; 78).
- Esophageal cancers are detected at an earlier stage during surveillance endoscopy than in patients not undergoing surveillance (172).
- Decision analysis modeling found that surveillance every 2 to 5 years provided the greatest quality-adjusted life expectancy (173; 174).
- There have been no prospective trials that show the clinical efficacy or cost-effectiveness of these recommendations, but each has expert consensus (165).
- The goal of surveillance is detection of dysplasia. The interval for surveillance if and when dysplasia is found is determined by the presence and grade of dysplasia seen on pathologic biopsy (74).

**Rationale**

- Barrett's esophagus increases the risk for developing esophageal adenocarcinoma. Early detection of dysplasia and/or cancer results in improved outcomes.

**Comments**

- Because active inflammation can be misinterpreted as dysplasia, mucosal healing should be achieved before biopsies are obtained.
- Consider referring patients to a gastroenterologist for management of Barrett's esophagus (see [Guidance Substatement](#)).
References


Gastroesophageal Reflux Disease


69. Benjamin SB, Gerhardt DC, Castell DO. High amplitude, peristaltic esophageal contractions associated with chest pain and/or dysphagia. Gastroenterol. 1979;77:478-83. (PMID: 456842)

70. Dakkak M, Hoare RC, Maslin SC, Bennett JR. Oesophagitis is as important as oesophageal structure diameter in determining dysphagia. Gut. 1993;34:152-5. (PMID: 8432464)
Gastroesophageal Reflux Disease


Gastroesophageal Reflux Disease


Gastroesophageal Reflux Disease


Gastroesophageal Reflux Disease


Glossary

ACE  
angiotensin-converting enzyme

bid  
twice daily

BMI  
body mass index

CAD  
coronary artery disease

CMV  
cytomegalovirus

GERD  
gastroesophageal reflux disease

GI  
gastrointestinal

H₂RA  
H₂ receptor antagonist

HSV  
herpes simplex virus

LES  
lower esophageal sphincter

NSAID  
nonsteroidal anti-inflammatory drug

OR  
odds ratio

OTC  
over the counter

PASS  
PPI Acid Suppression System (test)

PPI  
proton-pump inhibitor

qd  
once daily

qid  
four times daily
## Tables

### Laboratory and Other Studies for GERD

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose acid-suppression test</td>
<td>75-83</td>
<td>55</td>
<td>Empirical trial with double-dose PPI for at least 1 week</td>
</tr>
<tr>
<td>Upper endoscopy</td>
<td>50</td>
<td>100</td>
<td>Esophagitis establishes the diagnosis</td>
</tr>
<tr>
<td>Ambulatory pH monitoring</td>
<td>60-96</td>
<td>91-98</td>
<td>Best test to determine if abnormal amount of reflux is present and association with symptoms</td>
</tr>
<tr>
<td>Barium swallow</td>
<td>25 for mild esophagitis</td>
<td>80</td>
<td>Reflux of barium is neither sensitive nor specific</td>
</tr>
<tr>
<td>Provocative testing (i.e., Bernstein test)</td>
<td>10-50</td>
<td>86</td>
<td>Limited usefulness in routine diagnosis and therapy</td>
</tr>
<tr>
<td>Esophageal manometry</td>
<td>58</td>
<td>84</td>
<td>Used primarily to locate LES for pH probe placement or in preoperative evaluation</td>
</tr>
</tbody>
</table>

LES = lower esophageal sphincter; PPI = proton-pump inhibitor.
## Differential Diagnosis of GERD

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| GERD                                                                   | Typical symptoms of heartburn and regurgitation  
Patients with GERD can have normal-appearing esophagus on endoscopy |
| Pill esophagitis                                                       | Presents with dysphagia/odynophagia  
History of offending pill ingestion (e.g., potassium chloride, quinidine, tetracycline, NSAIDs, alendronate) |
| Infectious esophagitis                                                | Presents with dysphagia/odynophagia  
Often in immunocompromised patients with candidal, CMV, or HSV esophagitis |
| Esophageal motor disorders: achalasia, diffuse esophageal spasm, hypertensive/spastic motility disorders (e.g., 'nutcracker esophagus') | Dysphagia for liquids and solids; also may be associated with chest pain  
'Nutcracker esophagus' may be coincident with GERD; heartburn/chest pain in achalasia not due to reflux but to fermentation of retained esophageal contents or esophageal muscle spasm |
| Esophageal cancer                                                      | Presents with dysphagia and weight loss, often in patients with longstanding GERD  
Usually incurable by the time it presents clinically |
| CAD                                                                   | Chest pain that may be clinically indistinguishable from chest pain associated with GERD  
CAD should be ruled out before evaluating GERD as a cause |
| Functional syndrome                                                   | Chronic heartburn, chest pain, or dysphagia with typical symptoms of GERD but no objective evidence of abnormal acid reflux or esophageal motility  
Diagnosis of exclusion |
| Associated conditions: pregnancy                                      | Symptoms are experienced by 25%-50% of pregnant women  
The frequency and severity of symptoms increases throughout gestation |
| Associated conditions: hypersecretory states (e.g., Zollinger-Ellison syndrome) | 43% of patients with Zollinger-Ellison syndrome have endoscopic esophagitis (59)  
Patients also may have associated peptic ulceration or diarrhea |
| Associated conditions: connective tissue disorders (e.g., scleroderma) | Esophagus is involved in up to 90% of patients with scleroderma; often results in severe esophagitis and stricture formation  
Characterized by low or absent LES pressure and poor esophageal motor function |

**CAD** = coronary artery disease; **CMV** = cytomegalovirus; **GERD** = gastroesophageal reflux disease; **HSV** = herpes simplex virus; **NSAID** = non-steroidal anti-inflammatory drug.
### Drug Treatment for GERD

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Precautions</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antacids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium carbonate (Tums, RolaidS)</td>
<td>Chew 2 tablets. Repeat prn. Maximum 3000 mg elemental calcium total daily dose. Take with food</td>
<td>Hypercalcemia, constipation, gastric hypersecretion. Long-term use: hypophosphatemia</td>
<td>Caution with CrCl&lt;30</td>
<td>Mild or intermittent symptoms</td>
</tr>
<tr>
<td>Magnesium hydroxide (Milk of Magnesia)</td>
<td>Regular suspension: 5-15 mL qd-qid. Concentrated suspension: 2.5-7.5 mL qd-qid. Chewable tablets: 2-4 tablets qd-qid</td>
<td>Diarrhea, abdominal cramping, chalky taste, diuresis, dehydration, vomiting. Long-term use: hypermagnesemia</td>
<td>Avoid with CrCl&lt;10. Caution with CKD</td>
<td></td>
</tr>
<tr>
<td>Aluminum hydroxide</td>
<td>10-60 mL q4-6hr</td>
<td>Constipation. Long-term use: aluminum toxicity, hypophosphatemia, hypercalcemia</td>
<td>Caution with CKD</td>
<td></td>
</tr>
<tr>
<td><strong>H₂ receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine (Tagamet HB, Tagamet)</td>
<td>200-800 mg bid, or 400 mg qid</td>
<td>Headache, diarrhea, tolerance, confusion in elderly</td>
<td>May increase risk of pneumonia</td>
<td>Uncomplicated GERD. The lower dose strengths are available OTC</td>
</tr>
<tr>
<td>Famotidine (Pepcid AC, Pepcid)</td>
<td>10-40 mg bid</td>
<td>Gynecomastia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine (Zantac 75, Zantac 150, Zantac)</td>
<td>75-150 mg bid</td>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proton pump inhibitors</strong></td>
<td></td>
<td>Abdominal pain, diarrhea, nausea, flatulence, headache. Long-term use: hypomagnesemia, vitamin B₁₂ deficiency</td>
<td>May increase risk of: pneumonia, bone fracture, CDAD. Caution with clopidogrel. Substrates of CYPs 2C19, 3A4. Inhibitors of CYP2C19 to varying degrees</td>
<td>Moderate-severe GERD</td>
</tr>
<tr>
<td>Lansoprazole (Prevacid 24 hr, Prilosec)</td>
<td>15-30 mg qd</td>
<td></td>
<td>Consider decreased dose with: severe hepatic disease, Asian patients. Substrate and inhibitor of P-gp</td>
<td></td>
</tr>
<tr>
<td>Omeprazole (Prilosec OTC, Prilosec)</td>
<td>20-40 mg qd</td>
<td></td>
<td>Avoid with clopidogrel. Consider decreased dose with severe hepatic disease. Substrate and inhibitor of P-gp. Moderate-strong inhibitor of CYP2C19</td>
<td></td>
</tr>
<tr>
<td>Pantoprazole (Protonix)</td>
<td>40 mg qd</td>
<td></td>
<td>Limited data with severe hepatic disease. Substrate and inhibitor of P-gp</td>
<td></td>
</tr>
<tr>
<td>Rabeprazole (AcipHex)</td>
<td>20 mg qd</td>
<td></td>
<td>Limited data with severe hepatic disease</td>
<td></td>
</tr>
</tbody>
</table>
## Gastroesophageal Reflux Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole (Nexium)</td>
<td>20-40 mg qd</td>
<td>Avoid with clopidogrel. Maximum 20 mg qd with severe hepatic disease. Moderate-strong inhibitor of CYP2C19</td>
</tr>
<tr>
<td>Dexlansoprazole (Dexilant)</td>
<td>30-60 mg qd</td>
<td>Maximum 30 mg qd with moderate hepatic disease. No data with severe hepatic disease</td>
</tr>
<tr>
<td><strong>Combination agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium carbonate/Famotidine/Magnesium hydroxide (Pepcid Complete)</td>
<td>800/10/165 mg; chew one tablet. Maximum 2 tablets daily</td>
<td></td>
</tr>
<tr>
<td>Omeprazole/sodium bicarbonate (Zegerid OTC, Zegerid)</td>
<td>20-40 mg qd</td>
<td>Zegerid contains sodium bicarbonate which may not be appropriate for some patients. Avoid with clopidogrel. Consider decreased dose with severe hepatic disease. Substrate and inhibitor of P-gp. Moderate-strong inhibitor of CYP2C19</td>
</tr>
</tbody>
</table>

---

= first-line agent; = black box warning; bid = twice daily; CDAD = *Clostridium difficile*-associated diarrhea; CKD = chronic kidney disease; CNS = central nervous system; CrCl = creatinine clearance; CYP = cytochrome P450 isoenzyme; GERD = gastroesophageal reflux disease; GI = gastrointestinal; IM = intramuscular; IV = intravenous; OTC = over-the-counter (nonprescription); P-gp = P-glycoprotein; PO = oral; prn = as needed; qd = once daily; qid = four times daily; SC = subcutaneous; tid = three times daily.

PIER provides key prescribing information for practitioners but is not intended to be a source of comprehensive drug information.
## Relative Efficacies of Antireflux Therapies

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>PPI bid&lt;br&gt;PPI + promotility agent&lt;br&gt;PPI qd&lt;br&gt;H₂RA + promotility agent&lt;br&gt;H₂RA qd or promotility agent</td>
</tr>
<tr>
<td>Lowest</td>
<td>OTC H₂RA</td>
</tr>
</tbody>
</table>

bid = twice daily; H₂RA = H₂-receptor antagonists; OTC = over the counter; PPI = proton-pump inhibitor; qd = once daily.

Approach to the Treatment in the Primary Care Setting
Adapted with permission from Katz PO. Treatment of gastroesophageal reflux disease: use of algorithms to aid in management. Am J Gastroenterol. 1999;94:S3-10 (4).
Step-up vs. Step-down Drug Therapy

In patients who are refractory to standard-dose PPI therapy, consider referral for further treatment or additional diagnostic testing to confirm the diagnosis.

PPI = proton-pump inhibitor.
Proposed Surveillance and Management Algorithm for Patients with Barrett's Esophagus Based on Grade of Dysplasia Detected by Endoscopic Biopsy

High-grade dysplasia arm assumes confirmation as second opinion by an expert pathologist.