



## Gastroesophageal Reflux Disease (GERD)

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### Patient population: Adults

**Objective:** To implement a cost-effective and evidence-based strategy for the diagnosis and treatment of gastroesophageal reflux disease (GERD).

### Key Points:

#### ■ Diagnosis

**History.** If classic symptoms of heartburn and acid regurgitation dominate a patient's history, then they can help establish the diagnosis of GERD with sufficiently high specificity, although sensitivity remains low compared to 24-hour pH monitoring. The presence of atypical symptoms (Table 1), although common, cannot sufficiently support the clinical diagnosis of GERD [B\*].

**Testing.** No gold standard exists for the diagnosis of GERD [A\*]. Although 24-hour pH monitoring is accepted as the standard with a sensitivity of 85% and specificity of 95%, false positives and false negatives still exist [II B\*]. Endoscopy lacks sensitivity in determining pathologic reflux but can identify complications (eg, strictures, erosive esophagitis, Barrett's esophagus) [I A]. Barium radiography has limited usefulness in the diagnosis of GERD and is not recommended [III B\*].

**Therapeutic trial.** An empiric trial of anti-secretory therapy can identify patients with GERD who lack alarm or warning symptoms (Table 2) [I A\*] and may be helpful in the evaluation of those with atypical manifestations of GERD, specifically non-cardiac chest pain [II B\*].

#### ■ Treatment

**Lifestyle modifications.** Lifestyle modifications (Table 3) should be recommended throughout the treatment of GERD [II B], yet there is evidence-based data to support only weight loss and avoiding recumbency several hours after meals [II C\*].

**Pharmacologic treatment.** H2-receptor antagonists (H2RAs), proton pump inhibitors (PPIs), and prokinetics have proven efficacy in the treatment of GERD [I A\*]. Prokinetics are as effective as H2RAs but are currently unavailable [III A\*]. Carafate and antacids are ineffective [III A\*], but may be used as supplemental acid-neutralizing agents for certain patients with GERD [II D\*].

- **Non-erosive reflux disease (NERD):** *Step-up* (H2RA, then a PPI if no improvement) and *step-down* (PPI, then the lowest dose of acid suppression) therapy are equally effective for acute treatment and maintenance [I B\*]. *On demand* (patient-directed) therapy is the most cost-effective [I B].
- **Erosive esophagitis:** Initial PPI therapy is the treatment of choice for acute and maintenance therapy for patients with documented erosive esophagitis [I A\*].
- Take PPIs 30-60 minutes prior to breakfast (and also dinner if taking twice daily) to optimize effectiveness [I B\*]. Use generic and OTC formulations exclusively, eliminating need for prior authorizations.
- Patients should not be left on anti-secretory therapy without re-evaluation of symptoms to minimize cost and the potential adverse events from medications [I B].

**Surgery.** Anti-reflux surgery is an alternative modality in GERD treatment for patients with chronic reflux and recalcitrant symptoms [II A\*], yet has a significant complication rate (10-20%). Resumption of pre-operative medication treatment is common (> 50%) and may increase over time.

**Other endoscopic treatments.** While less invasive and with fewer complications, they have lower response rates than anti-reflux surgery [II C\*], and have not been shown to reduce acid exposure.

#### ■ Follow up

**Symptoms unchanged.** If symptoms remain unchanged in a patient with a prior normal endoscopy, repeating endoscopy has no benefit and is not recommended [III C\*].

**Warning signs.** Patients with warning or alarm signs and symptoms suggesting complications from GERD (Table 2) should be referred to a GERD specialist.

**Risk for complications.** Further diagnostic testing (eg, EGD [esophagogastroduodenoscopy], 24-hour pH monitoring) should be considered in patients who do not respond to acid suppression therapy [I C\*] and in patients with a chronic history of GERD who are at risk for complications. Chronic reflux has been suspected to play a major role in the development of Barrett's esophagus, yet it is unknown if outcomes can be improved through surveillance and medical treatment [D\*].

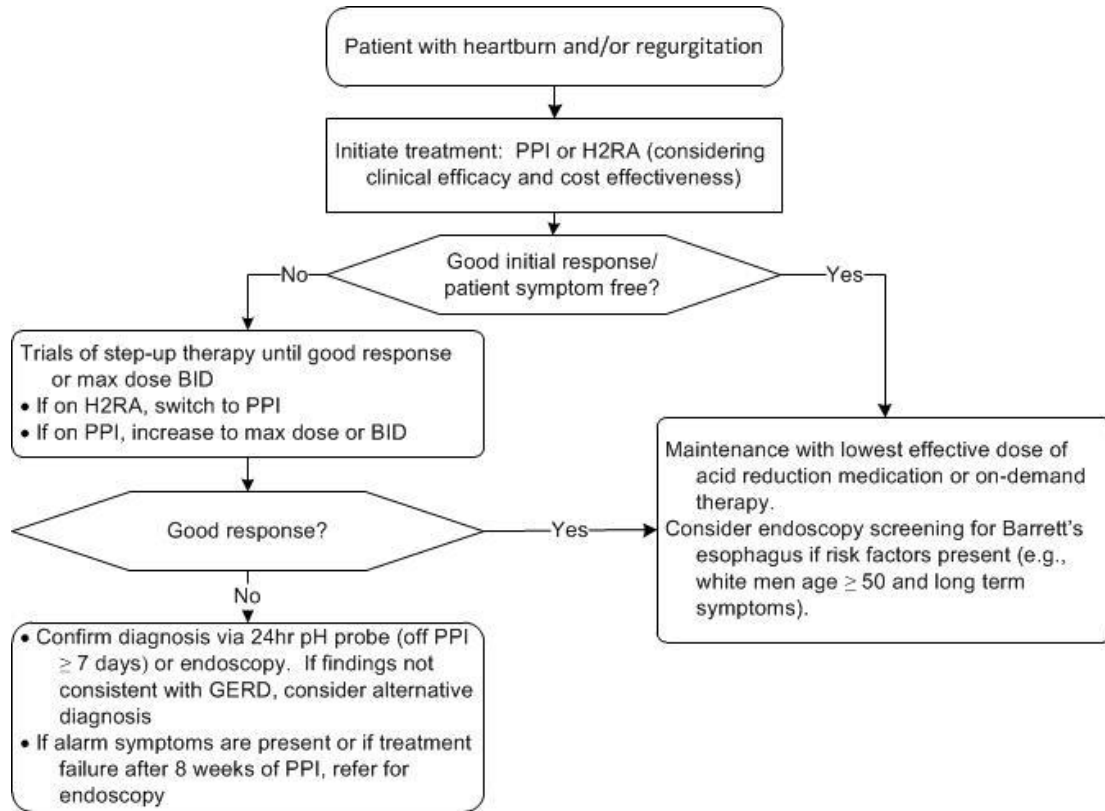
#### \* Strength of recommendation:

I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

#### Level of evidence supporting a diagnostic method or an intervention:

A=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.

**Figure 1. Diagnosis and Treatment of GERD**



**Table 1. Atypical Signs of GERD**

Chronic cough
Asthma
Recurrent sore throat
Recurrent laryngitis
Dental enamel loss
Subglottic stenosis
Globus sensation
Chest pain
Onset of symptoms at age > 50

**Table 2. Alarm or Warning Signs Suggesting Complicated GERD**

Dysphagia
Odynophagia
GI bleeding
Iron deficiency anemia
Weight loss
Early satiety
Vomiting

**Table 3. Lifestyle Modifications**

Elevate head of bed 6-8 inches
Decrease fatty meals
Stop smoking
Avoid recumbency or sleeping for 3-4 hours after eating
Avoid certain foods: chocolate, alcohol, peppermint, caffeinated coffee and other beverages, onions, garlic, fatty foods, citrus, tomato
Avoid large meals
Weight loss
Avoid medications that can potentiate symptoms: calcium channel blockers, beta-agonists, alpha-adrenergic agonists, theophylline, nitrates, and some sedatives (benzodiazepines).

**Table 4. Medications for Acute Treatment and Maintenance Regimens**

Drug	Dose Equivalents <sup>a</sup>	Dosage <sup>b</sup>	OTC	Generic <sup>c</sup>	Brand <sup>c</sup>
<b>H2 receptor antagonists</b>					
cimetidine (Tagamet HB)	200 mg twice daily	200 mg twice daily	\$25	\$25	NA
cimetidine (Tagamet)	400 mg twice daily	400 mg twice daily	\$12	\$25	NA
famotidine (Pepcid)	20 mg twice daily	20 mg twice daily	\$11	\$9	\$655
nizatidine (Axid)	150 mg twice daily	150 mg twice daily	\$43	\$37	NA
ranitidine (Zantac 150)	150 mg twice daily	150 mg twice daily	\$20	\$9	\$391
ranitidine (Zantac 300)	300 mg nightly	300 mg nightly	\$20	\$14	\$354
<b>Proton pump inhibitors</b>					
dexlansoprazole (Dexilant)	30 mg daily	30 mg once daily	NA	NA	\$296
esomeprazole (Nexium)	20 mg daily	20 to 40 mg daily	\$25-34	\$22-27	\$271
lansoprazole (Prevacid)	30 mg daily	15 or 30 mg daily before breakfast	\$15-29	\$15-24	\$448
omeprazole (Prilosec)	20 mg daily	20 or 40 mg daily before breakfast	\$15-30	\$5-8	NA
pantoprazole (Protonix)	40 mg daily	40 mg daily before breakfast	NA	\$6	\$465
rabeprazole (Aciphex)	20 mg daily	20 mg daily before breakfast	NA	\$21	\$567

<sup>a</sup> For each drug, the dose listed in this column has an effect similar to the doses listed in this column for other drugs.

<sup>b</sup> Maximum GERD dose for PPIs except dexlansoprazole is the highest listed dose amount, but given twice daily before breakfast and before dinner. Dexlansoprazole maximum dose is 60 mg once daily.

<sup>c</sup> Cost = For brand drugs, Average Wholesale Price minus 10%. AWP from Red Book Online 4/3/18. For generic drugs, Maximum Allowable Cost plus \$3 from BCBS of Michigan MAC List, 4/1/18. Prices calculated for 30-day supply unless otherwise noted.

## Clinical Background

### Clinical Problem

#### Incidence

Gastroesophageal reflux disease (GERD) is a common chronic, relapsing condition that carries a risk of significant morbidity and potential mortality from resultant complications. While many patients self-diagnose, self-treat and do not seek medical attention for their symptoms, others suffer from more severe disease with esophageal damage ranging from erosive to ulcerative esophagitis.

More than 60 million adult Americans suffer from heartburn at least once a month, and over 25 million experience heartburn daily. The National Ambulatory Medical Care Survey (NAMCS) found that 38.53 million annual adult outpatient visits were related to GERD. For patients presenting with GERD symptoms, 40-60% or more have reflux esophagitis. Up to 10% of these patients will have erosive esophagitis on upper endoscopy. GERD is more prevalent in pregnant women, and a higher complication rate exists among the elderly. Patients with GERD generally report decreases in productivity, quality of life and overall well-being. Many patients rate their quality of life to be lower than that reported by patients with untreated angina pectoris or chronic heart failure. GERD is a risk factor for the development of esophageal adenocarcinoma, further increasing the importance of its diagnosis and treatment.

Extraesophageal manifestations associated with GERD occur in up to 50% of patients with non-cardiac chest pain, 78% of patients with chronic hoarseness, and 82% of patients with asthma. Over 50% of patients with GERD have no

endoscopic evidence of disease. Although these diagnostic limitations occur less often when patients present with the classic symptoms of heartburn and acid regurgitation, diagnosis may be difficult in patients with recalcitrant courses and extraesophageal manifestations of this disease.

#### Diagnostic Problems

The lack of a gold standard in the diagnosis of GERD presents a clinical dilemma in treating patients with reflux symptomatology. Many related syndromes including dyspepsia, atypical GERD, *H. pylori*-induced gastritis, peptic ulcer disease and gastric cancer may present similarly, making accurate history taking important. The most common referral to a gastroenterologist from primary care is for evaluation of refractory GERD. Even in these cases the pre-test sensitivity and specificity for accurate diagnosis remain low. Invasive testing is over-utilized and not always cost-effective, given the relatively small risk of misdiagnosis based upon an accurate patient history. Empiric pharmacotherapy is advantageous based on both cost and convenience for the patient.

#### Treatment Decision Problems

Although empiric anti-secretory therapy with a histamine-2 receptor antagonist (H2RA) or a proton pump inhibitor (PPI) provides symptomatic relief from heartburn and regurgitation in most cases, the potential long-term adverse effects of anti-reflux medications are unknown. No cases of gastric cancer or carcinoid linked to use of the PPIs have been reported since the advent of this class of medication over 20 years ago.

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Complications from GERD (eg, Barrett's esophagus, adenocarcinoma of the esophagus) are rare but do exist; 10-15% with GERD will develop Barrett's esophagus, and 1-10% of those with Barrett's will develop adenocarcinoma over 10-20 years. Chronic reflux has been suspected to play a major role in the development of Barrett's esophagus (specialized columnar epithelium or intestinal metaplasia), yet it is unknown if outcomes can be improved through surveillance and medical treatment. anti-secretory therapy has been shown to reduce the need for recurrent dilation from esophageal stricture formation.

Previous cost-effectiveness models for endoscopic screening were flawed in that certain studies examined only patients with erosive esophagitis and excluded patients with non-erosive esophagitis (NERD), while some studies included data on anti-reflux surgery only for patients who failed medical therapy. These studies also viewed a short-term analysis of therapeutic efficacy, rather than following patients over a lifetime, and did not allow for the switching from one particular medication to another.

## Rationale for Recommendations

### Etiology

Most patients with GERD have normal baseline lower esophageal sphincter tone. The most common mechanism for acid reflux is transient relaxation of the lower esophageal sphincter ( $\geq 90\%$  of reflux episodes in normal subjects and 75% of episodes in patients with symptomatic GERD). Other mechanisms include breaching the lower esophageal sphincter because of increased intra-abdominal pressure (strain induced reflux) and a baseline low pressure at the lower esophageal sphincter. The latter two mechanisms increase in frequency with greater reflux severity. Other factors include delayed gastric emptying (co-factor in 20% of GERD patients), medication use (particularly calcium channel blockers), hiatal hernia (increased strain induced reflux and poor acid clearance from hernia sac), and poor esophageal acid clearance (eg, esophageal dysmotility, scleroderma, decreased salivary production).

### Natural History

Most GERD patients (80-90%) do not seek medical attention and will self-medicate with OTC anti-secretory therapy (50%). In patients seeing physicians, most will have chronic symptoms that will occur off treatment. Patients with more severe esophagitis will have symptoms recur more quickly and almost all will have recurrent symptoms and esophagitis if followed up for  $\geq 1$  year. Progression of disease can be seen in up to 25% of patients with esophagitis, but it is less likely to occur if esophagitis is not present or is mild. (Using the Los Angeles Classification for Gastroesophageal Reflux Disease, this would be LA grade A or B.) Complications such as Barrett's esophagus, esophageal ulcers, esophageal

stricture or adenocarcinoma of the esophagus are very rare unless the initial endoscopy shows esophagitis or Barrett's esophagus. A normal endoscopy with symptomatic GERD presents a good prognosis, and does not need to be repeated for 10 years unless alarm or warning symptoms are present (Table 2). Long-term natural history studies are limited.

### Diagnosis

Evidence-based limitations exist when trying to assess the validity of the diagnostic modalities for GERD. Most studies have flawed methods because no gold standard exists. However, the calculated numbers are helpful in providing a framework to assess available options. Recent studies suggest that combining diagnostic modalities (omeprazole challenge test [daily omeprazole for two weeks], 24-hour pH monitoring, and endoscopy) may increase the sensitivity for diagnosis of GERD (approaching 100%), but this approach is not practical in the routine clinical setting.

24-hour pH monitoring offers adequate sensitivity and specificity in establishing a diagnosis of GERD in cases that do not readily respond to anti-secretory therapy. It can also help with patient compliance by establishing that acid production has been eliminated or reduced to zero. The UMHS approach to 24-hour pH monitoring includes: scheduling, availability, report turnaround time, patient satisfaction, cost, and insurance coverage.

**History.** Since GERD occurs with few if any abnormal physical findings, a well-taken history is essential in establishing the diagnosis of GERD. Symptoms of classic burning in the chest, with sour or bitter taste, and acid regurgitation have been shown to correctly identify GERD with a sensitivity of 89% and specificity of 94%. Up to 1/3 of patients with GERD will not report the classic symptoms of heartburn and regurgitation. However, symptom frequency, duration and severity are equally distributed among patients with varying grades of esophagitis and Barrett's esophagus and cannot be used reliably to diagnose complications of GERD. There may also be some symptom overlap with other conditions (non-cardiac chest pain, cough, etc.).

**PPI diagnostic test.** A favorable symptomatic response to a short course of a PPI (once daily for two weeks) is considered to support a diagnosis of GERD when symptoms of non-cardiac chest pain are present. A meta-analysis found that a successful short-term trial of PPI therapy did not confidently establish a diagnosis of GERD (sensitivity 78%, specificity 54%) when 24-hour pH monitoring was used as the reference standard. This may be due to an observed clinical benefit of PPIs in treating other acid-related conditions (as seen in the heterogeneous dyspeptic population), patients with enhanced esophageal sensitivity to acid (without true GERD), or even due to a placebo effect. In those with non-cardiac chest pain, an empiric trial of high-dose omeprazole (40 mg AM, 20 mg PM) had a sensitivity of 78% and specificity of 85%. Standard dosages may have lower sensitivity and specificity.

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**Empiric or therapeutic trial.** Diagnostic modalities cannot reliably exclude GERD even if they are negative. Therefore, an empiric trial of anti-secretory therapy may be the most expeditious way in which to diagnose GERD in those with classic symptoms and who do not have symptoms suggestive of complications (eg, carcinoma, stricture). (See discussion of "step-up" therapy and "step-down" therapy in treatment section.)

Empiric therapy should be tried for two weeks for patients with typical GERD symptoms. Treatment can be initiated with standard dosage of either an H2RA twice daily (on demand, taken when symptoms occur) or a PPI (30-60 minutes prior to first meal of the day), with drug selection depending on clinical presentation and appropriate cost-effectiveness and the end point of complete symptom relief. (See Figure 1 and costs in Table 4). If symptom relief is not adequate and H2RA twice daily was initially used, then PPI daily should be used. If PPI daily was initially used, then increase to maximum dose PPI daily or twice daily (30-60 minutes prior to first and last meals).

For patients who initially present with more severe and more frequent symptoms of typical GERD, treatment may be initiated with higher and more frequent dosages of an H2RA or PPI. If symptom relief is not adequate from the initial dose (see Figure 1), then increase potency or frequency as needed to obtain complete symptom relief: high-dose H2RA to PPI daily, PPI daily or maximum dose PPI daily or twice daily. If there is no response when using maximal doses and frequencies, then diagnostic testing should be performed after 8 weeks of therapy.

If the patient responds with symptom relief, give 8-12 weeks of therapy, ie, enough to heal undiagnosed esophagitis. If the patient has complete symptom relief at 8-12 weeks, taper over 1 month to lowest effective dose of the medication that gives complete relief, eg, H2RA on demand, PPI every other day. If symptoms recur, put patient back on the lowest effective medication and dose, and consider further testing depending on clinical presentation and course.

Patients who present with atypical or extraesophageal manifestations take a longer time to respond to empiric therapy, and often require twice-daily dosing. If there is no improvement at all in symptoms after two months, further testing should be pursued.

**Endoscopy and biopsy in GERD.** Endoscopy is used to detect mucosal injury, esophageal stricture, Barrett's esophagus or esophageal cancer. Eosinophilic esophagitis, diagnosed by mucosal changes and biopsies (at least 5 in proximal and distal esophagus), is increasingly important. Mucosal injury is seen in less than 50% of patients with GERD symptoms, and therefore the diagnostic sensitivity is less than 50%, but specificity is 95%.

Esophagitis is best defined by the Los Angeles Classification of Gastroesophageal Reflux Disease (LA grades A through D). Alarm signs and severity of symptoms are not predictive

of complications (eg, Barrett's esophagus, cancer) but troublesome dysphagia and weight loss are predictive of complications. Endoscopy should be done for patients not responding to a twice-daily PPI.

Endoscopic biopsies are indicated to detect Barrett's esophagus and eosinophilic esophagitis, but are not indicated when the endoscopy is normal. Random biopsies and directed biopsies to nodular areas should be done if Barrett's esophagus is seen or eosinophilic esophagitis is suspected.

Routine endoscopy in the general population is not indicated. High-risk patients for esophageal adenocarcinoma such as age  $\geq$  50, males, chronic GERD, hiatal hernia, high body mass index, central obesity, and tobacco use, may warrant endoscopy.

**Esophageal manometry.** Esophageal manometry should be second line for diagnosis of GERD. Detection of achalasia, spastic achalasia, or distal esophageal spasm is critical if patient is having antireflux surgery. Adequate peristalsis is another prerequisite for anti-reflux surgery. Esophageal manometry is not indicated for the detection of GERD. High resolution manometry is superior to standard manometry in the detection of major motility disorders mimicking GERD.

**Other Testing for GERD.** Esophageal acid perfusion testing (also called Bernstein testing), esophageal sensory testing, and barium esophagram are not indicated for the diagnosis of GERD. Barium esophagram may be helpful in the preoperative phase of anti-reflux surgery or in the evaluation of major motor disorders (eg, achalasia, diffuse esophageal spasm) after a normal endoscopy.

## **Treatment**

**Lifestyle modifications.** For patients with a history typical for uncomplicated GERD, expert opinion is to discuss and offer various lifestyle modifications throughout the course of GERD therapy (see Table 3). Neither the efficacy nor the potential negative effects of lifestyle changes on a patient's quality of life have been adequately examined. With relatively little data available, it is reasonable to educate patients about factors that may precipitate reflux. Only recently has there been evidence to support weight loss and avoiding recumbency in favorable outcomes.

**Head elevation.** Numerous studies have indicated that elevating the head of a patient's bed by 4 to 8 inches, as well as avoiding recumbency for 3 hours or greater after a large or fatty meal, may decrease distal esophageal acid exposure. However, data reflecting the true efficacy of this maneuver in patient reported outcomes is lacking. It has also been suggested that patients should avoid sleeping on additional pillows, as this may increase abdominal pressure and lead to increased reflux.

**Avoid certain foods.** Several foods are believed to be direct esophageal irritants: citrus juices, carbonated beverages, coffee and caffeine, chocolate, spicy foods, fatty

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foods, or late evening meals. However, no randomized controlled trials are available to support recommendations to avoid or minimize these foods. Individualized dietary modification trials may be reasonable to help elucidate potential causative dietary factors.

Weight loss. A direct association among weight, reflux, and reflux complications has been demonstrated. Weight loss has been shown to improve global symptom scores, particularly if weight gain occurred before the onset of GERD symptoms.

Smoking cessation and alcohol minimization. Smoking cessation and the elimination or minimization of alcohol are also encouraged for a variety of health reasons. Both nicotine and alcohol have been shown to decrease lower esophageal sphincter pressure and lead to further esophageal irritation. A systematic review found that smoking was associated with an increase in GERD symptoms (over 1-2 days); yet smoking cessation was not shown to decrease GERD symptoms in 3 low-quality studies. Alcohol use may or may not be associated with reflux symptoms.

Avoid medications that decrease lower esophageal pressure or irritate the esophagus. Medications that decrease lower esophageal sphincter pressure should be avoided in patients with symptoms of GERD. These medications include calcium channel blockers, beta-agonists, alpha-adrenergic agonists, theophylline, nitrates, PDE-5 inhibitors (eg, avanafil, sildenafil, tadalafil, vardenafil), anticholinergics, narcotics, and some sedatives (benzodiazepines). Medications that irritate the esophagus include NSAIDs, ferrous sulfate, and bisphosphonates.

Avoid tight clothing around waist. Another anecdotal suggestion is that patients refrain from wearing tight clothing around the waist to minimize strain-induced reflux.

**Over-the-counter (OTC) remedies.** Antacids and OTC anti-secretory therapy (H2RAs, PPIs) are appropriate initial patient-directed therapy for GERD. Antacids (Tums, Rolaids, Maalox) and combined antacid with alginate acid (Gaviscon) have been shown to be more effective than placebo in the relief of daytime GERD symptoms. Two long-term studies suggest that approximately 20% of patients experience some relief from over-the-counter agents.

**H2 receptor antagonists (H2RAs).** All four of the histamine type-2 receptor antagonists (H2RAs: cimetidine, famotidine, nizatidine, and ranitidine) have been approved for use in the US as OTC preparations at a dose that is uniformly one-half of the standard lowest prescription dosage for each compound; ranitidine is now available in an OTC formulation at standard dose. At these dosages, the H2RAs decrease gastric acid production, particularly after eating a meal, without affecting esophago-gastric barrier dysfunction. The four H2RAs are virtually interchangeable at these dosages, with similarities in the rapidity and duration of action. The OTC costs are equivalent (although the generic costs differ by dosage). Some patients may predict

when they will suffer reflux symptomatology and may benefit from premedication with these OTC H2RAs. The OTC H2RAs are believed to be superior in efficacy when compared to antacids, alginate acid, and placebo.

Numerous randomized controlled trials have demonstrated that standard dose H2RAs are more effective than placebo at relieving heartburn in cases of GERD, with symptomatic relief reported in 60% of cases. A systematic review found that people in trials on H2RAs had faster healing rates than people in trials on placebo: over a 4-8 week period a healed esophagitis rate of 50% on H2RA and 24% on placebo.

Both higher doses and more frequent dosing of H2RAs appear to be more effective in the treatment of reflux symptoms and healing of esophagitis. If the patient is on maximal therapy, the disadvantages include cost and compliance. Some patients will develop tolerance to the H2RAs, with decreased efficacy observed after 30 days of treatment.

Most evidence describing adverse effects is from case reports or uncontrolled trials. H2RAs have been associated with rare cytopenias, gynecomastia, liver function test abnormalities, and hypersensitivity reactions. In the long-term, there have been no controlled trials with follow-up on the safety of chronic use of H2RAs. Cimetidine may cause gynecomastia or antiandrogenic side effects, and may interact with medications metabolized by cytochrome P450.

**Proton Pump Inhibitors (PPIs).** Several studies have demonstrated that on-demand therapy with PPIs is the most cost-effective method for non-erosive reflux disease (NERD). Evidence from numerous randomized controlled trials has shown that PPIs are more effective than both H2RAs and placebo in controlling symptoms from erosive reflux disease (83% compared to 60% and 27%, respectively) over a 4-8 week period. One systematic review compared the efficacy of PPIs and H2RAs and found that a greater number of people improved symptomatically with PPIs, yet the difference was not significant for heartburn remission. One randomized controlled trial showed that at 12 months, significantly more people were still in remission with omeprazole compared to ranitidine. Another randomized controlled trial found that treatment with omeprazole was more likely than ranitidine to improve symptom and psychological well-being scores.

In the treatment of erosive esophagitis, PPIs had faster healing rates than either H2RAs or placebo (78% compared to 50% and 24%, respectively) over a 4-8 week period. No randomized controlled trials have examined therapy for a longer period of time.

One randomized controlled trial found no evidence of a significant difference among four PPIs, including lansoprazole, omeprazole, pantoprazole, and rabeprazole in the healing of erosive esophagitis. Efficacy in pH changes was not studied. The least expensive PPIs are omeprazole and lansoprazole, which are available generically and OTC.

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A single study showed that esomeprazole, the S-isomer of omeprazole, at doses of 20 mg and 40 mg is more effective than omeprazole 20 mg in both healing and symptom resolution in GERD patients with reflux esophagitis, with a tolerability profile comparable to that of omeprazole. A randomized controlled trial compared esomeprazole 40 mg to lansoprazole 30 mg. Esomeprazole was superior in healing and symptom control, with superiority highest in more severe degrees of esophagitis.

The potential benefit of chronic PPI therapy in patients with chronic or complicated GERD generally outweighs any theoretical risk of adverse events. Risks associated with chronic PPI therapy include *Clostridium-difficile*-associated diarrhea (adjusted odds ratio [AOR] = 2.1 – 2.6); community-acquired pneumonia (AOR = 1.5 – 1.9); bone fracture (AOR = 1.4 – 1.6); vitamin B<sub>12</sub> deficiency (AOR = 1.0 – 4.46); antiplatelet interactions (AOR = 1.25). Data regarding risks of bone fracture and antiplatelet interactions are controversial. A 2011 FDA warning recommends periodic surveillance of serum magnesium levels due to potential hypomagnesemia.

Since all data were collected retrospectively, a definitive cause-and-effect relationship cannot be proven. All patients on long-term PPI therapy should be re-evaluated periodically to determine need and to weigh potential risks versus benefits of therapy.

### **Baclofen**

While not considered to be first-line therapy, baclofen has been shown to offer symptomatic relief for patients with GERD. This approach is aimed at decreasing the number of transient lower esophageal sphincter relaxations and increasing lower esophageal sphincter tone. These effects have been observed most significantly after eating a meal.

### **Prokinetics**

Previous prokinetic medications (eg, cisapride) were taken off the US market several years ago due to increased cardiovascular risks. Mosapride, a newer generation prokinetic not currently available in the US, has been shown to improve reflux symptoms and gastric emptying when combined with omeprazole.

### **Alternative Therapies**

No randomized controlled trials have been conducted to date to compare treatment outcomes between conventional anti-secretory therapy and alternative therapies. Use of demulcents (eg, licorice root, marshmallow), ginseng, and apple cider vinegar have shown varying degrees of symptomatic improvement in small numbers of patients. Acupuncture may also have some benefit, as one trial found this modality to be more effective than doubling the dose of a PPI in patients with non-erosive disease.

**Surgical treatment.** Anti-reflux surgery is an accepted alternative treatment for symptomatic reflux of acid or bile in certain patients. The basic tenets of surgery are reduction of the hiatal hernia, repair of the diaphragmatic hiatus, strengthening the attachment between the gastroesophageal junction and the posterior diaphragm, and strengthening the anti-reflux barrier by adding a gastric wrap around the gastroesophageal junction (fundoplication). Controlled trials comparing open and laparoscopic approaches have shown similar efficacy and complications, with lower morbidity and shorter hospital stays in the laparoscopic repair group.

Post-surgical complications are common, but they are typically short term and manageable in most instances. Short-term solid food dysphagia occurs in 10% of patients (2-3% have permanent symptoms) and gas bloating occurs in 7-10% of patients. Diarrhea, nausea, and early satiety occur more rarely. While some complication occurs in up to 20% of patients, major complications occur in only 3-4% of patients. Patient satisfaction is high when GERD symptoms are well controlled.

Controlled trials comparing anti-reflux surgery to antacids, H<sub>2</sub>RAs and PPIs have shown marginal superiority to surgery. Studies comparing surgery with proton pump inhibitors have shown similar efficacy if PPI could be titrated to response. Long-term follow-up trials have shown that 52% of patients are back on anti-reflux medications 3-5 years after surgery, most likely secondary to a combination of poor patient selection and surgical breakdown.

The choice to consider anti-reflux surgery must be individualized. Patients should have documented acid reflux, a defective anti-reflux barrier in the absence of poor gastric emptying, normal esophagus motility and at least a partial response to acid reduction therapy. Surgery appears to be most effective for heartburn and regurgitation (75-90%) and less effective for extraesophageal symptoms (50-75%).

**Other endoscopic treatments for GERD.** Radiofrequency heating of the GE junction (Stretta), endoscopic gastroplasty (Bard, Wilson Cook), polymer injections and full thickness gastroplication have been shown to improve quality of life in sham controlled trials. Duration of effect and acid control are less than surgical fundoplication (30-50% compared to > 70% at three years). Most of the commercial products for endoscopic anti-reflux treatments have been removed from the market mainly for non-coverage by insurance companies.

### **Treatment Failure**

Empiric treatment should be limited; if no response is seen after 8 weeks of anti-secretory therapy, consider referring the patient for upper endoscopy. Treatment response should be present in 2-4 weeks for patients with typical symptoms. Patients with atypical symptoms also have an initial response in one month, but may require 3-6 months for maximal response. Patients with atypical symptoms may require higher PPI doses for response.

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Empiric treatment in patients with atypical symptoms is appropriate if typical symptoms are also present. 24-hour esophageal pH monitoring off of anti-reflux medications might be the best diagnostic approach initially in patients with atypical symptoms only since  $\leq 30\%$  of patients will have GERD associated symptoms. If patients with atypical symptoms do not respond to treatment in 1-3 months, then GERD is not likely the cause and the other diagnoses should be entertained.

## Maintenance Regimens

The goal of maintenance anti-secretory therapy is to have a symptom-free individual without esophagitis. Multiple regimens are used to accomplish this. Increasing severity of esophagitis is associated with increasing need for potent acid reduction (ie, PPI long-term maintenance). Physicians should ask if symptoms have resolved or are persisting. When needed, an appropriate workup should be instituted (Figure 1). **Do not continue anti-secretory therapy indefinitely without re-evaluating symptoms. Regular re-evaluation can help avoid adverse events and minimize costs.**

Since most individuals with GERD do not undergo endoscopy, chronic acid suppression is tailored to the individual. Options include: step-up therapy (starting less potent agents and moving up for treatment response), step-down therapy (using potent acid suppression initially then decreasing the dose or moving to less potent agents to tailor to the individual's response), on demand (patient-directed) therapy, or surgery. All options have the goal of complete symptom relief.

**Step-up therapy.** If a patient does not respond to an H2RA within two weeks, the patient should be switched to a PPI, again emphasizing it be used 30 minutes to 1 hour prior to meals so that the PPI has time to interact with an activated pump.

If the patient does not respond to this program, double-dose PPI therapy (twice daily; 30 minutes before breakfast and 30 minutes before dinner) may be effective in reducing symptoms. If the patient does not respond to this program, the patient likely does not have reflux as a source of their symptoms, and diagnostic testing is appropriate.

Approximately 40% of patients requiring PPI therapy will need increasing dosage over time. Tolerance to H2RAs occurs over time. The main goal is to use the lowest dose and least potent medication to obtain a complete and sustained symptomatic response.

Breakthrough symptoms are common and can be treated with antacids and/or nocturnal H2RAs. This approach should be limited to those few individuals who are not getting symptomatic response, yet have defined reflux as their source of symptoms. H2RAs should not be administered at the same time as PPIs and should be taken at bedtime.

**Step-down therapy.** Once symptoms are controlled after step-up therapy, step-down therapy commences with the patient taking a PPI for 8 weeks, followed by an H2RA if GERD symptoms were adequately controlled with a PPI, then stepping down further to on-demand use of antacids if the patient was asymptomatic while taking an H2RA. The majority of patients who take more than a single daily dose of a PPI and who experience relief of symptoms can be successfully stepped down to single-dose therapy without a recurrence of reflux symptoms. However, a small percentage of patients with refractory GERD will need long-term therapy with higher doses of a PPI to control symptoms.

**On demand therapy.** Treatment can be initiated with standard dosage of either a PPI daily or an H2RA twice daily on demand (patient directed therapy). Drug selection depends on clinical presentation, cost-effectiveness, and end point of appropriate symptom relief.

## Special Circumstances

### Older Adults

In patients over the age of 50, new onset GERD is an alarm sign; endoscopy should be the initial diagnostic examination. If reflux is still considered the major cause after negative endoscopy, empiric therapy would then be appropriate.

### Pregnancy

New onset GERD symptoms are common during pregnancy due mainly to the mechanical pressure placed on the stomach and intestinal tract as the uterus enlarges. Therapy for GERD during pregnancy usually takes a step-wise approach, starting with lifestyle modifications often combined with a trial of calcium containing antacids. If this does not sufficiently treat the symptoms, H2RAs (eg ranitidine) are considered safe in pregnancy and can be taken to alleviate symptoms. If symptoms persist despite these efforts, PPIs can be considered (caution advised during pregnancy; possible risk of teratogenicity based on conflicting human data).

### Atypical Manifestations of GERD

As noted in Table 1, GERD may manifest atypically as pulmonary (asthma, chronic cough), laryngeal (laryngitis, hoarseness, sore throat, globus, throat clearing), or cardiac (chest pain) symptoms, often without symptoms of heartburn and regurgitation. Mechanisms include direct contact and microaspiration of small amounts of noxious gastric contents into the larynx and upper bronchial tree triggering local irritation, and cough, and acid stimulation of vagal afferent neurons in the distal esophagus causing non-cardiac chest pain and vagally-mediated bronchospasm or asthma. Laryngeal neuropathy has been implicated as a cause for laryngitis symptoms and cough.



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**Pulmonary symptoms.** Asthma and GERD are common conditions that often coexist, with 50-80% of asthmatics having GERD and up to 75% having abnormal pH testing. However, only 30% of patients who have both GERD and asthma will have GERD as the cause for their asthma. The causal relationship between asthma and GERD is difficult to establish because either condition can induce the other. GERD can cause asthma as noted above, and asthma can cause increased reflux by creating negative intrathoracic pressure and overcoming the lower esophageal sphincter barrier. Furthermore, medications used for asthma, such as bronchodilators, are associated with increased reflux symptoms. Historical clues to GERD-related asthma may include asthma symptoms that worsen with big meals, alcohol, or a supine position, or adult-onset and medically refractory asthma. Diagnostic testing with pH probe and EGD have limited utility in establishing causality in this population.

**Laryngeal symptoms.** In patients presenting with laryngeal symptoms, about 10% of hoarseness, up to 60% of chronic laryngitis and refractory sore throat, and 25-50% of globus sensation may be due to reflux. EGD and pH testing are frequently normal in this population. Reflux laryngitis is usually diagnosed based on laryngoscopic findings of laryngeal erythema and edema, posterior pharyngeal cobblestoning, contact ulcers, granulomas, and interarytenoid changes. However, a study found these signs to be nonspecific for GERD, noting at least 1 sign in 91 of 105 (87%) healthy people who did not have reflux or laryngeal complaints. Many of these signs may be due to other laryngeal irritants such as alcohol, smoking, postnasal drip, viral illness, voice overuse, or environmental allergens, suggesting their use may contribute to over-diagnosis of GERD. This also may explain why many patients (up to 40-50%) with laryngeal signs don't respond to aggressive acid therapy. Posterior laryngitis, medial erythema of false or true vocal cords and contact changes (ulcers and granulomas) are more common in GERD patients and predict a better response to acid reduction.

**Treatment.** Aggressive acid reduction using PPIs twice daily before meals for at least 2-3 months is now considered the standard treatment for atypical GERD and may be the best way to demonstrate a causal relationship between GERD and extraesophageal symptoms. Double blind, placebo controlled trials have not shown significant benefit for PPI twice daily treatment for laryngeal symptoms. Similar trials in asthma have shown marginal benefits in FEV<sub>1</sub> rates only when nocturnal GERD symptoms are also present. Both groups of studies demonstrate the need for better parameters for patient selection. Anti-reflux surgery aimed at controlling asthma through prevention of GERD has a lower rate of success than anti-reflux surgery aimed at treating heartburn (45-50% vs. 80-90% respectively).

A systematic review on chronic cough found there is insufficient evidence to definitely conclude that PPI treatment is beneficial for cough associated with GERD in

adults, although a small beneficial effect was seen in subgroup analysis.

## Controversial Areas

### Barrett's Esophagus Screening and Treatment

Barrett's esophagus is present when intestinal epithelium (intestinal metaplasia) replaces normal squamous epithelium in the tubular esophagus. Barrett's esophagus carries a small risk of progressing to esophageal adenocarcinoma. Most patients who develop esophageal adenocarcinoma are believed to progress from Barrett's epithelium to low-grade dysplasia, then to high-grade dysplasia, and then to cancer. The overall progression of non-dysplastic Barrett's epithelium to cancer is about 0.2% per year. Symptoms do not predict risk for cancer. Risk factors for progression include long-segment Barrett's esophagus, male sex, tobacco use, and likely abdominal obesity. Most patients with low-grade dysplasia will revert to non-dysplastic epithelium or remain low grade (60-80%); the progression of high-grade dysplasia to cancer is 6% per year.

Endoscopic surveillance of Barrett's esophagus is considered standard, but intervals are very controversial. Since progression is variable, the overall incidence of cancer is low (6,000-7,000 new cases per year), and surveillance of Barrett's esophagus at intervals of less than 5 years is cost-prohibitive ( $\geq$  \$100,000 per quality adjusted life-year). The diagnosis of all types of dysplasia is subject to sampling error and intra- and inter-observer bias. Most overcalling occurs between non-dysplastic and low-grade dysplasia and low-grade to high-grade dysplasia. Dysplasia should be confirmed by two experienced pathologists before surgery or endoscopic treatment is attempted.

Current accepted monitoring intervals are 3-5 years for no dysplasia, 6-12 months for low-grade dysplasia, and 3 months for high-grade dysplasia. Endoscopic biopsies should be done in a standard manner based on past histology. Biopsies from nodular areas should be examined separately. Endoscopy for Barrett's detection or monitoring should be done only after adequate GERD control for 3 months.

Prevention of cancer in Barrett's esophagus is also controversial. Proton pump inhibitors should be given to control GERD symptoms. Single dose and more intensive treatment to eliminate esophageal acid exposure have not been proven to reduce cancer risk. Low-dose aspirin reduces cancer risk, but should be reserved for Barrett's esophagus patients who have cardiovascular risk factors for which aspirin is indicated.

Endoscopic and surgical therapies for Barrett's esophagus are evolving. The use of radiofrequency ablation (RFA) or endoscopic mucosal resection (EMR) should be reserved for high-grade dysplasia confirmed by two pathologists. If treatment of non-dysplastic or low-grade dysplasia is being considered, the use of RFA or EMR should be a shared

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decision-making between the treating physician and the patient. Data to date show that reversion to squamous epithelium can persist for up to 5 years after endoscopic ablation.

Esophagectomy is the treatment of choice for esophageal adenocarcinoma. Most patients with high-grade dysplasia can be treated with endoscopic eradication (70-80%). Less morbidity is found with endoscopic ablation than esophagectomy with gastric pull-up. EMR is valuable to determine the existence of cancer with visible mucosal irregularities in dysplastic epithelium, and may effectively treat intramucosal cancers.

Before esophagectomy, patients with high-grade dysplasia or intramucosal carcinoma should be referred to surgical centers specializing in the treatment of foregut cancers and high-grade dysplasia.

### Treatment for *H. pylori*

Patients with predominant GERD symptoms have a similar or lower frequency of *H. pylori* positivity than the general population. Successful treatment of *H. pylori* has not been shown to reduce predominant GERD symptoms. Some studies have shown decreased PPI effectiveness after successful *H. pylori* treatment, but this is still controversial. One randomized controlled trial demonstrated that *H. pylori* eradication leads to more resilient GERD. Treatment of *H. pylori* is not indicated for patients with GERD.

### Related National Guidelines

This guideline is consistent with:

American College of Gastroenterology: Updated guidelines for the diagnosis and treatment of Gastroesophageal Reflux Disease, 2005

American Gastroenterological Association: Position statement on the management of gastroesophageal reflux disease, 2008

American Society for Gastrointestinal Endoscopy: Role of endoscopy in the management of GERD, 2007

Society of American Gastrointestinal and Endoscopic Surgeons: Guidelines for surgical treatment of gastroesophageal reflux disease, 2010

(See annotated references.)

### Strategy for Literature Search

The literature search began with the results of the literature searches performed through May 2006 for the previous versions of this guideline. The results of three more recent literature searches were initially reviewed and accepted as adequate through the time they were performed:

American Gastroenterological Association: Position statement on the management of gastroesophageal reflux disease, 2008, literature search through early 2007.

American Society for Gastrointestinal Endoscopy: Role of endoscopy in the management of GERD, 2007, literature search through March 2008.

Society of American Gastrointestinal and Endoscopic Surgeons: Guidelines for surgical treatment of gastroesophageal reflux disease, 2010, literature search through early 2006.

A search of more recent literature was conducted prospectively on Medline from January 2007 (end of AGA search) through March 2011, except January 2006 was the start date for endoscopy (since ASGE search) and January 2008 was the start date for surgical treatment (since SAGES search). The major keywords were: *gastroesophageal reflux disease (or GERD, NERD [non-erosive reflux disease], NEED [non-erosive esophageal disease]), human adults, English language, guidelines, clinical trials, and cohort studies*. Terms used for specific topic searches within the major key words included: *symptoms and classification (atypical symptoms, heartburn, retrosternal burning sensation precipitated by meals or a recumbent position, hoarseness, laryngitis, sore throat, chronic cough, chest pain, bronchospasm/asthma, dental erosions), eosinophil, lymphocytic esophagitis, non acid reflux and weekly acid reflux, nocturnal (or nocturnal breakthrough, night time), endoscopy, pH recording, manometry, provocative testing (Bernstein's), video esophagography, empiric/therapeutic trial to acid suppression, lifestyle measures/treatment (avoiding fatty foods, chocolate, peppermints, ethanol-containing beverages; recumbency for 3 hours after a meal; elevating head of bed; weight loss), antacids, alginic acid (gaviscon), carafate, prokinetic agents (cisapride, metoclopramide, bethanechol, dromperidone), H2 receptor antagonists (nizatidine, ranitidine, famotidine, cimetidine), proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole) – toxicity and adverse reactions/events, proton pump inhibitors – other references, baclofen, fundoplication (open vs. laparoscopy; endoscopic antireflux procedures), Barrett's esophagus (screening, surveillance)*. Detailed search terms and strategy available upon request.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent information available to expert members of the panel, including abstracts from recent meetings and results of clinical trials. Negative trials were specifically sought. The search was a single cycle.

Conclusions were based on prospective randomized controlled trials if available, to the exclusion of other data; if randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

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## Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

Team Member	Relationship	Company
Joel J Heidelbergbaugh, MD	None	
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## Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Medicine, and Gastroenterology. The Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

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2002: Clara Kim, MD, General Medicine; R. Van Harrison, PhD, Medical Education; Joel Heidelbergbaugh, MD, Family Medicine; Timothy Nostrant, MD, Gastroenterology.

2006: Joel J Heidelbergbaugh, MD, Family Medicine; Arvin S Gill, MD, Internal Medicine; R. Van Harrison, PhD, Medical Education; Timothy T Nostrant, MD, Gastroenterology.

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