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 Guideline Team**

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**Gastroesophageal Reflux Disease (GERD)**

**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 pH probe 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 (e.g. 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 (AST) can identify patients with GERD who lack alarm/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 (NCCP) [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 as followed by a PPI if no improvement) and *step-down* (PPI then followed by 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 strategy [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 PPI's 30-60 minutes prior to breakfast (and dinner if BID) to optimize effectiveness [I B\*]. Use generic and OTC formulations exclusively, eliminating need for prior authorizations.
- Patients should not be left on AST 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 modalities.** 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/alarm signs and symptoms suggesting complications from GERD (Table 2) should be referred to a GERD specialist.

**Risk for complications.** Further diagnostic testing (e.g., EGD [esophagogastroduodenoscopy], 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\*].

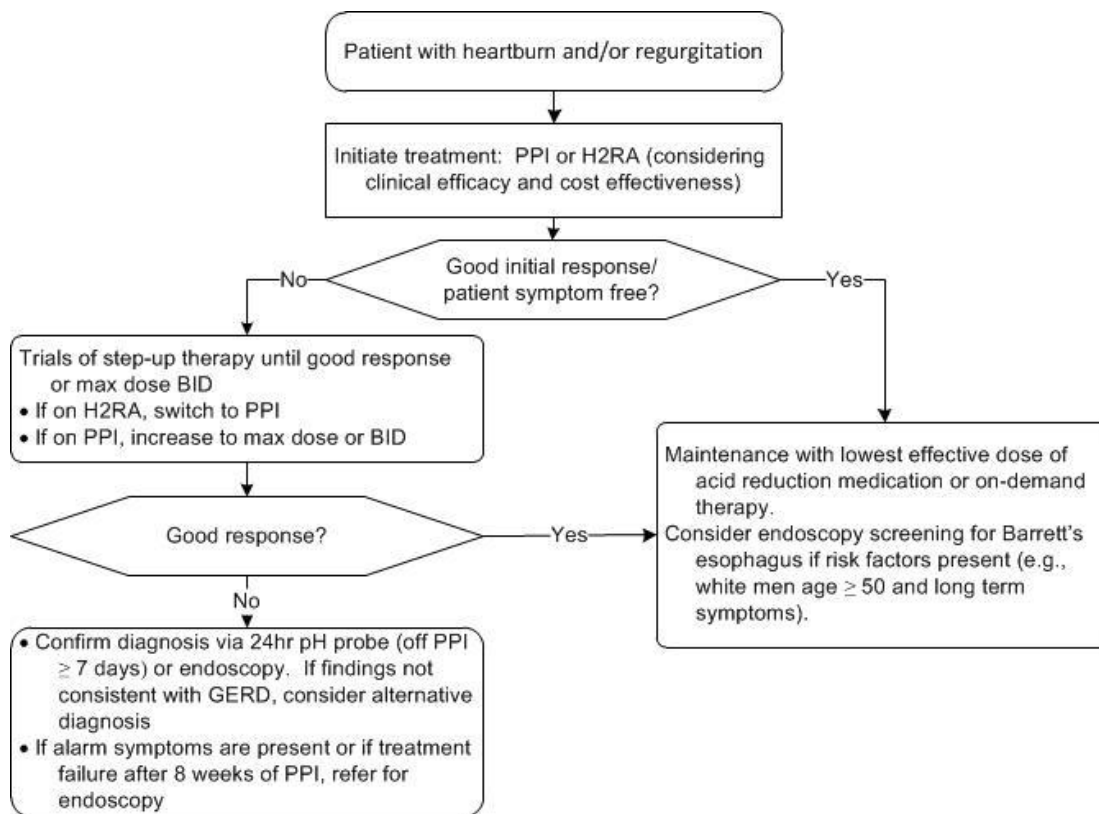
\* **Strength of recommendation:**

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/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/sleeping for 3-4 hours postprandially
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 antagonists</b>					
cimetidine (Tagamet HB)	200 mg BID	200 mg BID	\$15	NA	\$18
cimetidine (Tagamet)	400 mg BID	400 mg BID	\$30	\$11	\$36
famotidine (Pepcid)	20 mg BID	20 mg BID	\$34	\$8	\$130
ranitidine (Zantac)	150 mg BID	150 mg BID	\$20	\$29	\$220
ranitidine (Zantac)	300 mg nightly	300 mg nightly	\$40	\$48	\$187
<b>PPIs</b>					
lansoprazole (Prevacid)	30 mg daily	15/30 mg daily before breakfast	\$24-47	\$32-63	NA
omeprazole (Prilosec)	20 mg daily	20/40 mg daily before breakfast	\$16	\$18	\$180
pantoprazole (Protonix)	40 mg daily	40 mg daily before breakfast	NA	\$17	\$172
rabeprazole (Aciphex)	20 mg daily	20 mg daily before breakfast	NA	NA	\$240

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

<sup>b</sup> Maximum dose for PPIs is the highest listed dose amount, but given daily BID before breakfast and before dinner.

<sup>c</sup> For brand drugs, Average Wholesale Price minus 10%. AWP from Amerisource Bergen Wholesale Catalog 11/11. For generic drugs, Maximum Allowable Cost plus \$3 from BCBS of Michigan MAC List, 11/16/11.

## 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.

Extraneous 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 (AST) 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/carcinoid linked to use of the PPIs have been reported since the advent of this class of medication over 20 years ago.

Complications from GERD (e.g., Barrett's esophagus, adenocarcinoma of the esophagus) are rare but do exist; 10-15% with GERD will develop Barrett's esophagus, and 1-

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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/intestinal metaplasia), yet it is unknown if outcomes can be improved through surveillance and medical treatment. AST 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 LES (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 LES because of increased intra-abdominal pressure (strain induced reflux) and a baseline low LES pressure. 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 (e.g., esophageal dysmotility, scleroderma, decreased salivary production).

### Natural History

Most GERD patients (80-90%) do not seek medical attention and will self-medicate with OTC AST (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 (LA class A, 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 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 14 days], 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.

Classic symptoms of GERD are shown in Table 1. pH monitoring offers adequate sensitivity and specificity in establishing a diagnosis of GERD in cases that do not readily respond to AST. It may help with patient compliance by establishing that acid production has been eliminated / reduced to zero. The UMHS approach to 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.). Eosinophilic esophagitis is diagnosed via upper endoscopy with mucosal biopsy.

**PPI diagnostic test.** A favorable symptomatic response to a short course of a PPI (once daily for 2 weeks) is considered to support a diagnosis of GERD when symptoms of non-cardiac chest pain are present. A recent 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 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 NCCP (non-cardiac chest pain), empiric trial with 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/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 (e.g., 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 BID (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 BID was initially used, then PPI daily should be used. If PPI daily was initially used, then increase to maximum dose PPI daily or BID (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 initial dose (see figure 1), then increase potency/frequency as needed to obtain complete symptom relief: high-dose H2RA to PPI daily, PPI daily or maximum dose PPI daily or BID. If there is no response when using maximal doses and frequencies, then diagnostic testing should be performed after 8 weeks of therapy.

If patient responds with symptom relief, give 8-12 weeks of therapy, i.e., enough to heal undiagnosed esophagitis. If patient has complete symptom relief at 8-12 weeks, taper over 1 month to lowest effective dose of the medication that gives complete relief, e.g., H2RA on demand, PPI QOD. If symptoms recur, put patient back on 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 BID dosing. If there is no improvement at all in symptoms after two months, further testing should be pursued.

**Endoscopy/biopsy in GERD.** Endoscopy is used to detect mucosal injury, esophageal stricture, Barrett's esophagus or esophageal cancer. Eosinophilic esophagitis (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 diagnostic sensitivity is less than 50% but specificity in 95%.

Esophagitis is best defined by the LA Classification (A through D). Alarm signs and severity of symptoms are not predictive of complications (Barrett's, cancer) but

troublesome dysphagia and weight loss are predictive of complications. Endoscopy should be done for patients not responding to twice a day PPI.

Endoscopic biopsies are indicated to detect Barrett's esophagus and eosinophilic esophagitis, but are not indicated when 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 and 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.** Bernstein testing, esophageal sensory testing and barium esophagogram are not indicated for the diagnosis of GERD. Barium esophagogram may be helpful in the preoperative phase of anti-reflux surgery or in the evaluation of major motor disorders (achalasia, diffuse esophageal spasm) after a normal endoscopy.

## Treatment

**Lifestyle modifications.** For 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 for any of these modifications. 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 the elevation of 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 almost completely 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.

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**Avoid certain foods.** Several foods are believed to be direct esophageal irritants: citrus juices, carbonated beverages, coffee and caffeine, chocolate, spicy foods, fatty foods, or late evening meals. However, no randomized controlled trials 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 lower LES pressure and lead to further esophageal irritation. A recent 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 lower LES pressure or irritate the esophagus.** Medications that lower LES 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 (e.g., 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 AST (H2RAs, PPIs)** are appropriate, initial patient-directed therapy for GERD. Antacids (Tums, Roloids, Maalox) and combined antacid/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 antagonists (H2RAs).** All four of the **histamine type-2 receptors 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 in the postprandial state, without affecting esophagogastric barrier dysfunction. The four compounds 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 pre-medication 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, which may exceed or equal the cost of a proton-pump inhibitor, as well as 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 anandrogenic 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 to 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 RCT showed that at 12 months, significantly more people were still in remission with omeprazole compared to ranitidine. Another RCT 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 RCTs have examined therapy for a longer period of time.

One RCT found no evidence of a significant difference among the PPIs, including omeprazole, lansoprazole, rabeprazole and pantoprazole in the healing of erosive

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esophagitis. Efficacy in pH changes was not studied. The least expensive PPIs are omeprazole and lansoprazole, which are available generically and OTC. 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 healing and symptom resolution in GERD patients with reflux esophagitis, with a tolerability profile comparable to that of omeprazole. A recent 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 B12 deficiency (AOR = 1.0 – 4.46); antiplatelet interactions (AOR = 1.25). Data regarding risks of bone fracture and antiplatelet interactions are controversial. A recent 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. Their action is aimed at decreasing the number of transient lower esophageal sphincter relaxations and increase lower esophageal sphincter tone. These effects have been observed most significantly in the post-prandial state.

### **Prokinetics**

Previous prokinetics (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 RCTs have been conducted to date to compare treatment outcomes between conventional anti-secretory therapy and alternative therapies. Use of demulcents (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 acid/bile reflux. The basic tenets of surgery are reduction of the hiatal hernia, repair of the diaphragmatic hiatus, strengthening the gastroesophageal junction-posterior diaphragm attachment, and strengthening the anti-reflux barrier by adding a gastric wrap around the gastroesophageal junction (fundoplication). Open and laparoscopic surgical repairs are available. 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 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> receptor antagonists and proton pump inhibitors have shown marginal superiority to surgery. Recent 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%).

**Newer 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 trials should be limited and if no response is seen after 8 weeks of AST, then consider referring the patient for

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upper esophageal evaluation by a gastroenterologist or physician skilled in 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.

Empiric treatment in patients with atypical symptoms is appropriate if typical symptoms are also present. Esophageal pH monitoring off of anti-reflux medications might be the best 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 AST 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 (i.e. PPI long-term maintenance). Physicians should inquire regarding symptom resolution versus persistence and an appropriate workup should be instituted (Figure 1). **Patients should not simply be left on AST without re-evaluation of symptoms in order to minimize the potential for adverse events and 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 with decreasing dose or less potent agents to tailor to the individuals 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 2 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 (BID; 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 is likely not to have reflux as a source of their symptoms and diagnostic testing would be appropriate.

Approximately 40% of patients requiring PPI therapy will need increasing dosage over time. Tolerance to H2 receptor antagonists occurs over time. The main goal is to use the lowest dose and least potent medication to obtain a complete and sustained symptomatic response.

Break through symptoms are common and the patients can use antacids and/or nocturnal H2 receptor antagonists. These should be limited to individuals who are not getting symptomatic response, yet have defined reflux as their source of symptoms. This would be a very small number of patients. H2 receptor antagonists should not be administered at the same time as PPIs and should be taken 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 a patient over the age of 50, new onset of GERD is an alarm sign and 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 H2 blockers (e.g. ranitidine, category B) are considered safe in pregnancy and can be taken to alleviate symptoms. If symptoms persist despite these efforts, proton pump inhibitors (category C) can be considered.

#### Atypical Manifestations of GERD

As noted in Table 1, GERD may manifest atypically as pulmonary (asthma, chronic cough), ENT (laryngitis, hoarseness, sore throat, globus, throat clearing) or cardiac



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(chest pain) symptoms, often without symptoms of heartburn and regurgitation. Mechanisms for this 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/asthma). Laryngeal neuropathy has been implicated recently as a cause for laryngitis symptoms and cough.

**Pulmonary.** 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 causing asthma as above, and asthma causing increased reflux by creating negative intrathoracic pressure and overcoming LES barrier). Furthermore, medications used for asthma, such as bronchodilators, are associated with increased reflux symptomatology. Historical clues to GERD-related asthma may include asthma symptoms that worsen with big meals, alcohol, and 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.

**Ear, nose, and throat.** In patients presenting with ENT symptoms, 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 the laryngoscopic findings of laryngeal erythema and edema, posterior pharyngeal cobblestoning, contact ulcers, granulomas, and interarytenoid changes. However, a recent study found these signs to be nonspecific for GERD, noting at least 1 sign in 91 of 105 (87%) healthy people without 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/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 BID 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. Recent double blind, placebo controlled trials have not shown significant benefit for PPI BID 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/Treatment

Barrett's esophagus is intestinal epithelium (intestinal metaplasia) replacing 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 of 0.2%/year. Symptoms do not predict risk for cancer. Risk factors for progression include long segments of 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%) and the progression of high grade dysplasia to cancer is 6%/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) surveillance of Barrett's esophagus at intervals of less than 5 years ( $\geq$ \$100,000/quality adjusted life-year) is prohibitive. 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/endoscopic treatment is attempted.

Current accepted monitoring intervals are no dysplasia (3-5 years), low grade dysplasia (6-12 months) and high grade dysplasia (3 months). Endoscopic biopsies also should be done in a standard manner based on past histology, but very few patients are followed correctly. 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

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reduces cancer risk, but should be reserved for Barrett's esophagus patients with appropriate cardiovascular risk factors for which aspirin is indicated.

Endoscopic and surgical therapies for Barrett's 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 decision-making between 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 post successful *H. pylori* treatment, but this is still controversial. One RCT 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), eosinophile, 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.

## 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 Heidelbaugh, 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 Heidelbaugh, MD, Family Medicine, Timothy Nostrant, MD, Gastroenterology.

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

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