

## Management of Gastroesophageal Reflux Disease (GERD)

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

### UMHS Preferred Drugs version

### Patient population: Adults

**Objective:** Implement a cost-effective and evidence-based strategy in the diagnosis and treatment of gastroesophageal reflux disease.

### Key Points

#### ■ Diagnosis

**History.** A well-taken history is essential in establishing the diagnosis of GERD. If the classic symptoms of heartburn and acid regurgitation clearly dominate a patient's history, they can help establish the diagnosis of GERD with sufficiently high specificity. The sensitivity toward diagnosis remains low, however. Atypical symptoms (Table 1), although commonly present, cannot sufficiently make the clinical diagnosis of GERD. [evidence: 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 [B\*]. Endoscopy lacks sensitivity in determining pathological reflux. Barium radiology has limited usefulness in the diagnosis of GERD and thus is not recommended [B\*].

**Therapeutic trial.** An empiric trial of acid suppression therapy can identify patients with GERD who do not have alarm symptoms [A\*] and may be helpful in the evaluation of those with atypical manifestations of GERD, specifically, noncardiac chest pain (NCCP) [B\*].

#### ■ Treatment

**Lifestyle modifications.** Lifestyle modifications should be recommended throughout the treatment of GERD but there is little evidence to support this information [D\*].

**Pharmacologic treatment.** H2-receptor antagonists, prokinetics, and proton pump inhibitors have shown efficacy in the treatment of GERD [A\*]. Prokinetics have been as effective as H2 antagonists but are currently not available [A\*]. Carafate and antacids are ineffective in the treatment of GERD [A\*], but may be used as supplemental acid-neutralizing agents for certain patients with GERD [D\*].

- **Documented erosive esophagitis:** Initial Proton Pump Inhibitor (PPI) therapy is the treatment of choice in acute and maintenance therapy for patients with documented erosive esophagitis [A\*].
- **Non-erosive reflux disease:** step-up (H2 antagonists followed by PPI if no improvement) and step-down (PPI followed by the lowest dose of acid suppression) therapy are equally effective for both acute treatment and maintenance [C\*].
- PPI's should be given 30-60 minutes prior to a meal to optimize effectiveness [B\*].

**Surgery.** Antireflux surgery is an alternative modality in the treatment of GERD in patients who have documented chronic reflux with recalcitrant symptoms [A\*].

**Other endoscopic modalities.** Some alternative endoscopic modalities are less invasive and have fewer complications, but are also likely to have lower response rates than antireflux surgery [C\*].

#### ■ Follow up

**Symptoms unchanged.** If symptoms remain unchanged in a patient who has had a prior normal endoscopy, evidence for the need for repeat endoscopy is not known, but currently not recommended [C\*].

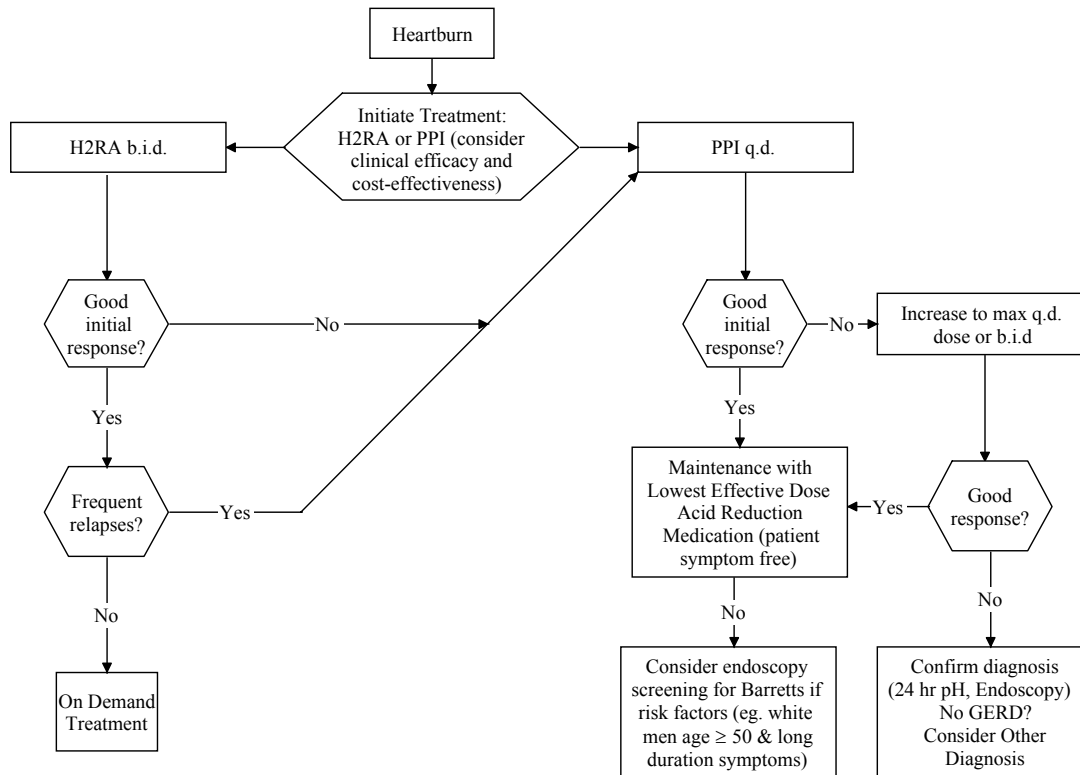
**Warning signs.** Patients with warning signs and symptoms suggesting complications from GERD (Table 2) should be referred to a GERD specialist.

**Risk for complications.** Consider further diagnostic testing (eg, EGD, pH monitoring) for those who do not respond to acid suppression therapy [C\*]. Further diagnostic testing should also occur in patients with a chronic history of GERD who are at risk for complications (e.g., Barrett's esophagitis, adenocarcinoma, stricture). 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\*]. Anti-reflux therapy has been shown to reduce the need for recurrent dilation from esophageal stricture formation [A\*].

\* Levels of evidence reflect the best available literature in support of an intervention or test:

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

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



Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease. American Journal of Gastroenterology. 94:6: 1434-1442. June 1999

**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. Warning Signs Suggesting Complicated GERD**

Dysphagia
Odynophagia
GI Bleeding
Fe Deficiency Anemia
Weight Loss
Early satiety
Vomiting

**Table 3. Lifestyle Modifications [D\*]**

Elevate head of bed
Decrease fat intake
Stop smoking
Avoid recumbency for 3 h postprandially
Avoid certain foods: chocolate, alcohol, peppermint, coffee, onions, garlic, fatty foods, citrus, tomato
Avoid large meals
Weight loss
Do not eat before sleeping
Avoid medications that can potentiate symptoms

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

Drug	Dose Equivalents	Dosage	Cost/Mo <sup>a</sup>
<b>H2 antagonists</b>			
Axid (nizatidine)	150 mg BID	150 / 300 mg BID	\$144 / <b>\$165</b> (brand) <b>\$89 / \$172</b> (generic)
Pepcid (famotidine)	20 mg BID	20 / 40 mg BID	\$110 / \$211(brand) <b>\$11 / \$19</b> (generic)
Tagamet (cimetidine)	400 mg BID	400 / 800 mg BID	<b>\$100</b> / <b>\$196</b> (brand) \$13 / \$20(generic)
Zantac (ranitidine)	150 mg BID	150 / 300 mg BID	<b>\$107</b> / <b>\$195</b> (brand) <b>\$14 / \$25</b> (generic)
<b>PPIs</b>			
Protonix (pantoprazole)	40 mg QD	40 mg QD / 80 mg QD / 40 mg BID	<b>\$95 / \$190 / \$190</b>
Prevacid (lansoprazole)	30 mg QD	30 mg QD / 60 mg QD / 30 mg BID	<b>\$120 / \$240 / \$240</b>
Aciphex (rabeprazole)	20 mg QD	20 mg QD / 40 mg QD / 20 mg BID	\$111 / \$222 / \$222
Prilosec (omeprazole)	20 mg QD	20 mg QD / 40 mg QD / 20 mg BID	\$120 / \$172 / \$240 <b>\$112 / \$224 / \$224(gen)</b>
Nexium (esomeprazole)	40 mg QD	20 mg QD / 40 mg QD / 40 mg BID	<b>\$115 / \$115 / \$230</b>

<sup>a</sup> For brand drugs, Average Wholesale Price minus 10%. AWP from Amerisource Bergen Wholesale Catalog 11/02.. For generic drugs, Maximum Allowable Cost plus \$3 from BCBS of Michigan MAC List, 1/15/03 UMHS preferred drugs in bold.

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## Clinical Background

### Clinical Problem

#### Incidence

Gastroesophageal reflux disease (GERD) is a common chronic, relapsing condition that carries a risk of significant morbidity and possible 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.

More than 60 million adult Americans suffer from heartburn at least once a month and over 25 million experience heartburn daily. For patients presenting with GERD symptoms, 40-60% or more have reflux esophagitis. Up to 10% of these patients will have erosive esophagitis after investigation. GERD appears to be 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 adenocarcinoma, further increasing the importance of its diagnosis and treatment.

Extrasophageal 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 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 extrasophageal 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 atypical GERD, *H. pylori*-induced gastritis, gastroduodenal ulcer and gastric cancer may present similarly, making accurate history taking important. 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 symptomatic relief generally occurs with empiric treatment, the long-term effects of anti-reflux medications are as yet unknown. Complications from GERD (e.g., Barrett's esophagus, adenocarcinoma) are rare but do exist; 10-15% with GERD will develop Barrett's esophagus, and 5-10% 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. Anti-reflux therapy has been shown to reduce the need for recurrent dilation from esophageal stricture formation.

Previous cost-effectiveness models 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 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 (esophageal dysmotility, scleroderma, decreased salivary production).

#### Natural History

Most GERD patients do not seek medical attention (80-90%) and self medicate (50%). In patients seeing physicians, most will have chronic symptoms which will occur off treatment. Patients with more severe esophagitis will recur more quickly and almost all will have recurrent symptoms and esophagitis if followed up for  $\geq 1$  yr.

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Progression 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. Long term natural history studies are few and are urgently needed.

## Diagnosis

Evidence-based limitations exist when trying to assess the validity of the diagnostic modalities for GERD. Most studies are flawed from a methodological standpoint as no gold standard exists. However, the calculated numbers as presented are helpful at least in providing a framework in which to thoughtfully assess the various options that exist.

**History.** A well-taken history is essential in establishing the diagnosis of GERD. Specificity is high when classic symptoms of heartburn (89%) and acid regurgitation (95%) clearly dominate a patient's history. However, the sensitivity remains low. Symptom frequency, duration and severity are equally distributed among patients with varying grades of esophagitis and Barrett's esophagus.

**PPI diagnostic test.** Proton pump inhibitors have been studied and tried more often than H2-receptor antagonists given their higher efficacy. An empiric trial of omeprazole at 20 mg BID had a sensitivity of 75% and specificity of 55% for symptom relief, which was equal to or better than pH testing or endoscopy. In another study that used pH monitoring as the gold standard, an omeprazole trial had a PPV of 68% and a NPV of 63%. In those with NCCP (noncardiac 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.

**Empiric/therapeutic trial.** Diagnostic modalities cannot reliably exclude GERD even if they are negative. Therefore an empiric trial 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). (Also see the 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) 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 Table 4). If symptom relief is not adequate and H2RA BID was initially used, then PPI QD should be used. If PPI QD was initially

used, then increase to maximum dose PPI QD or BID (30-60 minutes prior to first and last meals)

For those 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 increase potency/frequency as needed to obtain complete symptom relief: high dose H2RA to PPI QD, PPI QD to or maximum dose PPI QD or BID. If there is no response when using higher dosages, then diagnostic testing should be performed. If patient responds 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 reoccur, put patient back on initial 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. If there is no improvement in symptoms after one month, further testing should be pursued.

**Endoscopy.** Endoscopy is the primary technique for evaluating mucosal integrity, esophageal stricture formation, and Barrett's esophagus with a sensitivity of 50% and specificity of 95%. Endoscopic evidence of esophagitis occurs in less than 50% of people who have experienced heartburn greater than twice a week over a six-month time period.

Esophagitis is best defined by the LA classification system and identifies the degree to which mucosal breaks (erosions or ulcerations) occur, graded in severity from A to D, with D being the most severe. Specific definitions are:

- A One or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
- B One or more mucosal breaks more than 5 mm long, none of which extends beyond the tops of two mucosal folds
- C Mucosal breaks that extend between the tops of two or more mucosal folds, but which involves less than 75% of the esophageal circumference
- D Mucosal breaks which involve at least 75% of the esophageal circumference

(Dent, J et al. An evidence-based appraisal of reflux disease management-the Genval Workshop Report. Gut 1999;44(2S):1S-16S.)

Although biopsy is indicated in defining Barrett's esophagus, histological assessment has not been helpful in the diagnosis of GERD if endoscopy is negative for mucosal abnormalities. In addition, descriptives such as erythema, edema, and friability also are not clear indications of esophagitis.

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Endoscopy should be considered in those who present with warning symptoms (see Table 2) and who are suspected to have complications from GERD. Further testing should also occur for patients who do not respond to therapy, need continuous chronic therapy and have risk factors for Barrett's.

Repeating endoscopy is likely not to be worthwhile following a normal result. In observational studies, patients with an initial normal endoscopy have not been found to progress to severe esophagitis during a 10 year follow-up, thus arguing against repeat endoscopy in a select group of patients whose symptom complex has not changed during this time. However, some patients did progress to grade A esophagitis.

**PH probe.** Many patients do not have evidence of esophagitis on endoscopy and yet they respond to acid suppression and have behaviors and concerns that parallel those who have evidence of mucosal damage. Patients with endoscopic-negative GERD and who do not respond to medications are best evaluated by ambulatory pH monitoring. On average, patients with endoscopic-negative reflux have less acid exposure than those with esophagitis, but more compared to people without reflux. However, normal acid exposure has been found in up to 25% of patients with documented reflux esophagitis and in up to 33% of patients with endoscopic-negative GERD.

PH probe is used most often in the evaluation of atypical manifestations of GERD (see Table 1) and in difficult cases where there is no evidence of GERD on endoscopy and/or the individual remains refractory to acid suppression. However, patients with atypical symptoms frequently have normal pH monitoring.

Ambulatory pH monitoring is based upon the amount of time the intraesophageal pH is less than 4, with normal defined as less than 4% over a 24-hour period. Patients are expected to perform their usual activities with dietary and lifestyle restrictions minimized in order to improve the diagnostic yield.

Correlating symptoms with reflux events is important in those with EGD-negative GERD and is helpful in the evaluation of those with extraesophageal or sporadic symptoms. The symptom index associates symptoms with reflux events. Associations greater than 50% are clinically relevant.

The purpose for pH probe must be defined before proceeding: is it to diagnose GERD or to determine the adequacy of therapy? The test should be performed off therapy if the diagnosis is under question. The test should be performed on therapy if one is trying to determine the adequacy of treatment. The major indication for performing 24 ambulatory pH monitoring is in

documenting treatment failures, either to antireflux surgery or medical management.

**Other diagnostic modalities.** Other diagnostic modalities include manometry, Bernstein's test and gastroesophageal scintigraphy. Due to their many limitations, these tests should not be routinely ordered. Barium swallow should not be used in the evaluation of GERD although it was commonly used in the past. It is useful in the evaluation of dysphagia but limited in its ability as a screening test for GERD, as are all the aforementioned modalities.

## Treatment

**Lifestyle modifications.** For a history typical for uncomplicated GERD, expert opinion is to initiate and continue 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.

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, although data reflecting the true efficacy of this maneuver in patients 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.

Avoid certain foods. Foods such as coffee, chocolate, peppermint, spicy foods, citrus juices, and perhaps onions and garlic have been thought to be direct esophageal irritants and should be avoided or minimized, although randomized clinical trials are not available to test this hypothesis.

Weight loss. An association among weight, reflux and reflux complications has been shown recently, but weight loss has not been shown to improve reflux.

Smoking cessation and alcohol minimization. Smoking cessation and the elimination or minimization of alcohol are also encouraged, both for a variety of health reasons, as both nicotine and alcohol have been shown to lower LES pressure and lead to further esophageal irritation.

Avoid medications that lower LES pressure. Medications that lower LES pressure and should be avoided in patients with symptoms of GERD include calcium channel blockers,  $\beta$ -agonists,  $\alpha$ -adrenergic agonists, theophylline, nitrates, and some sedatives.

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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 acid suppressants are appropriate, initial patient-directed therapy for GERD. Antacids (Tums, Rolaids, Maalox) and combined antacid/alginate acid 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.

All four of the histamine type-2 receptors antagonists (H2RAs: ranitidine, cimetidine, famotidine, and nizatidine) 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. 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. **Ranitidine and cimetidine are preferred because they are available as generic products with lower acquisition costs.** 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.

**H2 antagonists (H2RAs).** Numerous randomized, controlled trials have demonstrated that standard prescription 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.

No randomized controlled trials exist to examine the course of incompletely treated GERD, nor is there any good data on the natural history of inflammatory esophageal disease. Little information is available on the level of gastric acid suppression that is needed to ensure adequate esophageal healing.

Patients seem to develop some tolerance to the H2RAs, with some decreased efficacy observed after 30 days of treatment.

In the short term, randomized controlled trials with patients on placebo found similar rates of adverse effects as compared to the RCTs with patients on H2RAs. 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, no controlled trials with follow-up on the safety of chronic use of H2RAs.

**Proton Pump Inhibitors (PPIs).** Solid evidence from several 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 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 esophagitis. Efficacy in pH changes was not studied. Pantoprazole is currently the least costly agent based on acquisition costs; omeprazole is the only agent this is currently available generically. Esomeprazole, the S-isomer of the parent compound omeprazole, has been recently introduced. A single study showed esomeprazole 20 mg and 40 mg to be 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. Decreased cobalamin absorption has been found, although a clinically significant decrease in serum vitamin B12 levels is not usually seen. PPIs cause a profound decrease in gastric acid secretion, which leads to an increase in gastrin production from the antral G-cells. No cases of gastric cancer/carcinoid linked to use of the PPIs have been reported since the advent of this class of medication over 16 years ago.

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**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 manageable in most instances. Solid food dysphagia occurs in 10% of patients with 2-3% having permanent symptoms. Gas bloating occurs in 7-10% of patients with diarrhea, nausea and early satiety occurring more rarely. Despite complications in up to 20% 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 against 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.** Radiofrequency heating of the GE junction (Stretta) and endoscopic gastroplasty (endocinch) attempt to reduce acid exposure by decreasing volume of acid exposure. Initial results with both treatments are encouraging, with 50-75% decreasing or eliminating acid reduction medications. Complications are few but follow-up is short. Less than 3,000 patients have been treated worldwide. Reduction in acid exposure appears to be in the range of 1 PPI dose/day.

### **Treatment Failure**

Empiric trials should be limited if no response is seen. Treatment response should be present in 2-4 weeks for patients with typical symptoms. Patients with atypical symptoms have a slower response, which may not be maximal for 3-6 months after treatment initiation. 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 therapy is to have a symptom free individual with no 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).

Since most individuals with GERD do not undergo endoscopy, chronic acid suppression is tailored to the individual. The goal of either 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), or surgery must be individualized. Treatment goals should again be complete symptom relief.

**Step-up therapy** (see Figure 1). When beginning step-up therapy, no more than 2 weeks is needed to determine if a dosage of medication will be effective. If a patient does not respond to an H<sub>2</sub> receptor antagonist within 2 weeks, the patient should be switched to a proton pump inhibitor, 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, a double dose program (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 H<sub>2</sub> 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 H<sub>2</sub> 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. H<sub>2</sub> receptor antagonists should not be administered at the same time as PPIs.

### **Special Circumstances**

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## 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.

## Asthma and GERD

Asthma and GERD are common conditions. Medications used for asthma, such as bronchodilators, are associated with increased reflux symptomatology. Only 30% of patients who have both GERD and asthma will have GERD as the cause for their asthma. Because of the low rate of causality, diagnostic testing prior to empiric treatment is considered to be standard. In general, diagnostic testing would include 24 hour pH monitoring and possibly endoscopy because of a slightly increased risk of complicated GERD (i.e. Barrett's and stricture formation) in patients who have GERD and asthma.

**Mechanism.** The mechanism of GERD and asthma is primarily microaspiration of gastric acid contents. A secondary mechanism is vagally mediated bronchoconstriction related to stimulation of afferent neurons by acid in the distal esophagus. Because micro aspiration is the major mechanism, small amounts of acid can produce significant symptoms.

**Treatment.** Aggressive acid reduction using PPIs bid before meals is now considered the standard treatment for this condition. Time for response may be slow. Within the first month significant improvement is usually noted if objective parameters are used.

If no response is obtained after 3 months, the association of asthma and GERD may be non causal. 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).

## Controversial Areas

### Screening for Barrett's Esophagus

GERD is the major cause for esophageal adenocarcinoma (68-90%). Adenocarcinoma is more common (30-60x) in patients with GERD and increases with increased frequency, severity and duration of reflux symptoms. Initial screening is appropriate especially in Caucasian males over age 50 and in patients with reflux symptoms for more than 10 years. If Barrett's esophagus and/or esophagitis is not found on initial endoscopy, repeat surveillance is not indicated unless the patient has a major change in symptoms.

Surveillance of known Barrett's esophagus is controversial because adenocarcinoma of the esophagus is rare in the US (6000-7000 cases/yr) and GERD/Barrett's occur in 0.4-0.8% of the population. The discounted cost per quality adjusted patient year for surveillance is expensive (\$100,000-\$500,000). Current recommendations are for repeat endoscopy every two years. Follow-up of patients with dysplasia should be more frequent. Surveillance should stop if patient's clinical situation would preclude esophageal resection. Endoscopic ablation treatments are being evaluated for Barrett's esophagus, dysplasia and superficially invasive esophageal carcinoma.

### Treatment for H. pylori

Patients with predominant GERD symptoms have a similar or lower frequency of H. pylori positivity than compared to 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. Treatment of H. pylori is not indicated for patients with GERD.

## Information the Patient Needs to Know

**Cause.** GERD is usually caused by random and transient episodes of relaxation of the lower esophageal sphincter as well as incompetence of this valve.

**Complete treatment.** Lifestyle measures should be recommended throughout treatment. Medications can help control symptoms and the type of medication prescribed by one's health care provider is tailored to the individual.

**Alarm symptoms.** Symptoms which require early follow-up include weight loss, early satiety, difficulty swallowing, blood in the stool, and onset of symptoms after age 50.

**Next option.** If symptoms persist despite adequate treatment or alarm symptoms trigger an early follow-up, you may need to undergo further testing. This may include endoscopy and/or pH testing.

## Related National Guidelines

This guideline is consistent with the American College of Gastroenterology's Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease published June 1999. (See annotated references.)

## Strategy for Literature Search

The literature search for this project was conducted on Medline prospectively using the major keywords of:

*gastroesophageal reflux, human adults, English language, clinical trials, and guidelines.* Terms used for specific topic searches within the major key words included: *symptoms (1988+), endoscopy (1995+), pH recording (1995+), manometry (1995+), video esophagography (1995+), acid suppression (1996+), lifestyle (1998+; diet therapy; weight loss: life style; health behavior; cacao; peppermint; dietary fats; ethanol; alcoholic beverages; posture; hob; recumbent; chocolate), antacids (1976+), alginic acid (1988+), carafate (1988+), prokinetic agents (1995+), H2 receptor antagonists (1978+), proton pump inhibitors (1988+), fundoplication (1980).* 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 clinical 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.

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### Annotated References

Dent, J. An evidence-based appraisal of reflux disease management – the Geneva Workshop Report. *Gut* 1999;44(2S):1S-16S.

An extensive authoritative report summarizing the recommendations from an evidence-based appraisal workshop with an emphasis on the management of GERD.

Devault, KR. Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease. *American Journal of Gastroenterology*. 94:6: 1434-1442. June 1999.

A consensus statement outlining the current recommendations by the American College of Gastroenterology in the diagnosis and treatment of GERD.

Kahrilas, PJ. Gastroesophageal Reflux Disease. *JAMA*. 1996;276(12):983-988.

A comprehensive review of treatment of GERD with less emphasis on diagnostic modalities.

Sridhar, S. Clinical economics review: cost-effectiveness of treatment alternatives for gastro-oesophageal reflux disease. *Alim Pharmacol Ther* 1996;10:865-873.

An economic appraisal reviewing different treatment modalities and their cost-effectiveness. Proton pump inhibitors are considered more cost effective than H2 receptor antagonists in those with documented erosive esophagitis.