Gastroesophageal Reflux Disease (GERD)

GERD Guideline Team

Team Leader

Joel J Heidelbaugh, MD
Family Medicine

Team Members

Arvin S Gill, MD
Internal Medicine

R Van Harrison, PhD
Medical Education

Timothy T Nostrant, MD
Gastroenterology

Updated
January, 2007

UMHS Guidelines Oversight Team

Connie J Standiford, MD
William E Chavey, MD
R Van Harrison, PhD

Literature search service
Taubman Medical Library

For more information call
GUIDES: 734-936-9771

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. A well-taken history is essential in establishing a 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, although sensitivity of clinical history 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 *[B*]*. Endoscopy lacks sensitivity in determining pathologic reflux. Barium radiology has limited usefulness in the diagnosis of GERD and 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, non-cardiac chest pain (NCCP) *[B*]*.

■ Treatment

Lifestyle modifications. Lifestyle modifications should be recommended throughout the treatment of GERD, but there is little evidence-based data to support their efficacy *[D*]*.

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

- Non-erosive reflux disease (NERD): Step-up (H2RAs followed by a 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*]*. Costs for step-down treatment are mainly medications, while step-up treatment requires more frequent endoscopy. On demand (patient-directed) therapy is the most cost-effective strategy.
- Documented erosive esophagitis: Initial PPI therapy is the treatment of choice for acute and maintenance therapy for patients with documented erosive esophagitis *[A*]*.
- PPI's should be taken 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*]*. Surgery has a significant complication rate (10-20%). Resumption of pre-operative medication treatment (>50%) is common and will likely increase over time.

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*]*, 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 *[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. Further diagnostic testing (e.g., EGD [esophagogastroduodenoscopy], pH monitoring) should be considered in patients who do not respond to acid suppression therapy *[C*]* and in patients with a chronic history of GERD who are at risk for complications (e.g., Barrett's esophagus, 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*]*. Costs of surveillance for Barrett's Esophagus without dysplasia are likely to be prohibitive *[B*]*. 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

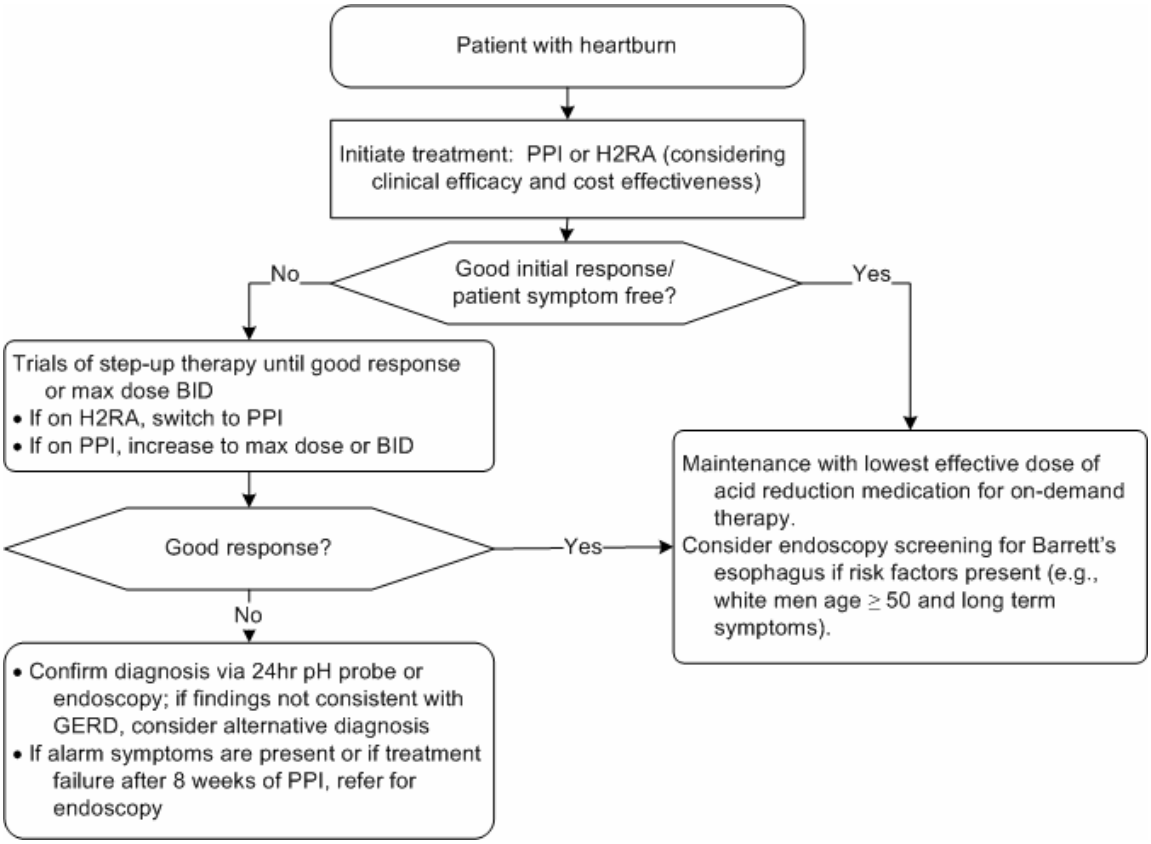

Table 1. Atypical Signs of GERD

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
Iron 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 hours 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/Month [a] Brand	Generic	OTC
H2 antagonists					
Zantac (ranitidine)	150 mg BID	150/300 mg BID	170/309	9/9	60/120 (75 mg tabs)
Pepcid (famotidine)	20 mg BID	20/40 mg BID	110/211	8/12	60/120 (10 mg tabs)
Tagamet (cimetidine)	400 mg BID	400/800 mg BID	133/266	8/19	60/120 (200 mg tabs)
Axid (nizatidine)	150 mg BID	150/300 mg BID	165/323	68/126	60/120 (75 mg tabs)
PPIs					
Prilosec (omeprazole)	20 mg daily	20 mg daily/40 mg daily/20 mg BID	128/190/256	27/51/51	36/72/72 (20 mg tabs)
Nexium (esomeprazole)	40 mg daily	20 mg daily/40 mg daily/40 mg BID	142/142/284	NA	NA
Protonix (pantoprazole)	40 mg daily	40 mg daily/80 mg daily/40 mg BID	114/228/228	NA	NA
Aciphex (rabeprazole)	20 mg daily	20 mg daily/40 mg daily/20 mg BID	142/284/284	NA	NA
Prevacid (lansoprazole)	30 mg daily	30 mg daily/60 mg daily/30 mg BID	144/288/288	NA	NA

[a] For brand drugs, Average Wholesale Price minus 10%. AWP from Amerisource Bergen Wholesale Catalog 10/06. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 8/8/06.

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 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.

Extraesophageal manifestations associated with GERD occur in up to 50% of patients with non-cardiac chest pain, 78% of patients with chronic hoarseness, and 82% of patients with asthma. Over 50% of patients with GERD have no endoscopic evidence of disease. Although 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 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 (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 (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 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. 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 methodologically because no gold standard exists. However, the calculated numbers are helpful in providing a framework to assess available options. Recent studies suggests that combining diagnostic modalities (omeprazole challenge test, 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.

History. 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%. 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.

PPI diagnostic test. A response to a short course of proton-pump inhibitors (PPIs) is commonly considered to support a diagnosis of GERD**.** PPIs have been studied and tried more often than H2-receptor antagonists given their higher efficacy. 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.

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 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 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, 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 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 at all 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 clinically useful in the diagnosis of GERD if endoscopy is positive for mucosal abnormalities. Descriptives such as erythema, edema, and friability also are not clear indications of esophagitis.

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 esophagus.

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 29% of patients with documented reflux esophagitis and in up to 33% of patients with endoscopic-negative GERD.

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.

Recent advances in "wireless" pH radiotelemetry capsule technology eliminates the need for the uncomfortable nasoesophageal tube, and increases diagnostic yield by allowing for longer monitoring (e.g., now 48-hour and soon 96-hour). Also, intraluminal impedance monitoring can detect "nonacid" (i.e. liquid/gas) reflux, which may be important in medically refractory patients with regurgitation who are being considered for surgery or in patients with atypical symptoms. 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 **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.

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 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. 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.

Weight loss. An 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. Medications that lower LES pressure should be avoided in patients with symptoms of GERD. These medications include calcium channel blockers, β-agonists, α-adrenergic agonists, theophylline, nitrates, and some sedatives.

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/alginic 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.

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, alginic 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 are good data available 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 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 esophagitis. Efficacy in pH changes was not studied. The least expensive PPI is omeprazole, which is 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. 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 20 years ago. PPIs have been associated with rare community-acquired pneumonia, Clostridium difficile colilis, and hip fracture.

Several studies have demonstrated that on-demand therapy with PPIs is the most cost-effective method for NERD treatment.

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_2 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. Radiofrequency heating of the GE junction (Stretta) and endoscopic gastroplasty (Bard, Wilson Cook), polymer injections to bolster the GE junction, and full thickness gastroplication have all been shown to improve symptoms and quality of life scores in sham controlled trials. None of these techniques have consistently reduced acid exposure. Polymer injections have been removed for safety concerns. Durability of response for all of these modalities (30-50% at 3 years) may limit long term usefulness. Complications are relatively rare in experienced hands and are less than with standard anti-reflux surgery.

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 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 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. 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. 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 H2 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 (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.

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.

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 (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 coblestoning, 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 overdiagnosis 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_1 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

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 treatments such as thermal ablation, photodynamic therapy and endoscopic mucosal resection offer promise to the patient who is not an operative candidate. They are likely to have fewer complications, but also lower effectiveness (60-70% loss of cancer/high grade dysplasia at 2 years follow-up). Hidden cancers or high grade dysplasia below the epithelial surface may hamper endoscopic monitoring.

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 the American College of Gastroenterology's Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease (2005) and the VA/DoD Clinical Practice Guideline for the Management of Adults with Gastroesophageal Reflux Disease in Primary Care Practice (2003). (See annotated references.)

Strategy for Literature Search

The literature search began with the results of the literature search performed through September 2000 for the previous version of this guideline. The results of two more recent literature searches were reviewed:

American College of Gastroenterology: Updated Guidelines for the diagnosis and treatment of gastroesophageal reflux disease (2005), literature search through early 2004.

VA/DOD Clinical Practice Guideline for the Management of Adults with Gastroesophageal Reflux Disease in Primary Care Practice (2003), literature search through May 2002.

A search of more recent literature was conducted prospectively on Medline from January 2004 through May 2006 using the major keywords of: *gastroesophageal reflux disease (or GERD, NERD [non-erosive reflux disease], NEED [non-erosive esophageal disease]), human adults, English language, clinical trials, and guidelines.* Terms used for specific topic searches within the major key words included: *symptoms (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)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 veverages; 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), fundoplication (open vs. laproscopy; endoscopic antireflux procedures), Barretts 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 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.

Team Member	Relationship	Company
Joel J Heidelbaugh, MD	(none)	
Arvin S Gill, MD	(none)	
R Van Harrison, PhD	(none)	
Timothy T Nostrant, MD	Consultant	Astra-Zeneca, Janssen (J & J), Sartoris, Tapp (Takeda), Wyeth)

Annotated References

American College of Gastroenterology: DeVault KR, Castell DO. Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease. American Journal of Gastroenterology, 2005; 100:190-200.

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

American College of Gastroenterology: DeVault KR. Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease. American Journal of Gastroenterology, 1999; 94(6):1434-1442.

This earlier consensus statement includes information that is simply referenced in the more recent update (above).

VA/DoD Clinical Practice Guideline for the Management of Adults with Gastroesophageal Reflux Disease in Primary Care Practice. Department of Veterans Affairs and Department of Defense, Draft 8a, March 12, 2003.

A 60 page report addressing each aspect of diagnosis and treatment in detail.

Heidelbaugh JJ, Nostrant TT. A Cost-Effective Approach to the Pharmacologic Management of Gastroesophageal Reflux Disease. Drug Benefit Trends 2004;16:463-471.

An in-depth examination of various cost-effective approaches to GERD treatment

Heidelbaugh JJ, Nostrant TT. Medical and surgical management of gastroesophageal reflux disease. In: Heidelbaugh JJ (ed). Clinics in Family Practice: Gastroenterology. Philadelphia, PA: Elsevier, September 2004, 6(3):547-568.

A systematic review of the literature and evidence-based recommendations for practice 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.

Numans Me, Lau J, deWit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Annals of Internal Medicine, 2004; 140(7):518-27.

A systematic review of this literature, with 15 studies showing the limited sensitivity and specificity of successful short-term treatment with PPI in establishing the diagnosis when GERD is defined by 24-hour pH monitoring.

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.

Vaezi, M. Gastroesophageal reflux disease and the larynx. J Clin Gastroenterol, 2003; 36(3):198-203.

Presents the rational for an approach to identifying patients whose laryngeal signs and symptoms are due to GERD.