GERD: Management Algorithms for the Primary Care Physician and the Specialist

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Gastroesophageal reflux disease (GERD) is a common and, for most patients, lifelong problem that can significantly impair quality of life. A comprehensive management scheme for GERD should include a patient education component that teaches individuals to recognize when their symptoms may be due to GERD and reinforces the value of lifestyle modifications that can help improve reflux symptoms; a cost-effective step-up approach for the primary care physician treating patients with typical GERD; and treatment options after a patient is referred to a gastroenterologist or gastrointestinal surgeon. The chronicity of GERD warrants a long-term management strategy. These considerations are addressed by a multidisciplinary panel of physicians in a "family" of management algorithms for GERD.

INTRODUCTION

The GERD Management Group, a multidisciplinary team of physicians in family practice, general internal medicine, gastroenterology, and gastrointestinal (GI) surgery, met on two occasions to develop a consensus approach to the patient with gastroesophageal reflux disease (GERD). At the onset of our discussion, we agreed that most treatment algorithms are too complex and, therefore, of little practical use. In addition, we felt that patient education was an important component of a comprehensive management scheme. As our deliberations progressed, it became clear that a total approach to the GERD patient might best consist of three components: a patient education vehicle, an algorithm offering a practical approach for the primary care physician, and a second algorithm outlining the approach to these patients by the specialist (gastroenterologist or surgeon). The patient education component is intended to teach individuals to recognize when their symptoms may be due to GERD, suggest changes in daily habits that can help them improve their reflux symptoms, and indicate when they should seek medical advice.

The primary care algorithm was constructed to provide a road map for approaching the majority of patients having heartburn and regurgitation as manifestations of their GERD. In addition, it was our intent to help physicians to recognize "alarm" symptoms that should encourage early referral to a specialist and to identify the

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atypical symptoms of GERD and their appropriate management. This algorithm incorporates a "step up" approach to the management of GERD because we believe this to be cost-effective. We also believe it is important for primary care physicians to have clear suggestions for referral of patients for diagnostic evaluation at various points in their overall management.

The specialist algorithm is intended to show the primary care physician the approach we believe most appropriate for the gastroenterologist or GI surgeon to follow in the majority of cases and is based on our belief that endoscopy is the most important initial diagnostic step for patients whose symptoms persist or suggest a more serious diagnosis. For patients with normal endoscopic findings or minimal esophagitis and no evidence of Barrett's esophagus, we agreed that whatever treatment approach successfully controls symptoms is the appropriate measure. Patients with more severe erosive esophagitis or complications (stricture, ulcer, or Barrett's esophagus) are likely to require either continuous therapy with a proton pump inhibitor (PPI) or fundoplication. Finally, we hope that this algorithm conveys the message that GERD is a chronic condition for which long-term therapy is usually necessary, and that both continuous medical therapy and surgery are reasonable options for long-term management.

PREVALENCE AND PATHOPHYSIOLOGY

Gastroesophageal reflux disease is defined by symptoms or tissue damage, or both, resulting from the movement of acidic gastric contents into the esophagus. Common reflux symptoms are listed in Table 1 (1). Patients with GERD typically complain of heartburn and regurgitation, which can occur postprandially. These symptoms are aggravated by lying down or bending over and are relieved by over-the-counter (OTC) histamine H_2-receptor antagonists (H_2RAs) and antacids. Atypical reflux symptoms include asthma, hoarseness, and unexplained chest pain (2). In about half of patients, reflux symptoms occur without esophageal mucosal erosions or ulcerations (3,4).

Gastroesophageal reflux disease is a common clinical problem for primary care physicians. Approximately 40% of adults in the United States have occasional heartburn (at least once a month), and 10% experience heartburn daily (5,6). The quality of life of patients with GERD can be as poor as that seen with angina or heart failure (7).

Table 1.
Common Symptoms of GERD.

Symptom	*Incidence (%)**
Heartburn	83
Regurgitation	70
Dysphagia	37
Respiratory symptoms	30
Abdominal pain	10
Chest pain	10
Nausea	8
Belching	7
Bleeding	4

*Base = 198 patients. (Adapted from Ref. 1.)

Symptoms of GERD result from prolonged contact of the esophageal mucosa with refluxed acid and other gastric contents. Many factors can contribute to GERD, but the primary underlying cause is abnormal motility. Retrograde movement of gastric acid is usually prevented by a competent lower esophageal sphincter (LES), aided by the crural diaphragm. Some patients with GERD may have defective resting LES pressures or reduced sphincter pressures during periods of increased intra-abdominal pressure, but much more frequently the underlying abnormality is an increased frequency of transient relaxations of the LES (8).

In healthy individuals, refluxed acid is promptly cleared from the esophagus. Delayed esophageal acid clearance may be due to a reduction in the frequency or strength of peristaltic contractions. In addition to esophageal motility, gravity and neutralization of acid by salivary bicarbonate help to effect esophageal acid clearance. It has been suggested that patients with a hiatal hernia develop GERD because the crural diaphragm does not effectively contribute to the antireflux barrier and because acid trapped in the distal esophagus is ineffectively cleared (9).

A delay in gastric emptying also may contribute to GERD (10). The composition of the refluxate (acid, pepsin, and bile) can determine the severity of disease (11). Much less is known about the role of epithelial

defense mechanisms in the esophagus (12). These protective factors may be important; up to 50% of patients with nonerosive GERD and a smaller proportion of those with erosive disease have acid exposure times comparable to those of healthy individuals (13).

NATURAL HISTORY

Despite the high prevalence of GERD, its natural history has not been well established. Few studies have prospectively followed patients with reflux symptoms. The best of these comes from a polyclinic in Lausanne, Switzerland, where 750 patients with grades I to III esophagitis were given empiric therapy and followed by endoscopy (14). Of these patients, 46% had an isolated episode of GERD and never required further therapy. However, 32% were found to have recurrent episodes without progression of their disease, and 23% experienced progressive disease. Half of the patients in the group with the most severe disease went on to develop strictures or esophageal ulceration. It is therefore clear that this common disorder remains a lifelong problem in most patients and becomes worse in one-fourth. The progression of GERD is usually associated with a change in the type or severity of symptoms. However, symptoms may not be a good measure of disease severity, since progression of disease is seen in asymptomatic patients. Moreover, esophagitis may progress even with intensive therapy. The chronicity of GERD is supported by the fact that 80% of patients relapse within 6 to 8 months of healing and cessation of therapy (15).

Barrett's esophagus is a condition in which the squamous lining of the esophagus is replaced by columnar epithelium, typically intestinal metaplasia. The presence of Barrett's esophagus indicates chronic severe GERD and is regarded as the worst form of esophagitis. In various endoscopic studies, Barrett's esophagus has been reported in approximately 10% to 15% of patients with chronic GERD symptoms (16). Most patients with Barrett's esophagus will give a history of reflux, but some will not have experienced symptoms and may progress to adenocarcinoma of the esophagus without ever having reflux symptoms. The risk of cancer in Barrett's esophagus is thought to be approximately 1% per year (17). When the diagnosis of Barrett's esophagus has been made, the patient should undergo endoscopic surveillance, and biopsy samples of the Barrett's mucosa should be evaluated for dysplasia and cancer.

INITIAL THERAPY

Patients with GERD are often aware that certain daily activities induce or exacerbate their symptoms. Antireflux treatment should begin with a review of possible risk factors for GERD and patient education as to why these activities may induce symptoms. This effort serves two purposes. First, it is a safe and inexpensive way to improve symptoms. Second, the patient is empowered to minimize the development of symptoms, an important concept in managed care medicine, particularly with a chronic condition such as GERD.

Simple changes in daily habits can improve symptoms in many patients with mild or moderate GERD (Table 2). As with other chronic conditions, adherence to these conservative measures should be lifelong, even when concomitant drug treatment is effective in relieving symptoms. The addition of lifestyle modifications to prescription H_2RA treatment significantly enhances the drug effect (18). Accordingly, conservative measures may allow successful control of symptoms with less aggressive drug therapy.

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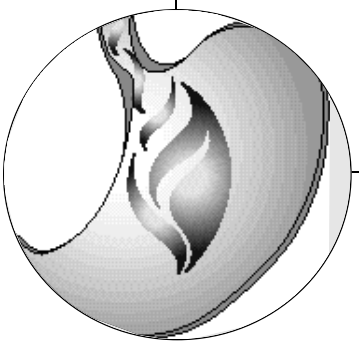
Table 2.
Recommended Lifestyle Modifications for GERD.

- Eat small meals
- Choose low-fat foods
- Reduce intake of chocolate, carminatives (peppermint or spearmint), and alcohol
- Limit consumption of beverages containing caffeine
- Limit consumption of carbonated beverages
- Stop cigarette smoking
- Suck hard candies or chew gum to increase saliva
- Don't lie down for 2 to 3 hours after eating
- Sleep with the head of the bed elevated 6 inches
- Wear loose-fitting clothing
- Take an OTC H_2-receptor antagonist or antacid as needed for symptoms

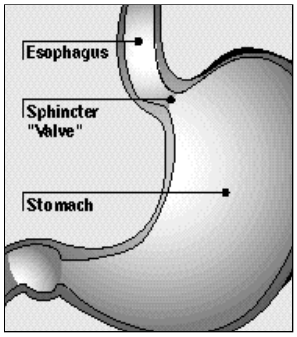
Patient Information

Two out of every five people get heartburn at least once a month.

How do I know if I have heartburn?



What *is* heartburn?



When you eat, your stomach produces acid to help you digest. Acid in the wrong place can lead to heartburn, or a burning feeling in the middle of the chest. You feel heartburn when food and stomach acid move up into the "food pipe," also known as the esophagus. This happens when the valve, or "gate," between the esophagus and stomach relaxes. Heartburn may worsen if the muscles in the stomach do not keep food and acid moving down the digestive tract.

To find out if you have heartburn, answer the following quiz:

Do I have heartburn?

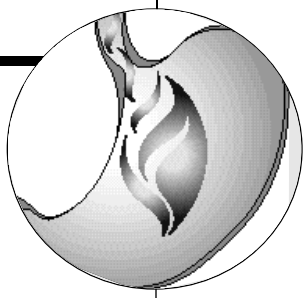
Check the appropriate response	Yes	No
I get a burning feeling in the middle of my chest.	☐	☐
I often have this feeling after a meal or at night.	☐	☐
This burning feeling gets worse when I lie down or bend over.	☐	☐
Over-the-counter medicines, such as acid reducers or antacids, help the burning go away.	☐	☐
I frequently regurgitate (burp up) my food.	☐	☐
There is a bitter or sour taste in the back of my throat.	☐	☐

If you checked yes to one or more of these statements, there is a good chance you have heartburn.

Figure 1. Caring for Your Heartburn.

Patient Information

What can I do to take control of my heartburn?



Do's

- Sleep with the head of the bed elevated 6 inches.
- Have smaller, more frequent meals.
- Choose low-fat foods.
- Suck hard candies (but not peppermint candies).
- Wear looser-fitting clothing and looser-fitting belts around the waist.

Don'ts

- Don't eat large meals, especially before sleep.
- Don't lie down for two to three hours after eating.
- Don't eat chocolate or peppermints.
- Don't smoke cigarettes.
- Don't drink alcohol.

What about over-the-counter medicines?

This is a good place to start. Over-the-counter acid reducers, like Pepcid AC, and antacids, like Mylanta, provide fast, effective relief of occasional heartburn. Some acid reducers also work well when you take them before meals that can cause your heartburn.

Should I see my doctor for heartburn?

You should see your doctor immediately if you have any of the following symptoms:

- pain or difficulty swallowing
- feeling full after eating only a small amount
- frequent vomiting
- unexplained weight loss
- severe hoarseness or wheezing

You should also speak to your doctor if you have heartburn more often than twice a week, if you keep on taking over-the-counter heartburn remedies for more than two weeks, or if you have frequent symptoms and are over 45 years old.

What else do I need to know about heartburn?

What about prescription medicines for heartburn?

If you have very frequent or severe heartburn, your doctor may prescribe a prescription-strength medication. Some medicines are good at tightening the valve between the esophagus and stomach, while others reduce the amount of acid your stomach produces. Talk to your doctor to determine if a prescription medication is right for you. And remember, whether you are on medication or not, lifestyle changes like the do's and don'ts listed above are an important part of managing heartburn.

Is surgery an option for treating heartburn?

If you have heartburn severe enough to require chronic medication, surgery may be an option. Surgery can repair the valve between the stomach and esophagus. Usually the surgery can be done videoscopically. The advantages of videoscopic surgery are a shorter hospital stay and quicker return to normal activities compared to conventional surgery. Talk to your doctor to determine what action plan for heartburn is right for you.

Figure 1. Caring for Your Heartburn (continued).

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We suggest that patients receive reminders of specific lifestyle modifications, along with other information (Figure 1).

Initial recommendations should focus on meal size and content. Eating small rather than large meals reduces the probability that gastric contents will reflux into the esophagus. Foods with high fat content, chocolate, and carminatives (such as peppermint or spearmint) should be avoided because they decrease LES pressure, thereby facilitating acid reflux. Weight reduction may be beneficial primarily because of the reduced quantity of fatty foods ingested. Caffeine-containing beverages should be limited because they increase acid secretion and possibly have a direct irritant effect in the esophagus. Carbonated beverages enhance gastric distention, which increases transient LES relaxations. Highly acidic foods such as citrus juices and tomatoes should be avoided because they may cause symptoms in acid-sensitive individuals by a direct esophageal irritant effect. Cigarette smoking should be curtailed because it is associated with decreased LES pressure. Increasing saliva production, by chewing gum or sucking candies, may also help to ameliorate symptoms. The alkaline saliva will neutralize refluxed acid contents. Additionally, swallowing will stimulate peristalsis and remove refluxed material from the esophagus.

It is generally recommended that individuals with reflux symptoms not lie down for at least 2 to 3 hours after eating and that they have the head of the bed elevated by 6 inches. The rationale for these recommendations is the observation that patients with chronic reflux often experience increased episodes of prolonged reflux and symptoms when supine. Sleeping with the head of the bed elevated enhances esophageal clearance of refluxed gastric acid and thereby substantially reduces acid contact time (19).

Finally, a number of frequently prescribed medications have the potential to exacerbate reflux symptoms. For example, calcium channel blockers, anticholinergic agents, theophylline, and progesterone relax the LES and may permit reflux. Although these medications may be necessary for the treatment of concurrent illnesses and often cannot be discontinued, the patient should understand the relationship between their use and the possible development of symptoms.

Over-the-Counter Medications

Antacids, in either liquid or tablet formulations, are widely promoted as initial treatment for reflux symptoms. They are thought to relieve symptoms by neutralizing gastric acid, thereby reducing the irritant potential of gastric contents refluxing into the esophagus. However, recent studies have emphasized the importance of a local neutralizing effect within the esophagus and defined a surprisingly long duration of action (20). Antacids decrease the acidity (raise the pH) of refluxate into the esophagus (21) and are more effective than placebo in relieving heartburn (22). A combination product that contains a weak antacid and alginic acid is also available; it provides a foam barrier in the gastric cardia. This barrier decreases acid reflux into the esophagus. Despite their efficacy, liquid antacids are not popular for daytime use because of the inconvenience associated with their bulky containers.

Newer nonprescription therapies are the OTC formulations of H_2RAs. Provided in lower dose forms than their prescription counterparts (Table 3), these medications are marketed for either acute treatment or prophylaxis before consumption of foods that are anticipated to cause reflux symptoms.

Since information about antacids and OTC H_2RAs is directed toward the same group of heartburn sufferers, it is desirable that consumers know the advantages of each therapy. Antacids are nonsystemic and locally acting, while H_2RAs are systemically absorbed. A recent study highlighted differences by showing that calcium carbonate tablets had a more rapid onset of acid neutralization, while an H_2RA, famotidine, with a 15- to 30-minute onset, demon-

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Table 3.
Over-the-Counter Histamine H_2-Receptor Antagonists.

Drug	*Brand name*	*Dosage for episodic heartburn*
Cimetidine	Tagamet HB	100 mg
Famotidine	Pepcid AC	10 mg
Nizatidine	Axid AR	75 mg
Ranitidine	Zantac 75	75 mg

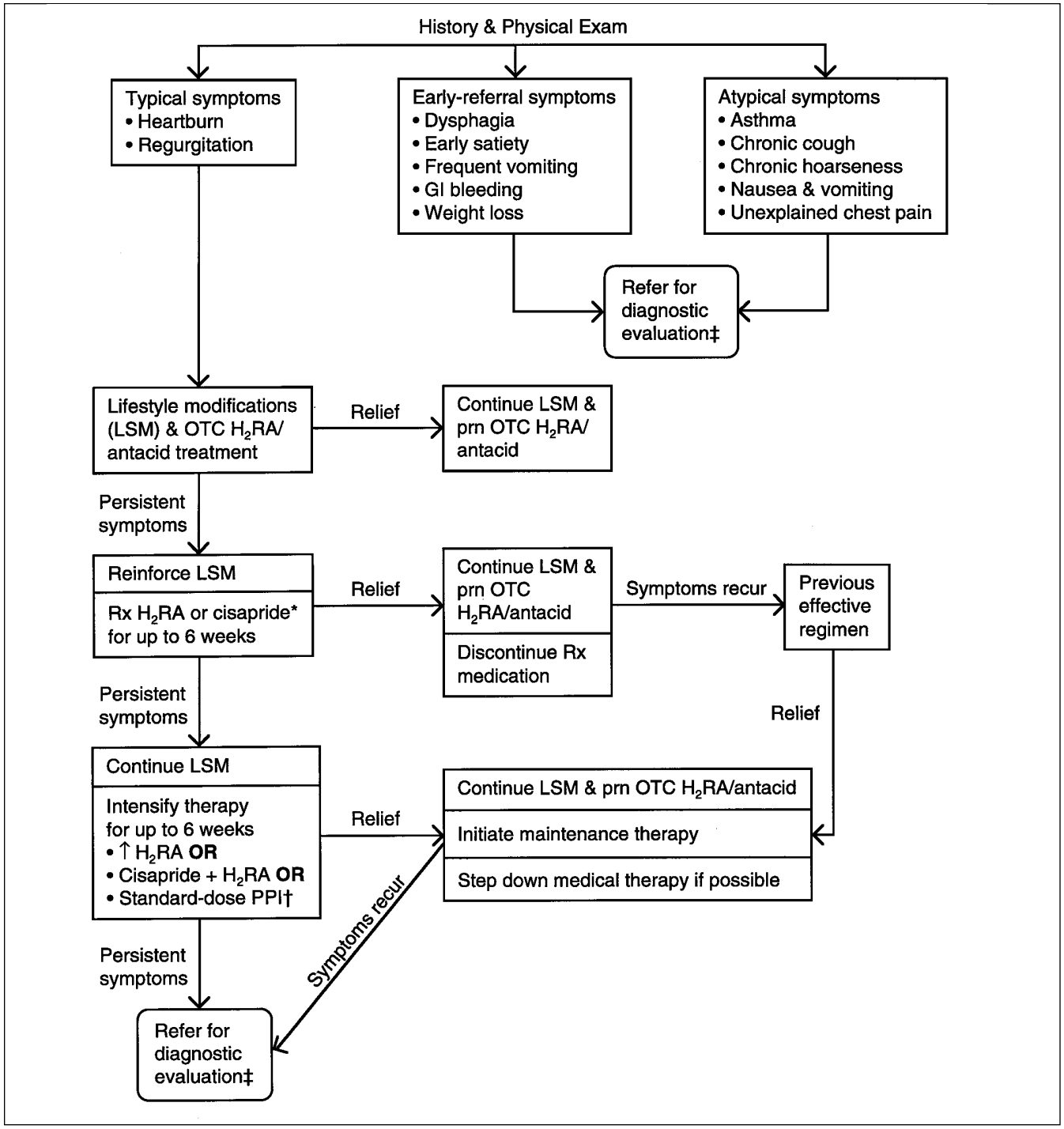

Figure 2. Algorithm for heartburn/GERD in adults: primary care approach. *Cisapride 10 mg qid or 20 mg bid should be considered particularly if belching, bloating, or other postprandial symptom is present. †Endoscopy should be considered if PPI use is required beyond 6 weeks. ‡See algorithm on overview of specialist evaluation and treatment approach. H_2RA = histamine H_2-receptor antagonist; LSM = lifestyle modifications; OTC = over the counter (nonprescription); PPI = proton pump inhibitor.

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strated a longer duration of acid inhibition (23). The more rapid onset of antacid effect may provide faster relief (24), while a prolonged period of acid inhibition may prevent heartburn for extended periods throughout the day or night (25).

It has been proposed that the long-lasting effect of OTC H_2RAs would reduce the cost of care for GERD because patients would have easy access to an effective medication. Consequently, there would be less need for visits to the physician or for the prescription of other medications to treat reflux symptoms. Although some pharmacoeconomic studies have suggested that OTC medications reduce the total cost of care for patients with GERD, other studies have not identified significant savings (26,27).

When reflux symptoms persist despite use of OTC products, primary care physicians may initiate empiric therapy based on the history and physical examination or refer the patient for further diagnostic evaluation.

EMPIRIC THERAPY FOR GERD

Empiric therapy is treatment provided in the absence of a definitive diagnosis. Common conditions for which the treatment is relatively benign are most appropriately treated empirically. Nevertheless, avoiding the invasiveness and expense of diagnostic procedures must be weighed against the risk of initiating and continuing a course of treatment in the event the suspected condition is not present.

Given the prevalence of GERD in the general population, the relative specificity of heartburn as a cardinal manifestation, the fact that most GERD patients do not have severe erosive disease, and the availability of safe and effective treatments, antireflux therapy is often initiated solely on clinical suspicion, without definitive diagnostic studies. In fact, most cases are likely to be self-treated before the patient seeks medical care. Once a presumptive diagnosis of GERD has been made, a treatment regimen should be prescribed that is likely to provide satisfactory symptom relief. The frequency and severity of symptoms and response to empiric treatment will usually determine the pace of intervention. As GERD is most often a chronic condition with the acute morbidity being discomfort, in the absence of "early referral" symptoms, the clinician can safely pursue a step-up approach, titrating treatment to symptom relief (Figure 2).

Episodic, mild heartburn may be adequately relieved with lifestyle modifications, OTC H_2RAs, and antacids (with or without alginate) taken as needed. More frequent or severe heartburn may respond to the regular, once- or twice-a-day use of OTC H_2RAs. Some patients may not have adequately attempted this treatment before seeking care, and it is entirely appropriate for the clinician to initiate therapy with these medications. The lower cost of the OTC products compared with their prescription counterparts can be an important consideration.

If a heartburn patient does not achieve satisfactory relief with OTC products, empiric therapy should be initiated with a full prescription dose of an H_2RA or a prokinetic agent. Cisapride is recommended as a safe and effective prokinetic compound and may be a good choice for initial prescription drug therapy when heartburn is accompanied by prominent postprandial symptoms, such as fullness or bloating, suggestive of upper GI tract dysmotility.

With symptom relief, the initial treatment regimen is continued for 4 to 6 weeks; then a trial off medications, but with continued lifestyle modifications, should be considered. Many patients will have episodic disease that recurs infrequently or not at all. Identifying these patients may allow the avoidance of unnecessary long-term prescription drug treatment. Should symptoms recur, the patient may be treated with the previously effective regimen.

If symptoms persist after 4 to 6 weeks on the initial regimen, drug therapy may be intensified. Several approaches are possible; they include increasing the dose of the H_2RA (to double the initial dose), combining the H_2RA with cisapride, and discontinuing the H_2RA or cisapride in favor of a PPI. Once satisfactory symptom relief is achieved, treatment with the agent(s) and dosages effecting relief should be continued for a total of up to 6 weeks. At that time, an attempt should be made to step down treatment or initiate a trial off medications to determine whether symptoms recur. If step-down treatment is unsuccessful or symptoms return soon after discontinuation of therapy, endoscopy is indicated to make a definitive diagnosis and evaluate for GERD complications.

DIAGNOSTIC EVALUATION

When a patient has symptoms suggestive of a serious non-GERD diagnosis (ie, early-referral symptoms, Table 4) or has atypical GERD symptoms (Table 5), it is appropriate to refer promptly for diagnostic evaluation (Figure 3). Diagnostic evaluation is also warranted when GERD symptoms persist after more than one course of empiric treatment or when PPI use exceeds 6 weeks.

On referral to a specialist, the patient is most frequently evaluated by endoscopy (esophagogastroduodenoscopy [EGD]). At least half of heartburn patients have either normal endoscopic findings or mild to moderate esophagitis. In cases of endoscopy-negative GERD symptoms, some centers will perform ambula-

Table 4.
Early-Referral Symptoms in Patients With Suspected GERD.

- Dysphagia, odynophagia
- Early satiety
- Frequent vomiting
- Gastrointestinal bleeding
- Unexplained weight loss

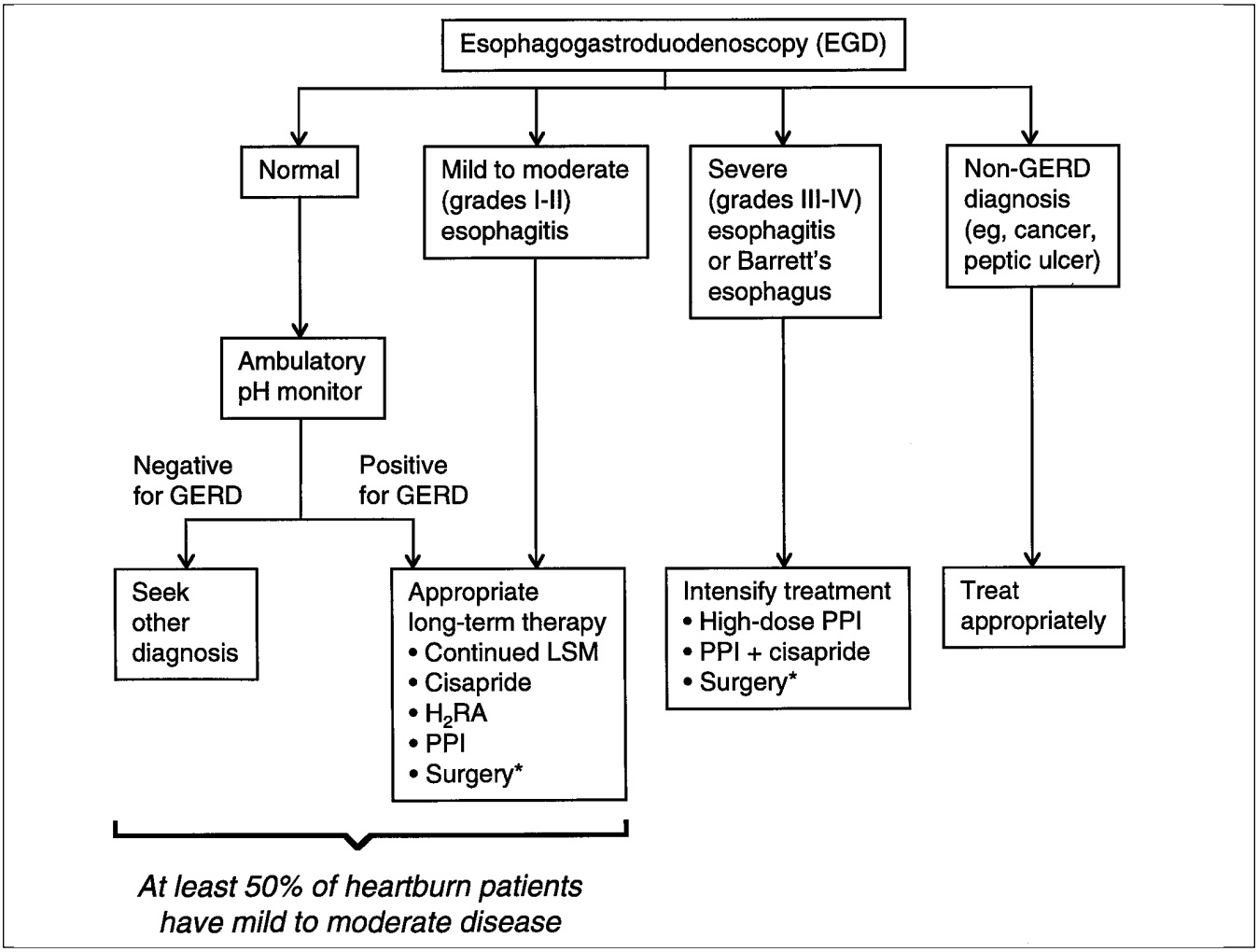

Figure 3. Algorithm for heartburn/GERD in adults: overview of specialist evaluation and treatment approach. *Motility, pH studies before surgery. H_2RA = histamine H_2-receptor antagonist; LSM = lifestyle modifications; PPI = proton pump inhibitor.

tory pH monitoring to confirm the presence of abnormal gastroesophageal reflux. When endoscopy suggests a non-GERD diagnosis, such as cancer or peptic ulcer disease, further diagnostic testing and appropriate treatment are the next steps.

THERAPY AFTER DIAGNOSTIC EVALUATION

When endoscopy reveals mild or moderate esophagitis, continued intensification of antireflux therapy is warranted; dosages are listed in Table 6. Proton pump inhibitors are highly effective in controlling reflux symptoms and healing erosive esophagitis. In patients with grade III or IV esophagitis (Table 7), a standard-dose PPI regimen for 6 to 8 weeks should be considered. Treatment may be intensified by raising the PPI dose or adding cisapride. Although antireflux surgery has traditionally been considered primarily for patients whose disease is refractory to intensive medical treatment, we believe it should be an option for many patients with chronic symptoms.

LONG-TERM TREATMENT

Frequent symptom recurrence suggests that long-term maintenance therapy will be required. Maintenance therapy should be instituted at the lowest effective dose, with encouragement that lifestyle modifications be continued. Early in the course of long-term treatment, patients with an unconfirmed diagnosis of GERD should be referred for endoscopy.

In those with grade I or II esophagitis, a number of long-term options are effective, including monotherapy with cisapride, an H_2RA, or a PPI in standard or low doses. Long-term treatment in patients with grade III or IV esophagitis is frequently initiated with the regimen effective in healing the esophagitis. If possible, the long-term regimen should be stepped down after effective symptom control has been achieved and maintained for 6 to 8 weeks. For example, some patients may be stepped down to monotherapy after short-term treat-

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Table 5.
Atypical Symptoms of GERD.

- Asthma
- Chronic cough
- Chronic hoarseness
- Nausea and vomiting
- Unexplained chest pain

(From Ref. 2.)

Table 6.
Medical Therapies for GERD.

Drug	*Dosage*
Initial Empiric Options	
H_2-receptor antagonists:	
Cimetidine (Tagamet)	400 mg bid (800 mg bid*)
Famotidine (Pepcid)	20 mg bid (40 mg bid*)
Nizatidine (Axid)	150 mg bid (150 mg bid*)
Ranitidine (Zantac)	150 mg bid (150 mg qid*)
Prokinetic agents:	
Cisapride (Propulsid)	10 mg qid or 20 mg bid
Metoclopramide (Reglan)	10 mg qid
Intensive Empiric Options	
H_2-receptor antagonists	Double the dosing frequency with standard doses
Combination of standard-dose H_2-receptor antagonist plus prokinetic agent	
Proton pump inhibitors:	
Lansoprazole (Prevacid)	30 mg once daily
Omeprazole (Prilosec)	20 mg once daily
Maintenance Therapy	
H_2-receptor antagonists	Same as initial empiric dosages
Prokinetic agents:	
Cisapride	10 mg bid or 20 mg hs
Proton pump inhibitors:	
Lansoprazole	15 or 30 mg once daily, in the morning before food
Omeprazole	20 mg once daily, in the morning before food

*H_2RA dosage for healing of erosive esophagitis.

(continued from page 34)

Table 7.
Savary-Miller Grading System for Esophagitis.

Grade I	Linear, nonconfluent erosions
Grade II	Longitudinal, confluent, noncircumferential erosions
Grade III	Longitudinal, confluent, circumferential erosions that bleed easily
Grade IVa	One or several esophageal ulcerations in the mucosal transition zone, which can be accompanied by stricture or metaplasia
Grade IVb	Presence of a stricture but no indications of erosions or ulcerations

(From: Miller LS: Endoscopy of the esophagus. In: Castell DO, ed. *The Esophagus.* 2nd ed. Boston: Little Brown and Co; 1995:94.)

ment with a combination regimen. Other patients, whose acute symptoms were treated with a PPI, may be stepped down to cisapride or an H_2RA. The step-down approach is particularly effective in patients with mild to moderate esophagitis. Antireflux surgery should be considered a long-term option for patients requiring continuous drug therapy or increasing doses of medication.

A review of the various antireflux treatment options follows.

ROLE OF PROKINETIC AGENTS

Prokinetic, or promotility, drugs improve motility-related pathophysiology in patients with GERD. These drugs can strengthen the amplitude of esophageal peristaltic contractions, increase LES pressure, accelerate gastric emptying, and coordinate upper GI motor activity. Currently available prokinetic drugs—bethanechol, metoclopramide, and cisapride—exert their actions by a variety of mechanisms.

Bethanechol, a direct cholinergic agonist, enhances esophageal peristalsis and increases LES pressure, but an absence of effect on antroduodenal coordination and gastric emptying is thought to diminish its effectiveness as a prokinetic agent. Adverse effects, such as abdominal cramps, diarrhea, bradycardia, and blurred vision, which occur in 10% to 15% of patients, have limited the use of bethanechol.

Metoclopramide is structurally related to procainamide but has no antiarrhythmic or local anesthetic properties. Its GI prokinetic effect results mainly from enhanced acetylcholine release from intrinsic cholinergic neurons; antidopaminergic actions contribute to antiemetic as well as prokinetic properties. Adverse effects have been reported in 10% to 30% of metoclopramide users and can be severe and persist until withdrawal of the drug (28). Metoclopramide crosses the blood-brain barrier and can produce symptoms ranging from drowsiness, anxiety, and confusion to motor restlessness, tardive dyskinesia, and other dystonic reactions. Gynecomastia may occur, owing to enhanced prolactin release. The frequency and severity of adverse effects have diminished enthusiasm for the use of metoclopramide.

Cisapride, a serotonin ($5\text{-}HT_4$) agonist, causes release of acetylcholine at the myenteric plexus. In addition to increasing GI motility, it enhances the flow of saliva and thus its buffering capacity. Significant improvements in daytime and nocturnal heartburn have been demonstrated with cisapride 10 mg qid (29) and 20 mg bid (30). The incidence and severity of other GERD symptoms compatible with upper GI tract dysmotility, especially postprandial bloating, fullness, early satiety, belching, and regurgitation, also have been reduced significantly by cisapride (30,31). A comparison of symptom relief with cisapride and H_2RAs showed comparable efficacy (32). Cisapride is at least as effective as H_2RAs in healing mild to moderate esophagitis (33,34). The combination of cisapride with cimetidine or ranitidine produced significant advantages for esophagitis healing and symptom control when compared with either H_2RA alone (35-37). Monotherapy with cisapride 10 mg bid and 20 mg at bedtime has been effective in preventing GERD relapse (38,39). In general, although relapse rates were lowest in patients with grade I or II esophagitis, patients with all grades of the condition benefited from cisapride therapy, compared with placebo.

Cisapride may be useful as part of a step-down approach following healing of esophagitis with a PPI: initiation of cisapride, at dosages of 5–10 mg tid or 20

mg at bedtime, either during or immediately following a course of therapy with omeprazole 20–40 mg daily resulted in significant decreases in the need to return to full-dose PPI therapy (39–41). The addition of cisapride to a maintenance regimen of omeprazole 20 mg daily was shown to decrease recurrence of GERD symptoms and erosive esophagitis (41).

Cisapride is safe and well tolerated; the main side effects are headache, abdominal cramps, and diarrhea. It does not cross the blood-brain barrier and has no central or peripheral antidopaminergic effects.

ROLE OF H_2-RECEPTOR ANTAGONISTS

H_2-receptor antagonists, used either alone or in combination with prokinetic agents, were the major treatments for GERD symptoms before the availability of PPIs, which are more potent inhibitors of acid secretion. The available H_2RAs—cimetidine, famotidine, nizatidine, and ranitidine—are of equivalent efficacy and safety.

Several broad conclusions can be reached regarding the clinical utility of H_2RAs (42,43): almost half the patients treated with standard H_2RA doses obtain complete relief of GERD symptoms, and many others experience partial improvement. Symptomatic improvement does not correlate with healing of esophagitis, however. Endoscopic healing of mucosal damage was observed in only 40% of patients after 6 weeks of therapy and in only 50% of patients by week 12 (44). High-dose H_2RA therapy can increase the rate of healing of erosive esophagitis to 77% after 12 weeks (45).

Some studies have suggested that maintenance therapy for erosive esophagitis with H_2RAs is not more effective than placebo. Other reports indicate remission in 50% of patients with healed esophagitis who were treated with ranitidine (41,46). In general, the more severe the erosive disease, the less likely sustained remission will be achieved with H_2RAs.

ROLE OF PROTON PUMP INHIBITORS

The enzyme responsible for secretion of H^+ ions from parietal cells into the gastric lumen is an H^+/K^+ ATPase called the "proton pump." Compounds that bind this enzyme, known as proton pump inhibitors, have a profound inhibitory effect on gastric acidity. Currently available PPIs are lansoprazole and omeprazole; other compounds are in development.

Initial studies from Europe and Australia with omeprazole reported high rates of symptom relief and healing of esophagitis in patients with GERD and marked superiority in direct comparison with ranitidine (15,47,48). Many subsequent studies encourage the use of PPIs as the most effective medical therapy to control symptoms of GERD and heal esophagitis. Omeprazole 20 mg or lansoprazole 30 mg daily has been shown to be more effective in healing erosive esophagitis than either placebo or standard doses of H_2RA, with mean symptomatic relief in 78% of cases (range, 62%–94%) and esophagitis healing in a mean of 83% (range, 71%–96%) over a 4- to 8-week period. A large US multicenter study has shown that omeprazole 20 mg and lansoprazole 30 mg healed esophagitis at equal rates: 90% after 8 weeks (49). There was some evidence for superiority of lansoprazole in early symptom relief. However, the greater the severity of esophagitis, the lower the healing rate, and larger doses are often required for higher grades of esophagitis (50). Recent evidence suggests that occasional patients will continue to secrete gastric acid, particularly during the night, and have gastroesophageal reflux at omeprazole doses of 20 mg bid (51).

The impressive record of PPIs in the short-term (4–8 weeks) treatment of GERD does not obviate the need for effective long-term therapy. The rapid return of symptoms when PPIs are discontinued supports the concept that effective maintenance therapy for GERD frequently requires continuation of full daily doses of medication. Studies from around the world confirm the efficacy of PPIs in maintaining symptom relief and healing of esophagitis in 80% to 100% of patients over periods of 1 to 5 years (41,52–54).

Early concerns about adverse side effects with long-term PPI use have markedly diminished with increasing experience with these compounds. Omeprazole has been available in the United States for approximately 8 years and in Europe for almost 15 years. The benign carcinoid tumors observed in rats during initial premarketing safety studies have not been found to occur in humans in carefully monitored trials. Related concerns about chronic elevations in serum gastrin concentration have faded. A recent observation of

atrophic changes in the gastric mucosa after 5 years of continuous omeprazole therapy has generated new concerns (55). These potential histologic changes occurred in GERD patients who were *Helicobacter pylori*-positive. At present, however, these changes are considered unlikely to progress. Some physicians choose to eradicate *H. pylori* when detected in a patient receiving long-term PPI therapy. However, this may lead to increased gastric acid secretion.

ANTIREFLUX SURGERY

Two developments over the past decade have significantly changed both the outcome and the acceptance of antireflux surgery. The first, an appreciation of the importance of a short, loose, "floppy" fundoplication, markedly lessened the postoperative sequelae associated with antireflux surgery, including dysphagia and "gas bloat" (56,57). Most patients are able to belch normally, and long-term dysphagia is now uncommon following Nissen fundoplication. Importantly, these benefits were achieved without sacrificing efficacy in controlling reflux of gastric contents into the esophagus. The second development was the introduction of laparoscopic Nissen fundoplication, which dramatically reduced the pain and the disruption of patients' lives associated with major surgery (58,59). These advances have catalyzed renewed interest in surgical therapy for GERD.

Indications

Antireflux surgery is indicated for the treatment of objectively documented, relatively severe GERD. Candidates for surgery include not only patients with erosive esophagitis, stricture, and Barrett's esophagus but also those without severe mucosal injury who are dependent on PPIs for long-term symptom relief. Patients with atypical or respiratory symptoms who have a good response to intensive medical treatment are also candidates. The option of antireflux surgery should be given to all patients who have demonstrated the need for long-term aggressive medical therapy, particularly if escalating doses of PPIs are needed to control symptoms. Antireflux surgery may be the preferred option in patients younger than 50 years of age, those for whom medications are a financial burden, those who are noncompliant with their drug regimen, and those who prefer a single intervention to long-term drug treatment (Figure 4).

Diagnostic Evaluation

Diagnostic evaluation prior to surgery is critical to determine that gastroesophageal reflux is the underlying cause of the patient's symptoms (60). Objective evidence of GERD is most commonly obtained by 24-hour esophageal pH testing.

Selection of partial versus complete fundoplication and the preferred surgical approach are based on an assessment of esophageal contractility and length (61). Laparoscopic fundoplication is used in patients with normal esophageal contractility and length. Esophageal body function should be assessed via manometry to ensure that the esophagus has sufficient power to propel a bolus of food through a newly reconstructed valve. Patients with normal peristaltic contractions do well with a 360° Nissen fundoplication. When peristalsis is absent or severely disordered (more than 50% simultaneous contractions), or when the amplitude of the contraction in one or more of the lower esophageal segments is less than 30 mm Hg, a partial fundoplication is the procedure of choice.

Anatomic shortening of the esophagus can compromise the ability to perform adequate repair without tension and lead to an increased incidence of breakdown or thoracic displacement of the repair. Esophageal length is best assessed using videoroentgenographic contrast studies and endoscopy. A short esophagus should be suspected if there is a large (greater than 5 cm) hiatal hernia, particularly if it fails to reduce in the upright position on a video barium esophagogram.

Surgical Technique

Antireflux surgery is designed to improve the function of an organ that will remain in the patient. The results depend greatly on appropriate patient selection and the technical elements of the procedure. In patients with normal esophageal contractility and length, laparoscopic fundoplication has now replaced traditional open Nissen fundoplication as the procedure of choice.

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GERD: Management Algorithms

A SPECIAL ARTICLE

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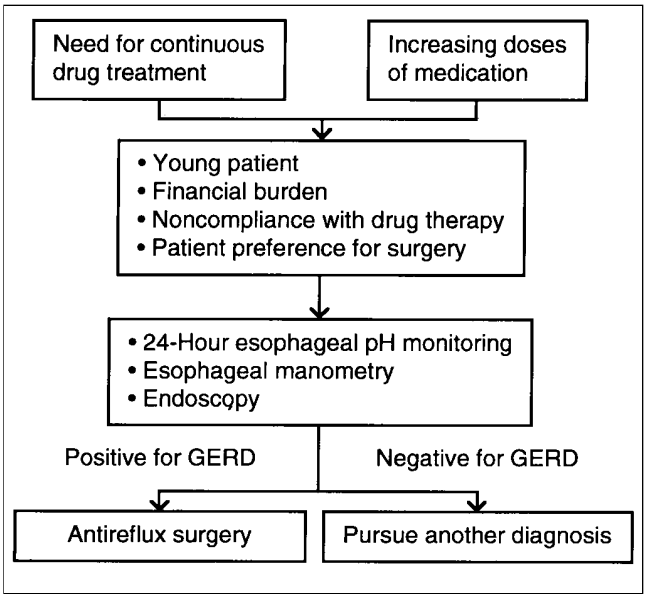

Figure 4. Considerations for antireflux surgery.

Clinical Results

Complications following elective antireflux surgery are uncommon. This is particularly true in the era of laparoscopic fundoplication. Mortality is rare, whether the procedure is open or closed. In a recent collective review, only four deaths occurred among 2453 patients (62). Complications arise, on average, in 10% to 15% of patients and tend to be minor (63). Laparoscopic fundoplication has further decreased complications associated with surgical access and postoperative recovery. Unrecognized perforation of the esophagus or stomach is the most life-threatening sequela and is related to the surgeon's experience (64).

Results of several excellent series of laparoscopic fundoplication have now been published. Three of the best come from Atlanta, Omaha, and Adelaide (1,65,66). These reports document the ability of laparoscopic fundoplication to relieve typical reflux symptoms (heartburn, regurgitation, and dysphagia) in more than 90% of patients. The average length of follow-up is approaching 3 years. These results compare favorably with those of the "modern" era of open fundoplication. Overall, these papers report a 4.2% rate of conversion to open surgery, a 0.5% rate of early reoperation, and excellent to good symptomatic improvement in 91% of patients. The incidence of postoperative dysphagia has decreased to 3% to 5% with increasing experience and attention to technical details (67). Lower esophageal sphincter characteristics and esophageal acid exposure are returned to normal in nearly all patients.

Thus, surgery can be an appropriate treatment for selected patients. The laparoscopic technique holds significant promise, but the excellent results reviewed above are from centers with extensive experience. Accordingly, when deciding whether to recommend surgical treatment, one must evaluate the experience and results obtained at a particular surgical center and also consider whether referral to a more experienced surgical center is appropriate.

COST-EFFECTIVENESS CONSIDERATIONS

Recognition is increasing that antireflux treatment options should be compared prospectively in terms not only of efficacy and safety but also of cost-effectiveness. Cost-effectiveness studies should take into account both direct costs, such as the drug acquisition cost, and indirect costs, such as time lost from work. Furthermore, comparisons should reflect effects on the patient's quality of life (QOL). Recent QOL studies suggest that we are moving in this direction (68).

The chronicity of GERD has warranted development of long-term management strategies. Evaluations of long-term medical therapy versus antireflux surgery are now based not only on traditional outcomes such as symptom resolution and improvement in esophagitis (69) but also on cost factors and QOL (70). Published studies have focused on patients with erosive esophagitis, but endoscopy-negative GERD needs to be investigated as well.

CONCLUDING REMARKS

The GERD management algorithms discussed in this article are designed to offer practical support to the clinician in diagnosing and treating this common problem. These algorithms encourage cost-effective practice by reinforcing the need for lifestyle modifications in addition to pharmacologic therapy; advocating the step-up, then step-down approach to achieve use of the lowest effective dose of medication; defining appropriate use

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of diagnostic studies; and promoting identification of patients at low risk of recurrence to avoid unnecessary long-term drug therapy. These algorithms allow clinicians the flexibility to select among several pharmacologic agents and make rational treatment decisions.

For any management algorithm to be "cost-effective"—that is, to justify the expense of its development—it should have an impact on clinical practice. Toward that end, an implementation plan is important. Physician education efforts and patient education tools, thus, are the final, and necessary, components of this family of algorithms.

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