

Treatment of Gastroesophageal Reflux Disease: Use of Algorithms to Aid in Management

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ABSTRACT

Effective treatment of gastroesophageal reflux disease demands an awareness of several factors: the disease spectrum, its varied symptom presentation, and potential complications; when to refer to a gastroenterologist or surgeon; and the various treatment options available. By taking these factors into consideration, algorithms can provide a useful framework within which clinicians can approach decision making regarding management of gastroesophageal reflux disease. As such, algorithms can be a good clinical tool for meeting the goals of effective disease management. Presented below are treatment algorithms for the primary care physician, gastroenterologist, and surgeon. Improved understanding of these algorithms can assist clinicians in the care of patients with this common disease. (Am J Gastroenterol 1999;94(Suppl.):S3–S10. © 1999 by Am. Coll. of Gastroenterology)

INTRODUCTION

Gastroesophageal reflux disease (GERD) is perhaps the most common problem seen in medical practice. Approximately 10% of the U.S. population experiences heartburn daily, and 40% of the population has heartburn monthly. Almost 40 million individuals use over-the-counter antacids or histamine-2 (H₂) receptor antagonists at least twice weekly to relieve symptoms.

Effective treatment requires an awareness of the clinical spectrum of GERD, its varied symptomatology and potential complications, the reasons for referral, and the many treatment options available. An effective management algorithm, care pathway, or clinical “roadmap” for GERD can assist physicians in selecting appropriate treatment. At the same time, it can educate physicians by providing a review of symptom presentation, indications for specialist referral, and a stepped-care treatment approach. The ideal algorithm is flexible, with appropriate emphasis on the inherent variability of disease presentation and the treatment options available. This review discusses the components of three GERD management algorithms—for primary care physicians, subspecialists, and surgeons—useful to physicians who regularly treat and refer patients with GERD.

The primary care algorithm (Fig. 1) (1) provides a framework for management that focuses on both acute and long-

term maintenance therapy—the key to managing a disease that is usually chronic. The algorithm emphasizes the typical presentations of GERD, those that may be treated empirically, and the atypical and alarm symptoms that suggest early referral to a specialist.

The subspecialist algorithm (Fig. 2) (1) uses endoscopy as a focal point for evaluation and ambulatory pH monitoring as a diagnostic adjunct. As such, it outlines different management approaches for erosive and nonerosive esophagitis and intestinal metaplasia (Barrett’s esophagus). The surgery algorithm reviews the indications and preoperative workup for antireflux surgery (Fig. 3) (1).

CLINICAL PRESENTATION AND NATURAL HISTORY

Typical Symptoms

The most common symptom of GERD is heartburn, a sometimes burning pain behind the breastbone, which is seen daily in up to 10% of the U.S. population and at least monthly in about 40% of the population (2–4). Millions seek treatment regularly using over-the-counter antireflux products. Regurgitation, the spontaneous return of gastric contents into the esophagus or mouth, is another common symptom (3). When present together, heartburn and regurgitation establish the diagnosis of GERD with more than 90% certainty, and patients can be treated empirically without further diagnostic testing (Fig. 1).

Large meals, high-fat meals, spicy foods, and citrus products are more likely to produce heartburn. Cola drinks, coffee, tea, and beer can have an acidic pH and alter the pressure of the lower esophageal sphincter, causing symptoms when ingested. Late-night meals, eaten before bedtime or accompanied by alcohol, can predispose patients to nighttime symptoms (Table 1).

Heartburn is highly specific for GERD, and it is almost always diagnostic. If it is the only presenting esophageal symptom, it is likely due to GERD. There is one major exception. A heartburn-like symptom, believed to be due to esophageal stasis from outflow obstruction, is often described in patients with achalasia. Fermentation of undigested food in the esophagus, coupled with inflammation, can create a heartburn-like sensation in the absence of true GERD.

The presence or the frequency of heartburn is not predic-

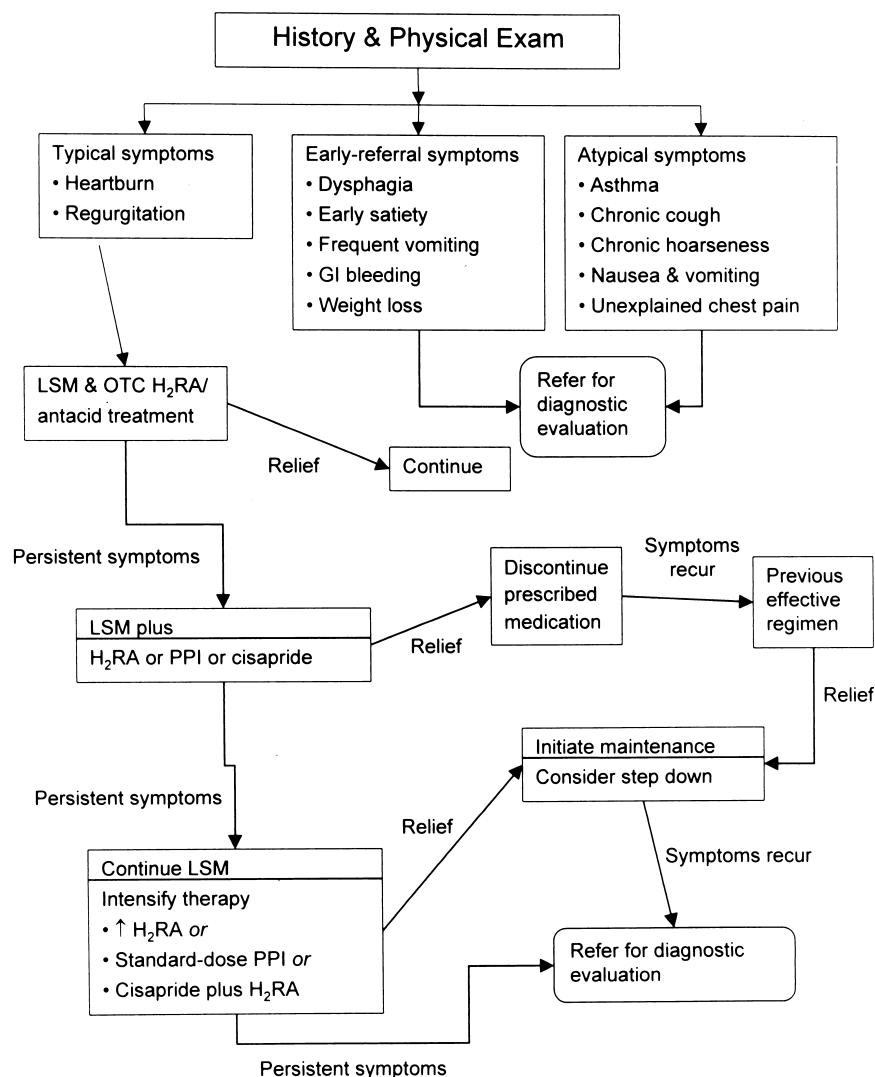


Figure 1. A primary care approach to gastroesophageal reflux disease. LSM = lifestyle modifications; OTC = over the counter; H₂RA = H₂-receptor antagonist; PPI = proton pump inhibitor. Adapted with permission from (1).

tive of the degree of endoscopic damage to the distal esophagus. Only 50–60% of patients with heartburn who seek medical attention have erosive esophagitis on endoscopy. The remainder will be diagnosed with nonerosive GERD (5). Severe disease, including Barrett's esophagus and peptic strictures, can occur with infrequent or no heartburn, just as many patients with daily heartburn will show no endoscopic abnormalities.

The natural history of GERD is not well studied. Although symptoms are chronic and recurrent, most patients with esophagitis will not progress beyond the endoscopic stage seen at initial examination. In a series of 701 patients followed for up to 29 years, only 23% progressed to a more serious grade of esophagitis (6). Among patients with reflux symptoms and no esophagitis (nonerosive GERD), less than 15% progressed to a higher grade over 6 months (7).

Extraesophageal (Atypical) Symptoms

Many atypical or extraesophageal symptoms (Fig. 1) are associated with GERD, including unexplained substernal chest pain without evidence of coronary artery disease (non-cardiac chest pain), asthma, bronchitis, chronic cough, recurrent pneumonia, hoarseness, chronic posterior laryngitis, globus sensation, otalgia, aphthous ulcers, hiccups, and erosion of dental enamel. The prevalence of these atypical or extraesophageal symptoms and their frequency in the general population have not been studied as extensively as has heartburn. A large survey (3) designed to assess the prevalence of GERD in the general population found that 23% experienced unexplained chest pain at some point within a year and 40% had symptoms occurring over more than 5 years. Asthma was reported by 9%, bronchitis by 20%, and chronic hoarseness by 15% of patients with typical GERD

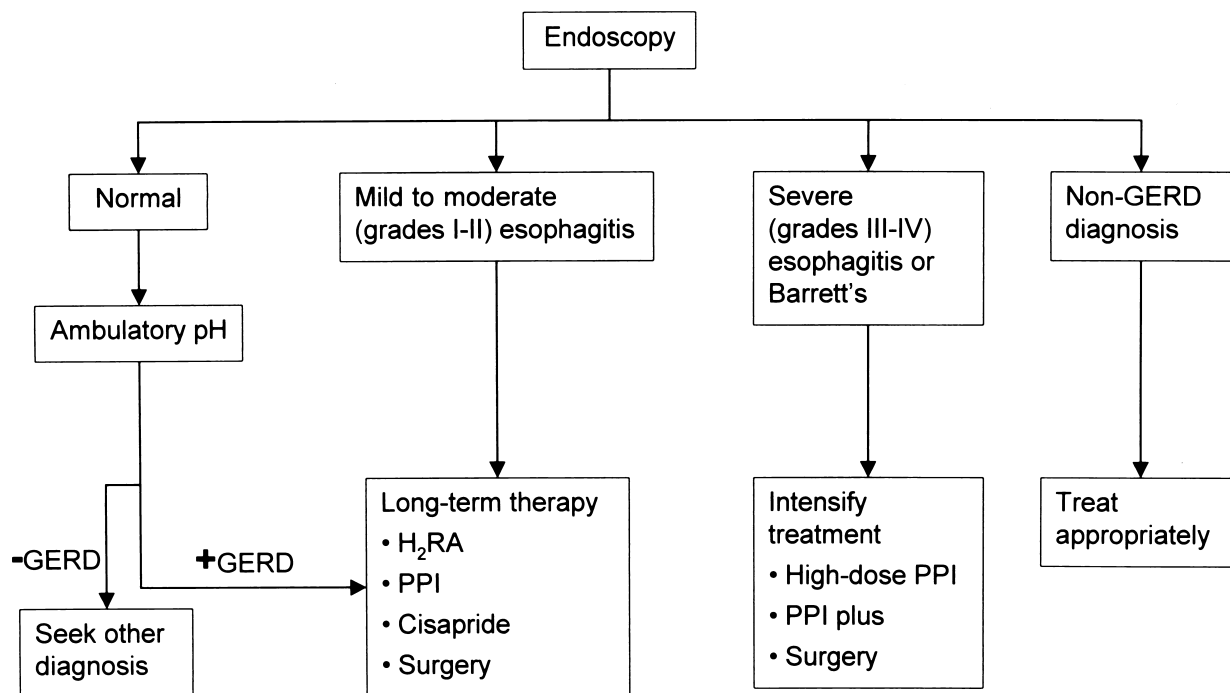


Figure 2. A subspecialist (gastroenterologist) approach to diagnosing heartburn/gastroesophageal reflux disease (GERD) symptoms that are severe, atypical, or refractory to therapy. H₂RA = H₂-receptor antagonist; PPI = proton pump inhibitor. Adapted with permission from (1).

symptoms. In comparison, asthma and bronchitis each affect about 6% of the general population (8).

The frequency of heartburn and regurgitation among patients with atypical symptoms has been debated. In the

population-based study noted above (3), patients with heartburn and regurgitation experienced atypical symptoms about 80% of the time. Such symptoms were more common among patients with frequent heartburn than among those

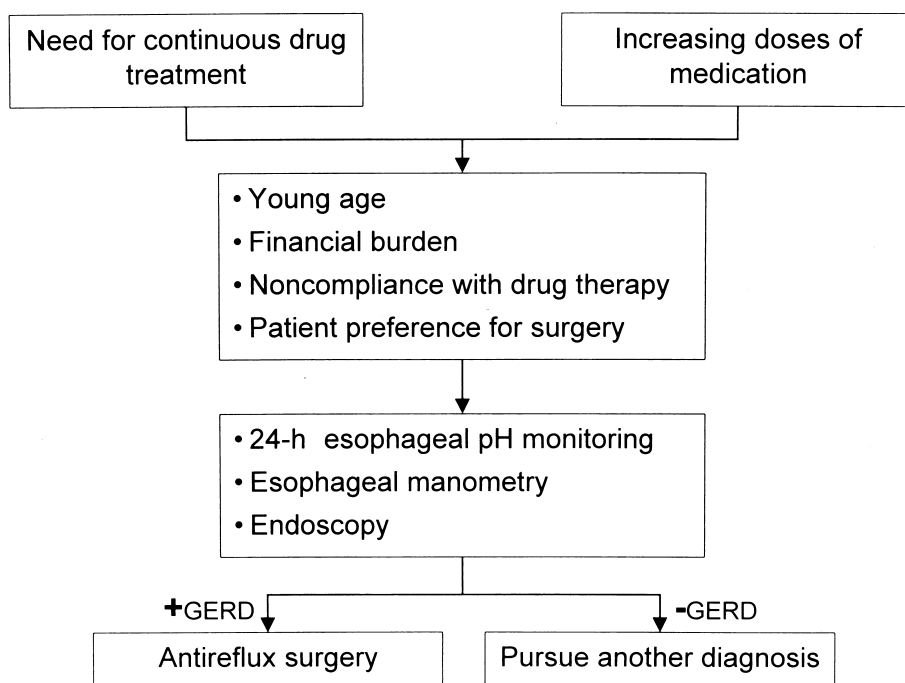


Figure 3. A surgical approach to gastroesophageal reflux disease (GERD). Adapted with permission from (1).

Table 1. Lifestyle Modifications Useful in Patients With GERD

Elevate head of bed (6 inches); avoid waterbed
Sleep on left side
Make dietary modifications
Eat less fat, more protein
Avoid irritants
Citrus juice
Tomato products
Coffee
Cola
Alcohol
Chocolate
Do not eat before sleeping (allow ≥ 2 h)
Decrease or stop smoking
Avoid potentially harmful medications
Anticholinergics
Sedatives/tranquilizers
Theophylline
Prostaglandins
Calcium channel blockers
Alendronate
Take antacids or alginic acid
Take over-the-counter doses of H ₂ -receptor antagonists (can be used prophylactically)

with no GERD symptoms. Among patients with unexplained chest pain, more than 80% had heartburn or regurgitation. Among patients with asthma, bronchitis, hoarseness, or pneumonia, approximately 60% had heartburn or regurgitation. Heartburn was not predictive of otolaryngological symptoms (3). In a recent case-control study from the Veterans Administration, patients with a discharge diagnosis of erosive esophagitis had twice the prevalence of associated otolaryngological symptoms as control patients without esophagitis (9). The absence of heartburn and regurgitation should not preclude a diagnosis of GERD in patients with atypical symptoms.

Prospective studies using endoscopy and ambulatory pH monitoring have found GERD in as many as 75% of patients with chronic hoarseness (10), in 70–80% of patients with asthma (11, 12), and in 20% of patients with chronic cough (13). Approximately 45% of patients with unexplained chest pain and normal coronary arteries have GERD (14). Esophagitis is seen in less than 10% of patients with GERD (15). Endoscopic esophagitis is seen in 30–40% of patients with asthma (16, 17) and in about 20% of patients with reflux laryngitis.

The cause-and-effect relation between GERD and asthma is unclear. A careful history among patients with asthma reveals heartburn or regurgitation in 50%. Late onset, the absence of a seasonal or allergic component, and onset after ingestion of a large meal or alcohol suggest GERD-related asthma. Reflux is the third most common cause of chronic cough, after postnasal drip and bronchitis. Hoarseness is the most common otolaryngological symptom of GERD. Although most studies suggest that heartburn is present in about 50% of patients who experience hoarseness, in our experience a careful history reveals heartburn in about 75%

(18). Other associated symptoms include halitosis, throat clearing, dry cough, coated tongue, globus sensation, tickle in the throat, chronic sore throat, and postnasal drip. Nausea and erosion of dental enamel can also occur with GERD.

GERD COMPLICATIONS

GERD can present with severe complications, including peptic stricture, ulceration, iron deficiency anemia, and, most important, Barrett's esophagus. The latter is characterized by a change from normal squamous epithelium to a metaplastic intestinal-type epithelium with typical special staining. It is a premalignant condition. Approximately 2–10% of GERD patients have strictures (10) and 9–12% have Barrett's esophagus (5, 19). Complicated GERD is suggested by a number of warning symptoms: dysphagia, odynophagia, early satiety, vomiting, or bleeding (Fig. 1). Slowly progressive dysphagia, particularly for solids, suggests peptic strictures. Liquid and solid dysphagia suggests a GERD-related motility disorder. Odynophagia is rare in reflux and, when present, suggests ulceration or inflammation, most frequently associated with infectious or pill-induced esophagitis. Ineffective esophageal motility is also more prevalent among reflux patients with associated respiratory symptoms (20). Occasionally, esophagitis presents with occult upper GI bleeding or iron deficiency anemia (21). These warning symptoms mandate early diagnostic intervention to rule out a diagnosis other than GERD (Fig. 2).

GERD CHRONICITY

Ample evidence shows that patients with reflux esophagitis will have endoscopic and symptomatic relapse up to 80% of the time if therapy is discontinued or drug dosage is decreased. Studies in patients with extraesophageal (atypical) GERD suggest similar findings. Recurrence of hoarseness was seen within 6 months of therapy in one study (22). The clinical impression is that all GERD is chronic, with individual patients expressing this chronicity in different ways. Most patients, especially those with erosive esophagitis or extraesophageal disease, will require continuous medical therapy or surgery to achieve adequate symptom relief.

TREATMENT

Patient Education and Lifestyle Modification

Patient education regarding lifestyle modification is the foundation of therapy in GERD. Simple changes in lifestyle can be effective in controlling heartburn and dyspepsia (Table 1). The basics of therapy include instructing patients to decrease their fat intake, eat small meals, refrain from eating within 2–3 hours of bedtime, avoid lying down after meals, stop smoking, and elevate the head of the bed 6 inches. Overnight pH-monitoring studies show that a significant decrease in total esophageal acid exposure is

achieved by elevating the head of the bed, with the improvement more pronounced in combination with drug therapy (23). A similar effect can be achieved by placing a foam rubber wedge (10-inch maximal elevation) under the patient's head on top of the mattress. A recent study suggests that sleeping on the right side results in more frequent reflux compared with sleeping on the left side or in the supine position (24).

Potential esophageal irritants such as citrus juices, tomato products, coffee, colas, and alcohol should be restricted. Medications that can decrease esophageal pressures and promote reflux include anticholinergics, sedatives or tranquilizers (particularly benzodiazepines), tricyclic antidepressants, theophylline, prostaglandins, and calcium channel blockers. Pills such as potassium tablets, nonsteroidal anti-inflammatory drugs, and alendronate can cause esophagitis. The intermittent use of antacids, alginic acid, or over-the-counter H₂-receptor antagonists (which are available in half the prescription strength and are indicated for up to 2 weeks of continuous use) can improve symptoms. These medications can be used as they are needed or expected to be needed.

H₂-Receptor Antagonists

H₂-receptor antagonists have been the mainstays of therapy for patients with heartburn and dyspepsia. The four such available agents—cimetidine, ranitidine, famotidine, and nizatidine—have only one known mechanism of action in treating patients with reflux disease, namely, a decrease in gastric acid production. They have no clinical effect on lower esophageal sphincter pressure or esophageal or gastric emptying. Used in standard doses (equivalent to ranitidine 150 mg twice daily), these drugs can achieve symptomatic relief in about 60% of patients (25, 26). Endoscopic resolution of documented esophagitis is seen in about 50% of patients (27). Smaller doses are effective in symptom relief or prevention, thus supporting the over-the-counter availability of half-strength H₂-receptor antagonists.

High-dose H₂-receptor antagonists (ranitidine 150 mg *q.i.d.* or its equivalent) result in healing rates of up to 75% (28). The cost of this larger dosage, coupled with compliance issues, makes this choice a less efficacious one than proton pump inhibitors (PPIs), which provide equal or greater efficacy with once-daily therapy.

Prokinetic Agents

The pathogenesis of GERD is related to defects in esophago-gastric motility, lower esophageal sphincter incompetence, poor esophageal clearance, and delayed gastric emptying. Therapy directed at correcting these defects allows improvement in GERD symptoms without suppression of gastric acid. Cisapride, the most widely prescribed prokinetic agent, increases GI motility and enhances salivary flow, thus enhancing its buffering capacity. Improvements in daytime and nocturnal heartburn have been demonstrated with cisapride 10 mg *q.i.d.* (29) and 20 mg *b.i.d.* (30).

GERD symptoms suggestive of dysmotility, such as postprandial bloating, fullness, early satiety, belching, and regurgitation, are also significantly reduced by cisapride (31, 32). Cisapride and H₂-receptor antagonists show comparable efficacy (32) and healing of mild to moderate esophagitis (33, 34). The combination of cisapride with cimetidine or ranitidine enhances healing and symptom relief compared with either agent alone (35–37). However, the cost and side effects of this regimen compared with PPIs have diminished its use. Cisapride 10 mg *b.i.d.* and 20 mg at bedtime is effective in preventing relapse (38, 39), especially among patients with grade I or II esophagitis. Ample evidence demonstrates that both H₂-receptor antagonists and cisapride can provide effective long-term control of GERD in about 50% of patients, and both are most likely to be effective in patients with less severe degrees of esophagitis (40).

Proton Pump Inhibitors

Many studies suggest that PPIs are the most effective medical therapy to control GERD symptoms and heal esophagitis. Omeprazole 20 mg or lansoprazole 30 mg daily is more effective than either placebo or standard-dose H₂-receptor antagonists in this regard, with mean symptomatic relief in more than 80% of patients and esophagitis healing in upward of 90% (41–43) over 4–8 weeks. Omeprazole 20 mg and lansoprazole 30 mg have shown equal healing rates (>90%) in direct comparisons (44). In grades III and IV esophagitis, however, the healing rate is lower (80%), often necessitating higher doses (45). Recent evidence shows that some patients will continue to secrete gastric acid and have gastroesophageal reflux even at doses of omeprazole as high as 20 mg *b.i.d.* or lansoprazole 30 mg *b.i.d.* (46).

Klinkenberg-Knol *et al.* (47) first documented effective long-term control of GERD with a PPI. Continuous therapy with omeprazole at 20–60 mg/d maintained esophagitis healing for up to 5 years. They also emphasized the need for larger doses among some patients for effective long-term maintenance. Other investigators have reported similar findings (48). These reports suggest that long-term maintenance therapy can be effective in up to 100% of GERD patients if appropriate doses are used. The study of Klinkenberg-Knol *et al.* has been extended to 11 years and supports continued efficacy (49).

Rabeprazole, a new agent in this class awaiting U.S. clinical approval, has been shown in comparative clinical trials to be similar in efficacy to omeprazole for the treatment of GERD (50, 51). Initial clinical trials suggest that it is highly effective in preventing long-term relapse of esophagitis and heartburn among patients with erosive or ulcerative GERD. Moreover, it appears to be well tolerated and to have a favorable safety profile in early clinical trials (51, 52). Pantoprazole, another new PPI awaiting clinical approval, has been shown in a 1-year clinical trial to be highly effective for long-term prophylaxis of reflux esophagitis

(53). Results of this study indicate that it also has a good safety profile.

The need for larger doses of PPIs has increased the use of combined intragastric and esophageal pH monitoring to evaluate the adequacy of acid suppression and reflux control among patients with continued symptoms or in those in whom profound acid suppression is desired (*e.g.*, patients with Barrett's esophagus) (54–56). The same technique can be used to monitor the level of PPI therapy required for each patient and, as such, it has redefined medical failure (57). This technique has an important use in the patient who fails to respond to treatment because of overnight recovery of acid secretion accompanied by reflux, which might not cause symptoms during sleep (46).

Antireflux Surgery

Refinements, including the use of laparoscopic techniques, have changed our approach to antireflux surgery. The good success rate of fundoplication—about 90% after 3 years, with minimal complications—makes it an attractive option for some patients. Use of a short, loose, “floppy” fundoplication markedly reduces the postoperative sequelae associated with antireflux surgery, including dysphagia and “gas bloat” (58, 59). Most patients are able to belch normally, and long-term dysphagia is now uncommon after fundoplication. These benefits are achieved without sacrificing efficacy in controlling reflux of gastric contents in the esophagus.

Indications for surgery (Fig. 3) in the patient with GERD are controversial. Medical failure is rare and in itself is not an indication for surgery. Antireflux surgery should be considered for the treatment of patients with objectively documented, relatively severe GERD, including patients with erosive esophagitis, stricture, and Barrett's esophagus, and for those without severe mucosal injury who require continuous high-dose PPIs for long-term symptom relief. Patients with atypical or respiratory symptoms who respond well to intensive medical treatment should be considered. The option of antireflux surgery should be given to all patients who require long-term aggressive medical therapy, particularly if escalating doses of PPIs are needed to control symptoms. Antireflux surgery may be the preferred option for patients less than 50 years of age, for those whose medications are a financial burden, for those who are non-compliant with their drug regimen, and for those who prefer a single intervention to long-term drug treatment. Patients who do not respond to PPI therapy and those with atypical chest pain are not likely to benefit from surgery.

Diagnostic evaluation before surgery is critical to determine whether gastroesophageal reflux is the underlying cause of the patient's symptoms (60). Objective evidence of GERD is usually obtained by 24-hour esophageal pH testing. The preferred surgical approach is based on an assessment of esophageal motility (61). Patients with normal contractions do well with a 360° Nissen fundoplication. When peristalsis is absent or severely disordered (>50%

simultaneous contractions) or when motility is ineffective (amplitude <30 mm Hg or nontransmitted contractions in >30% of wet swallows), partial fundoplication is the procedure of choice. A short esophagus can affect the ability to perform an adequate repair and thereby increase the risk of surgical failure. Esophageal length is best assessed using barium swallow and endoscopy. A short esophagus should be suspected if a large (>5 cm) hiatal hernia is present, particularly if it fails to reduce in the upright position on a video barium esophagram.

Complications after elective antireflux surgery are uncommon, particularly with laparoscopic fundoplication. Death is rare, whether the procedure is open or closed. In a recent collective review, 4 of 2453 patients died (62). Complications arise, on average, in 10–15% of patients and tend to be minor (63). Laparoscopic fundoplication has further decreased the 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 (58).

The results of several series of laparoscopic fundoplication have now been published (59, 64, 65). Relief of typical reflux symptoms (heartburn, regurgitation, and dysphagia) is seen in more than 90% of patients after up to 3 years of follow-up. A conversion rate of 4.2% to open surgery, a 0.5% rate of early reoperation, and excellent to good symptomatic improvement in 91% of patients are reported. Postoperative dysphagia has decreased to a rate of 3–5% with increasing experience and attention to technical details (66). Esophageal acid exposure returns to normal in nearly all patients.

Although the laparoscopic technique is exciting, these excellent results 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.

APPROACH TO THE PATIENT

The approach to the patient must be individualized. Patients with heartburn and regurgitation as their primary symptoms can be treated empirically with consideration given to the stepped-care approach outlined in Figure 1. Each level of therapeutic trial should last 4–8 weeks before moving to the next step. Several options are available at each step, and decisions should be based on cost, patient and physician familiarity with the agent, and the possibility of side effects from drug interactions. Complete symptom relief should be the goal of acute therapy. Maintenance should be attempted with the least costly agent available. Consideration should be given to a trial off medications (continuing lifestyle modifications) to see whether symptoms recur.

Early diagnostic evaluation is suggested for patients with extraesophageal (atypical) symptoms (Fig. 1) or warning

symptoms of dysphagia, early satiety, weight loss, or bleeding (Figs. 1 and 2). Referral should be considered in patients with persistent symptoms after a course of empirical therapy or in patients who require continuous daily therapy. Diagnostic evaluation usually begins with endoscopy (Fig. 2), with ambulatory pH monitoring used in patients with negative findings or atypical symptoms. Patients with grade III or IV erosive esophagitis or atypical symptoms should be treated with PPIs, with increasing dosage if symptoms are refractory. Combination therapy with a prokinetic agent can be considered, particularly in patients with abnormal gastric emptying. Antireflux surgery should also be considered for such patients after documentation of adequate symptom relief.

Every patient should be treated with the goal of achieving complete long-term symptom relief. A careful, thoughtful approach to the patient with GERD should produce a successful outcome in nearly all patients. The algorithms presented here will aid in that process.

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