GERD and Its Complications

STUART JON SPECHLER, M.D.

Abstract

Gastroesophageal reflux disease (GERD) is the condition that results when gastric material that refluxes into the esophagus or oropharynx causes symptoms, tissue injury, or both. Endoscopic examination usually is not required merely to establish a diagnosis of GERD, but endoscopy is the best diagnostic test for Barrett's esophagus, a sequela of GERD that predisposes to esophageal adenocarcinoma. Patients found to have Barrett's esophagus will require regular endoscopic surveillance for early, curable neoplasia. Esophageal pH monitoring is useful for patients who have symptoms or signs suggestive of GERD, but who have little or no response to antisecretory therapy. For patients who have severe, ulcerative reflux esophagitis, the clinician has only two reasonable therapeutic options: (1) lifelong antisecretory therapy with proton pump inhibitors or (2) antireflux surgery. There are no absolute indications for antireflux surgery, but the operation can be considered for patients with severe GERD who are unwilling to accept lifelong medical therapy or for young patients whose GERD symptoms respond only to proton pump inhibitors administered in high dosages. **Key Words:** Gastroesophageal reflux disease.

GASTROESOPHAGEAL REFLUX DISEASE (GERD) is the condition that results when gastric material that refluxes into the esophagus or oropharynx causes symptoms, tissue injury, or both (1). Reflux-induced esophageal injury (reflux esophagitis) can be complicated by the development of esophageal erosions and ulcerations. Esophageal ulcerations that stimulate the deposition of fibrous tissue result in esophageal strictures, and ulcerated esophageal squamous epithelium can be replaced by a metaplastic, intestinal-type epithelium that has a malignant predisposition (a condition called Barrett's esophagus). Refluxed gastric juice that crosses the upper esophageal sphincter to enter the oropharynx can damage the oropharyngeal mucosa and erode the dental enamel. Aspiration of refluxed material into the airway can result in laryngitis and pulmonary disorders such as asthma and bronchitis. Thus, GERD can have both esophageal and extra-esophageal manifestations. The esophageal symptoms of GERD such as heartburn and odynophagia usually respond quickly and dramatically to conventional medical antireflux therapy (2). In contrast, resolution of the extra-esophageal symptoms of GERD may require high doses of potent acid-suppressive medications administered for many months (3).

Who Needs Endoscopy?

For patients with GERD, an endoscopic examination of the esophagus can answer the four clinical questions listed below:

- Is there reflux esophagitis?
- Is the esophagitis severe?
- Is there an esophageal stricture?
- Is there Barrett's esophagus?

Answers to these questions may have clinical importance in certain situations. For example, the endoscopic demonstration of reflux esophagitis establishes a diagnosis of GERD, and the demonstration of severe esophagitis suggests that med-

From the Dallas Department of Veterans Affairs Medical Center and The University of Texas Southwestern Medical Center at Dallas, Dallas, TX.

Address correspondence to Stuart Jon Spechler, M.D., Chief, Division of Gastroenterology (111B1), Dallas VA Medical Center, 4500 South Lancaster Road, Dallas, TX 75216.

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ical treatment with agents other than proton pump inhibitors will not be effective. The demonstration of an esophageal stricture indicates that esophageal dilation may be required in addition to intensive antisecretory therapy. Furthermore, endoscopy is required to establish a diagnosis of Barrett's esophagus.

The clinician should appreciate that endoscopy does not always answer the question, "Does the patient have GERD?" Although the endoscopic finding of reflux esophagitis establishes a diagnosis of GERD, a normal endoscopic examination does not eliminate GERD as a cause of symptoms. Gastroesophageal reflux can cause disabling symptoms without causing visible esophageal damage (4). Endoscopic examination reveals esophagitis in fewer than 50% of patients who complain of frequent heartburn (1), and the esophagus typically appears normal endoscopically in patients who only have extra-esophageal symptoms of GERD (5). Patients with classic heartburn who respond readily to conventional antireflux therapy can be assumed to have GERD, and endoscopy is not necessary simply to confirm that diagnosis. Without endoscopic examination, however, it is not possible to answer all of the four clinical questions listed above. For patients with GERD symptoms, the physician must decide whether the benefits of answering these questions outweigh the inconvenience, small risk, and considerable expense of endoscopy. The American Society for Gastrointestinal Endoscopy (6) has recommended diagnostic endoscopy for patients who have "esophageal reflux symptoms which are persistent or recurrent despite appropriate therapy," and has advised that diagnostic esophagogastroduodenoscopy (EGD) is generally not indicated for evaluating "uncomplicated heartburn responding to medical therapy" (6). More recently, the Practice Parameters Committee of the American College of Gastroenterology (7) has endorsed a similar policy. This policy states: "If the patient's history is typical for uncomplicated GERD, an initial trial of empiric therapy (including lifestyle modification) is appropriate. Patients in whom empiric therapy is unsuccessful or who have symptoms suggesting complicated disease should have further diagnostic testing." Presumably, symptoms that might suggest complicated disease would include fever, anorexia, weight loss, dysphagia, odynophagia, and bleeding. The policy further states that "selected individuals who have longstanding symptoms or who require continuous therapy may need endoscopic screening for Barrett's esophagus." Although these proposed approaches to patient management seem reasonable, it is important to recognize that they are merely committee recommendations whose efficacy has not been established by formal clinical investigation. Also, there is no clear consensus regarding which is the most appropriate medication to use for initial empiric therapy of GERD, i.e., a histamine H2-receptor blocker, a prokinetic drug, or a proton pump inhibitor. Proton pump inhibitors clearly are most effective for eliminating the signs and symptoms of GERD, but the H2-blockers and prokinetics will control symptoms in most patients who have GERD of mild to moderate severity. Patients with GERD whose symptoms are refractory to H2-blocker therapy tend to have severe and complicated disease. For such patients, early diagnostic evaluation may be important to tailor therapy and to prevent further complications. Therefore, I usually begin empiric therapy for GERD with an H2-blocker, and reserve the use of proton pump inhibitors (PPIs) for patients whose diagnosis has been established by endoscopic examination.

Who Needs 24-Hour Esophageal pH Monitoring?

Ambulatory monitoring of esophageal pH can be used to document the pattern, frequency, and duration of acid reflux, and to seek a correlation between reflux episodes and symptoms (8, 9). In most ambulatory systems, an episode of acid reflux is defined (somewhat arbitrarily) as a drop in esophageal pH below 4. Standard 24-hour pH monitoring records a number of different variables such as the total number of reflux episodes, the number of episodes longer than 5 minutes in duration, and the duration of the longest episode. The single most clinically applicable variable appears to be the total percentage of the monitoring period that esophageal pH remains below 4 (9). In normal individuals, esophageal pH remains below 4 for less than 4.5% of the 24-hour monitoring period. Most patients who have both endoscopic signs and symptoms of GERD also have abnormal 24-hour esophageal pH monitoring studies, whereas subjects with no such signs and symptoms usually have normal studies. It is difficult to determine the precise sensitivity and specificity of the test, however, because there is no universally accepted "gold standard" for the diagnosis of GERD.

In theory, protracted esophageal pH monitoring should be very useful in establishing acid reflux as the cause of symptoms in individual patients. In practice, however, the correlation between discrete episodes of acid reflux and

symptoms often is poor. For example, although normal individuals often experience brief episodes of acid reflux during the day (particularly after meals), these episodes usually are not associated with heartburn (10). Even in patients with heartburn who have endoscopic evidence of reflux esophagitis, 24-hour esophageal monitoring reveals that fewer than 20% of episodes of acid reflux are accompanied by heartburn (11).

For patients who have classic symptoms of GERD, endoscopic evidence of reflux esophagitis and a good response to conventional antireflux therapy, ambulatory esophageal pH monitoring usually is a superfluous test that provides little important clinical information. For patients with atypical symptoms, the test occasionally can be useful to establish an association of symptoms with abnormal acid reflux. Perhaps the best application of 24-hour esophageal pH monitoring is for patients who have symptoms or signs suggestive of GERD, but who have little or no response to potent antisecretory therapy. For such patients, the test is often most useful if antisecretory therapy is continued during the monitoring period. The objective demonstration that antisecretory therapy has successfully eliminated acid reflux, but that symptoms persist nevertheless, indicates that acid reflux is not the cause of the symptoms. Alternatively, the demonstration that acid reflux persists despite antisecretory therapy suggests that alternative antireflux therapies must be used. For patients with extra-esophageal symptoms such as hoarseness, esophageal pH monitoring during therapy should not be performed until the patient has had treatment for an adequate period of at least 2 – 3 months.

Who Needs Proton Pump Inhibitors?

The proton pump inhibitors (e.g., omeprazole, lansoprazole, rabeprazole, pantoprazole) are the most effective medications available for the treatment of GERD. In patients with mild to moderately severe reflux esophagitis treated with conventional doses of these agents, healing rates of 80 – 100% can be expected within 8 weeks (7, 12 – 14). The efficacy of any medication for GERD is inversely proportional to the severity of the underlying esophagitis, and patients with severe, ulcerative reflux esophagitis often do not respond well to H2-blocker therapy (15). PPIs have been shown to heal esophagitis that is refractory to H2-blocker treatment, and therefore PPIs appear to be the agents of choice for the medical treatment of patients who have severe forms of reflux esophagitis. Very severe (grade 4) reflux esophagitis may persist despite PPI therapy administered in conventional dosages in up to 40% of cases. In almost all such cases, however, the severe reflux esophagitis that is refractory to conventional dose PPI therapy can be healed simply by increasing the dose of the PPI (16). Also, recent studies have shown that PPI treatment can improve dysphagia and decrease the need for esophageal dilation in patients who have peptic esophageal strictures (17, 18). Therefore, PPI therapy also is indicated for the medical treatment of patients with peptic strictures.

Although PPIs are highly effective in healing esophagitis, they do little to correct the underlying diathesis for reflux. In the majority of patients with severe GERD, symptoms recur shortly after stopping these agents and maintenance therapy usually is required. For most patients, the dose of PPI necessary to maintain remission is at least the dose required to heal the acute esophagitis (19). Furthermore, for patients with severe GERD, the maintenance dose of PPI may increase with time. Klinkenberg-Knol et al. recently studied a group of patients with severe GERD, all of whom had been refractory to H2-blockers (16). The patients were treated with a high dose of omeprazole, and the esophagitis healed in every case. Patients then were switched to maintenance omeprazole in a dose of 20 mg per day, and were followed for up to 5 years. During that time, almost one-half of the patients had a relapse of GERD despite maintenance therapy. In every case, the esophagitis could be healed again simply by increasing the dose of omeprazole. By years 3 – 5, a substantial number of patients required double and triple doses of omeprazole to maintain remission. Also, 11% of the patients developed substantial elevations of their serum gastrin levels. This study shows that PPIs can heal esophagitis very effectively over the long term if one is willing to pay the price, both in dollars and in the potential for side effects.

Recent studies suggest that a course of PPI therapy can be used as a diagnostic test for GERD-related symptoms. In one study of 37 patients with atypical chest pain who had heart disease excluded by a cardiologic evaluation, endoscopy and 24-hour pH monitoring were performed at baseline to establish an objective diagnosis of GERD (20). In a double-blind, placebo-controlled, crossover trial, patients were randomly assigned to receive either omeprazole (40 mg AM, 20 mg PM) or placebo for one week. Omeprazole treatment resulted in a > 50% decrease in chest pain (a positive omeprazole test)

in 78% of patients with GERD, whereas only 14% of patients without GERD had such a response. The authors estimated that the omeprazole test for GERD-associated noncardiac chest pain had a sensitivity of 78% and a specificity of 86%, and resulted in a cost-saving of $573 per patient compared to a conventional diagnostic work-up that might include an endoscopy and/or 24-hour pH monitoring study.

Who Needs Laparoscopic Antireflux Surgery?

Different antireflux operations such as the Nissen fundoplication, the Hill posterior gastropexy, and the Belsey fundoplication all share several fundamental features (21). In all of these procedures, the surgeon creates an intra-abdominal segment of esophagus, reduces the hiatal hernia, approximates the diaphragmatic crura, and wraps a portion of the gastric fundus around the distal esophagus. As a result, the surgery narrows the angle of His (the angle formed by the junction of esophagus with stomach) which may create an antireflux flap-valve effect (22). Restoration of the distal esophagus to the positive pressure environment of the abdomen also may prevent reflux. Reduction of the hiatal hernia and approximation of the diaphragmatic crura may restore the normal antireflux function of the crural diaphragm. The fundoplication itself may act as a one-way valve, and may prevent distention of the gastric fundus that can trigger transient lower esophageal sphincter (LES) relaxations. Finally, LES pressures increase after fundoplication for reasons that are not clear.

A large cooperative study conducted in the late 1980s compared the efficacy of available medical and surgical therapies for GERD (23). The 247 study subjects all had GERD complicated by Barrett's esophagus, esophageal ulceration, esophageal stricture, or severe erosive esophagitis. Antireflux lifestyle modifications were prescribed for all study subjects regardless of treatment group. Patients were randomly assigned to receive one of three types of treatment: continuous medical therapy, symptomatic medical therapy, or surgical therapy. Continuous medical therapy included antacid tablets and ranitidine taken on a daily basis regardless of symptoms; metoclopramide and sucralfate were added in a stepwise fashion for patients who remained symptomatic. For patients in the symptomatic medical therapy group, drug therapy was used only for control of symptoms. Therapy in these patients began with antacid tablets; ranitidine, metoclopramide, and sucralfate were added in a stepwise fashion for symptoms that could not be controlled with antacids alone. Patients in the surgical therapy group had Nissen fundoplications. All three therapies resulted in significant improvements in the symptoms and endoscopic signs of GERD for up to two years. However, surgical therapy was significantly better than either medical therapy for the two-year duration of the study. Overall satisfaction with therapy also was better for patients in the surgical group. Although this prospective, randomized study predated the availability of omeprazole, the investigation clearly demonstrated that surgical therapy is superior to medical therapy without proton pump inhibitors. Although there is no reported study that has compared the efficacy of antireflux surgery with proton pump inhibitors, it is anticipated that the results of these two forms of therapy will be similar.

Antireflux surgery now can be performed laparoscopically, and a number of reports have described the short-term results of laparoscopic fundoplication (24–26). For the Nissen fundoplication, these results can be summarized in Table 1.

These complication rates, mortality rates, and outcome results are comparable to those reported for the open procedure (27). Compared to the open procedure, the expected advantages of laparoscopic fundoplication are listed in Table 2.

Presently, there are few published data that substantiate all of the proposed advantages for laparoscopic fundoplication over the open procedure (28). Fundoplication performed by a skilled surgeon is a highly effective form of therapy for GERD whether the operation is done by the open or laparoscopic approach. At least one study has shown that the primary factor involved in postoperative patient satisfaction is the relief of GERD

TABLE 1
Results of Laparoscopic Nissen Fundoplication

Complication rate	4–26%
Mortality rate	< 1%
Conversion to open procedure	2–14%
Median hospital stay	2–7 days
Good or excellent outcome	> 85%

TABLE 2
Proposed Advantages for Laparoscopic Antireflux Surgery (Compared to Open Procedure)

Fewer complications	Faster return to work
Less postoperative discomfort	Better esthetic result
Shorter hospital stays	Greater patient satisfaction
Less expensive	

symptoms rather than the operative approach (open vs. laparoscopic) (29). These findings suggest that the availability of laparoscopic surgery should not influence the physician's decision regarding the advisability of fundoplication. The primary decision for the clinician is whether or not the patient should have an antireflux operation, not how the operation should be performed.

Major indications for antireflux surgery include the following:

- Patients with severe GERD who are unwilling to accept lifelong medical therapy.
- Patients who have signs and symptoms of GERD (esophageal or extra-esophageal) that are responsive only to PPIs administered in high dosages.
- Patients who are young and require longtime use of PPIs for GERD control.

Although none of the above can be considered absolute indications for antireflux surgery, the option should at least be considered and discussed with the patient. Lifelong medical therapy for severe GERD is expensive, and there are theoretical risks involved. The patient should be well informed of the risks and benefits of both medical and surgical treatments for GERD.

Note that medical intractability is not listed as an indication for antireflux surgery. Prior to the advent of PPIs, internists primarily recommended antireflux surgery for patients whose GERD failed to respond to medical therapy. Today, this practice is not tenable. Modern medical therapy is extraordinarily effective in healing reflux esophagitis, and it is decidedly unusual to encounter patients who are truly refractory to medical treatment. Indeed, the very diagnosis of GERD must be questioned for patients whose esophageal signs and symptoms are unaffected by the administration of PPIs in high dosages. It is ironic that in an era when highly effective medical therapy for GERD is available, surgical therapy is best reserved for patients who are medical successes, not failures. Patients who respond well to medical therapy usually do well with fundoplication surgery. In the large majority of patients whose symptoms fail to respond to PPIs, esophageal pH monitoring reveals that these agents have controlled acid reflux. Such patients almost certainly would have a poor response to antireflux surgery.

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