Gastroesophageal Reflux Disease in Adults: Pathophysiology, Diagnosis, and Management

Douglas K. Rex, MD
Indianapolis, Indiana

Gastroesophageal reflux disease (GERD) refers to symptoms or tissue damage that result from gastroesophageal reflux. Reflux esophagitis is a subset of GERD and implies the presence of esophageal inflammation, ie, esophageal erosions that are visible endoscopically, or nonerosive inflammation that can be documented by biopsies. Heartburn is the most common and specific symptom of GERD. In some patients, chest pain or respiratory symptoms may be the only presenting signs. In patients aged <50 years with uncomplicated GERD, empiric therapy (typically with antacids or an H_2-receptor antagonist) is appropriate. For older patients, those with complications, and those whose symptoms do not respond to empiric therapy, endoscopic evaluation is indicated. Many patients will improve with standard twice-daily dosing of an H_2-receptor antagonist. However, GERD is generally more resistant to antisecretory pharmacologic therapy than is peptic ulcer disease. Those patients who fail to respond to standard dosing of an H_2-receptor antagonist may get relief from high-dose H_2-receptor antagonists or omeprazole therapy.

Key words. Gastroesophageal reflux; histamine antagonists; omeprazole; antacids. *J Fam Pract 1992; 35:673-681.*

Gastroesophageal reflux occurs commonly in normal persons. Patients who have either symptoms or tissue damage resulting from reflux are said to have gastroesophageal reflux disease (GERD). "Reflux esophagitis" is often used as a synonym for GERD. Strictly speaking, however, reflux esophagitis is a subset of GERD in which there is evidence of esophageal inflammation demonstrated either by gross inspection during endoscopy or by microscopic examination of biopsy specimens. A number of reviews of GERD and its treatment have been published.[1–4] This review addresses the pathophysiology, diagnosis, and management of GERD in adults.

Incidence and Prevalence

Gastroesophageal reflux is very common in adults. Approximately one third of the general population experience heartburn on a monthly basis (or more frequently) and 7% experience heartburn daily.[5] Among medical patients, 14% of those hospitalized and 15% of outpatients experience daily heartburn. About 25% of pregnant women have daily heartburn. Other than in pregnancy, there is no correlation in adults between age and sex and prevalence of reflux symptoms.[5] One study estimated the prevalence of GERD in the elderly at 5%.[6] Another study reported heartburn in 14% of elderly ambulatory outpatients and abnormal reflux in 20% of this population by ambulatory pH monitoring.[7]

The frequency of GERD is reflected in the heavy use of antacids in the United States.[8] Marketing surveys indicate that one half of American adults have used antacids and 4% of adults are "heavy users"—those who take 6 or more doses a week. Ninety-five percent of heavy users of antacids had symptoms consistent with GERD. The majority of persons with gastroesophageal reflux experience mild, intermittent symptoms and treat themselves effectively with diet modification and antacids. Those patients with more severe or prolonged symptoms and those with complications are more likely to visit a physician.

Pathophysiology

Mechanisms of Gastroesophageal Reflux Disease

Abnormalities of lower esophageal sphincter (LES) function, esophageal clearance, gastric emptying, and esophageal mucosal defense have been demonstrated in patients with GERD.

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From the Department of Medicine, Division of Gastroenterology/Hepatology, Indiana University School of Medicine, Indianapolis. Requests for reprints should be addressed to Douglas K. Rex, MD, University Hospital, Suite 2300, 926 W Michigan St, Indianapolis, IN 46202.

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The LES is critical to the antireflux mechanism. Resting pressure in the LES, however, is decreased in only about one third of patients with GERD.[9] When LES pressure is very low, there may be a greater potential for developing reflux disease. Nevertheless, most patients with GERD have normal resting LES pressures but demonstrate an increased frequency and duration of transient LES relaxations.[9] These LES transient relaxations are complete relaxations of the LES that are not preceded by esophageal peristaltic waves. LES transient relaxations occur and result in reflux even in normal individuals. In patients with GERD, however, they occur more frequently and are longer in duration.

Esophageal clearance is the restoration of a normal intraluminal pH in the esophagus after acid reflux. In normal persons a volume of refluxed acid is rapidly emptied from the esophagus by an immediate secondary peristaltic wave initiated by the refluxate.[10] Following this, the esophageal pH returns to normal in a series of stepped increases corresponding to a sequence of peristaltic waves induced by swallowing. Residual acid in the esophagus is neutralized by the bicarbonate in swallowed saliva. Increasingly, abnormalities of this esophageal clearance mechanism are being recognized as important factors in the genesis of reflux esophagitis.

Impaired esophageal clearance leads to prolonged exposure of the esophagus to refluxed acid and other injurious components of the refluxate. Several factors contribute to impaired esophageal clearance in GERD. About 50% of patients with reflux esophagitis exhibit impaired esophageal peristalsis.[11] It is still not certain, however, whether peristaltic abnormalities represent a primary motility disturbance in GERD or are the result of esophagitis, fibrosis, and secondary impairment of esophageal muscle function. Hiatal hernias can impair esophageal clearance by serving as an acid trap that promotes reflux during relaxation of the LES induced by swallowing.[12] Horizontal body position may impair esophageal clearance, particularly in GERD patients. Sleep impairs esophageal peristalsis even in normal subjects. Thus, even minor amounts of reflux occurring at night may result in significant esophageal damage.

Delayed gastric emptying can be documented in 41% of patients with GERD.[13] Delayed gastric emptying results in gastric distention and increased gastric volume, both of which predispose the patient to reflux.

Impaired mucosal defense certainly contributes to esophagitis, but the role of epithelial protection is not as well understood in the esophagus as it is in the stomach and duodenum. Important elements of esophageal mucosal defense include the esophageal mucus layer, the unstirred water layer, the epithelium itself, and the mucosal blood flow. The mucus layer serves as a barrier to large molecules such as pepsin.[14] The unstirred water layer is an area of low turbulence adjacent to the epithelial surface which mixes poorly with luminal contents. This layer acts as a sink for bicarbonate,[15] which can then neutralize hydrogen ion as it diffuses toward the epithelium. In animal models, prostaglandins augment the resistance of the esophageal epithelium.

Irritant Factors in the Refluxate

The dominant irritant factors in the refluxate are gastric acid and pepsin. Treatments that neutralize or reduce acid are often effective in GERD.

Some patients (eg, after total gastrectomy or in the presence of pernicious anemia and achlorhydria) have esophagitis in the absence of acid secretion. That they do demonstrates that other components of the refluxate, such as bile acids and pancreatic enzymes, are also important irritant factors in GERD.[16,17]

Dietary Factors and Physical Conditions Predisposing to GERD

Several dietary and social factors may increase the likelihood of gastroesophageal reflux. Cigarette smoking, alcohol, caffeine, peppermint, and chocolate decrease LES pressure. Fatty meals delay gastric emptying and decrease LES pressure.

Physical factors, such as obesity, predispose patients to GERD. Obesity increases intra-abdominal pressure and may lower the strength of the LES. Pregnancy may result in GERD since circulating progesterone reduces LES pressure and the growing fetus increases intra-abdominal pressure. Hiatal hernia sacs serve as a reservoir for the collection of gastric secretions, predisposing to reflux. Most patients with severe esophagitis or with Barrett's esophagus have a hiatal hernia. Many patients with hiatal hernias are asymptomatic, however, and esophagitis is often seen in the absence of hernia. Whenever a hiatal hernia is encountered, its importance must be considered in the context of the individual patient's symptoms and extent of esophagitis.

Clinical Presentation

Classic Symptoms

The classic presentation of GERD is heartburn (defined as retrosternal sensation of burning and discomfort that is worse after eating) and, less frequently, regurgitation. The use of antacids for symptom relief is common. Water

brash (excessive salivation in response to reflux) is occasionally reported. Dysphagia always demands imaging of the esophagus and is the one upper gastrointestinal (GI) tract symptom that is still often first evaluated by barium radiograph rather than endoscopy. Odynophagia (painful swallowing) is more typical of infectious esophagitis due to *Candida*, cytomegalovirus, or herpesvirus, but is reported by some patients with erosive reflux esophagitis. The astute physician should be aware that atypical symptoms, such as respiratory symptoms, chest pain, and laryngeal or oropharyngeal symptoms, may be caused by GERD.

Respiratory Symptoms

In recent years, an association between GERD and pulmonary problems has been recognized. Abnormal reflux was found during pH monitoring in more than 80% of patients with asthma[18] and in 62% of patients with chronic bronchitis.[19] In a small percentage of those patients, GERD appears to be a major causative factor in bronchiectasis and even in recurrent pneumonitis.[20]

Two mechanisms may explain respiratory complications of gastroesophageal reflux: (1) direct laryngeal and pulmonary aspiration of refluxed gastric contents and (2) vagally mediated reflex bronchoconstriction initiated by refluxate-induced irritation of the esophageal lining.[21] Asthma patients in whom GERD should be considered a possible causative factor are those with reflux symptoms, those with primarily nocturnal cough or wheezing, and those without an allergic component to their asthma. Asthma and other pulmonary symptoms have improved or resolved after medical or surgical therapy for GERD. In addition to respiratory symptoms, reflux may damage the oropharynx and larynx, resulting in sore throat, earache, poor dentition, cough, and hoarseness.

Angina-like Chest Pain

Both GERD and coronary artery disease are common diseases and may coexist in the same patient. In some patients GERD can precipitate angina. Apparently, irritation of the distal esophagus by acid initiates a neural reflex that can cause vasoconstriction of coronary arteries.[22,23] This association should be kept in mind in patients with concurrent heartburn and angina.

In addition to precipitating angina, GERD itself may present as angina-like chest pain rather than heartburn. Certainly initial evaluation of angina-like chest pain involves a careful search for cardiac disease. However, 20% of patients referred for coronary angiography are found to be normal. In one study, approximately half of the patients with a history of chest pain showed esophageal dysfunction as the cause of their pain.[24] Both GERD and esophageal motility disorders can produce typical angina-like chest pain. Of these two disorders, GERD is the more common cause of noncardiac chest pain. Motility disturbances may, in fact, be precipitated by GERD. The goals of evaluation are to reassure the patient by verifying that the esophagus is the origin of the pain and to develop a rationale for therapy. Evaluation generally includes initial endoscopy, and if esophagitis is found, aggressive therapy for GERD is indicated. If endoscopy is negative, other testing may be indicated (see below).

Diagnostic Studies

Young patients with simple heartburn and regurgitation are diagnosed with GERD by history alone, and empiric therapy can be initiated. Diagnostic evaluation is needed only when these patients fail to respond to empiric therapy. In patients with dysphagia, anemia, weight loss, or occult blood in the stool, or who develop these symptoms after 50 years of age, imaging of the upper GI tract must be performed. Many experts prefer to evaluate dysphagia first by barium esophagram and then by endoscopy, but other symptoms and findings are most effectively evaluated by initial endoscopy. The purpose of the upper GI radiograph or endoscopy is to rule out other structural diseases, such as cancer and peptic ulcer disease, and to assess the degree of damage to the esophageal mucosa. Collection of esophageal biopsies increases the sensitivity of endoscopy for detection of reflux esophagitis.[25]

Other diagnostic tests are also available for the evaluation of GERD. These tests are generally needed only in patients with GERD when special situations arise. For example, esophageal manometry is primarily helpful in evaluating GERD in the preoperative assessment of patients being considered for reflux surgery. It is occasionally used in planning the long-term therapy of GERD. Very low LES pressure is associated with a greater likelihood of failure of medical therapy[26] and of relapse after successful medical therapy.[27] Thus, low LES pressure may suggest patients more likely to benefit from antireflux surgery.

Another special situation in which diagnostic testing may be indicated is the patient with atypical symptoms such as angina-like chest pain. If endoscopy is normal, then either the Bernstein test or the ambulatory pH probe can be used to correlate chest pain with an acid pH in the esophagus. The Bernstein test is performed by infusion of dilute hydrochloric acid into the mid-esoph-

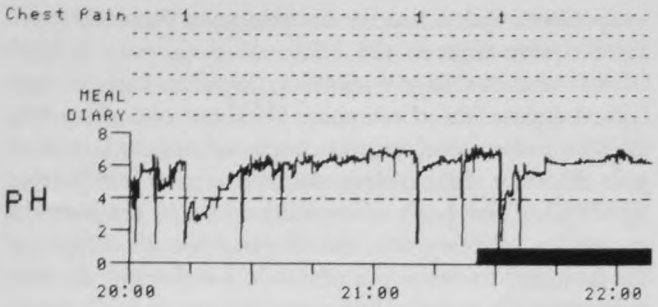

Figure 1. Results of an ambulatory pH monitoring. A pH sensitive electrode is placed 5 cm above the manometrically located lower esophageal sphincter. Just over 2 hours of a 24-hour ambulatory recording are shown. The last meal was at 7:30 PM (not shown). Decreases in pH level below 4 are considered reflux episodes. The patient indicated three episodes of chest pain using the event marker (each indicated by a "1" on the chest pain line). Two of the three episodes were associated with prolonged reflux. Several very brief episodes of reflux were not associated with chest pain. The correlation between chest pain and reflux would be considered good in this patient.

agus through a nasogastric tube and utilizes a saline control infusion. Reproduction of the patient's usual symptoms by acid infusion but not with saline infusion is a positive test. The Bernstein test has the advantage of being an office test but, in reality, few primary care physicians ever perform it. It has average sensitivity and specificity of 80% for reflux disease in general but the sensitivity is much lower in patients with angina-like chest pain.[24] A better test for correlation of atypical symptoms with reflux is the 24-hour ambulatory pH probe (Figure 1).[28] Esophageal manometry is also sometimes useful in evaluation of atypical chest pain.[24] However, many episodes of chest pain in these patients are associated with neither reflux nor a manometric abnormality.[29] Recent investigation has focused on abnormal esophageal visceral afferent function in atypical chest pain.[30] The entire evaluation of noncardiac chest pain is made even more complex by the recent recognition of microvascular angina.[31]

In some patients diagnostic testing may be necessary to resolve a question as to the presence of reflux (Table 1). In this setting, tests that can document reflux events are useful. The most widely available test to demonstrate reflux is the upper GI barium radiograph. However, this test has a sensitivity of only 30%.[32] The addition of special maneuvers such as water-sipping in the head-down position increases the sensitivity but unacceptably lowers the specificity.[33] The standard acid reflux test employs an esophageal pH electrode to measure reflux, which may occur spontaneously or after infusion of hydrochloric acid into the stomach. If necessary, various maneuvers such as Valsalva's or Muller's or abdominal compression can be employed to precipitate reflux. The sensitivity and specificity of these tests are each about 80%. Radionuclide scans can document reflux, but wide variation in sensitivity has been reported.[34–36] They may be helpful when a noninvasive test is desired (Figures 2 and 3).

Currently the most accurate test for determining the presence of abnormal reflux is prolonged intraesophageal pH monitoring (Figure 1). The test is now available on a widespread basis in medical centers and in many private practice gastroenterology groups. Depending on the criteria examined, the sensitivity and specificity are each approximately 90%.[37]

Management

Nonpharmacologic Therapy

Certain nonpharmacologic treatments involving lifestyle changes and diet modification should be pursued aggressively in patients with GERD. The number of appropriate nonpharmacologic therapies will vary among patients. Many patients will already have recognized the importance

Table 1. Diagnostic Tests for Gastroesophageal Reflux Disease (GERD)

Goal	Tests
To image the esophagus and upper GI tract; to rule out other diseases and assess damage to the esophagus	Endoscopy Upper GI series
To determine if atypical symptoms (chest pain or pulmonary symptoms) are caused by GERD	24-Hour ambulatory pH monitor (best) Bernstein (less sensitive)
To answer the question; is reflux occurring?	24-Hour ambulatory pH monitor (best) Nuclear medicine reflux scintiscan Standard acid reflux testing Upper GI radiograph (least sensitive)
To assess esophageal peristalsis before resorting to reflux surgery	Esophageal manometry

of many of these measures when they are first interviewed. Education of patients regarding nonpharmacologic measures can be facilitated by an instruction sheet for distribution to GERD patients (Table 2). It is important to emphasize to the patient that these measures are not a short-term solution. Gastroesophageal reflux disease is a chronic condition, and lifestyle changes must be incorporated on a long-term basis. Patients of normal weight should be advised to eat frequent, smaller meals in order to avoid gastric distention. Patients who are overweight should lose weight. Avoiding meals within 3 hours of bedtime and remaining upright after eating is also helpful. Certain foods (fatty foods, alcohol, coffee, peppermint, chocolate) decrease LES pressure while others (citrus and tomato juice) may directly irritate the esophageal mucosa. Smoking reduces LES pressure and should be avoided. Drugs that can reduce LES pressure or interfere with esophageal peristalsis should be avoided if feasible (Table 3).

Elevating the head of the bed on 6- or 8-in. blocks is an effective strategy for improving esophageal acid clearance and thus reducing the harmful effects of reflux,[38] and it has been found to enhance the effects of an H_2-receptor antagonist.[39] For patients who are unwilling to elevate the head of the bed on blocks or who have waterbeds, an alternative is a commercially available wedge-shaped foam rubber pillow.

Pharmacologic and Surgical Therapy

Patients with mild symptoms may often respond to nonpharmacologic therapy alone. However, drug therapy (Table 4) is indicated when symptoms are refractory or severe in character, or when esophagitis is present at endoscopy.

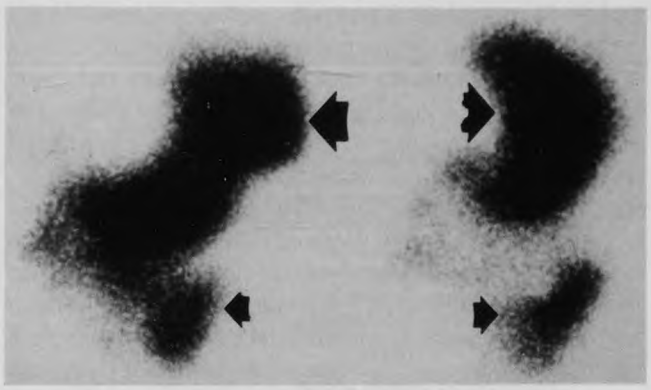

Figure 2. Negative reflux scintiscan. Two scans, one taken with the patient in the upright position (left) and one with the patient in the supine position (right), show radionuclide in both the stomach (large arrows) and small bowel (small arrows) but not in the esophagus. No reflux of radionuclide was documented in this patient.

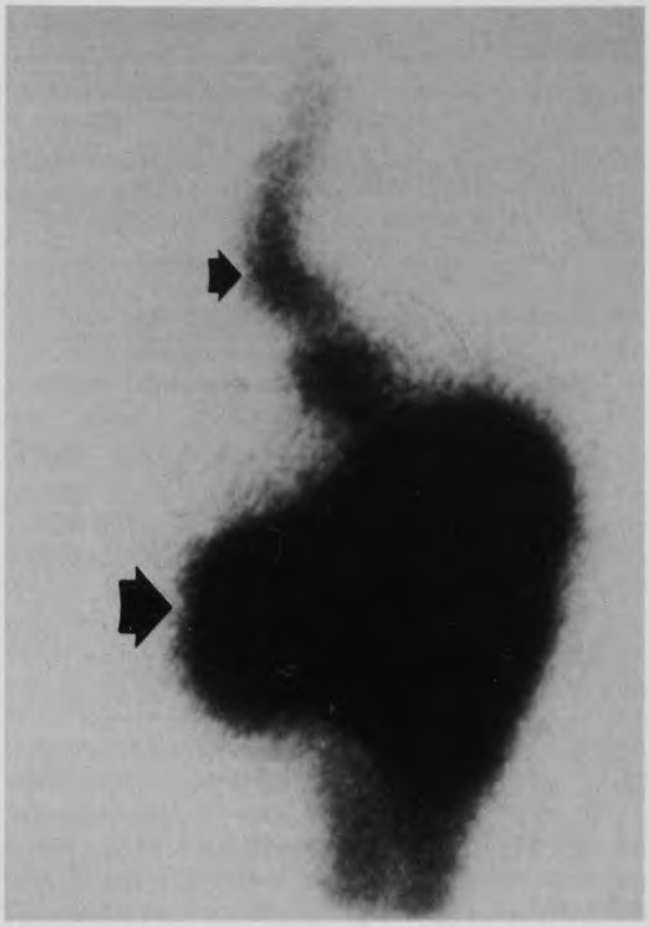

Figure 3. Positive reflux scintiscan. Radionuclide is in the stomach (large arrow) and freely refluxing up the esophagus (small arrow).

ANTACIDS AND ALGINIC ACID

Reports on the effectiveness of antacids in relieving symptoms and improving esophagitis are conflicting. Nevertheless, for patients with mild to moderate symptoms, antacids are an acceptable first choice. The frequent dosing and associated diarrhea, however, can negatively affect patient compliance. Alginic acid is the major active ingredient in Gaviscon. Alginic acid does not neutralize stomach acid, rather it creates a floating barrier between gastric contents and esophageal mucosa. Gaviscon, a nonprescription drug, appears to be at least as effective as antacid,[40] but probably only works for heartburn when the patient is in the upright position.

H_2-RECEPTOR ANTAGONISTS

H_2-receptor antagonists, which act by reducing gastric acid production, are in widespread use for the management of GERD. The advantages of H_2-receptor antagonists in treating GERD are that they provide symptom

Table 2. Nonpharmacologic Therapy for Patients With Gastroesophageal Reflux Disease

1. *Decrease or eliminate* your intake of fatty and spicy foods, alcohol, coffee (caffeinated or decaffeinated), chocolate, peppermint, and citrus juice.
2. Eat *smaller* meals. *Do not* eat for 3 hours before bedtime. Stay *upright* for 2 hours after meals.
3. If overweight, *lose weight* and achieve your ideal body weight.
4. *Stop* smoking cigarettes.
5. *Avoid* bending or stooping if they cause your symptoms.
6. *Avoid* tight clothing over the abdominal area.
7. Try *lozenges* to stimulate saliva secretion.
8. *Avoid* aspirin and other arthritis medication *unless* instructed by your physician.
9. *Elevate* the head of your bed on 6- to 8-in. blocks.

relief in most patients and have a remarkably good safety profile. These drugs are not as effective for GERD, however, as they are for peptic ulcer disease. For duodenal ulcer, for example, standard doses of any H_2-receptor antagonist will give symptom relief and ulcer healing in 90% of patients after 8 weeks of therapy. Similar doses of H_2-receptor antagonists for GERD will produce symptom relief in about 75% of patients and healing of erosive esophagitis in about one third of patients. Thus, healing rates for GERD using standard doses of H_2-receptor antagonists are less than half the healing rates seen for peptic ulcer disease. This underscores the important clinical concept that erosive esophagitis is much more refractory to antisecretory therapy than is peptic ulcer disease.

When H_2-receptor antagonists are used for GERD, it is preferable to give split-dose (twice daily or more frequently) therapy. Bedtime single-dose therapy has proved to be effective for peptic ulcer disease, particularly duodenal ulcer, but is less effective than split-dose therapy for GERD.[41]

The H_2-receptor antagonists differ in their potency. This difference has no apparent clinical importance in peptic ulcer disease but may be a factor in their efficacy in GERD. Thus, higher doses of a less potent agent such as cimetidine are needed to demonstrate healing of erosive esophagitis.[42,43] The more potent H_2 antagonists, ranitidine, nizatidine, and famotidine, are more likely to be effective at standard duodenal ulcer doses. Ranitidine has been approved by the FDA at a dosage of 150 mg four times daily for healing erosive esophagitis, and at 150 mg twice daily for relief of GERD symptoms. Nizatidine, the newest of the H_2-receptor antagonists, was the first to be approved by the Food and Drug Administration for both symptom relief and healing of esophagitis at standard duodenal ulcer doses (150 mg twice per day). This approval was the result of two large clinical trials demonstrating its efficacy.[44,45] Recently famotidine has also received approval for symptom relief and healing of erosive esophagitis at standard duodenal ulcer dosage (20 mg twice daily), and at a higher dosage (40 mg twice daily) for severe esophagitis. [46]

In patients refractory to standard doses of H_2-receptor antagonists, it is safe and often effective to increase the dose. Because of the cost of the H_2-receptor antagonists, however, it is usually not reasonable to exceed double the standard dosage. Even with double doses, fewer than 75% of patients will have healing of erosive esophagitis after 12 weeks of therapy.[43]

Few safety differences exist between the H_2-receptor antagonists. Contrary to widely held beliefs, all of the H_2-receptor antagonists occasionally cause central nervous system toxicity with little difference in incidence. Cimetidine and, to a lesser extent, ranitidine bind to the cytochrome P450 system and can increase blood levels of drugs metabolized by this system. This interaction may be important for drugs with a narrow toxic therapeutic ratio such as warfarin, phenytoin, and theophylline.[47]

Table 3. Drugs That Exacerbate Gastroesophageal Reflux Disease

Alpha-adrenergic antagonists
Anticholinergics
Beta-adrenergic agonists
Calcium-channel blockers
Diazepam
Dopamine
Narcotics
Progesterone
Theophylline
Nitrates

Table 4. Pharmacologic Therapy for Gastroesophageal Reflux Disease

Barrier agents
Alginic acid
Antacids
Anti-secretory agents
H_2-receptor antagonists
Cimetidine
Ranitidine
Famotidine
Nizatidine
Omeprazole
Prokinetic agents
Metoclopramide
Bethanechol
Cisapride*
Domperidone*
Sucralfate

* *Not yet available in the United States.*

Because of the current medical-legal climate, I recommend avoiding cimetidine when patients are concurrently taking one of these medications. Nizatidine and famotidine have no significant interaction with the cytochrome P450 system.

Gastroesophageal reflux disease is a chronic illness often requiring long-term therapy. Because of their established safety records, the H_2-receptor antagonists are the agents best suited for continuous long-term therapy. Reduction of H_2-receptor antagonists to half doses at bedtime, in a fashion analogous to that used in maintenance therapy for duodenal ulcer, is seldom successful for GERD. Most GERD patients require at least full split-dose therapy when H_2 antagonists are used for chronic continuous treatment.

In summary, H_2 blockers are effective in relieving heartburn and somewhat effective in healing esophagitis. Because of their excellent safety profile, they are still the primary prescription pharmacologic agents used in the treatment of GERD.

OMEPRAZOLE

Omeprazole, which irreversibly inhibits the hydrogen ion pump on the luminal surface of the parietal cell, is a potent inhibitor of gastric acid. Omeprazole has demonstrated a high rate of endoscopic healing (81%) compared with that of placebo (6%).[48] Endoscopic healing was accompanied by relief of symptoms and histologic healing. Omeprazole is indicated for use in patients with severe erosive esophagitis and also for GERD that is refractory to H_2-receptor antagonists. Short-term therapy is recommended because of a theoretical risk of developing gastric carcinoid tumors with long-term therapy. This concern is based on the observation that rats treated with high-dose omeprazole developed malignant gastric carcinoids.[49] There is currently no evidence, however, that an increase in gastric carcinoid tumors occurs in humans who have been given omeprazole on a long-term basis.

Because of the need for long-term therapy for GERD, the best approach for patients who are candidates for omeprazole therapy is an 8-week course of omeprazole followed by long-term H_2-receptor antagonist therapy. If patients with severe esophagitis receiving long-term H_2 antagonist therapy relapse (as they often do), then intermittent courses of omeprazole are an option. Occasionally, patients with severe GERD prove themselves dependent on omeprazole for control of reflux symptoms or esophagitis. Elderly patients and those in poor health may be candidates for continuous omeprazole therapy. The rationale for continuous therapy should be appropriately documented. Young patients in good general health who prove themselves to be dependent on omeprazole for control of reflux symptoms may be considered for anti-reflux surgery. The efficacy of omeprazole should not be used by patients to avoid adherence to the nonpharmacologic lifestyle changes mentioned above.

PROKINETIC AGENTS

The prokinetic agents include metoclopramide and bethanechol, and the newer compounds cisapride and domperidone. These drugs improve the rate of gastric emptying, enhance esophageal clearance, and increase LES pressure. Bethanechol is actually not a true prokinetic agent since it only increases the amplitude of gastrointestinal contractions and does not improve their coordination. These agents are useful primarily as adjunctive therapy with H_2-receptor antagonists.

The principal limitation of bethanechol and metoclopramide is their potential for toxicity. Bethanechol may produce side effects, such as abdominal discomfort and excessive salivation, and occasionally more serious reactions such as wheezing and bradycardia. Metoclopramide commonly results in drowsiness, jitteriness, or nightmares and may cause anxiety or depression. Occasionally more impressive neurologic reactions may be seen. Dystonic reactions are seen, particularly in young women; elderly patients may experience neurologic reactions resembling parkinsonism. With the availability of omeprazole for GERD refractory to H_2-receptor antagonists, the already limited use of metoclopramide and bethanechol for treating GERD is likely to further decline.

In most patients, the safest and most effective therapeutic progression is from antacids to H_2-receptor antagonists to omeprazole. Metoclopramide, used intermittently or as needed, can be considered in GERD with significant associated nausea or documented impairment of gastric emptying.

Domperidone and cisapride, new prokinetic agents, appear to have better side-effect profiles. Neither of these agents is commercially available in the United States at this time. Limited data are available regarding the efficacy of domperidone. Cisapride demonstrated superiority to placebo in patients with GERD in terms of antacid use, heartburn, symptomatology, and severity of esophagitis.[50] Combination therapy with cisapride and cimetidine produced a significant improvement in daytime and nighttime heartburn when compared with that achieved with cimetidine therapy alone.[51] Endoscopic healing was also superior with the combination regimen. When cisapride becomes available in the United States it will

almost certainly increase the importance of prokinetic agents in the management of GERD.

SUCRALFATE

Sucralfate is being investigated for its potential to enhance mucosal resistance to injury. In one study, a 1-g sucralfate suspension given four times daily produced results comparable to those of cimetidine in patients with reflux esophagitis.[52] Sucralfate appears to bind to the esophageal mucosa and may prevent mucosal injury by acting as a physical barrier. If selected for therapy, the dose should be 1 g dissolved in 1 oz of warm water and taken four times daily. Its role in the treatment of GERD is still being defined.

SURGERY

Surgery is considered for patients with GERD who have persistent symptoms despite aggressive medical therapy or for those who develop serious reflux-related complications. The Nissen fundoplication is the most commonly performed operation, and good results are reported by experienced surgeons. Anti-reflux surgery, however, may be associated with complications such as dysphagia and the gas-bloat syndrome. Therefore, patients must be carefully selected, and preoperative consultation with a gastroenterologist is generally appropriate. Only a very small percentage of those with GERD will need surgery.

LONG-TERM THERAPY

Gastroesophageal reflux disease is a chronic disease. Patients treated with antisecretory agents for GERD and then withdrawn from therapy generally experience recurrence of reflux symptoms. This underscores the importance of patient education regarding nonpharmacologic measures for treatment of GERD. Careful adherence to these nondrug measures may reduce or eliminate the need for drug therapy. In some patients, however, long-term continuous drug therapy is needed. Because of their efficacy and outstanding safety profile, the H_2-receptor antagonists are well suited to this role. At least full doses, given twice daily or more frequently, are generally needed. Metoclopramide, because of its toxicity, is less appropriate for long-term therapy. With rare exception, metoclopramide should be either avoided in the long-term therapy of GERD or used only on an as-needed basis. For severe GERD, intermittent courses of omeprazole interspersed with H_2-receptor antagonist therapy are an acceptable long-term option. The role of surgery in long-term therapy was discussed above.

Summary

Gastroesophageal reflux disease is a common problem with a wide spectrum of clinical severity. A variety of tests are available to evaluate patients with GERD, and physicians must be aware of the type of information that each test can provide. Conservative measures employing nonpharmacologic therapy are appropriate for all patients. Initial pharmacologic therapy usually involves an H_2-receptor antagonist or antacids. In many patients, long-term continuous therapy with an H_2-receptor antagonist given in split doses is needed. Omeprazole is indicated for short-term therapy of severe erosive esophagitis and symptoms refractory to H_2-receptor antagonists.

References

1. Waterfall WE, Craven MA, Allen CJ. Gastroesophageal reflux: clinical presentations, diagnosis and management. Can Med Assoc J 1986; 135:1101–9.
2. Castell DO. Introduction to pathophysiology of gastroesophageal reflux. In: Castell DO, Wu WC, Ott DJ, eds. Gastroesophageal reflux disease: pathogenesis, diagnosis, therapy. Mount Kisco, NY: Futura Publishing Company, 1985:3–9.
3. Ott DJ, Katz PO, Wu WC. Anti-reflux barrier. In: Castell DO, Wu WC, Ott DJ, eds. Gastroesophageal reflux disease: pathogenesis, diagnosis, therapy. Mount Kisco, NY: Futura Publishing Company, 1985:35–54.
4. Castell DO. Medical therapy for reflux esophagitis: 1986 and beyond. Ann Intern Med 1986;104:112–4.
5. Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. Am J Dig Dis 1976; 21:953–6.
6. Weinbeck M, Barnert J. Epidemiology of reflux disease and reflux esophagitis. Scand J Gastroenterol 1989; 24(Suppl 156):7–13.
7. Mold JW, Reed LE, Davis AB, Allen ML, Decktor DL, Robinson M. Prevalence of gastroesophageal reflux in elderly patients in a primary care setting. Am J Gastroenterol 1991; 86:965–70.
8. Graham DY, Smith JL, Patterson DJ. Why do apparently healthy people use antacid tablets? Am J Gastroenterol 1983; 78:257–60.
9. Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 1982; 307:1547–52.
10. Helm JF, Dodds WJ, Pelc LR, Palmer DW, Hogan WT, Teeter BC. Effect of esophageal emptying and saliva on clearance of acid from the esophagus. N Engl J Med 1984; 310:284–8.
11. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology 1986; 91:897–904.
12. Mittal RK, Lange RC, McCallum RW. Identification and mechanism of delayed esophageal acid clearance in subjects with hiatus hernia. Gastroenterology 1987; 92:130–5.
13. McCallum RW, Berkowitz DM, Lerner E. Gastric emptying in patients with gastroesophageal reflux. Gastroenterology 1981; 80: 285–91.
14. Orlando RC. Esophageal epithelial resistance. J Clin Gastroenterol 1986; 8(Suppl 1):12–6.
15. Allen A, Garner A. Mucus and bicarbonate secretion in the stomach and their possible role in mucosal protection. Gut 1980; 21:249–62.
16. Pellegrini CA, DeMeester TR, Wernly JA, Johnson LF, Skinner DB. Alkaline gastroesophageal reflux. Am J Surg 1978; 135:177–84.

17. Orlando RC, Bozymski EM. Heartburn in pernicious anemia—a consequence of bile reflux. New Engl J Med 1973; 289:522–3.
18. Sontag SJ, O'Connell S, Khandelwal S, et al. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology 1990; 99:613–20.
19. David P, Denis P, Nouvet G, Pasquis P, Lefrancois R, Morere P. Lung function and gastroesophageal reflux during chronic bronchitis. Bull Eur Physiopathol Respir 1982; 18:81–6.
20. Davis MV. Relationship between pulmonary disease, hiatal hernia, and gastroesophageal reflux. NY State J Med 1972; 72:935–8.
21. Barish CF, Wu WC, Castell DO. Respiratory complications of gastroesophageal reflux. Arch Intern Med 1985; 145:1882–8.
22. Davies HA, Page Z, Rush EM, Brown AL, Lewis MJ, Petch MC. Oesophageal stimulation lowers exertional angina threshold. Lancet 1985; 2:1011–4.
23. Mellow MH, Simpson AG, Watt L, Schoolmeester L, Haye OL. Esophageal acid perfusion in coronary artery disease. Induction of myocardial ischemia. Gastroenterology 1983; 85:306–12.
24. Katz PO, Dalton CB, Richter JE, Wu WC, Castell DO. Esophageal testing in patients with non-cardiac chest pain or dysphagia: Results of 3 years' experience with 1161 patients. Ann Intern Med 1987; 106:593–7.
25. Goldman H, Antonioli DA. Mucosal biopsy of the esophagus, stomach and duodenum. Hum Pathol 1982; 13:423–48.
26. Saco LS, Orlando RC, Levinson SL, Bozymski EM, Jones JD, Frakes JT. Double-blind controlled trial of bethanechol and antacid versus placebo and antacid in the treatment of erosive esophagitis. Gastroenterology 1982; 82:1369–73.
27. Lieberman DA. Medical therapy for chronic reflux esophagitis. Arch Intern Med 1987; 147:1717–20.
28. DeMeester TR, Sullivan GC, Bermudez G, Midell AI, Cimochowski GE, O'Drobinak J. Esophageal function in patients with angina-type chest pain and normal coronary angiograms. Ann Surg 1982; 196:488–98.
29. Peters LJ, Maas LC, Petty DA, et al. Spontaneous non-cardiac chest pain: evaluation by 24-hr ambulatory motility and pH monitoring. Gastroenterology 1988; 94:878–86.
30. Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. Gastroenterology 1986; 91:845–52.
31. Cannon RO III, Epstein SE. Microvascular angina as a cause of chest pain with angiographically normal coronary arteries. Am J Cardiol 1988; 61:1338–43.
32. Ott DJ, Gefland DW, Wu WC. Reflux esophagitis; radiographic and endoscopic correlation. Radiology 1979; 130:583–8.
33. Linsman JF. Gastroesophageal reflux elicited while drinking water (water-siphonage test): its clinical correlation with pyrosis. AJR 1964; 94:325–32.
34. Velasco N, Pope CE, Gannan RM, Roberts P, Hill LD. Measurement of esophageal reflux by scintigraphy. Dig Dis Sci 1984; 29:977–82.
35. Hoffman GC, Vansant JH. The gastroesophageal scintiscan; comparison of methods to demonstrate gastroesophageal reflux. Arch Surg 1979; 114:727–8.
36. Menin RA, Malmud LS, Petersen RP, Maier WP, Fisher RS. Gastroesophageal scintigraphy to assess the severity of gastroesophageal reflux disease. Ann Surg 1980; 191:66–71.
37. Schindlbeck NE, Heinrich C, Dendorfer A, Pace F, Müller-Lissner SA. Influence of smoking and esophageal intubation on esophageal pH-metry. Gastroenterology 1987; 92:1994–7.
38. Johnson LF, DeMeester TR. Evaluation of elevation of the head of the bed, bethanechol, and antacid foam tablets on gastroesophageal reflux. Dig Dis Sci 1981; 26:673–80.
39. Harvey RF, Hadley N, Gill TR, et al. Effects of sleeping with the bed-head raised and of ranitidine in patients with severe peptic oesophagitis. Lancet 1987; 2:1200–3.
40. Graham DY, Lanza F, Dorsch ER. Symptomatic reflux esophagitis: a double-blind controlled comparison of antacids and alginate. Curr Ther Res 1977; 22:653–8.
41. Feldman M, Burton ME. Histamine$_2$-receptor antagonists: standard therapy for acid-peptic diseases (second of two parts). N Engl J Med 1990; 323:1749–55.
42. Tytgat GNJ, Nicolai JJ, Reman FC. Efficacy of different doses of cimetidine in the treatment of reflux esophagitis. Gastroenterology 1990; 99:629–34.
43. Palmer RH, Frank WO, Rockhold FW, Wetherington JD, Young MD. Cimetidine 800 mg twice daily for healing erosions and ulcers in gastroesophageal reflux disease. J Clin Gastroenterol 1990; 12(Suppl 2):S29–S34.
44. Cloud ML, Offen WW, the Nizatidine Gastroesophageal Reflux Disease Study Group. Nizatidine versus placebo in gastroesophageal reflux disease: a 6-week, multicenter, randomized, double-blind study. Dig Dis Sci 1991 (in press).
45. Cloud ML, Offen WW, Robinson M. Nizatidine versus placebo in gastroesophageal reflux disease: a 12-week, multicenter, randomized, double-blind study. Am J Gastroenterol 1991; 86:1735–42.
46. Sabesin SM, Schaffner JA, Bradstreet DJ, Walton-Bowen K, Humphries TJ. Famotidine-symptomatic relief and healing in patients with reflux esophagitis (RE): results of a US multicenter trial [abstract]. Gastroenterology 1990; 98(suppl):A117.
47. Schunack W. Pharmacology of H_2-receptor antagonists: an overview. J Intern Med Res 1989; 17(Suppl 1):9A–16A.
48. Hetzel DJ, Dent J, Reed WD, et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 1988; 95:903–12.
49. Ekman L, Hansson E, Havu N, Carlsson E, Lundberg G. Toxicological studies on omeprazole. Scand J Gastroenterol 1985; 20(Suppl 108):53–69.
50. Dodds W, Champion M, Orr W, et al. Oral cisapride in GERD: a double-blind placebo-controlled, multicenter trial [abstract]. Gastroenterology 1989; 96:A126.
51. Galmiche P, Brandstätter G, Evreux M, et al. Combined therapy with cisapride and cimetidine in severe reflux oesophagitis: a double-blind controlled trial. Gut 1988; 29:675–81.
52. Hameeteman W, v. d. Boomgaard DM, Dekker W, Schrijver M, Wesdorp IC, Tytgat GN. Sucralfate versus cimetidine in reflux esophagitis. A single-blind multicenter study. J Clin Gastroenterol 1987; 9:390–4.