CLINICAL PRACTICE

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Gastroesophageal Reflux Disease

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 55-year-old woman presents with symptoms of heartburn and an 8-year history of a sour, bitter taste in her mouth. Her symptoms have increased in frequency and severity over the past year and now occur daily, typically after meals and at nighttime. She has no dysphagia, odynophagia, weight loss, anorexia, or upper gastrointestinal bleeding. Her medical history includes hypertension (treated with lisinopril) and obesity; the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) is 31. She smoked a half pack of cigarettes daily for 20 years but stopped 15 years ago. She eats late dinners that usually include wine. She has tried antacids and famotidine (at a dose of 20 mg twice daily) for a few months with minimal effect on the symptoms. How would you manage this case?

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This article was updated on September 29, 2022, at NEJM.org.

N Engl J Med 2022;387:1207-16.
DOI: 10.1056/NEJMcp2114026

CME at NEJM.org

THE CLINICAL PROBLEM

Gastroesophageal reflux disease (GERD) is a condition in which the reflux of stomach contents causes troublesome symptoms and complications.[1] In population-based studies, mild symptoms that occurred at least 2 days a week and moderate-to-severe symptoms that occurred at least 1 day a week were often considered troublesome by patients.[1-3] Although heartburn and regurgitation are considered typical, a broad range of manifestations have been associated with GERD,[1,4] including chronic cough, a globus sensation, wheezing, posterior laryngitis, dental erosions, and idiopathic pulmonary fibrosis (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[5]

The estimated prevalence of GERD is 13.3% of the population worldwide and 15.4% in North America, and costs related to GERD in the United States are estimated at $10 billion annually.[6,7] Risk factors for GERD include an age of 50 years or older, current smoking, use of nonsteroidal antiinflammatory drugs, obesity (BMI >30), low socioeconomic status, and female sex.[6,7] In a U.S. study that involved participants who completed a national survey on gastrointestinal symptoms, 44.1% of the participants reported a history of GERD symptoms, 30.9% reported having had symptoms in the past week, and 54.1% had persistent symptoms despite daily use of proton-pump inhibitors (PPIs).[8]

The phenotypic presentations of GERD include nonerosive reflux disease (in 60 to 70% of patients), erosive esophagitis (in 30%), and Barrett's esophagus (in 5 to 12%).[9] The focus of the present article is on the first two conditions. Nonerosive reflux disease is associated with abnormal exposure to esophageal acid in the absence of findings of mucosal breaks on endoscopy,[10-13] and erosive esophagitis is characterized by breaks in the esophageal mucosa (Fig. 1).[1] The natural course of GERD

KEY CLINICAL POINTS

GASTROESOPHAGEAL REFLUX DISEASE

- Patients with heartburn and symptoms such as dysphagia, odynophagia, weight loss, anorexia, gastrointestinal bleeding, and vomiting (known as "alarm symptoms") should undergo an upper endoscopy.
- Patients without documented gastroesophageal reflux disease (GERD) who have heartburn that is refractory to treatment and a normal endoscopy should undergo reflux testing while not receiving treatment, whereas patients with documented GERD and with heartburn that is refractory to treatment should undergo impedance–pH testing while receiving treatment.
- Lifestyle modifications are a key part of the medical management of GERD; currently, proton-pump inhibitors (PPIs) are the most effective medications.
- In patients with uncomplicated GERD that is responsive to 8 weeks of PPI therapy, discontinuation of therapy is an appropriate consideration.
- Patients should take the lowest dose of PPI that controls their symptoms, and the need for long-term PPI treatment should be periodically evaluated.
- Other interventions for GERD include endoscopic treatment and surgery (fundoplication or, in patients with a body-mass index [the weight in kilograms divided by the square of the height in meters] of >35, gastric bypass).

remains incompletely understood, but evidence suggests that there is limited progression (from nonerosive reflux disease to erosive esophagitis, and from erosive esophagitis to Barrett's esophagus) and regression (from erosive esophagitis to nonerosive reflux disease) over time.[9,14,15]

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

A diagnosis of GERD in practice is commonly made on the basis of the presence of characteristic symptoms, particularly heartburn and acid regurgitation. However, these symptoms may be present in other disorders (e.g., supragastric belching, vomiting syndromes, gastric and esophageal motility disorders, esophageal mucosal disorders, and functional esophageal disorders).[16] Functional heartburn (defined as burning retrosternal discomfort or pain in the absence of GERD) and reflux hypersensitivity (defined as heartburn and chest pain with symptoms triggered by reflux events but with normal esophageal mucosa and acid exposure) account for approximately 50% of patients who present with heartburn and a normal endoscopy.[10]

There is no difference in heartburn severity among GERD phenotypes or between GERD and functional esophageal disorders such as functional heartburn.[17] Although patients with functional heartburn do not have a response to antireflux treatment, those with reflux hypersensitivity have some, albeit limited, response to antireflux treatment.

Patients should be queried about the frequency, severity, and duration of symptoms; specific triggers (dietary or nondietary); timing of symptoms (daytime, nighttime, or both); and the presence of associated symptoms such as dysphagia, odynophagia, weight loss, anorexia, vomiting, and upper gastrointestinal bleeding (known as "alarm symptoms"). In the absence of alarm symptoms, empirical antireflux treatment for 2 months is a reasonable initial diagnostic and therapeutic approach. Another option in patients with typical symptoms is the PPI test, which is a short course (1 to 2 weeks) of high-dose PPI taken twice daily.[18] A recent meta-analysis of studies that evaluated the PPI test showed a pooled sensitivity of 79% (95% confidence interval [CI], 72 to 84) and a pooled specificity of 45% (95% CI, 40 to 49) for GERD in patients who had undergone endoscopy and, if an endoscopy was negative, had subsequently undergone pH testing.[19]

OTHER TESTING

Upper endoscopy is generally limited to patients with GERD who report alarm symptoms, who have no response or an incomplete response to treatment or have recurrent GERD after a successful 8-week course of empirical therapy, who are candidates for antireflux or bariatric surgery, or who are at increased risk for Barrett's esophagus (i.e., have chronic [≥5 years] GERD symptoms and three or more of the following risk factors: male sex, an age of >50 years, White race, tobacco smoking, obesity, or a family his-

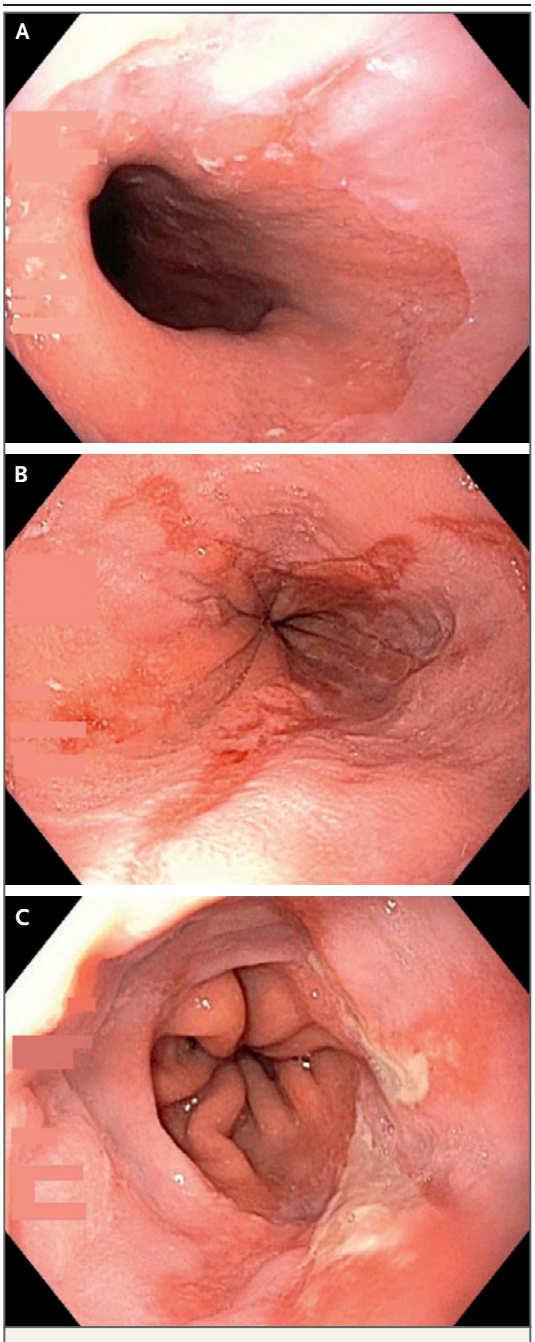

Figure 1. Erosive Esophagitis.

Shown are a single esophageal mucosal break (Panel A), several esophageal mucosal breaks (Panel B), and esophageal mucosal breaks and ulceration (Panel C).

tory of Barrett's esophagus or esophageal adenocarcinoma).[20] Upper endoscopy is highly specific for GERD but has low sensitivity because most patients have a normal-appearing esophagus on upper endoscopy.[21] The severity of erosive esophagitis is classified with the use of the Los Angeles classification system (Table S2).[22] Advanced technologies (e.g., high-magnification endoscopy and narrow-band imaging) may increase the diagnostic yield of upper endoscopy in GERD but are not routinely used.[23] Esophageal biopsy is primarily performed to rule out other esophageal mucosal disorders, such as eosinophilic esophagitis.

Reflux testing allows for assessment of the degree, height, and type (acidic or weakly acidic) of gastroesophageal reflux and the correlation between symptoms and reflux events.[24] Ambulatory 24-hour pH monitoring[25] is highly sensitive (79 to 96%) and specific (85 to 100%) in patients with erosive esophagitis but less so in patients with nonerosive reflux disease. During reflux testing, a pH catheter is introduced into the nose and placed 5 cm above the proximal margin of the lower esophageal sphincter. The ambulatory 24-hour esophageal impedance–pH monitoring system includes sensors that can detect impedance changes in response to liquid reflux or belched air. This technique has a sensitivity of approximately 90%[26] and can also identify reflux with lower acidity (pH level, >4). In addition, impedance–pH testing can characterize reflux composition as liquid, gas, or mixed. An alternative approach is the wireless pH capsule, which provides an extended recording time of up to 96 hours, which overcomes the day-to-day variability observed when intraesophageal changes in pH level are recorded. The capsule is introduced orally by means of a delivery device and attached to the distal esophagus. A sensor records pH changes and transmits the data to a recording device worn by the patient. This technique has fewer adverse effects in patients than catheter-based pH monitoring. Prolonged recording of the pH level increases the likelihood of identifying abnormal acid reflux, especially in patients with infrequent symptoms.[24]

Guidelines from the American College of Gastroenterology recommend ambulatory reflux monitoring as preferential to both patient-reported GERD questionnaires and assessment of response to PPI therapy (albeit based on very-low-quality evidence) for use in making a conclusive diagnosis of GERD in patients with suggestive symptoms.[24] Appropriate candidates for reflux monitoring include patients who have GERD symptoms despite twice-daily PPI treat-

Table 1. Lifestyle Measures for Patients with Gastroesophageal Reflux Disease (GERD).

Avoid eating within 3 hr before bedtime; sleep on the right side (use special positional pillows) and observe good sleep hygiene.
Avoid alcohol, caffeine, carbonated beverages, and smoking.
Lose weight (any amount).
Elevate the head of the bed 15 to 20 cm (6 to 8 in) or use a bed wedge and incline mattress.
Keep meal sizes small. Consider four or five small meals instead of three large meals during the day.
Avoid spicy foods and high-fat meals. Avoid lying down or napping immediately after a meal.
Identify dietary triggers and minimize common precipitants (e.g., peppermint, onion, fresh citrus juices, tomato paste, and chocolate).
Avoid tight-fitting garments.
Avoid bending over.
Chew gum to promote salivation, which neutralizes acid reflux.
Avoid medications that relax the lower esophageal sphincter (e.g., benzodiazepines, theophylline, calcium-channel blockers, tricyclic antidepressants, anticholinergics, progesterone, and sildenafil).
Engage in stress-reduction techniques.

ment and normal findings on endoscopy. For patients without previous evidence of GERD, any one of the aforementioned reflux tests performed while the patient is not receiving PPI treatment is recommended; the wireless pH capsule is preferred, if available.[27] For patients with previously documented GERD, impedance–pH testing while the patient is receiving PPI treatment is recommended. Reflux testing is also indicated in symptomatic patients with normal findings on endoscopy who are candidates for antireflux surgery or endoscopic treatment, patients with relapse of symptoms after having undergone endoscopic or surgical intervention for GERD, patients with new reflux symptoms after having undergone bariatric surgery, and patients with GERD complications for whom confirmation of acid control would be beneficial.

Esophageal manometry has no role in the diagnosis of GERD but is used to guide the placement of reflux-testing probes, to rule out esophageal motor disorders in patients with GERD who have dysphagia or chest pain, and to assess esophageal function before antireflux surgery. The double-contrast barium esophagram has low sensitivity and specificity for GERD and is not recommended.[28]

TREATMENT

Treatment of patients with GERD includes lifestyle modifications alone or in combination with pharmacologic, endoscopic, or surgical interventions, depending on the severity of the disease.

LIFESTYLE CHANGES

Patients should be counseled about common reflux precipitants and encouraged to avoid lifestyle and dietary habits that exacerbate their symptoms (Table 1). The evidence is strongest for the benefits of weight loss, elevation of the head of the bed, and the avoidance of food for at least 3 hours before bedtime.[29,30] In a prospective study, women who adhered to several antireflux lifestyle approaches (maintaining normal weight; never smoking; engaging in moderate or greater physical activity; avoiding more than 2 cups of coffee, tea, or soda daily; and eating a prudent diet) had only half the risk of GERD symptoms as women who adhered to none of the lifestyle approaches.[31]

PHARMACOLOGIC

Pharmacologic treatment for GERD includes medications taken as needed or daily. The medications that are most frequently used are antacids, histamine$_2$ blockers, and PPIs; other medications are used less frequently (Table 2).

Antacids

Antacids have an immediate and very short-term effect. Alginate-based formulations include a gelatinous polysaccharide extract from brown algae and sodium bicarbonate or potassium bicarbonate. In the presence of gastric acid, alginates precipitate into a gel and create a foamy raft that displaces the postprandial acid pocket. Patients with breakthrough symptoms can take antacids and alginates either on demand or in addition to daily PPI therapy. A meta-analysis showed that the relative percentage of patients who reported positive results was 11% higher with antacids and 60% higher with alginates than with placebo.[32] Alginates have been shown to be more effective than antacids in controlling postprandial exposure to esophageal acid.[33]

Mucosal Protectants

Sucralfate is a topical mucosal protective agent that is superior to placebo for symptom control,

healing of erosive esophagitis, and prevention of symptom recurrence.[34] The level of symptom control provided by sucralfate has been reported to be similar to that of alginate plus antacids and histamine$_2$-receptor antagonists.[25,35]

Histamine$_2$-Receptor Antagonists

Histamine$_2$-receptor antagonists are used on demand for treatment of postprandial heartburn or daily for mild-to-moderate GERD symptoms or low-grade erosive esophagitis and as a bedtime add-on for breakthrough symptoms in patients who have not had a response to PPI therapy. The available histamine$_2$-receptor antagonists are similar in their antisecretory and clinical effects. Daily use of histamine$_2$-receptor antagonists may result in tachyphylaxis that cannot be overcome by higher doses and that persists for several days after drug discontinuation.[36]

PPIs

PPIs are the most effective medication for GERD symptom relief, healing of erosive esophagitis, and prevention of disease relapse and complications. In a meta-analysis of randomized, controlled trials of antireflux therapies in patients with erosive esophagitis, the percentage of patients with esophageal healing within 12 weeks after starting treatment was 51.9% with histamine$_2$-receptor antagonists as compared with 83.6% with PPIs, and healing was more rapid with PPIs. Moreover, PPIs were superior to histamine$_2$-receptor antagonists in relieving symptoms (in 77.4% vs. 47.6% of patients), maintaining symptom relief, and preventing complications.[37]

The seven currently available PPIs differ in pharmacokinetics and pharmacodynamics but have similar clinical effects. PPIs should be taken 30 to 60 minutes before eating, preferably in the morning, and used regularly to achieve a maximum clinical effect.

PPIs are the first-line treatment in patients with moderate-to-severe erosive esophagitis (Los Angeles classification grade C or D, with grades ranging from A to D and higher grades indicating erosion of a greater area of the esophagus), complications of GERD (esophageal ulcer or stricture), Barrett's esophagus, and extraesophageal manifestations. Recommendations for the use of PPI therapy are summarized in Table 3.

Long-term treatment with PPIs has been associated in large observational studies with a variety of adverse events, including *Clostridium difficile* infection, bacterial gastroenteritis, bacterial overgrowth in the small intestine, pneumonia, chronic kidney disease, bone fracture, dementia, and myocardial infarction. However, confounding remains possible, and these studies cannot be used to determine causality. In a randomized, double-blind, placebo-controlled trial involving 17,598 participants, the administration of pantoprazole at a dose of 40 mg daily for 3 years was associated with a significant but small increase in the incidence of enteric infections (1.4% with pantoprazole vs. 1% with placebo) but no other adverse events.[39] To be prudent, PPIs should be used at the lowest dose that controls the patient's symptoms and esophageal inflammation, and the appropriateness of treatment should be periodically reevaluated (Table 3).[38]

ENDOSCOPIC TREATMENT

Endoscopic techniques are alternative approaches in the treatment of patients with GERD; they work by augmenting the antireflux barrier. Among these techniques are esophageal radiofrequency energy delivery (Stretta), which increases the thickness of the esophagogastric-junction musculature, and transoral incisionless fundoplication, which forms a partial wrap around the lower esophagus.[40] These procedures are options for patients who are not candidates for (or do not want to undergo) antireflux surgery or long-term medical treatment and have nonerosive reflux disease or low-grade erosive esophagitis, a hiatal hernia smaller than 3 cm, and have had a complete or partial response to treatment with PPIs. The experience level of the endoscopist and careful patient selection are critical to the success of these procedures. Concerns have been raised about the limited effect of endoscopic procedures on objective clinical end points (e.g., healing of erosive esophagitis and normalization of esophageal acid exposure).[41]

SURGICAL TREATMENT

Antireflux surgery and hiatal hernia repair (if a hernia is present) mechanically augment the antireflux barrier. Candidates for these procedures include persons who choose not to take PPIs or have had adverse effects with PPI therapy and those who have severe regurgitation, large hiatal hernia (>5 cm), persistent objective GERD despite taking PPIs twice daily, or symptoms

Table 2. Pharmacologic Agents for GERD.*

Class and Drug	Dose	Adverse Effects	Comment
Antacid			As needed for episodic heartburn; taken alone or in combination with a PPI
Aluminum and magnesium hydroxide, calcium carbonate, sodium citrate, sodium bicarbonate	Varied	Diarrhea, constipation, nausea, vomiting	
Alginate compounds	2 to 4 tablets administered orally four times daily	Constipation, diarrhea	
Mucosal protectant			Taken alone or in combination with a PPI
Sucralfate†	1 g administered orally two to four times daily	Constipation, diarrhea, nausea, vomiting, indigestion, gas	
Histamine$_2$-receptor antagonist			Taken alone for mild-to-moderate GERD and in combination with a PPI in refractory GERD
Cimetidine	400 mg administered orally twice daily	Headache, drowsiness, nausea	
Famotidine	20 mg administered orally twice daily	Constipation, dizziness, headache	
Nizatidine	150 mg administered orally twice daily	Drowsiness	
PPI‡			Most effective treatment; in patients with refractory GERD, there is no value of taking PPI more than twice daily§
Dexlansoprazole	30 to 60 mg administered orally once daily	Diarrhea, headache	
Esomeprazole	40 mg administered orally once daily¶	Bloating, constipation, nausea	
Lansoprazole	30 mg administered orally once daily¶	Diarrhea, nausea	
Omeprazole	20 mg administered orally once daily¶	Headache, nausea, vomiting	
Pantoprazole	40 mg administered orally once daily¶	Dizziness, headache, nausea	
Rabeprazole	20 mg administered orally once daily¶	Constipation, headache, gas	
Immediate-release omeprazole	20 mg administered orally once daily¶	Headache, nausea, diarrhea, gas	
TLESR reducer			May be used in combination with a PPI in patients with refractory GERD§
Baclofen‖	10 to 20 mg administered orally three times daily	Confusion, somnolence, drowsiness, dizziness, insomnia	
Prokinetic agent			Generally limited to patients who also have hypocontractile esophagus, gastroparesis, or both

Table 2. (Continued.)

Class and Drug	Dose	Adverse Effects	Comment
Metoclopramide	5–10 mg administered orally every 6 to 8 hr	Drowsiness, agitation, insomnia, dizziness, fatigue, uncontrolled muscle movements	

* PPI denotes proton-pump inhibitors, and TLESR transient lower esophageal sphincter relaxation.
† American College of Gastroenterology guidelines suggest that, given limited data, sucralfate be used only for treatment of GERD-related symptoms during pregnancy.[20,26]
‡ Listed are adverse effects that have been associated predominantly with short-term treatment. Potential long-term adverse effects are described in the text.
§ Refractory GERD is defined as GERD that is partially responsive or nonresponsive to a stable double dose of PPI administered over a treatment period of at least 8 weeks in patients who had previous objective evidence of GERD.
¶ Administration twice daily has not been approved by the Food and Drug Administration. However, a double dose is commonly used in clinical practice in patients who did not have a response to once-daily treatment, and the definition of refractory GERD requires a lack of alleviation of symptoms with a twice-daily dose.
‖ Use of baclofen for the treatment of GERD has not been approved by the Food and Drug Administration.

Table 3. Recommendations for Use of PPIs.*

PPIs should be taken 30 to 60 min before a meal, preferably in the morning.
In patients who do not have a response when receiving PPI once daily, therapy should be optimized before doubling the dose:
Confirm daily adherence to PPI regimen and correct timing of ingestion.
If appropriate adherence and timing are confirmed, try splitting the standard dose, giving half before breakfast and half before dinner.
Reemphasize lifestyle recommendations.
Patients with uncomplicated GERD who have a response to short-term PPI therapy should attempt to stop therapy; if symptoms recur, therapy should be reinitiated at the lowest dose that controls the symptoms.†
Long-term PPI therapy should be considered in patients with Barrett's esophagus and symptomatic GERD.
Dose levels that are used for long-term PPI therapy should be periodically evaluated so that the lowest effective PPI dose can be prescribed.
Long-term PPI use is not an indication for routine use of probiotics to prevent infections (e.g., gastroenteritis, *Clostridium difficile* colitis, and pneumonia); increased intake of calcium, vitamin B_{12}, or magnesium beyond the recommended dietary allowance (with the goal of preventing osteoporosis, anemia, or magnesium deficiency); or routine monitoring of bone mineral density or levels of serum creatinine, magnesium, or vitamin B_{12}.
Patients with erosive esophagitis or GERD-related complications (e.g., grade C or D erosive esophagitis, peptic stricture, or esophageal ulcer) should receive long-term PPI therapy for healing, symptom control, and prevention of recurrence.
In patients with nonerosive reflux disease and episodic heartburn, on-demand or intermittent therapy with a PPI can serve as an alternative to daily PPI treatment.

* Recommendations for long-term use of PPIs were adapted from best-practice advice from the American Gastroenterological Association.[38]
† In a patient whose symptoms recur with PPI tapering, an upper endoscopy should be performed if not already done; if findings on endoscopy are normal, reflux testing should be considered to distinguish GERD from functional or other esophageal disorders before committing the patient to long-term PPI use.

caused by weakly acidic reflux. Before undergoing antireflux surgery, patients should undergo an upper endoscopy and, if the endoscopy findings are normal, should undergo reflux testing; esophageal manometry and, possibly, a barium-swallow examination should be performed.

A recent systematic review that included both randomized, controlled trials and observational studies concluded that patients who underwent surgery had better short-term quality of life but no significant improvement in short-term or long-term symptom control as compared with medi-

cally treated patients.[42] However, the available evidence was noted to be at a high risk for bias. In a small, randomized trial involving patients with GERD and refractory heartburn, the percentage of patients who had a successful outcome (≥50% improvement in scores on GERD-related quality-of-life assessments at 1 year) was significantly higher with antireflux surgery (67%) than with medication (28%).[43] More than 25% of patients who undergo antireflux surgery receive PPI treatment during long-term follow-up (>5 years).[44] Complications of surgery include gas-bloat syndrome (an inability to properly vent the stomach, resulting in a bloating sensation), dysphagia, diarrhea, and relapse of heartburn. Preoperative predictors of a successful antireflux surgery outcome include abnormal esophageal exposure to acid, erosive esophagitis, typical GERD symptoms, the response to antireflux medications, hiatal hernia, absence of esophageal outflow obstruction, and a highly experienced surgeon.[44]

The magnetic sphincter augmentation system (LINX) is a small, flexible band of titanium beads with a magnetic core that is placed, by means of a laparoscope, around the end of the esophagus to augment the antireflux barrier. Its effects on acid regurgitation have been reported to be superior to PPIs.[45] Long-term information about the efficacy and safety of magnetic sphincter augmentation remains limited.

Roux-en-Y gastric bypass is the preferred surgical intervention for patients with class II obesity (BMI >35) and GERD, owing to a higher incidence of failure after surgical fundoplication in this patient population. The effect of surgery on the reduction of GERD symptoms and signs is related to the resultant weight loss.

AREAS OF UNCERTAINTY

The appropriate approach to managing GERD without alarm symptoms is a controversial issue. Although the initiation of empiric antireflux treatment is common, some experts propose that patients first undergo phenotyping by means of diagnostic tests so that therapy can be individualized. Whether treatment should be with a step-up approach (starting with the least potent antireflux medication and escalating treatment on the basis of the patient's response) or a step-down approach (starting with the most potent medication and deescalating therapy if the patient has a response) is unclear. Clinical criteria for endoscopic treatment or referral to antireflux surgery remain poorly defined. Establishing the true risks of long-term PPI treatment requires further study. More data are needed from randomized, controlled trials to determine the value of on-demand or intermittent treatment as compared with continued daily PPI treatment in a subset of patients with GERD; to compare outcomes of medical, endoscopic, and surgical therapies for GERD; and to guide the treatment of patients with refractory GERD or extraesophageal manifestations of GERD.

GUIDELINES

Guidelines regarding GERD have been published nationally and internationally, including U.S. guidelines for the diagnosis and overall management of GERD and the roles of endoscopy and surgical management.[26,44,46,47] Recommendations in this article are generally consistent with U.S. guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has symptoms consistent with GERD. The patient should first undergo an upper endoscopy because she meets the recommended screening criteria for possible Barrett's esophagus. If low-grade erosive esophagitis or Barrett's esophagus is observed, once-daily PPI taken 30 minutes before breakfast is recommended. Histamine$_2$-receptor antagonists should not be considered in this patient because her symptoms did not abate with a previous course of famotidine. If advanced erosive esophagitis or an esophageal ulcer is present, PPI taken twice daily (before breakfast and before dinner) for 2 months is recommended, along with a follow-up endoscopy to rule out Barrett's esophagus. If findings on the endoscopy are normal, I would start the patient on a standard dose of PPI for 2 months and reassess for symptom response (recognizing that other esophageal disorders, such as functional heartburn, remain on the differential diagnosis). The patient should also be counseled regarding

weight loss, smoking cessation, avoidance of late-night meals and alcohol consumption, and stress reduction. If the patient chooses to forego treatment with medication, endoscopic treatment or antireflux surgery could be considered; however, if endoscopy was normal, these nonmedical interventions could be considered only if she is found to have abnormal esophageal exposure to acid while she is not taking antireflux medication.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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