

Treatment of Gastroesophageal Reflux Disease

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Therapeutic modalities for gastroesophageal reflux disease (GERD) continue to evolve despite the introduction of proton pump inhibitors (PPIs), the most successful antireflux class of drugs. On-demand modalities such as antacids and alginates as well as histamine type-2 receptor antagonists continue to be popular with GERD patients who seek temporary relief of symptoms. The PPIs have revolutionized the treatment of patients with severe erosive esophagitis, complications of GERD, and atypical or extraesophageal manifestations of GERD. Antireflux surgery, commonly performed via laparoscopy, remains popular among patients who do not wish to take medications long term. In addition, the recent introduction of various endoscopic techniques offers GERD patients a long-term solution with less morbidity and lower cost than antireflux surgery. *Clinical Cornerstone*® Vol. 5, No. 4. Copyright © 2003 Excerpta Medica, Inc.

The diverse clinical manifestations of gastroesophageal reflux disease (GERD) result from the reflux of gastric and/or duodenal content into the esophagus. Patients may report typical symptoms such as heartburn and acid regurgitation or atypical/extraesophageal symptoms such as chest pain, hoarseness, chronic cough, and asthma (1,2).

GERD has been traditionally approached as a spectrum of disease in which nonerosive reflux disease (NERD) is considered the mild form and erosive esophagitis, as well as GERD complications, the severe form (1–3). This prevailing concept has led investigators to focus almost exclusively on therapeutic studies of patients with erosive esophagitis. The assumption is that whatever applies to patients with esophageal mucosal injury will definitely apply to those without esophageal

mucosal involvement. A new paradigm suggests that GERD has 3 unique phenotypic presentations: NERD, erosive esophagitis, and Barrett's esophagus. This concept shifts our traditional focus on esophageal mucosal injury to GERD symptomatology (2,4). A total of 44% of the US population experience GERD symptoms at least once a month and approximately 20% at least once a week (1,5). Consequently, rapid and complete symptom relief has become the immediate goal of physicians and the desired outcome of patients. Because GERD is a chronic disease with a high relapse rate, long-term maintenance treatment is warranted in most, if not all, patients. This updated review describes the ever-growing therapeutic modalities for GERD and discusses different GERD-related disorders (Table I).

TABLE I. THERAPEUTIC OPTIONS FOR GERD

Medical	
Antacids and alginates Sucralfate (Carafate®)	1 g po qid
Promotility Agents Metoclopramide (Reglan®) Tegaserod (Zelnorm®)	5–10 mg po q6–8h 6 mg po bid
Histamine Type-2 Receptor Antagonists Cimetidine (Tagamet®) Ranitidine (Zantac®) Famotidine (Pepcid®) Nizatidine (Axid®)	400 mg po bid (OTC – 200 mg) 150 mg po bid (OTC – 75 mg) 20 mg po bid (OTC – 10 mg) 150 mg po bid
Proton Pump Inhibitors Omeprazole (Prilosec®) Rabeprazole (Aciphex®) Pantoprazole (Protonix®) Lansoprazole (Prevacid®) Esomeprazole (Nexium®)	20 mg po qd (OTC – 20 mg) 20 mg po qd 40 mg po qd 30 mg po qd 40 mg po qd
Transient Lower Esophageal Sphincter Relaxation Reducers Baclofen	10 mg – 20 mg po tid
Surgical	
Laparoscopic Open	
Endoscopic	
Endoscopic suturing Radiofrequency energy procedure Submucosal bulking	

GERD = gastroesophageal reflux disease; OTC = over the counter.

THERAPEUTIC MODALITIES

Lifestyle Modifications

Lifestyle modifications include weight loss, smoking cessation, avoidance of postprandial recumbency for a period of 3 hours, elevation of the head of the bed, avoidance of tight-fitting garments, and avoidance of food and drink that exacerbate GERD symptoms (Table II). Although of limited value as sole treatment of GERD, lifestyle modifications commonly serve as adjunct to medical therapy (6,7). For many patients, lifestyle modifications

may be difficult to follow long term and may adversely affect quality of life.

Antacids and Alginates

Antacids are basic compounds composed of different combinations of acid-neutralizing agents such as aluminum and magnesium hydroxide, calcium carbonate, sodium citrate, and sodium bicarbonate. Considered the standard medical treatment for peptic ulcer disease for more than a century, antacids have been the most widely used remedy for GERD symptoms (8,9). They provide transient symptom relief but do not contribute to the healing or prevention of GERD complications (8,10). Nevertheless, antacids are a very popular on-demand treatment for patients seeking rapid symptom relief.

Alginates create a foamy raft above the gastric content. With both alginic acid and antacid present, the raft acts as a barrier between the gastric content and the esophagus while the antacid serves to neutralize the gastric content. This mechanism is thought to protect the esophageal epitheli-

KEY POINT

Although lifestyle modifications are commonly recommended to patients with GERD, few data support their efficacy.

TABLE II. LIFESTYLE MODIFICATIONS FOR THE TREATMENT OF GERD

- Avoid medications that exacerbate gastroesophageal reflux: anticholinergics, tricyclics and other antidepressants, calcium channel blockers, benzodiazepines.
- Avoid smoking or drinking alcohol.
- Avoid eating large fatty meals, spicy food, chocolate, peppermint, coffee, onions, and citrus juices.
- Avoid carbonated beverages.
- Reduce weight (if overweight).
- Avoid tight-fitting garments.
- Elevate the head of the bed.
- Avoid assuming a supine position up to 3 hours after a meal.

GERD = gastroesophageal reflux disease.

um and to alleviate GERD symptoms. However, as with antacids alone, alginates provide rapid, transient relief of symptoms but play no role in healing erosive esophagitis or preventing symptom relapse or GERD complications.

Sucralfate

Sucralfate is composed of basic aluminum salt of sucrose octasulphate and provides mucosal protection by creating an adherent complex with the proteinaceous exudates of the denuded esophageal mucosa. It also has pepsin-binding and bile acid-binding capacities that enhance tissue resistance. The release of sucrose sulfate, which coats the damaged esophageal mucosa during reflux, is dependent on the acidity of the stomach; therefore, its effectiveness will depend on both the stomach's acidity and the simultaneous presence of the drug in the esophagus. Sucralfate has lost favor as an antireflux treatment because it has limited efficacy and requires multiple (qid) dosing.

Promotility/Prokinetic Drugs

Motility-modifying drugs may affect gastroesophageal reflux (GER) by increasing lower esophageal sphincter (LES) pressure, improving esophageal peristalsis and thus acid clearance, and facilitating gastric emptying.

*Metoclopramide** is a dopamine antagonist and a cholinomimetic that crosses the blood–brain

barrier and neutralizes the inhibitory effect of dopamine in the central nervous system and on the gastrointestinal (GI) smooth muscle. Its therapeutic efficacy in GERD, however, is limited because of multiple adverse effects of neurological or psychotropic nature that include lethargy, mental status changes, and extrapyramidal abnormalities (11). Elderly subjects are particularly vulnerable to these effects, and some (extrapyramidal) effects are not reversible after discontinuation of the drug. Additionally, metoclopramide has demonstrated little effect on esophageal healing.

Domperidone,[†] which is available only outside the United States, is a potent peripheral dopamine antagonist whose properties are similar to metoclopramide. Unlike metoclopramide, however, it does not readily cross the blood–brain barrier. The most significant adverse effect reported so far is prolactin release (11). Domperidone is commonly used to treat GERD in patients who have delayed gastric emptying.

Tegaserod,[‡] a partial 5-hydroxytryptamine-4 (HT₄) receptor agonist, has been prescribed primarily for women with constipation-predominant irritable bowel syndrome. A potent promotility agent throughout the GI tract, tegaserod may improve delayed gastric emptying in patients with GERD. Although its role in GERD has not been clearly established, early studies have demonstrated a lim-

* FDA approved for short-term use only.

[†] Not FDA approved.

[‡] Not FDA approved for the treatment of GERD.

ited transient lower esophageal sphincter relaxation (TLESR) reducing effect that may result in fewer GER events (12).

KEY POINT

The main beneficial effect of promotility agents in treating GERD is improvement of gastric emptying.

Histamine Type-2 Receptor Antagonists

Histamine type-2 receptor antagonists (H₂RAs), or H₂-blockers as they are commonly known, are still widely used for the treatment of GERD. This class of drugs reduces gastric acid output by competitive inhibition of histamine at H₂-receptors on the parietal cells. H₂RAs reduce pepsin output by an unknown mechanism and reduce gastric acid volume as well (13). As a class, the different H₂RAs are considered equivalent in suppressing gastric acid output when administered in equipotent doses. The pharmacokinetic differences among the agents appear to be clinically insignificant (14). Although H₂RAs are effective in controlling basal acid secretion, they are less effective in suppressing postprandial acid secretion. Standard doses have been proven to be effective in controlling symptoms and healing mild to moderate erosive esophagitis. The more severe forms of erosive esophagitis require greater acid suppression, which the H₂RAs are less able to provide. Clinical trials with higher doses of H₂RAs to address this concern have yielded conflicting results. Ranitidine 300 mg bid was proven to be no better than the standard dose of 150 mg bid (15). Cimetidine 800 mg bid was likewise shown to have a similar outcome to 400 mg bid (16). In a multicenter trial comparing ranitidine 300 mg qid with 150 mg bid, healing rates among patients with grades I–III erosive esophagitis were much higher in those receiving the higher dose (75% vs 54%) (17). However, the authors neglected to elaborate on the increased cost of multiple dosing as well as the impact on patient compliance. In contrast, Kahrilas et al (18) demonstrated that

doubling the standard dose of ranitidine (from 150 mg bid to 300 mg bid) failed to improve symptom control of >50% of patients who persistently experienced heartburn symptoms after 6 weeks of standard H₂RA therapy.

The potential effect of H₂RAs on the nighttime histamine-driven surge of gastric acid secretion led to the popular use of these drugs at bedtime by patients who continued to be symptomatic on a standard or double-dose proton pump inhibitor (PPI) (19). However, tachyphylaxis develops quickly with H₂RAs, limiting their regular use in clinical practice (20). The main appeal of H₂RAs is their usage as an on-demand therapy. Their rapid effect on GERD symptoms, unsurpassed by any of the currently available PPIs, makes this class of drugs a very popular over-the-counter (OTC) remedy for many GERD sufferers who never seek medical attention.

KEY POINT

H₂RAs provide a rapid effect on GERD symptoms that is unsurpassed by any of the currently available PPIs, making them a successful on-demand therapeutic modality.

Proton Pump Inhibitors

The introduction of PPIs has revolutionized the treatment of acid-related disorders, and they are currently considered the best therapeutic option for GERD (21). PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) are the most potent gastric acid suppressants because of their ability to inhibit the proton pump H⁺, K⁺-ATPase, which is the final common pathway of gastric acid secretion. They suppress nocturnal and daytime as well as food-stimulated gastric acid secretion (22). Because of their profound and sustained acid inhibition, PPIs are now the most successful antisecretory agents in terms of symptom relief and mucosal healing (13,23). Additionally, PPIs provide faster symptom resolution and healing of the esophageal mucosa compared with the

H₂RAs (23). The main impact of PPIs has been on advanced erosive esophagitis, complications of GERD (such as peptic stricture), atypical/extra-esophageal manifestations of GERD, and Barrett's esophagus. Overall, the PPIs have made the greatest impact of all antireflux medications in improving quality of life.

Transient Lower Esophageal Sphincter Relaxation Reducers

None of the aforementioned treatments for GERD address the underlying cause of reflux; consequently, investigators have studied different therapeutic modalities that may interfere with TLESR, the most common underlying mechanism for physiological or pathological GER. Only *baclofen** has shown promising results in reducing the rate of TLESRs. A gamma-aminobutyric acid-B (GABA-B) agonist, baclofen appears to inhibit both monosynaptic and polysynaptic reflexes at the spinal cord level, possibly by hyperpolarization of primary afferent fiber terminals (24). Several recent studies in normal subjects and GERD patients have demonstrated that baclofen ($P < 0.05$) decreases significantly the number of acidic and nonacidic reflux events, percent total time pH <4, and reported GERD symptoms. Although baclofen has been administered in doses of 10 mg qid, in one recent study baclofen 20 mg tid reduced duodenal reflux and improved GERD symptoms in patients where treatment with PPIs failed (24).

EROSIVE ESOPHAGITIS

Patients with erosive esophagitis appear to be a much more homogeneous group of patients compared with those who have NERD (2). Differences in healing and symptom resolution have been attributed to the extent of esophageal mucosal injury (25). It should be noted, however, that up to 15% of patients with erosive esophagitis continue to report GERD symptoms despite complete mucosal healing (25). The refractoriness of symptoms in this group of patients is not clearly understood, but hypersensitivity to acid or potentially other mechanisms have been postulated (2).

In a meta-analysis, Chiba et al (23) demonstrated that after 12 weeks of treatment, healing rates were 83.6% with PPIs, 51.9% with H₂RAs, 39.2% with sucralfate, and 28.2% with placebo. Furthermore, PPIs provided faster healing rates of esophageal inflammation as well as superior resolution of symptoms. Erosive esophagitis healing has been shown to correlate with the time intragastric pH is >4 (26). All PPIs appear to be effective in healing erosive esophagitis, with failure rates that range between 5% to 15% (25,27); however, the effect on erosive esophagitis healing decreases with the increase in severity of esophageal inflammation (25). Failure rates of PPIs in high grades of erosive esophagitis (Los Angeles grades C and D) range from 13% to 40% (25). Patients with erosive esophagitis require maintenance therapy to prevent symptom relapse, inflammation, or potential progression to complications such as ulceration, stricture, and GI bleeding. Vigneri et al (28) showed that the combination of omeprazole (20 mg daily) and cisapride (10 mg tid) provided the highest remission rate (89%) in patients with erosive esophagitis, followed by omeprazole once daily (80%), ranitidine (150 mg tid) and cisapride (66%), cisapride (54%), and ranitidine alone (49%) after 12 months of treatment. As a sole therapeutic modality, PPIs by far provide the best maintenance treatment for erosive esophagitis. Lansoprazole and rabeprazole claim to offer faster control of symptoms in patients with erosive esophagitis, but comparison studies with other PPIs are scarce (29). Faster onset of action and thus more rapid control of gastric pH were reported for both PPIs.

NERD

Most patients with GERD have NERD (50% to 70%) (1,2). For decades NERD was assumed to be just a mild form of GERD because of the absence of esophageal mucosal injury. However, therapeutic trials have repeatedly demonstrated that NERD patients are less likely to respond to antireflux treatment than patients with erosive esophagitis (30). Symptom control is achievable in only 40% to 50% of NERD patients compared with 75% of those with erosive esophagitis after 4 weeks of treatment with a standard dose PPI (30). The low

* Not FDA approved for the treatment of GERD.

response rate to PPI treatment by NERD patients (30) is due to the marked heterogeneity of these patients, resulting in an unpredictable response to antireflux treatment (31). Of all NERD patients, those with abnormal acid exposure, as documented by pH testing, demonstrate the highest symptom response rate to PPI therapy (30). In contrast, NERD patients with normal esophageal acid exposure (functional heartburn) demonstrate the lowest response rate to PPIs (40% to 50%), primarily because of the subset of patients with nonacid-related stimuli responsible for their symptoms (30).

As with erosive esophagitis, the goals of therapy are the rapid and complete resolution of symptoms and the prevention of symptom relapse. Recent studies suggest that most NERD patients never progress to developing erosive esophagitis or Barrett's esophagus (4). Consequently, therapeutic approaches such as on-demand or intermittent therapies have become an attractive option for patients with NERD.

KEY POINT

Patients with NERD demonstrate a lower symptom response rate to PPIs than patients with erosive esophagitis.

BARRETT'S ESOPHAGUS

The goals of medical and surgical therapy in patients with Barrett's esophagus include symptom control; healing of concomitant esophageal inflammation if present; prevention of symptom recurrence and complications (stricture, etc.); and, potentially, prevention of neoplastic transformation (from intestinal metaplasia to low- and high-grade dysplasia).

As a group, Barrett's patients have demonstrated the highest acid exposure in the distal esophagus (31), suggesting the need for more aggressive antireflux treatment. Although the rates of symptom relief with PPI treatment are approaching 80%, it appears that symptom resolution is not synonymous with complete acid control. It is now

well recognized that 20% to 40% of Barrett's patients who symptomatically respond to PPI treatment would still have abnormal esophageal acid exposure as shown by 24-hour esophageal pH monitoring (32,33). Even at high doses, treatment with PPIs rarely results in a significant regression of Barrett's epithelium (34). Furthermore, no clinical data suggest that PPIs prevent neoplastic progression and the development of esophageal adenocarcinoma. Moreover, no current data support survival benefit with acid reduction therapy, and no consensus exists as to whether the treatment endpoint in these patients should be symptom control or acid control. Nevertheless, on the basis of our current knowledge it seems prudent and logical to treat Barrett's patients with a PPI (standard dose initially) for symptom relief and healing of esophageal inflammation.

STEP-UP, STEP-DOWN, OR STEP-IN?

Concerns about cost have been raised in relation to PPIs for the long-term treatment of GERD; consequently, several therapeutic approaches have been suggested to offset the cost. The step-up approach starts with lifestyle modifications and upgrade treatment based on symptom response (OTC H₂RA → H₂RA full dose → PPI once daily, etc.). This conservative approach has received the endorsement of institutions and third-party payers and is currently the most commonly advocated (35). In contrast, the step-down approach favors initiating therapy with a PPI standard dose and stepping down to an H₂RA. In a recent study, 58% of GERD patients were stepped down successfully from a PPI once daily to an H₂RA or a prokinetic, or no treatment after 1 year of follow-up (36). Ofman et al (37) compared the step-up approach to the step-down approach (using initially the PPI test) and found that the latter approach resulted in improved symptom relief and quality of life over 1 year and more appropriate utilization of invasive diagnostic testing at a small marginal increase in total cost. Furthermore, ~80% of subjects on multiple dosing of PPIs were able to step down to a PPI once daily after 6 months' follow-up on a single-dose PPI. Howden et al (38) demonstrated that continuous PPI therapy (step-in) over a period of 20 weeks was the best

strategy for keeping patients symptom free compared with either continuous H₂RA therapy or the step-up or step-down approach.

Although controversy continues as to which therapeutic strategy for GERD is best, the transition of PPIs to a generic or OTC medication will result in a substantial reduction of cost, and thus the step-in approach will become a more acceptable strategy by third-party payers.

NONCARDIAC CHEST PAIN

The recent introduction of the PPI therapeutic trial has provided an attractive therapeutic modality as well as a simple, readily available, and inexpensive diagnostic test (39,40). High-dose omeprazole (40 mg AM and 20 mg PM) over a period of 7 days yielded in a double-blind, placebo-controlled, randomized trial a sensitivity of 78.3% and a specificity of 85.7% in diagnosing GERD-related noncardiac chest pain (NCCP). When using other PPIs such as lansoprazole (41) and rabeprazole (42) as a diagnostic test, similar efficacy was noted with a sensitivity of 68% and 83% and a specificity of 80% and 75%, respectively. NCCP patients who demonstrate a positive clinical response to the PPI test should be treated with a long-term PPI as maintenance therapy. The dosage and duration of maintenance therapy are yet to be determined and require further studies. Achem et al (43) demonstrated in a double-blind, placebo-controlled trial that omeprazole 20 mg bid given over a period of 8 weeks was significantly better ($P < 0.05$) than placebo in controlling chest pain symptoms in patients

with GERD-related NCCP. This study underscores the need for at least a double dose of PPIs to control chest pain. Additionally, step-down therapy to a standard dose PPI is a reasonable approach, although studies supporting it are lacking. As with extraesophageal manifestations of GERD, the PPI dose that induces remission is the one likely needed to maintain it.

KEY POINT

The PPI test, a short course of a high-dose PPI, is a simple, readily available, and sensitive tool for diagnosing GERD-related NCCP.

ATYPICAL/EXTRAESOPHAGEAL MANIFESTATIONS OF GERD

Table III summarizes key points for the successful treatment of atypical/extraesophageal manifestations of GERD.

Laryngeal Manifestations

In recent years evidence has emerged about the possible benefit of PPI therapy in posterior laryngitis. Wo et al (44) recently reviewed some of the therapeutic trials in patients with GERD-related ear-nose-throat (ENT) manifestations. The reviewers pointed out that comparison of the different studies was limited due to the usage of various

TABLE III.

KEY POINTS FOR SUCCESSFUL TREATMENT OF ATYPICAL/EXTRAESOPHAGEAL MANIFESTATIONS OF GERD

- H₂RAs have no role.
- Treat with PPIs.
- Initial treatment with at least a double-dose PPI.
- If initial treatment with a PPI bid is successful, a step-down to PPI once daily for maintenance is a reasonable approach.
- Response may lag for up to 6 months.
- A small subset of patients may require even higher dose of PPI (> bid).

GERD = gastroesophageal reflux disease; H₂RAs = histamine type-2 receptor antagonists; PPIs = proton pump inhibitors.

doses of PPIs (omeprazole 20 to 40 mg), standard doses of H₂-blockers, and surgery over different periods of time, which ranged from 4 to 24 weeks. Regardless of the mode of therapy, the response rates in these studies ranged from 50% to 96%. One study that used omeprazole 40 mg daily for 8 weeks as an empirical therapy for posterior laryngitis demonstrated that two thirds of the patients were either symptom free or satisfied with their symptom improvement at the conclusion of the study. The remaining patients were classified as nonresponders, and when ambulatory 24-hour esophageal pH monitoring was performed, 80% still demonstrated an abnormal amount of esophageal acid exposure. This finding raises the question of adequate compliance in the latter group (45).

In a recent randomized, double-blind, placebo-controlled study, the effect of lansoprazole 30 mg bid was evaluated in patients with idiopathic chronic laryngitis; 20 patients were randomly assigned to lansoprazole or placebo for 3 months. The groups were matched by pH test results, endoscopic findings, and laryngeal signs and symptoms. At the end of the study, 50% of the patients in the lansoprazole group but only 10% in the placebo group reported complete resolution of their laryngeal symptoms. Laryngeal signs completely or partially resolved in 58% of the patients in the lansoprazole group but only in 30% of the patients in the placebo group. The investigators concluded that the use of an empirical trial of a PPI as the first line of therapy is an effective therapeutic approach in patients with chronic recurrent laryngitis (46).

As with therapeutic trials in GERD-related asthma, patients with GERD-related ENT abnormalities benefit the most from PPIs in at least double the standard dose for a minimum period of 8 to 12 weeks. H₂RAs have no role in this patient population.

Chronic Cough

Recent guidelines for the diagnosis and treatment of chronic cough advise that after excluding common non-GERD related causes (postnasal drip, asthma, etc.) aggressive treatment with PPIs should be initiated, lifestyle modifications recommended, and promotility drugs considered as an additive

modality. Treatment should be continued for at least 3 months before reevaluation. After 3 to 6 months of therapy, ambulatory 24-hour esophageal pH monitoring of PPI therapy should be considered in nonresponders to identify those with inadequate acid control who consequently need a high-dose PPI. As with other manifestations of GERD, long-term and possibly lifelong treatment with PPIs would likely be needed to prevent recurrence (47).

Recently, Irwin and Madison (48) reviewed retrospectively and prospectively conducted uncontrolled trials that used PPIs or H₂RAs to treat chronic cough. Response rates to acid-suppressive therapy were between 70% and 100% in these studies. PPIs (omeprazole 20 mg or 40 mg daily) provided a much faster response rate (mean of 53 days), and many patients already had responded during the first 1 to 2 weeks of treatment. In contrast, the response time of H₂RAs was longer and occurred over a period of 3 to 6 months. A 2-week trial of omeprazole 40 mg bid was found to be an excellent diagnostic approach for GERD-related chronic cough as well as a clinical predictive factor for successful response to antireflux treatment (49).

Pulmonary Manifestations

H₂RAs have no role in the treatment of GERD-related asthma. Overall, studies have demonstrated that these patients require profound and consistent acid suppression that is presently provided only by PPIs. Not uncommonly, high doses of PPIs for prolonged periods of time are needed. Double-dose PPI therapy for a minimum period of 3 months is an acceptable approach for patients with asthma. Because GERD-related asthma is a chronic process, long-term therapy is likely to be essential for the prevention of symptom relapse.

Studies have tried to evaluate the value of PPI therapy in the management of asthma. Harding et al (50) studied 30 patients with documented asthma and GERD (defined by symptoms and abnormal pH test). Patients were treated for 3 months with omeprazole until esophageal acid exposure was normalized as documented by 24-hour esophageal pH testing. Twenty-two patients demonstrated improvement in pulmonary function tests and/or symptoms while receiving PPI therapy;

20 patients reported marked improvement in asthma symptoms and 4 of those also had an improvement in pulmonary function tests. Responders had their asthma symptoms reduced by 57% but had a minimal although statistically significant ($P < 0.05$) improvement in their pulmonary function test. Another important clinical observation made by this study was that 27% of the patients needed omeprazole 40 or 60 mg to achieve adequate suppression of esophageal acid exposure. Additionally, a time lag was observed between improvement in reflux symptoms and asthma symptoms. Whereas reflux symptoms tended to improve relatively fast, improvement in asthma symptoms appeared later, with only 30% of the patients improving after 1 month, 43% after 2 months, and 57% after 3 months of therapy. Improvement was ongoing after 3 months of therapy. Lastly, the presence of acid regurgitation or abnormal proximal esophageal acid exposure had a sensitivity of 100%, negative predictive value of 100%, and a positive predictive value of 79% for asthma response to omeprazole therapy (51).

SURGICAL TREATMENT OF GERD

Antireflux surgery is offered to patients in the hope of obviating the need for continuous medical therapy, which may result in patient inconvenience, increased costs, and concerns about safety (52). Nissen fundoplication remains the most commonly performed surgery and consists of a 360° wrap of the gastric fundus around the distal esophagus, which results in augmentation of LES basal pressure and a decrease in the rate of TLESR. At this time, fundoplication is commonly done laparoscopically, which, compared with open surgery, is less costly, has less postoperative morbidity, and requires a shorter hospital stay. Postoperatively, however, dysphagia appears to be more common in patients who underwent laparoscopic Nissen fundoplication. Complications due to antireflux surgery are also determined by the expertise of the surgeon, which has been shown to closely correlate with the number of procedures performed.

Offering surgery to young patients because of the prospect of long-term medical therapy should be individualized and discussed in an unbiased

approach. Ultimately, the success of antireflux surgery depends on selecting the appropriate patients and surgeon. Presurgical evaluation includes an esophageal manometry, primarily to exclude achalasia and ineffective peristalsis (amplitude of esophageal body contractions < 30 mm Hg), upper endoscopy, and 24-hour esophageal pH monitoring in those patients without erosive esophagitis (53).

Positive response to medical therapy is the best predictor of successful surgical outcome. Additionally, age < 50 years and the presence of typical GERD symptoms were also found to be positive predictors. However, approximately half of the patients are referred for antireflux surgery because medical therapy has failed (54). When clinical outcome of antireflux surgery was compared with treatment with omeprazole, as long as patients were allowed to adjust the needed dose no great difference in treatment failure was observed between the 2 therapeutic strategies (55). However, a recent publication has reported that 10 years after antireflux surgery, more than half the patients require medical therapy (many on PPIs) to control their GERD symptoms (56).

Practitioners should be aware of the different side effects that patients may encounter after antireflux surgery, which may include persistent dysphagia, “gas-bloat” syndrome, inability to vomit, vagal nerve injury, and diarrhea.

ENDOSCOPIC TREATMENT OF GERD

Several endoscopic techniques have recently been introduced for the treatment of GERD. They include endoscopic suturing, radiofrequency energy procedure, and submucosal bulking. The primary aim of the various endoscopic techniques is to augment LES basal pressure and possibly reduce the rate of TLESR. Thus far, most of the studies published have shown a good safety profile, patient satisfaction with the clinical outcome, and good feasibility in performing these procedures.

The radiofrequency energy procedure involves the delivery of radiofrequency energy to the esophageal and cardia muscle, resulting in an increase in collagen deposition and probably dam-

age to the sensory afferents located within the esophageal mucosa (51). The net result is augmentation of the LES basal pressure, decreased rate of TLESR, and probably decreased perception of intraesophageal stimuli (9,57). Endoscopic suturing involves the placement of sutures (on average 2–3 per procedure) in the cardia, thus creating a gastric tube along the lesser curve (42), which lengthens the LES and increases LES basal pressure. The submucosal bulking technique utilizes an implantable substance that is biocompatible but not biodegradable (26,58). The net effect is primarily improvement in LES basal pressure.

Thus far, most of the endoscopic procedure trials were not randomized, did not have a placebo arm, included a small number of participants, and had a follow-up duration that was relatively short. Furthermore, the patient population studied was highly selective and included mostly mild to moderate erosive esophagitis cases with small (<3 cm) hiatal hernias. Additionally, endoscopic procedures are not without complications, which may include bleeding, fever, chest pain, vomiting, aspiration pneumonia, dysphagia, perforation, and death.

KEY POINT

Endoscopic treatment of GERD should remain within the realm of well-designed clinical studies until more data clarify its exact role.

The first sham-controlled trial using the radiofrequency energy procedure was recently published (56). The study revealed that subjective parameters such as quality of life and heartburn scores significantly improved ($P < 0.05$), but none of the objective parameters, such as esophageal acid exposure, LES basal pressure, or antireflux medication usage, were affected. This study raised the concern that the main impact of the radiofrequency energy procedure is on sensory afferent terminals in the esophageal mucosa rather than on GER.

SUMMARY

The new paradigm for GERD suggests that GERD has 3 unique phenotypic presentations: NERD, erosive esophagitis, and Barrett's esophagus, which shifts the traditional focus on esophageal mucosal injury to symptomatology. Because GERD is a chronic disease with a high relapse rate, long-term treatment is warranted in most if not all patients. Therapeutic modalities continue to evolve with some more successful than others depending on the physician's treatment goal and the patient's desired outcome. The PPIs are considered the best therapeutic option for GERD, especially for long-term maintenance, providing fast symptom resolution and healing of the esophageal mucosa. On-demand medications such as antacids, alginates, and the H₂RAs continue to be popular with patients who seek fast, temporary relief. Antireflux surgery is an option for patients who do not wish to take medication long term, although patient selection is critical. The recent introduction of various endoscopic techniques promises a long-term solution with less morbidity and lower cost to patients than antireflux surgery.

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Dialogue Box

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How do H₂RAs compare with PPIs in the management of GERD?

FASS

As an acid suppressant used episodically on an as-needed basis, H₂RAs work much more rapidly and thus are more effective. Used long term on a daily basis, H₂RAs are much less effective than PPIs in terms of acid suppression, symptom relief, and healing of lesions. The bottom line—if you have a patient who does not want to take medication on a regular basis and you have the choice of prescribing either a PPI or an H₂RA, the H₂RA would do a better job because it has a much more rapid effect. But if the patient will be taking an acid suppressant on a regular basis, the PPI is a superior agent because it has a profound and consistent effect on gastric acid secretion.

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Why do patients with NERD who have normal esophageal pH studies demonstrate a response rate to PPIs greater than that seen for placebo?

FASS

Because a subset of those patients have a hypersensitive esophagus that causes them to have symptoms even in the face of “normal” exposure to acid; that is, they don’t have to be within what we would consider an abnormal range on esophageal pH studies to have symptoms. Eliminating the small amount of acid with a PPI appears to be a difficult task in these patients, but gratifying if achieved.

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How do you dose PPI therapy?

FASS

First of all you need to take a PPI a half hour

before a meal, which is essential to obtain the maximum effect since PPIs work only on the pumps that are activated by a meal and not on the proton pumps that are dormant. Typically I will initiate PPI therapy with a single-dose regimen and adjust as needed to achieve the desired response. Although treatment could be based on 24-hour esophageal pH monitoring or on the healing of erosive esophagitis on upper gastrointestinal endoscopy, in clinical practice it is based primarily on the alleviation of symptoms. If the patient fails to respond, the next step is to double the dose. If you double the dose, studies have shown that the best way to go is to split the dose and give the first dose half an hour before breakfast and the second dose half an hour before dinner. That way you get the best control of acid secretion.

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Are there any patients in whom you would initiate therapy with double-dose PPI therapy?

FASS

An argument can be made for beginning with double-dose therapy in patients with Grade C and Grade D erosive esophagitis; 30% of patients with GERD have erosive esophagitis and ~30% of them have Grade C and D disease. Although the majority of patients with even Grade C and D disease will respond to single-dose PPI therapy, 20% to 30% of them will not, thus some gastroenterologists may opt to initiate double-dose therapy for patients in the more severe categories. The other group of patients who may be less likely to respond to a single dose are patients with Barrett’s esophagus. About 20% of these patients are likely to fail with a single dose.

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What do you think of the strategy of initially

Dialogue Box

treating all patients with suspected GERD, particularly those with suspected NERD and NCCP, with a high-dose PPI as a diagnostic trial and, in those who respond, tapering the dose down from there?

FASS

I would have no problems with that. What you're suggesting is to start them on a PPI trial and use it as a diagnostic tool. If they respond, you taper down to the lowest dose of PPI that controls their symptoms or possibly, for some, switch them to an H₂RA. The only issue is that the PPI test has a very good sensitivity but not great specificity in GERD patients.

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*Cisapride** is no longer available in the United States. Is there a new version on the horizon for the treatment of GERD?

FASS

Let me say that it remains uncertain whether the beneficial effect of promotility drugs like cisapride, which was indicated for nocturnal heartburn, actually stemmed from their ability to raise LES pressure and augment the amplitude contractions in the esophagus. Instead, many of us think that although there may have been a component of this, their major benefit is treating GERD patients who have a significant component of delayed gastric emptying. I don't really see a need for future promotility drugs to treat GERD now that we have even better PPIs in the pipeline. There is another promotility drug that recently became available called *tegaserod*.† Tegaserod is a partial 5HT-4 agonist that has been very helpful to patients with

predominant irritable bowel syndrome (IBS) constipation. Although currently FDA approved only for female patients with constipation-predominant IBS at a dose of 6 mg bid, tegaserod is a promotility drug that has an effect throughout the GI tract including the stomach. It thus also functions as a progastric emptying drug, although the dose required for that is higher (6 mg tid). I'm aware of at least one study that showed tegaserod perhaps also has an effect on the rate of TLESR, although it's not certain if it's a weak or strong effect. If it were to be confirmed that tegaserod also has a beneficial impact on TLESR, that might prove to be an attractive GERD treatment since it could then be used to reduce the number or the rate of TLESRs.

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What dose of PPI therapy do you favor in patients with extraesophageal GERD who do not have heartburn symptoms that can be monitored and what dosing regimens do you use?

FASS

In all atypical and extraesophageal manifestations of GERD, I start with a PPI bid as a diagnostic tool. For NCCP, I give omeprazole 40 mg in the morning and 20 mg in the evening for 1 week. To diagnose GERD-related chronic cough, I begin with 40 mg bid for 2 weeks. Since there is a lag in response in extraesophageal manifestations of GERD in some patients, you may need to treat these patients bid for up to 6 months. Once you get the desired response, I would taper them down to the lowest PPI dosage that controls their symptoms.

* Not FDA approved.

† Not FDA approved for the treatment of GERD.