Management of Gastroesophageal Reflux Disease

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ABSTRACT: Gastroesophageal reflux disease (GERD) is a chronic condition requiring long-term treatment. Simple lifestyle modifications are the first methods employed by patients and, because of their low cost and simplicity, should be continued even when more potent therapies are initiated. Potent acid-suppressive therapy is currently the most important and successful medical therapy. Whereas healing of the esophageal mucosa is achieved with a single dose of any proton pump inhibitor (PPI) in more than 80% of cases, symptoms are more difficult to control. Patients with persistent symptoms on therapy should be tested (preferably with combined multichannel intraluminal impedance and pH) for association of symptoms with acid, nonacid, or no GER. Long-term follow-up studies indicate that PPIs are efficacious, tolerable, and safe medication. So far, promotility agents have shown limited efficacy, and their side-effect profile outweighs their benefits. Antireflux surgery in carefully selected patients (ie, young, typical GERD symptoms, abnormal pH study, and good response to PPI) is as effective as PPI therapy and should be offered to these patients as an alternative to medication. Still, patients should be informed about the risks of antireflux surgery (ie, risk of postoperative dysphagia; decreased ability to belch, possibly leading to bloating; increased flatulence). Endoscopic antireflux procedures are recommended only in selected patients and given the relative short experience with these techniques, patients treated with endoscopic procedures should be enrolled in a rigorous follow-up program. KEY INDEXING TERMS: Gastroesophageal reflux disease (GERD); Proton pump inhibitors; Antireflux surgery.

Approximately 40% of the US population has symptoms of gastroesophageal reflux disease (GERD), making it the fourth most prevalent gastrointestinal disease in the United States. GERD is a chronic disease requiring long-term therapy. As a general rule, the management of GERD should follow a step-wise approach, starting with simple therapeutic modalities and gradually advancing to more potent and more aggressive modalities based on 2 goals: healing of lesions and alleviation of symptoms.

The pattern of presentation and therapy is well-expressed by the “heartburn iceberg” shown in Figure 1. The vast majority of patients have only occasional symptoms and will empirically treat heartburn with over-the-counter (OTC) medications and not seek medical attention. Patients with frequent symptoms will seek medical attention and are often evaluated by primary care physicians and given prescriptions for acid-suppressive therapy. Because acid-suppressive therapy is very effective and has few side effects, specialists (gastroenterologists and gastrointestinal surgeons) are likely to see only the “tip of the iceberg” represented by patients with severe or persistent symptoms not responsive to standard treatment. When evaluated by gastroenterologists, treatment targets reduction of esophageal acid exposure. Supported by a good correlation between control of intragastric pH and healing of erosive esophagitis, medical strategies employ pharmacological suppression of gastric acid production, whereas surgical and endoscopic strategies employ augmentation of the gastroesophageal junction.

The above concepts have primarily been studied in patients with so-called “typical” symptoms of GERD (heartburn, regurgitation) but apply equally to those with atypical (chest pain, asthma/cough, hoarseness, sore throat) symptoms or complications (ulceration, strictures, metaplasia) of the disease.

Simple Therapeutic Modalities (Lifestyle Modifications)

In the current days of very potent acid-suppressive therapy, simple, alternative, patient-driven, and less expensive GERD treatments tend to be forgotten. Most of these methods were the main therapeutic modalities before the late 1970s and include elevation of head of the bed, wearing loose-
fitting clothing, avoidance of meals before bedtime, weight loss, and restriction of smoking, alcohol, coffee, and fat.6 Today, these lifestyle modifications often also include use of antacids, alginate, and over-the-counter (OTC) doses of histamine-2 receptor antagonists (H2RA).

Elevation of the head of the bed helps improvement of esophageal acid clearance and decreases the total recumbent acid exposure.7 These hypotheses are supported by studies indicating significant reduction in nocturnal acid clearance time and total nocturnal acid exposure using 6-inch blocks to elevate the head of the bed.8 A more patient-friendly alternative is to sleep predominantly on the left side.9 Avoidance of meals for 3 hours before bedtime is based on studies indicating that postprandial recumbency leads to a significant increase in the number and duration of reflux events10

Wearing loose-fitting clothing as a measure to reduce gastroesophageal reflux is based on the hypothesis that tight clothing increases intragastric pressure and therefore the gastroesophageal pressure gradient across the lower esophageal sphincter (LES),11 the so-called “tight pants syndrome.” Even though there are no good studies supporting this hypothesis, this relatively simple and intuitive measure should not be ignored.

Based on studies showing a correlation of morbid obesity with reflux and lower LES pressures,12 weight reduction in the attempt to improve GERD is a rational approach. Even though not formally studied, it is commonly believed that typical GERD symptoms improve in patients during weight reduction.

Recommendations to avoid certain foods and limit smoking and alcohol are based on studies indicating decreases in LES pressures and/or increased number of gastroesophageal reflux episodes. Ingestion of high-fat meals decreases LES pressure,13 increases frequency of transient lower esophageal relaxations,14 and increases esophageal acid exposure for up to 3 hours after meals.15 Increased esophageal acid exposure has been documented after ingestion of chocolate16 and alcohol17 and after smoking.18,19

The use of antacids in treatment of GERD relies on the neutralizing capabilities of these compounds on gastric secretions. The superiority of antacids over placebo was proven in double-blind studies in patients with reflux esophagitis.20,21 Other placebo-controlled studies have shown the superiority of an alginic acid-antacid combination in controlling reflux symptoms.22 The observation of the floating nature of alginic acid within the stomach suggested that it might work well in patients with symptoms during the upright position,23 a hypothesis supported in subsequent studies.24

After several years of proven efficacy and safety of standard-dose H2RAs, the class of medication became available as low-dose over-the-counter (OTC) preparations for “conservative” treatment of GERD. There is only limited information available showing symptomatic improvement with OTC doses of H2RAs,25 although several studies have documented the ability of these preparations to decrease intragastric acidity.26,27 In 2002, the American Gastroenterology Association (AGA) issued a consensus statement declaring OTC H2RA and antacid the first line of treatment for patients with mild GERD symptoms. The combination H2RA/antacid was considered better at symptom relief than its constituent components alone.

Table 1 summarizes the life-style modification approach to GERD. Even though recently developed acid-suppressive agents are highly effective in treatment of GERD, these simple measures should be discussed with patients. Their simplicity and low cost justify them as phase 1 therapy to be continued in all patients suffering from this disorder. OTC antacids or even H2RAs should be recommended for occasional “breakthrough” symptoms while patients are receiving more potent therapies.

Figure 1. Pattern of presentation and therapy of GERD patients expressed by the “heartburn iceberg.” Endo, endoscopic antireflux procedure.

Table 1. Lifestyle Modifications That Can Help Improve GERD Symptoms

<table>
<thead>
<tr>
<th>Symptom Level</th>
<th>Therapy</th>
<th>Care Provider</th>
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<tbody>
<tr>
<td>Severe symptoms</td>
<td>PPI high Surgery Endo</td>
<td>Gastroenterologist GI surgeon</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>PPI low H2RA</td>
<td>Primary care physician</td>
</tr>
<tr>
<td>Mild symptoms</td>
<td>Life style modification OTC (H2RA, antacids)</td>
<td>Self medicate</td>
</tr>
</tbody>
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Sleep with the head of the bed elevated
Sleep on the left side
Avoid late meals/avoid recumbent position 3 hours after meals
Avoid high-fat meals
Use smaller meals
Use saliva-stimulating agents (ie, hard candies, chewing gum)
Wear loose-fitting clothing
Restrict smoking, alcohol, coffee, chocolate
Lose weight
Pharmacologic Management of GERD

The objectives of pharmacological treatment of GERD are relief of symptoms, avoidance of complications, and healing of esophageal mucosa. The principal classes of pharmacological agents are: acid suppressive drugs (H2RAs, proton pump inhibitors (PPIs)), promotility agents (bethanechol, metoclopramide, cisapride, domperidone, erythromycin, tegaserod), mucosal protective agents (sucralfate), and agents to reduce transient lower esophageal sphincter relaxation (TLESR) (baclofen).

Acid-Suppressive Drugs

Histamine-2 Receptor Antagonists. H2RAs were the antisecretory therapy of choice from the mid-1970s until the introduction of PPIs into clinical practice in the late 1980s.28 Currently in the United States, 4 H2RAs are available for clinical use: ranitidine (Zantac), famotidine (Pepcid), cimetidine (Tagamet), and nizatidine (Axid). Even though the more recently developed PPIs have been shown to be superior, the H2RAs still remain useful in treatment of milder forms of the disease and for on-demand therapy, particularly for nocturnal GERD symptoms.

Prescription dosages of H2RAs can be grouped into standard dose (150 mg of ranitidine, 20 mg of famotidine, 400 mg of cimetidine, and 150 mg of nizatidine, each twice daily) and high dose (obtained by doubling the standard doses). The healing rates with H2RAs range between 50 and 70% at 8 weeks and 60 to 80% at 12 weeks.29 Most studies have shown superiority of H2RAs to placebo but no significant differences among high and standard doses (possible type II error, because most studies were powered to show differences from placebo). Even though the more recently developed PPIs have been shown to be superior, the H2RAs still remain useful in treatment of milder forms of the disease and for on-demand therapy, particularly for nocturnal GERD symptoms.

Proton Pump Inhibitors. PPIs are superior to H2RAs in treating erosive esophagitis36 and its complications,37 relieving symptoms from erosive and nonerosive GERD,38,39 and preventing recurrence of GERD-associated symptoms.40 Studies by Zeitoun,41 Lundell et al,42 Vantrappen et al,43 and Klinkenberg-Knol et al36 indicate superiority of the PPI versus H2RA. Thus, they have surpassed H2RAs as the antisecretory agents of choice (Figure 2). PPIs are substituted benzimidazoles that irreversibly bind the H+/K+-ATPase, the final common step in acid secretion.44

Currently, 5 PPIs are commercially available in the United States: omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. FDA-approved doses (20- and 40-mg omeprazole, 15- and 30-mg lansoprazole, 20-mg rabeprazole, 40-mg pantoprazole, and 40-mg esomeprazole) are for use once daily, which provides sufficient acid suppression to effectively treat most patients. Symptom relief can be expected in about 78% of cases (range, 62–94%) and esophagitis healing in 83% (range, 71–96%).45

Figure 2. Comparison of omeprazole versus ranitidine in healing reflux esophagitis after 8 weeks of treatment. Studies by Zeitoun,41 Lundell et al,42 Vantrappen et al,43 and Klinkenberg-Knol et al36 indicate superiority of the PPI versus H2RA. Numbers indicate dose of omeprazole used in the study.
switching to another PPI as the first step in patients not responding to one PPI.

The most recent “second-generation” PPI, esomeprazole, the active S-isomer in the racemic mixture of omeprazole, has been reported to have slightly better effect on GERD. Results from a large, double-blind study suggest that the advantages of esomeprazole become more important in patients with more severe disease (Figure 4).

The timing of administering the PPI in relation with meals is important. The ideal window to take the PPI is 15 to 30 minutes before meals. This allows the medication to be absorbed to be available to the proton pumps when they are activated by the meal. PPIs taken before meals provide better intragastric pH control compared with being taken after the meal. Inadequate timing is frequently seen clinically, especially when patients are prescribed PPI twice daily without further instructions; patients frequently take the medication in the morning and before bedtime (without a meal).

Despite the efficacy of single-dose proton pump inhibitor in controlling intragastric acidity, improving symptoms, and healing of erosive esophagitis, some patients do not heal as well and may require increased dosing. In addition, patients with extraphageal presentations (asthma, cough, or laryngitis) may require higher doses for effective symptom control. Rather than doubling the single dose amount, it is preferable to give the PPI twice daily. This recommendation is based on studies in healthy subjects indicating that 20 mg of omeprazole before breakfast and before dinner was superior in controlling intragastric pH compared with 40 mg of omeprazole before breakfast or before dinner.

A more recent discovery has been that PPIs may not achieve adequate control of intragastric pH; even with twice-daily dosing, they are not always able to control nocturnal acid breakthrough. A single dose of H2RAs added at bedtime to the PPI can reduce nocturnal acid breakthrough (Figure 5). Concerns that combination of PPI and H2RAs...
might decrease the efficacy of PPIs were cleared by studies indicating similar intragastric acid control on daily PPI after placebo or H2RAs the night before. Therefore H2RAs are still potentially effective drugs for on-demand therapy of both daytime and nocturnal GERD symptoms.

Based on existing data we propose the step-up therapeutic approach to acid suppression guided as illustrated in Table 2. Symptom response to a trial of PPI therapy is currently a popular recommended diagnostic approach to GERD (“PPI-trial”). Patients failing PPI trials or not responding to PPI therapy should undergo reflux testing to evaluate the amount of reflux and its relation to symptoms. For more than 20 years, esophageal pH testing has been the accepted standard for diagnosing GERD. For optimal study interpretation patients should be off PPI therapy for at least 7 days before undergoing esophageal pH testing. Patients with GERD who failed to respond to standard PPI treatment because of insufficient dosing might experience symptom exacerbation during this period that may help clarify the diagnosis.

An important alternative diagnosis in patients with persistent symptoms on therapy is the possibility of symptomatic nonacid reflux, which will be missed by conventional pH testing because of the limitations of this technique in identifying nonacid reflux. Currently, combined multichannel intraluminal impedance and pH (MII-pH) is evolving as dual modality reflux testing. Because MII-pH detects reflux by changes in intraluminal electric conductivity, both acid and nonacid reflux events can be identified. Preliminary data from a multicenter collaborative study suggest that only 20% of patients with persistent symptoms on acid-suppressive therapy have their symptoms related to acid reflux. The other 80% usually present a diagnostic dilemma as to whether their symptoms are associated with nonacid reflux or not associated with any type of GER. Combined MII-pH will further clarifying this possible association, including recognition that 40% of patients with persistent symptoms on therapy have no temporal correlation between symptoms and any type of reflux. Therefore, we believe that combined MII-pH should be considered the next step in diagnostic management of patients not responding to PPI therapy (Figure 6).

As mentioned before, GERD is a chronic disease requiring long-standing therapy. Although daily maintenance therapy on standard-dose PPI sustains relapse rates well under 20% for 12 months, change to H2RAs or placebo will increase the relapse to more than 50 to 70% and 70 to 90%, respectively. Long-term safety and efficacy of standard PPI doses are supported by European studies with patient follow-up over a decade.

**Promotility Agents (PMAs)**

The rationale for using PMAs in treatment of GERD is based on the hypothesis that normalizing underlying dysmotility or augmenting existing motility would decrease esophageal acid contact time. An overall comment regarding PMAs in GERD is that as a group, they have limited effectiveness or undesirable side effects.

Bethanechol is a cholinergic agonist that will increase esophageal peristalsis and LES pressure but also stimulate gastric secretion. Compared with placebo, it will improve GERD symptoms but has no advantages in healing esophagitis. At the recommended dose for treatment of GERD (25 mg 4 times per day), it may have cholinergic side effects, including diarrhea, abdominal cramping, fatigue, and blurred vision.

Metoclopramide is a smooth-muscle stimulant that inhibits dopamine receptors. It enhances gastric emptying and LES pressure but also stimulate gastric secretion. Compared with placebo, it will improve GERD symptoms but has no advantages in healing esophagitis. At the recommended dose for treatment of GERD (25 mg 4 times per day), it may have cholinergic side effects, including diarrhea, abdominal cramping, fatigue, and blurred vision.

Cisapride stimulates acetylcholine release, increasing LES pressure, aiding esophageal peristalsis, and accelerating gastric emptying. Placebo-controlled trials have shown significant improvements

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**Table 2. Suggested Approach to Acid Suppressive Therapy**

<table>
<thead>
<tr>
<th>Step</th>
<th>Medical regimen</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Single-dose PPI (AM before meals)</td>
</tr>
<tr>
<td>2</td>
<td>Switch to another PPI</td>
</tr>
<tr>
<td>3</td>
<td>PPI AM plus evening (or bedtime) H2RA</td>
</tr>
<tr>
<td>4</td>
<td>PPI twice daily before meals</td>
</tr>
<tr>
<td>5</td>
<td>PPI twice daily before meals plus H2RA at bedtime</td>
</tr>
</tbody>
</table>

**Figure 6. Suggested diagnostic GERD algorithm.**
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In GERD symptoms, because of its cardiovascular side effects, however, it is no longer available. Tegaserod, a selective 5-HT4 receptor partial agonist, is a potent promotility agent throughout the gastrointestinal tract that is also considered to decrease visceral sensitivity and promote gastric emptying. In 1 study in GERD patients, it was shown to decrease postprandial esophageal acid exposure suggesting a potential role in treatment of GERD. Domperidone and erythromycin are the other promotility agents currently being investigated for treatment of GERD. Both agents enhance gastric emptying but do not have significant effects on esophageal peristalsis. Their side effect profiles may also limit their clinical utility.

Mucosal Protective Agents

The role of sucralfate in treatment of GERD has not been studied as extensively as H2RAs and PPIs. Sucralfate is believed to physically adhere to injured mucosa and thereby create a protective barrier against acid gastric secretions. Randomized comparisons showed superiority to placebo and healing comparable with standard dose H2RAs.

Agents to Reduce TLESRs

Recently, transient lower esophageal sphincter relaxations (TLESRs) have been recognized to be the major mechanism of gastroesophageal reflux. Baclofen, an agonist of γ-aminobutyric acid type B, was shown to reduce the rate of postprandial TLESRs and acid reflux episodes in healthy volunteers and patients with reflux esophagitis. In a mechanistic study using combined MII-pH in healthy volunteers and patients with GERD, a single dose of 40 mg of baclofen significantly reduced all types (acid and nonacid) of postprandial reflux. The side-effect profile of dizziness or nausea may restrict its clinical utility.

Surgical Management of GERD

Surgical antireflux procedures are highly effective treatment modalities in appropriately selected patients. Before potent acid suppressive therapy became available, surgery was considered superior to medical therapies. The rationales for antireflux surgery have evolved parallel to clarifications in pathophysiologic mechanisms of reflux disease. Although hiatal hernia was considered to be of major importance in production of GERD, antireflux surgery was performed to reduce the hiatal hernia and keep the LES within the abdominal cavity. Reports showing that only 9% of patients with hiatal hernia had typical reflux symptoms suggested that other factors might play a more important role. When low LES pressures were considered the major factor in gastroesophageal junction incompetence, antireflux procedures were done to increase LES pressure. At present, given that TLESR is considered the main mechanism by which GERD occurs, surgery is done to lengthen the intraabdominal portion of the LES, to reduce the volume of the gastric fundus and prevent effacing of the LES during gastric distention in the postprandial period.

Preoperative evaluation of patients undergoing antireflux surgery includes: esophageal manometry, upper gastrointestinal endoscopy, 24-hour esophageal pH monitoring, barium esophagogram, and gastric emptying studies. This is necessary to select the ideal candidates for the procedure, who should be young (because they will require long-term GERD therapy), should have typical GERD symptoms (heartburn, regurgitation), should have an abnormal ambulatory pH test, and should have responded to PPI therapy. Antireflux procedures should be used with caution in patients with atypical manifestations (ie, chest pain, acid taste), in patients not responding to PPI therapy, and patients with ineffective esophageal motility. Contraindications to perform surgical interventions are major esophageal motility abnormalities (ie, achalasia, scleroderma). Recently, a randomized clinical trial in 310 patients comparing surgery and omeprazole showed similar success/failure rates over a 5-year period. Results from community hospitals report rates of complications/defective fundoplication (ie, dysphagia, bloating, flatulence, and recurrent esophagitis) during a 78-month follow-up, which underlined the importance of having an experienced surgeon in a hospital that has a high procedure volume.

Endoscopic Management of GERD

Recent development in endoscopic techniques proposed a series of procedures to treat GERD. Radiofrequency ablation of the lower esophageal sphincter (Stretta procedure) uses a balloon-tipped 4-needle catheter that delivers radiofrequency (RF) energy to the smooth muscle of the gastroesophageal junction. The initial proposed mechanism of action was considered to be generation of a scarring tissue that would decrease the amount of reflux. Subsequently, it was proposed that RF ablation of the LES might in fact decrease the number of transient lower esophageal sphincter relaxations. This procedure is recommended in patients suffering from chronic heartburn requiring maintenance antisecretory therapy but without a hiatal hernia >2 cm, severe esophagitis, or complications of gastroesophageal reflux disease. After the initial success, more recent studies indicate that the procedure improves symptoms (ie, severity of GERD, scores on GERD-related questionnaires), but results regarding improvement of esophageal acid exposure are conflicting.

Around the same time, the FDA approved a sec-
ond endoscopic antireflux technique (EndoCinch) that is based on endoscopic placement of sutures below the gastroesophageal junction. This procedure is not indicated in the presence of dysphagia, grade 3 or 4 esophagitis, obesity, or hiatal hernia >2 cm in length. Initial results and recently published follow-up studies indicate symptomatic improvement as well as improvement in esophageal acid exposure parameters.99,100 Other endoscopic antireflux procedures are currently in advanced stages of evaluation using injected materials, endoscopic fundoplication, etc.

Summary

Gastroesophageal reflux disease (GERD) is a chronic condition requiring long-term treatment. Simple, life-style modifications are the first methods employed by patients; because of their low cost and simplicity, they should be continued even when more potent therapies are initiated.

Potent acid-suppressive therapy is currently the most important and successful medical therapy. Although healing of esophageal mucosa is achieved with a single dose of any PPI in more than 80% of cases, symptoms are more difficult to control. For symptom control, additional dosing or combination therapy with H2RA might be required. Patients with persistent symptoms on therapy should be tested (preferable with combined MII-pH) for association of symptoms with acid, nonacid, or no GER. Long-term follow-up studies indicate that PPIs are effective, tolerable, and safe medications. So far, PMAs have shown limited efficacy and their side-effect profiles outweigh benefits.

Antireflux surgery, in carefully selected patients (ie, young, typical GERD symptoms, abnormal pH study, and good response to PPI) is as effective as PPI therapy and should be offered to these patients as an alternative to medication. Still, patients should be informed about the risks of antireflux surgery (ie, risk of postoperative dysphagia; decreased ability to belch, possibly leading to bloating and increased flatulence).

Endoscopic antireflux procedures are recommended only in selected patients; given the relatively short experience with these techniques, patients treated with endoscopic procedures should be enrolled in a rigorous follow-up program.

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