

## Advances in the Management of Gastroesophageal Reflux Disease

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**G**astroesophageal reflux disease (GERD) is a very common disease—of the United States adult population, 44% experience heartburn at least once per month, 14% weekly, and 7% daily.<sup>1</sup> What portion of the asymptomatic population is affected by GERD is unclear; however, one study estimated that 30% of patients with GERD are asymptomatic.<sup>2</sup> GERD involves abnormal exposure of the esophagus to acid, which may lead to various intra- and extra-esophageal complications. GERD is now recognized as a chronic disease, although not always a progressive disease.

The understanding of the mechanisms that underlie GERD has advanced markedly in the past decade. Transient lower esophageal sphincter (LES) relaxation, a sudden decrease in LES pressure that is not precipitated by primary or secondary peristalsis, is considered to be the most common cause for exposure of the esophagus to acid and is the cause of 94% of cases of physiologic acid exposure and 65% of cases of pathologic acid exposure. Other less common mechanisms that involve the LES include increased intra-abdominal pressure (stress reflux) and reduced LES pressure, resulting in spontaneous reflux.<sup>3</sup> Delayed gastric emptying, ineffective clearance mechanisms, impaired mucosal integrity, duodenogastric reflux, and the presence of a hiatal hernia have all been demonstrated to contribute to abnormal esophageal acid exposure.

The perception of GERD symptoms by patients with GERD has attracted much attention recently because of the lack of association between esophageal mucosal injury or acid exposure and symptom assessment by the patient. This lack of correlation between injury or acid exposure and symptoms is particularly accentuated in elderly patients (ie, older than age 60 years) with GERD.<sup>4</sup> Up to 20% of the patients with symptoms of heartburn exhibit no evidence of excess acid exposure or esophageal mucosal injury; this syndrome is therefore termed *functional heartburn*.<sup>5</sup> For the purpose of this discussion, however, heartburn and acid regurgitation are considered typical GERD symptoms.

The symptoms of GERD usually appear approximately 30 minutes postprandially and are exacerbated by the patient lying flat, engaging in physical exertion, or bending over. GERD symptoms are relieved by ingestion of antacid.<sup>6</sup> Belching may also indicate acid reflux because the mechanism of both belching and reflux is similar. Alarming symptoms of GERD include dysphagia, upper gastrointestinal bleeding, weight loss, hoarseness, wheezing, cough, and recurrent pneumonia—these symptoms indicate the need for further, timely diagnostic evaluation.

Therapeutic management of GERD has changed dramatically in the past decade because of the introduction of potent acid inhibitors and new promotility drugs with improved safety profiles. Both the traditional and newer therapies are aimed at reducing acid production, enhancing LES competency, and improving esophageal clearance and gastric emptying. Behavioral and lifestyle modification, termed *phase 1 management*, remains an integral component of any therapeutic approach. Healing rate, mucosal injury resolution, and maintenance of remission are correlated with reduced esophageal acid exposure.<sup>7</sup> Each patient presenting with the symptoms of GERD should receive individualized therapy, and treatment goals that are appropriate for the patient's status should be established, including symptom relief in patients without erosive esophagitis, symptom relief and mucosal healing in patients with erosive esophagitis, and relapse prevention in patients in remission.

### PHASE 1 MANAGEMENT

#### Lifestyle and Dietary Modifications

Lifestyle modifications, as listed in **Table 1**, are an important adjunct to any treatment program. Lifestyle modifications can include behavioral modifications—

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**Table 1.** Lifestyle and Dietary Modifications for Gastroesophageal Reflux Disease

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Avoid large meals
Avoid specific dietary sources
Fatty foods
Citrus juices
Carbonated beverages
Tomatoes
Onions
Chocolate
Peppermint
Coffee
Avoid eating 3–4 hours before bedtime
Stop smoking and avoid alcohol
Lose excess weight
Avoid tight-fitting garments
Elevate head of bed or use a bed wedge
Remain upright for 2–3 hours after meals
Avoid drugs that reduce lower esophageal sphincter pressure
Theophylline
Anticholinergics
Calcium channel blockers
Nitrates
$\alpha$ -Adrenergic antagonists
$\beta$ -Adrenergic agonists
Diazepam
Progesterone
Meperidine
Avoid drugs that may cause direct mucosal injury: aspirin, nonsteroidal anti-inflammatory drugs

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such as weight loss, cessation of smoking and alcohol ingestion, and avoidance of drugs that reduce LES pressure—and postural methods—such as remaining upright after meals and elevating the head of the bed or using a bed wedge. Dietary modifications are also effective: patients should avoid large meals and any food products that appear to aggravate the symptoms of GERD. In addition, food products that affect LES function, such as fatty foods, coffee, chocolate, peppermint, and highly acidic beverages (citrus juices, certain carbonated beverages), should be avoided.<sup>7</sup>

Although lifestyle modifications can be beneficial to patients with GERD at every stage of medical therapy, both physicians and patients tend to discount this

important therapeutic adjunct. In a multicenter study, fewer than 50% of patients reported receiving lifestyle modification recommendations from health-care providers.<sup>8</sup> Elderly patients were less likely than younger patients to report receiving lifestyle modification recommendations from health-care providers, whereas obese patients were more likely to report receiving diet-related recommendations.

#### Antacids

The most common agents used by patients with GERD symptoms are antacids because of their easy availability and rapid symptom relief. Because of rapid esophageal clearance, however, antacids provide only short-term relief of the symptoms of GERD and have no role in controlling nocturnal acid secretion, healing esophagitis, or preventing complications.<sup>7</sup> In antacid users with frequent symptoms of heartburn (four times per week or more), 47% were found to have erosive esophagitis on upper endoscopy and 6% had nondysplastic Barrett's esophagus.<sup>9</sup> An alginic acid/antacid combination that prevents contact of acid refluxate with esophageal mucosa provides better symptom relief than antacids and may maintain remission in patients whose mild to moderate esophagitis has healed with histamine<sub>2</sub> receptor (H<sub>2</sub>) blockers or proton pump inhibitor (PPI) therapy.

#### Alternative Medicine

Alternative medicine has also been recruited to combat GERD but has not yet been subjected to randomized studies. Progressive muscle relaxation training has been demonstrated to improve GERD symptoms and reduce acid exposure, particularly in patients who experience increased symptoms during stress. Acupuncture, hypnosis, and other alternative modalities are used as well, primarily for symptom relief.

#### Nonprescription Histamine<sub>2</sub> Receptor Blockers

Nonprescription H<sub>2</sub> blockers were recently introduced into the market. A list of common H<sub>2</sub> blockers currently available is presented in **Table 2**. Famotidine (10 mg) has been demonstrated to be superior to placebo or antacids in relieving GERD symptoms.<sup>10</sup> For episodic heartburn, 10-mg famotidine induced an effect that was comparable to prescription-strength ranitidine and cimetidine.<sup>11</sup> Increasing the availability to the general public of drugs for GERD that are more potent than antacids was expected to decrease antacid consumption. The availability of nonprescription H<sub>2</sub> blockers was also expected to reduce time lost from work because of the drugs' increased effectiveness and

to decrease medical office visits because more patients could self-medicate. The impact of nonprescription drugs on the public's behavior in seeking medical assistance has not yet been fully elucidated, but one study documented that up to 50% of antacid users had tried nonprescription H<sub>2</sub> blockers within several months of introduction of the drugs.<sup>12</sup> However, additional randomized comparison studies are needed to evaluate the efficacy and cost savings of nonprescription H<sub>2</sub> blockers.

#### PHASE 2 MEDICAL THERAPY

In patients with typical symptoms of GERD who have never sought medical attention and who are without associated alarming symptoms, empiric therapy with an H<sub>2</sub> blocker or a promotility drug is appropriate. If a patient presents with alarming, refractory, or persistent symptoms, however, further evaluation using upper endoscopy and/or 24-hour esophageal pH monitoring is required to establish the diagnosis of GERD and to exclude GERD-related complications. A barium swallow, as the first diagnostic procedure, is probably justified only in patients with dysphagia.

#### Histamine<sub>2</sub> Receptor Blockers

H<sub>2</sub> blockers have been the mainstay treatment of GERD for 20 years, but their role should be redefined in the era of PPIs. The specific niche of each class of drugs should be determined on the basis of therapeutic studies, cost analyses, safety profile, and flexibility in changing doses. Goals of therapy should be established prior to starting therapy.

H<sub>2</sub> blockers competitively inhibit histamine from binding to the receptor protein by binding more avidly to the relevant amino acids than does histamine itself.<sup>13</sup> In 1977, cimetidine became the first H<sub>2</sub> blocker to obtain United States Food and Drug Administration approval, initially approved for healing duodenal ulcers. Subsequent approval came for ranitidine in 1983, famotidine in 1987, and nizatidine in 1988. Famotidine is 20 to 50 times and nizatidine and ranitidine are four to 10 times more potent than cimetidine, as reflected in their different doses. With appropriate dosing, however, all H<sub>2</sub> blockers have similar efficacy.<sup>13</sup>

Healing and symptom control in patients with GERD are directly related to maintaining an intra-esophageal pH of greater than 4, a level at which pepsin is inactivated. Standard doses of H<sub>2</sub> blockers inhibit 60% to 70% of 24-hour acid secretion, thereby effectively increasing intra-esophageal pH.<sup>14</sup> Efficacy is markedly improved with increased dose and frequency

**Table 2.** Nonprescription Histamine<sub>2</sub> Receptor Blockers for Gastroesophageal Reflux Disease

Drug	Dose/unit, mg	Dose/day, mg
Cimetidine	100	100, not to exceed 400 mg/day
Famotidine	10	10, not to exceed 20 mg/day
Nizatidine	75	75, not to exceed 150 mg/day

of administration.<sup>15</sup> Famotidine achieved a 48% healing rate after 6 to 8 weeks of treatment with 40 mg twice daily compared with a 32% healing rate with 20 mg twice daily.<sup>15</sup> When a standard dose of ranitidine was administered four times daily, the healing rate reached 71%, emphasizing the need for multiple dosing during the day and dosing at bedtime. Similarly, nizatidine at a dose of 150 mg twice daily provided a higher 6-week healing rate (41.1%) than one nighttime dose of 300 mg or placebo.<sup>16</sup>

Although healing rates improve with increased amount and frequency of the dose, the effectiveness of H<sub>2</sub> blockers in healing erosive esophagitis is also determined inversely by the severity of mucosal injury. Nizatidine (150 mg twice daily for 3 months) provided healing rates of 55%, 42%, 28%, and 32% in patients with grade 1, 2, 3, and 4 esophagitis, respectively.<sup>17</sup> Thus, these drugs appear to be effective mainly for healing and symptom relief in patients with mild to moderate erosive esophagitis. H<sub>2</sub> blockers are very effective in alleviating symptoms of GERD as well.<sup>7</sup> Standard doses of H<sub>2</sub> blockers provide symptomatic relief in 32% to 82% of cases with documented erosive esophagitis and healing in 0% to 82% of cases.<sup>18</sup> In a recent study, a single 10-mg dose of famotidine produced a significantly more profound antisecretory effect than a single 10-mg or 20-mg dose of the PPI omeprazole.<sup>19</sup> Thus, famotidine appears to be superior to PPIs for episodic symptom relief of heartburn, although correlation with symptoms was not evaluated.

#### Promotility Agents

Although GERD is primarily considered to be a motility disorder, the clinical response in patients treated with promotility drugs has not been satisfactory. Promotility drugs improve esophageal peristalsis and thus enhance esophageal clearance and neutralization of acid by saliva, increase LES pressure, and improve gastric emptying.<sup>20</sup> However, few of the promotility agents have proven efficacious in the clinical management of GERD, and many promotility agents have

been associated with an unacceptable incidence of side effects.<sup>20</sup> Bethanechol, a cholinergic agonist, has been associated with significant side effects, profoundly limiting its use in GERD patients.

**Metoclopramide.** Metoclopramide was the first substituted benzamide derivative with prokinetic and antiemetic effects. Metoclopramide significantly increases basal LES pressure and decreases reflux episodes, commonly during the third and fourth hours postprandially.<sup>21</sup> However, the clinical efficacy of this drug as a sole treatment for GERD has not been consistently substantiated, and the side-effect profile of metoclopramide makes the drug unattractive for regular use.<sup>22</sup> The drug's action is mediated through blockade of the central and gut dopaminergic receptors and the release of acetylcholine from postganglionic nerves in the myenteric plexus. The ability of metoclopramide to cross the blood-brain barrier has resulted in various side effects such as extrapyramidal movement disorders, restlessness, confusion, insomnia, and drowsiness. These side effects may occur in up to 30% of patients, and elderly patients appear to be most vulnerable to these adverse events.

**Cisapride.** The introduction of cisapride has made available a safer prokinetic drug with more reliable data to support its use in treating GERD. Cisapride is a serotonin receptor agonist, which enhances the release of acetylcholine from postganglionic nerve endings in the myenteric plexus.<sup>7</sup> Cisapride is as effective as standard doses of cimetidine or ranitidine and is somewhat more effective than metoclopramide.<sup>22</sup> The drug is administered four times daily, which may adversely affect patient compliance. However, cisapride at a dose of 20 mg twice daily was found to be as effective as 10 mg four times daily in symptom control and esophagitis healing.<sup>23</sup> Furthermore, a recent study demonstrated that cisapride at a dose of 20 mg four times daily was superior to 10 mg four times daily in improvement of both daytime and nighttime heartburn and healing of erosive esophagitis.<sup>24</sup> Overall, the drug appears to be most useful in patients with mild to moderate GERD.

**Other promotility drugs.** Other promotility drugs, such as erythromycin and domperidone, have not yet been found to have a significant clinical role in the management of GERD. However, several macrolide derivatives are currently being evaluated for mild to moderate GERD.

#### Proton Pump Inhibitors

PPIs were recently introduced to the market for GERD and rapidly gained popularity because of their profound acid inhibitory effect. PPIs, of which only

omeprazole and lansoprazole are currently available in the United States, irreversibly and noncompetitively inactivate the parietal cell H<sup>+</sup> - K<sup>+</sup> -ATPase (ie, the proton pump) located in the secretory apparatus of the parietal cell membrane.<sup>7</sup> Omeprazole (20 mg/day) is more effective than placebo or standard doses of H<sub>2</sub> blockers: symptomatic relief occurred in a mean of 83% of cases (62% to 94%) during a period of 4 to 8 weeks, and esophagitis healing occurred in 78% of cases (62% to 94%) in a comparable period.<sup>18</sup>

The response to PPIs decreases with more advanced esophagitis. Treatment with omeprazole at a dose of 20 mg/day or 40 mg/day for 4 weeks achieved a healing rate for grade 2 esophagitis of 87% of cases and 97% of cases, respectively; for grade 3 esophagitis, the same dosages and length of treatment achieved a healing rate of 67% of cases and 88% of cases, respectively.<sup>25</sup> For grade 4 esophagitis, however, omeprazole at a dose of 20 mg/day resulted in a healing rate of only 48% of cases, which was not significantly different from the 44% healing rate achieved by 40 mg/day.<sup>25</sup> Lansoprazole at a dose of 30 mg twice daily is as effective as omeprazole at a dose of 40 mg/day in an intent-to-treat analysis of symptom relief.<sup>26</sup> Although both drugs appear to be equally effective in equivalent doses, at least one report suggests faster symptom relief with lansoprazole.<sup>27</sup> This finding is probably a result of the higher bioavailability of lansoprazole compared with omeprazole.

#### MAINTENANCE THERAPY

GERD is a chronic disease that requires maintenance treatment in most patients. Patients with severe disease are most prone to relapse after discontinuing medical treatment, regardless of the therapy.<sup>7</sup> Furthermore, patients with erosive esophagitis may suffer a relapse to a more severe grade of esophagitis or even develop a GERD-related complication.<sup>28</sup> A recent study compared five antireflux regimens in maintaining GERD patients who were healed with omeprazole at a dose of 40 mg/day.<sup>29</sup> Efficacy of treatment was determined by the absence of esophageal mucosal injury after 12 months. In an intent-to-treat analysis, the patients who remained in remission were 49% of the ranitidine group, 54% of the cisapride group, 66% of the ranitidine-plus-cisapride group, 80% of the omeprazole group, and 89% of the omeprazole-plus-cisapride group. Although the number of patients in each group was relatively small, this study demonstrated the superiority of PPIs in long-term maintenance therapy. Lansoprazole at a dose of 15 mg/day was as effective as 30 mg/day in maintaining healing and

controlling symptoms.<sup>30</sup> In contrast, omeprazole demonstrated a dose-response relationship, in which 20 mg/day provided significantly better endoscopic healing and symptomatic relief than 10 mg/day.<sup>31</sup>

PPIs are well tolerated by most patients and are associated with minimal side effects, but several concerns about their long-term use have recently been raised. Long-term maintenance therapy with omeprazole was accompanied by a two-fold to three-fold persistent increase in gastrin levels and an increase in micro-nodular argyrophil cell hyperplasia and subatrophic or atrophic gastritis.<sup>32</sup> A more recent study suggested that the presence of *Helicobacter pylori* increases the risk for the development of atrophic gastritis in patients treated with long-term omeprazole.<sup>33</sup> Although the latter issue remains controversial, many physicians have adopted the practice of eradicating *H. pylori* before initiating long-term treatment with a PPI. However, enthusiasm about this practice should be tempered because early reports indicate that eradication of *H. pylori* appears to significantly increase acid reflux, possibly by disappearance of gastritis and recovery of acid secretion. Thus, it appears that *H. pylori* may have a protective role against GERD.<sup>34-37</sup> In addition, discontinuation of long-term high-dose omeprazole or replacement by an H<sub>2</sub> blocker has been associated with gastric acid hypersecretion and parietal cell hyperplasia, which revert toward normal by 3 months.<sup>38</sup> This reversion may suggest the need for tapering the PPI dose to avoid possible complications of gastric acid hypersecretion. In one study, abrupt withdrawal of a high-dose PPI resulted in rapid progression to esophageal stricture and duodenal ulcer formation in patients with prior normal upper endoscopy.<sup>38</sup>

Antacids and sodium alginate provide only short-term relief of symptoms and thus have no role in maintenance therapy. Studies assessing the role of promotility drugs in maintaining remission are scarce. Cisapride has been demonstrated to significantly increase symptomatic and endoscopic remission rates compared with placebo, but cisapride was ineffective in patients with severe erosive esophagitis before healing. H<sub>2</sub> blockers are effective in preventing relapse in patients with mild or no esophagitis. However, increased doses are often needed, and tolerance may develop over time.

In young adults with GERD, who may require life-long treatment with a PPI, antireflux surgery offers a more cost-effective alternative.<sup>39</sup> Nissen fundoplication, which provides a 360-degree wrap around the lower esophageal sphincter, is the most common technique and can be performed by means of laparoscopy. This option and its advantages and disadvantages

should be discussed first with the patient, who should be referred only to a surgeon skilled and experienced in performing this procedure.

#### Maintenance Therapy for Patients with Refractory Disease

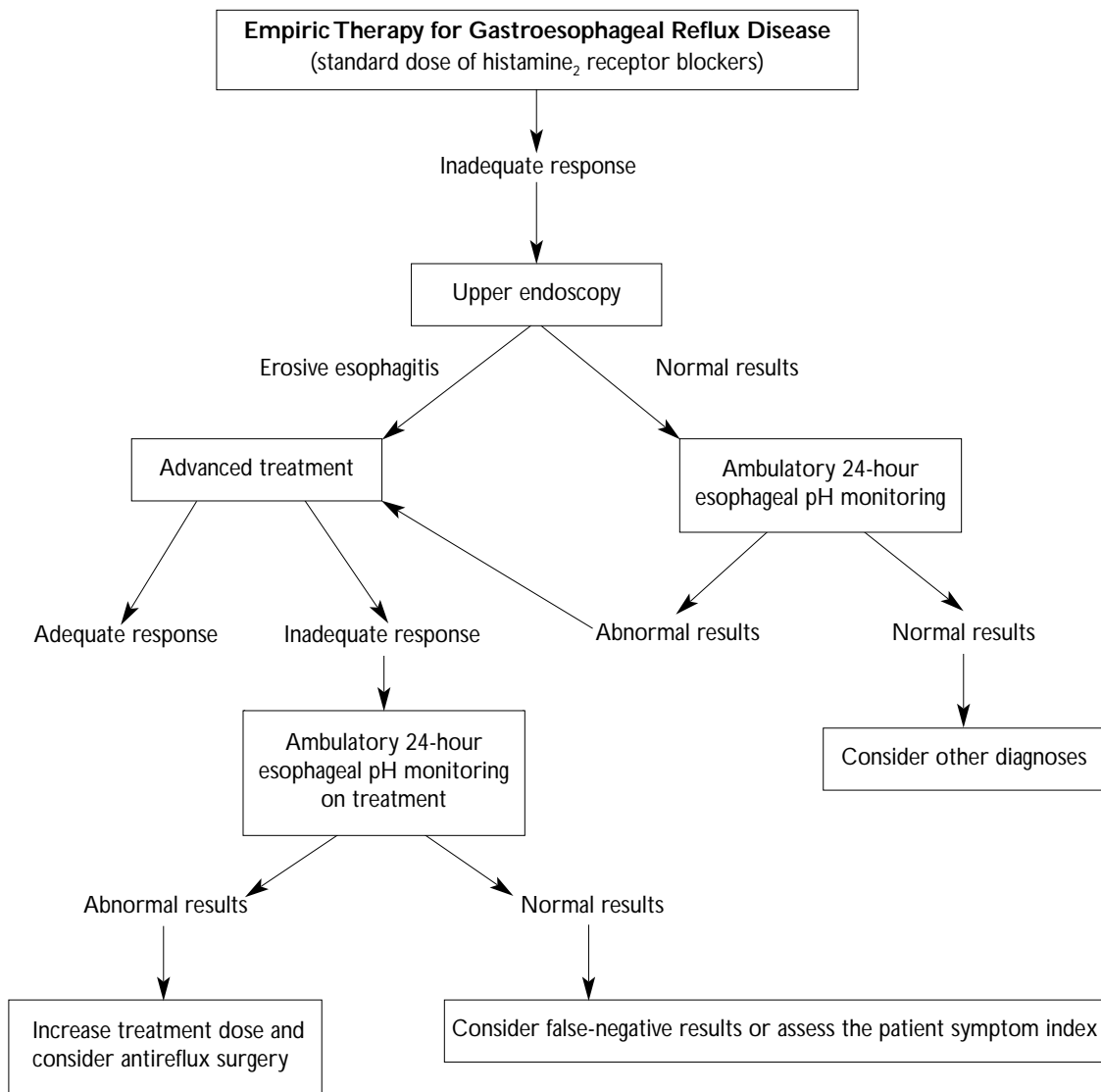
Patients who remain symptomatic on standard doses of H<sub>2</sub> blockers require further evaluation. Upper endoscopy permits direct visualization of esophageal mucosa and identification of active inflammation. In addition, this procedure can also detect complications of GERD, such as esophageal ulceration, stricture, and Barrett's esophagus. A discussion of the treatment of these complications is beyond the scope of this review.

In patients who still demonstrate esophageal mucosal injury, several treatment options are available. Higher doses of some H<sub>2</sub> blockers (ranitidine at a dose of 150 mg to 300 mg and famotidine at a dose of 20 mg to 40 mg, twice daily) may be required to promote esophageal healing and symptom relief.<sup>7</sup> In some patients, doses of ranitidine as high as 3000 mg/day have been used to achieve endoscopic healing. Nizatidine, however, is the only H<sub>2</sub> blocker that is currently approved for erosive and ulcerative esophagitis with a standard dose. Combining H<sub>2</sub> blockers with promotility drugs may achieve a modestly improved clinical response. Metoclopramide plus cimetidine has been shown to improve endoscopic healing in 42% to 55% of cases.<sup>40</sup> Similarly, cisapride enhances the effectiveness of cimetidine for esophageal healing.<sup>41</sup> On the basis of cost considerations and clinical efficacy, however, initiating treatment with a PPI in refractory GERD patients is superior to combination therapy or increased H<sub>2</sub> blocker doses.

In patients who fail PPI therapy, ambulatory 24-hour esophageal pH monitoring is warranted. This evaluation, which is performed while the patient is receiving treatment, is used to determine the extent of residual acid exposure. In select patients, doses as high as 80 mg/day of omeprazole are needed to adequately suppress gastric acid secretion.<sup>7</sup> In this group of patients, the option of surgical intervention should be considered. The recent introduction of laparoscopic Nissen fundoplication has increased the popularity of this intervention compared with long-term aggressive medical therapy. However, comparison studies of surgical treatment versus optimal medical management have not yet been performed.

#### COST CONSIDERATIONS

Figure 1 suggests an algorithm for the clinical management of patients with typical GERD symptoms.

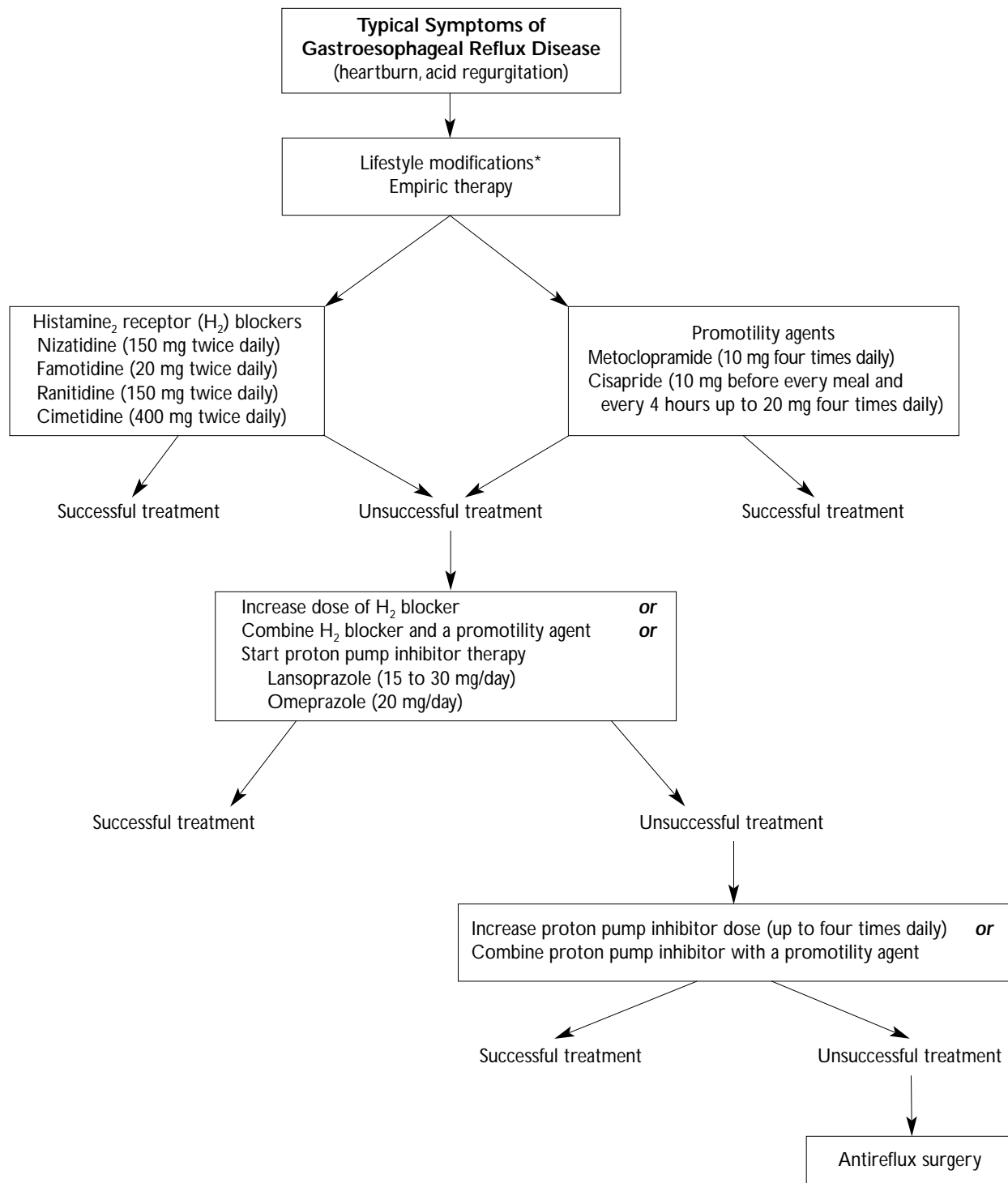


**Figure 1.** Empiric therapy for patients with gastroesophageal reflux disease.

Initiating empirical therapy is far more cost effective than evaluating all patients with GERD symptoms. An important exception to this approach is the patient with alarming symptoms, a case in which further evaluation is clinically indicated. Treatment can be tailored to the patient's symptoms and advanced gradually from H<sub>2</sub> blockers to PPIs until symptom relief is achieved. This "step-up" approach is illustrated in **Figure 2**. Another option is to start treatment with a PPI and gradually step down to the lowest regimen that provides the patient with symptom relief (ie, the "step-down" approach). However, switching from a PPI to an H<sub>2</sub> blocker or a promotility agent may result in a surge

of GERD symptoms, which may necessitate tapering the PPI dose.

In the era of managed care, cost considerations are an increasingly important incentive for choosing therapy for patients with GERD. In GERD, inexpensive treatment does not always equal cost-effective treatment.<sup>42</sup> The most cost-effective strategy is the one that cures the patient and prevents relapse.<sup>42</sup> Thus, in patients with erosive esophagitis, starting with a PPI, which is more expensive than H<sub>2</sub> blockers, may reduce the cost of additional visits to the physician, supplemental therapy, or even further investigation. However, prescribing an H<sub>2</sub> blocker rather than a PPI



**Figure 2.** Algorithm for the “step-up” approach to the treatment of gastroesophageal reflux disease.

to treat less severe GERD may still represent an effective and inexpensive therapeutic option.

The introduction of laparoscopic Nissen fundoplication has shifted attention back to surgical management. The new technique reduces incisional pain and disability and shortens hospital stay after surgery. In a large multicenter study that compared surgical therapy with medical management, surgery was found to be significantly more effective in improving symptoms and endoscopic signs of esophagitis for up to 2 years.<sup>43</sup> Although PPIs were not used in this study, an economic analysis revealed that surgery is more cost-effective in young patients than medical management that included omeprazole.

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