

## Acid-Related Disorders: Successful Management Strategies in Primary Care

### What We Know About Acid-Related Disorders

- 60 million Americans have heartburn at least once a month
- Only about 5% of people with moderately severe heartburn seek a clinician's care

### Learning Objectives

After completing this activity, participants should be better able to:

- Identify patients at risk for gastrointestinal (GI) complications of acid-related disorders
- Describe effective strategies for managing gastroesophageal reflux disease (GERD)
- Discuss options for minimizing GI risk in patients requiring nonsteroidal anti-inflammatory drug (NSAID) therapy

### GERD: Common Yet Undertreated

Almost everyone occasionally has acid reflux—a sour taste and a burning sensation caused when noxious stomach contents surge through the lower esophageal sphincter (LES) into the esophagus. For many people, gastroesophageal reflux occurs often enough to cause chronic physical symptoms and, according to an evidence-based definition from the 1997 Genval Workshop Expert Panel, “clinically significant impairment of health-related well-being (quality of life) due to reflux-related symptoms.”<sup>1</sup>

**A successful trial of PPI therapy confirms GERD diagnosis in patients with heartburn and regurgitation**

**Does hiatal hernia contribute to GERD?**  
See page 98

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Although difficult to determine accurately, the prevalence of GERD usually is based on the estimated frequency and severity of the hallmark symptoms of regurgitation and heartburn.<sup>2</sup> The American College of Gastroenterology (ACG) estimates that more than 60 million people in the United States have heartburn at least once a month, and some surveys indicate that more than 15 million Americans have symptoms daily.<sup>3</sup> Several North American population-based studies conducted in the 1990s reported that 13% to 20% of participants reported weekly heartburn and/or regurgitation.<sup>4</sup> Although these numbers suggest that GERD is common, most people with GERD symptoms do not seek a clinician's advice: in 1 survey, only 5.4% of respondents with long-standing, moderately severe heartburn indicated that they sought medical care because of their symptoms.<sup>5</sup>

### GERD Versus NERD

The term *GERD* can include any complaint or complication caused by the passage of gastric juice from the stomach into the esophagus. In addition, there is a broad range of manifestations of GERD. The best-characterized cases of GERD are those that appear on endoscopy. This group includes patients with erosive esophagitis, esophageal strictures, esophageal ulcerations with the potential to bleed, Barrett's metaplasia (also called Barrett's esophagus: a premalignant condition in which the normal pink squamous epithelium of the esophagus is replaced by abnormal red tissue resembling the intestinal lining), and esophageal adenocarcinoma, which is the most severe complication of GERD. More commonly, patients have symptoms of GERD and a negative endoscopy, a condition called nonerosive reflux disease (NERD). Although gastroesophageal reflux in NERD does not cause macroscopic injury to the esophageal lining, patients often complain of symptoms as severe as those reported by patients with esophageal damage.<sup>2</sup> Thus, the focus of management in NERD is on relieving symptoms and improving quality of life.<sup>6</sup> In addition to esophageal symptoms (eg, heartburn, regurgitation) and damage, a patient with GERD may have signs and symptoms that are not directly related to the esophagus, such as chronic cough, hoarseness, asthma, noncardiac chest pain, and other disorders of the mouth, throat, and airway.<sup>6</sup>

### GERD: Not Just a Matter of Acid

Contrary to what is widely believed, acid-reflux disease usually is not caused by too much acid. Instead, it is a signal that acid is in the wrong place. Causes include transient relaxations of the LES and other anatomic or functional faults that compromise the antireflux barrier at the junction of the esophagus and the stomach. Other causes include delayed acid clearance, ineffective esophageal motility, impaired tissue resistance to injury, and pH of the refluxate.<sup>2</sup>

The development and severity of acid-related disease depend on the balance between aggressive and protective mechanisms.<sup>2</sup> Aggressive factors—how often acid reflux occurs, the caustic nature of the refluxed acidic gastric juice—are the primary determinants, with defensive factors—esophageal tissue resistance, acid clearance—close runners-up.<sup>2,7</sup> Possibly the most important defensive factor is the esophagogastric junction comprising the LES and the crural diaphragm, which work in tandem to stop the flow-back of

stomach contents into the esophagus.<sup>2</sup> While it may be more accurate to describe GERD as an esophageal motor disorder rather than an acid-peptic disorder, the disease usually is considered acid mediated because the overall burden of acid in the esophagus and how the esophageal mucosa responds to this burden are the factors that determine whether symptoms will develop.

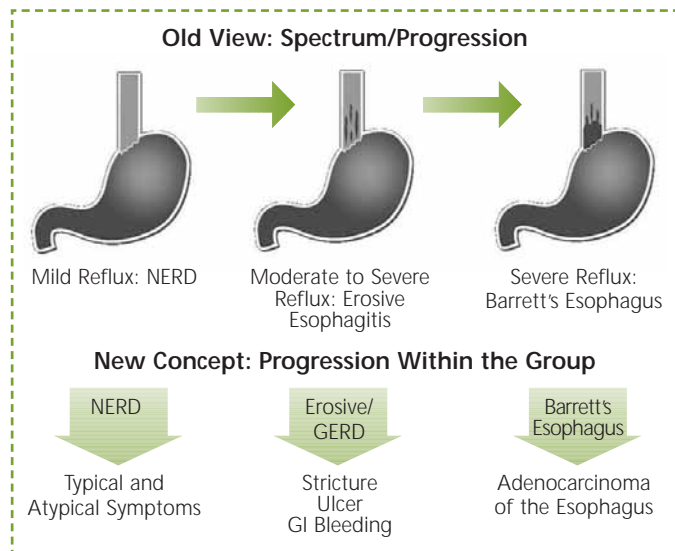
The primary therapeutic goal in GERD is to make the refluxate less caustic.<sup>8</sup> A few existing medical therapies can curb the frequency of reflux events, but these agents are not available in the United States and/or have unacceptable side effect profiles. None are effective as monotherapy for GERD. In addition, because there are no noninvasive therapies that correct the anatomic and motor abnormalities known to cause GERD, current treatment approaches are compensatory rather than curative.<sup>8</sup>

## The Natural History of GERD: A New Concept

A solid understanding of GERD's natural history is essential in planning a long-term management strategy. As the disease profile of patients with NERD has emerged, notions of disease progression in GERD have veered from a strictly linear model. Traditionally, GERD was viewed as a disease spectrum with patients with NERD on the less severe end. As the disorder progressed, the defensive mechanisms in the esophageal mucosa weakened causing erosive esophagitis and progressively more severe manifestations, such as Barrett's esophagus and esophageal adenocarcinoma (Figure 1).<sup>4</sup>

Although patients with NERD may develop mild esophageal erosions, most will not progress to erosive disease. Moreover, it is inaccurate to label NERD as a less severe form of GERD. Many patients with NERD have symptoms that are as severe as those in patients with esophageal erosions, and results of studies with acid-mediating GERD therapies show that patients with NERD generally need therapy as intensive as patients with erosive esophagitis, but are less responsive to such treatments.<sup>6</sup>

Prompted by these findings, a new conceptual framework for GERD classifies patients according to phenotypic presentation (Figure 1). According to this framework, patients are



**Figure 1.** Old view and new concept of progression in GERD. Adapted from Fass R et al.<sup>6</sup>

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classified into 1 of 3 groups of acid-related disease based on their initial presentation: the NERD group, the erosive/GERD group, and the group with Barrett's esophagus.<sup>6</sup> Patients who present with NERD continue to have NERD and, in the large majority of cases, do not develop erosive esophagitis. Patients who present with erosive esophagitis may develop esophageal strictures and ulcers that can bleed. Finally, patients with Barrett's esophagus may develop esophageal adenocarcinoma.<sup>6</sup>

This is not to suggest that patients with GERD and Barrett's esophagus are the only ones at risk of developing esophageal adenocarcinoma. The relationship between this most severe GERD complication and GERD symptoms is an important consideration in the natural history and management of GERD. A landmark, population-based, case-control study investigated the association between GERD symptom frequency and severity and the risk of esophageal adenocarcinoma in 1438 patients in Sweden. As the frequency, severity, and duration of symptoms increased, so did the risk of esophageal adenocarcinoma. For example, the risk of adenocarcinoma in patients who had reflux symptoms at least once a week was almost 8 times higher than in those with no symptoms. Patients who had symptoms for more than 20 years had an odds ratio (OR) for esophageal adenocarcinoma of 16.4, while those with the most severe symptoms had an OR of 20.0. The association between frequent, severe, and persistent GERD symptoms and esophageal adenocarcinoma risk is substantial.<sup>9</sup>

With regard to the natural history of GERD, critical considerations include the likelihood of disease progression for certain patient groups and the adoption of the best management approach based on the likelihood of progression. The majority of patients who present with NERD will never develop esophageal erosions; a small percentage may develop esophagitis, which is usually mild and never severe. Erosions resulting from esophagitis may be healed with acid-mediating therapy, but symptoms will continue. If left untreated, this group of patients can progress to worse complications, such as esophageal ulcer or stricture. Barrett's esophagus can develop after years of reflux disease, but usually is diagnosed on initial endoscopy and typically persists despite antireflux therapy. This condition may progress to adenocarcinoma; however,

a sizable proportion of adenocarcinoma diagnoses are made without prior evidence of Barrett's esophagus.<sup>6</sup>

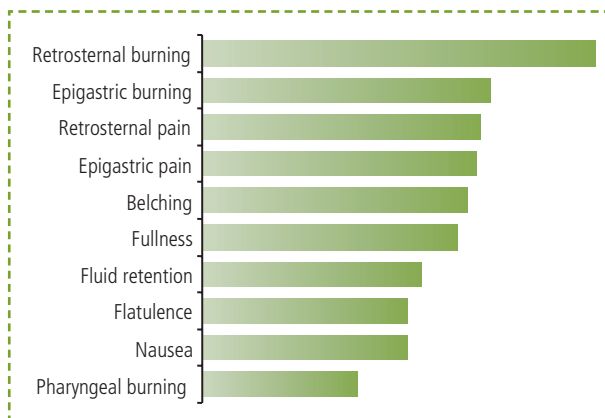


Figure 2. Symptoms reported by patients with GERD.

### GERD Symptoms: Diagnosis and Management

Symptoms of heartburn and regurgitation are specific for GERD. Thus, patients who present with these hallmark symptoms are appropriate candidates for empiric therapy.<sup>8</sup> A representative study

evaluated symptomatology in 304 patients referred for 24-hour esophageal pH monitoring. Of a range of symptoms considered to be related to GERD, only heartburn (68% vs 48%) and acid reflux (60% vs 48%) occurred in more patients with GERD determined by pH monitoring than in patients with normal pH on monitoring.<sup>10</sup>

Symptoms do not predict the extent or severity of esophagitis, nor do they reliably predict complications of GERD, including Barrett's metaplasia. Endoscopic biopsy is needed to determine whether Barrett's metaplasia is present, but it is vital to understand that while endoscopy showing evidence of Barrett's metaplasia or esophagitis confirms the diagnosis of GERD, a normal endoscopy does not rule out GERD. In addition, documentation of the presence or absence of esophagitis usually does not determine how the clinician initially approaches management of a patient with GERD.<sup>8</sup> Patients reporting heartburn and regurgitation may also complain of flatulence, nausea, fluid retention, and fullness, but these symptoms are not typically predominant and may indicate a functional component in the pathology (Figure 2).

Empiric proton pump inhibitor (PPI) therapy is a reasonable initial measure in primary care. If successful, it confirms the presence of GERD in patients who present with heartburn and regurgitation.<sup>8</sup> The hallmark symptoms of heartburn and regurgitation have a positive predictive value of >80% for GERD, and most patients with these symptoms are candidates for PPI therapy. According to the ACG 2005 updated practice guidelines, "If the patient's history is typical for uncomplicated GERD, an initial trial of empirical therapy (including lifestyle modification) is appropriate."<sup>8</sup> However, even when the most effective therapy is prescribed, some patients will continue to reflux acid.<sup>8</sup> Additional diagnostic testing should be considered in patients who do not respond to therapy, present with alarm symptoms that indicate complicated disease, or have symptoms long enough to put them at risk for Barrett's metaplasia (Table 1). Typical alarm symptoms are dysphagia, odynophagia, bleeding, unintentional weight loss, and anemia.<sup>8</sup>

Less clear-cut is the decision to screen for Barrett's esophagus. Although no single study shows that endoscopic screening for Barrett's can prevent further complications or that screening is cost effective, there is general agreement that patients aged >50 years or who have had heartburn for at least 5 years are at risk for Barrett's esophagus and should undergo endoscopy.<sup>11</sup>

### When to Refer a Patient With GERD for Further Testing

- Alarm symptoms
  - Refer a patient with any of these symptoms for further testing: dysphagia, odynophagia, persistent vomiting, anorexia, unintentional weight loss, anemia, fever, GI bleeding (occult or overt)
- Failure of empiric therapy
  - No response to trial of PPI
- Screening for Barrett's esophagus
  - Symptoms ≥5 years
  - Age >50 years

Adapted from DeVault KR et al<sup>8</sup>; Sampliner RE.<sup>11</sup>

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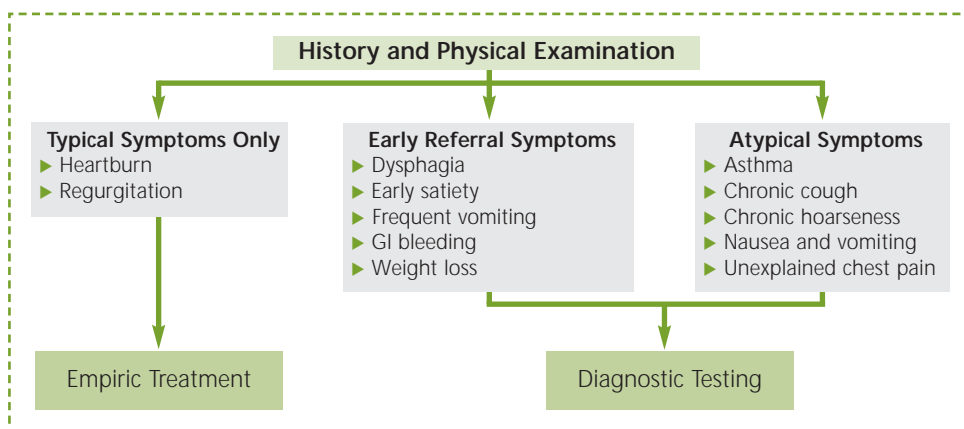


Figure 3. Managing patients with GERD symptoms. Adapted from Katz PO.<sup>12</sup>

### Diagnostic Approaches

For patients with the typical GERD symptoms of heartburn and regurgitation, primary care providers may initiate a trial of PPI therapy (Figure 3).<sup>12</sup> Referral for diagnostic testing is warranted when patients have alarm symptoms or other symptoms outside the typical picture of GERD.<sup>12</sup> However, a trial of empiric therapy may be indicated for certain patients with atypical symptoms. For example, if a patient with chronic cough, hoarseness, or laryngitis is not responding to appropriate therapies and questioning elicits a GERD symptom profile, it would be reasonable for the primary care clinician to initiate PPI therapy and evaluate the response before referring the patient for endoscopy or pH monitoring.

Diagnostic techniques for GERD include endoscopy, ambulatory pH monitoring, esophageal manometry, and barium esophagogram. Each of these tests has its place in investigating different aspects of reflux disease. Techniques most often used are endoscopy and esophageal pH monitoring.

*Endoscopy* allows direct visualization of the esophagus and should be considered at the outset if a patient has symptoms suggesting complicated GERD or is at risk for Barrett's esophagus. It is the technique of choice to diagnose GERD-related damage such as erosions and strictures and may uncover an alternative diagnosis, such as eosinophilic esophagitis, in patients who do not respond to PPI therapy (Figure 4).

*Ambulatory pH monitoring* is used to determine the pH of the distal—and sometimes the proximal—esophagus, identify

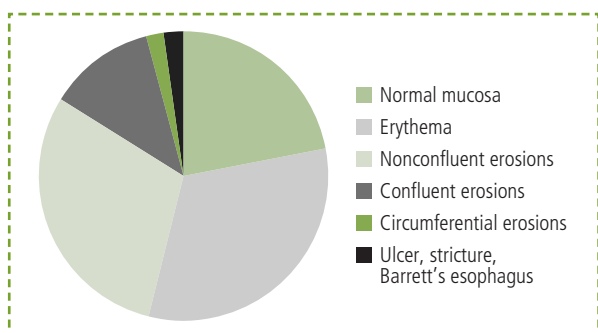


Figure 4. Esophageal conditions commonly shown on endoscopy in patients with GERD.

patients with excessive esophageal acid exposure (EAE), and correlate symptoms with EAE. This technique helps confirm acid reflux in patients with persistent symptoms who have no endoscopic evidence of mucosal damage, especially when a trial of acid-suppression therapy has failed. Ambulatory pH monitoring also helps the clinician know how well reflux is controlled in patients who continue to have symptoms despite therapy.

*Esophageal manometry* has limited use for the actual diagnosis of GERD and is used mostly to guide the placement of pH monitoring probes. Manometric evaluation of esophageal motility also may be helpful prior to antireflux surgery to exclude achalasia and severe esophageal motor abnormalities.

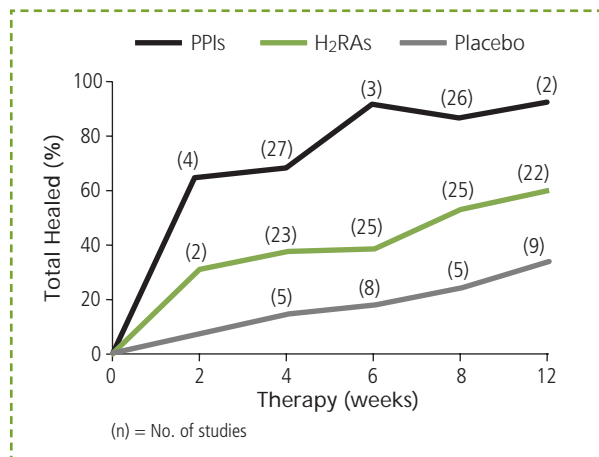
A *barium esophagogram* is no longer recommended for routine GERD diagnosis, but is reasonably accurate for detecting severe esophagitis. It is much less accurate for diagnosing mild esophagitis and is not accurate for diagnosing Barrett's esophagus.<sup>8</sup> Newer diagnostic techniques, such as impedance and tubeless pH monitoring, hold promise for improving GERD detection. However, additional study is needed to determine their value in GERD management.<sup>8</sup>

## Acid-Suppression Therapy

For most patients, acid-peptic disorders, including GI effects of NSAIDs, can be managed with medical therapy in the primary care setting. Currently, acid suppression, which is the primary goal of GERD treatment, relies on 2 classes of agents: histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) and PPIs. Antacids, which alter the pH of the refluxate but not through acid suppression, are of limited use beyond supplemental or rescue therapy in patients with anything worse than mild GERD symptoms.<sup>8</sup>

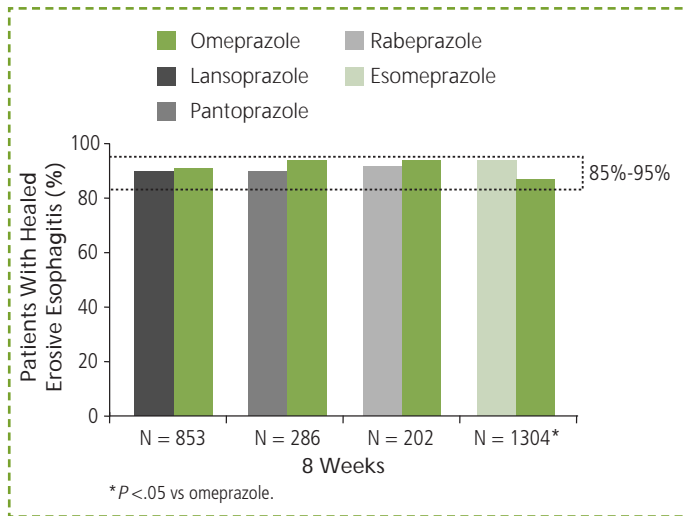
## Choosing Among Agents

Numerous studies and meta-analyses have confirmed that PPIs are superior to H<sub>2</sub>RAs in terms of overall efficacy in GERD. A meta-analysis of 43 studies (N = 7635) showed that PPIs were more effective than H<sub>2</sub>RAs, which, in turn, were more effective than placebo in healing esophageal erosions over 2 to 12 weeks of treatment (Figure 5).<sup>13</sup> The overall healing rate was 83.6% for PPIs compared with 51.9% for H<sub>2</sub>RAs and 28.2% for placebo. The mean percentage of patients who were heart-burn free was highest with



**Figure 5.** Meta-analysis: rates of healing of erosive esophagitis: PPIs, H<sub>2</sub>RAs, and placebo. Adapted from Chiba N et al.<sup>13</sup>

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**Figure 6.** Healing of erosive esophagitis: PPIs vs omeprazole. Adapted from Castell DO et al<sup>15</sup>; Mössner J et al<sup>16</sup>; Dekkers CP et al<sup>17</sup>; Kahrilas PJ et al.<sup>18</sup>

PPIs (77.4%) compared with H<sub>2</sub>RAs (47.6%), and PPIs resulted in more rapid healing and symptom relief.<sup>13</sup>

A more recent meta-analysis comparing individual PPIs with ranitidine showed that each agent was more effective than the H<sub>2</sub>RA, with varying healing rate ratios.<sup>14</sup> The analysis of 53 randomized, controlled clinical studies assessed acute healing and healing maintenance rates in endoscopically documented erosive esophagitis. Protocols included a PPI in at least 1 treatment arm. The healing rate ratio over 8 weeks compared with ranitidine was 1.62 (95% confidence interval [CI], 1.46-1.76) for lansoprazole, 1.36 (95% CI, 1.20-1.54) for rabeprazole, 1.60 (95% CI, 1.33-1.96) for pantoprazole, and 1.58 (95% CI, 1.41-1.78) for omeprazole. Each of the agents was more efficacious than the H<sub>2</sub>RA.<sup>14</sup>

Regardless of the PPI chosen, treatment with this class of agents is extremely effective. Results of studies comparing pantoprazole, lansoprazole, rabeprazole, and esomeprazole with omeprazole, the oldest PPI, show a healing range of 85% to 95% for all PPIs (Figure 6).<sup>15-18</sup> Notably, the study investigating healing with esomeprazole demonstrated a statistically significant difference for that agent compared with omeprazole; however, the study population of >1300 patients<sup>18</sup> was much larger than the study population in the studies of lansoprazole, pantoprazole, and rabeprazole, which enabled the results to show statistical significance. Additionally, efficacy varies according to the severity of esophagitis. Healing rates in patients with more severe erosions tend to be lower than in patients with mild esophagitis.

### A Long-Term Condition Needs Long-Term Treatment

Most patients with GERD need long-term treatment. After erosive esophagitis has been healed with acute PPI treatment, therapy must continue to maintain healing. A Cochrane literature review confirms that maintenance therapy with the same PPI dose used acutely to heal erosive esophagitis is most effective in preventing relapse.<sup>19</sup> This review evaluated the data concerning the efficacy of acute healing doses and standard maintenance doses of

PPIs, as well as H<sub>2</sub>RAs and placebo, in preventing erosive esophagitis relapse over 24 to 52 weeks of follow-up. Approximately 58% to 66% of patients relapsed on H<sub>2</sub>RA maintenance therapy. By comparison, 29% to 39% of patients relapsed on maintenance PPI therapy, and only 18% to 23% of patients relapsed when continued at the acute healing dose of PPIs.<sup>19</sup>

### **Benefits of Continuous Treatment**

Motivating patients to continue daily maintenance treatment for any chronic condition poses a challenge. Several studies have investigated less-than-daily use of PPIs as on-demand or intermittent therapy for maintaining symptom relief and/or healing esophageal erosions.<sup>20-23</sup> As expected, using a PPI on demand and less often than daily is not as effective as daily (ie, continuous) therapy for maintaining healing. In a study comparing continuous and intermittent esomeprazole regimens for maintaining healing of erosive esophagitis, 81% of patients were in remission after 6 months of continuous treatment versus 58% of patients who took the PPI on demand.<sup>20</sup>

Efficacy of both regimens decreased as the severity of disease increased. For example, 93% and 78% of patients with Los Angeles (LA) classification A (ie, mild) erosive esophagitis remained in remission with continuous and on-demand therapy, respectively. These percentages dropped to 80% and 44%, respectively, in patients with LA grade D (ie, severe) disease.<sup>20</sup> On-demand therapy is not appropriate for erosive esophagitis. These patients need continuous therapy.

### **NERD: A Special Case**

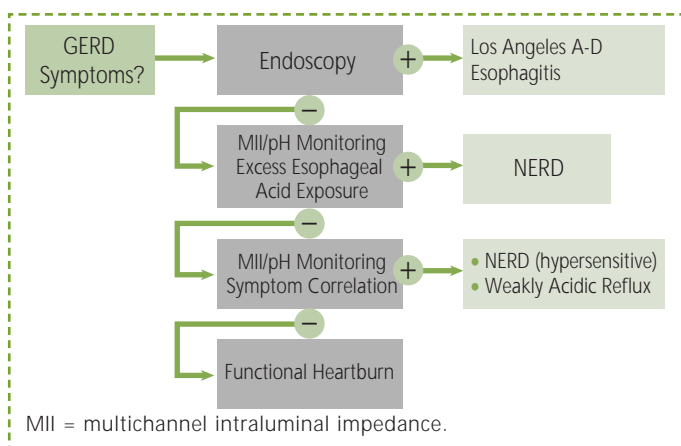
Symptom relief is the primary measure of therapeutic efficacy in patients with NERD because they have no esophageal injury to heal. Several randomized, placebo-controlled studies have shown that on-demand PPI treatment can be effective in patients with NERD.<sup>21-23</sup> The results of studies with lansoprazole, rabeprazole, and esomeprazole showed that on-demand PPI therapy was significantly more effective than placebo for the end point of time to treatment discontinuation due to inadequate heartburn control ( $P < .05$ ). In each trial, asymptomatic patients took part in an on-demand extension after symptoms had been controlled with acute treatment. Discontinuation due to inadequate heartburn control with lansoprazole 15 mg on demand was 16% versus 28% with placebo.<sup>21</sup> For rabeprazole, 6% of patients discontinued treatment versus 20% with placebo, and for esomeprazole, 5% and 9% of patients taking the 20-mg and 40-mg doses, respectively, discontinued treatment compared with 36% of patients on placebo.<sup>22,23</sup>

### **When Patients Don't Respond to Acid-Suppression Therapy**

There is no consensus on what constitutes lack of response to PPI treatment. Judgment differs according to the clinician's preference and the patient's satisfaction. However, several investigators consider lack of response to be persistent symptoms despite treatment with double the Food and Drug Administration (FDA)-approved standard dose of a PPI.<sup>24</sup>

An abnormal pH monitoring test (ie, an abnormal level of EAE) in patients taking double-dose PPI therapy is rare.<sup>24</sup> Therefore, if pH testing is necessary, it should be delayed until after the conclusion of a trial of double-dose PPI.

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**Figure 7.**  
Suggested evaluation of  
PPI nonresponders.

### Other Causes of Esophageal Symptoms

- ➔ Motor disorders
- ➔ Achalasia
- ➔ Diffuse esophageal spasm
- ➔ Eosinophilic esophagitis
- ➔ Functional heartburn

Why do some patients not respond to acid-suppression therapy? The answer may be that such patients do not have reflux disease. Esophageal symptoms can arise from etiologies other than abnormal EAE (Table 2).<sup>25,26</sup>

A protocol for evaluating patients with continued GERD symptoms despite PPI treatment is shown in Figure 7. Most of the time, these patients do not have erosive esophagitis. In the absence of esophageal erosions, patients undergo ambulatory pH monitoring or combined impedance pH monitoring to investigate the persistence of excessive EAE. If the EAE level is in the normal range, pH monitoring is used to correlate symptoms with reflux.

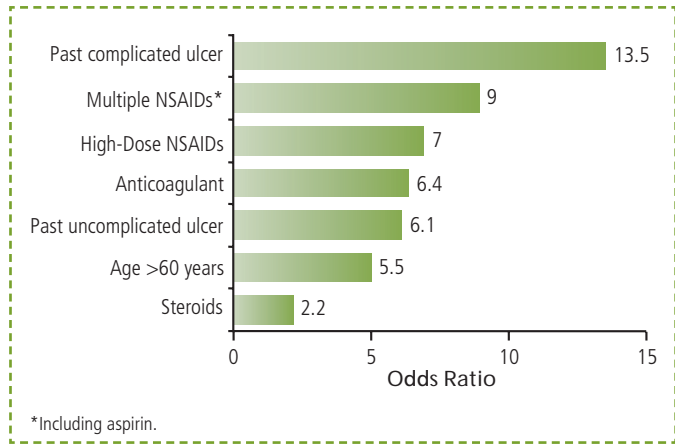
These patients have NERD with a hypersensitive esophagus; they experience symptoms at less-than-pathologic levels of EAE.<sup>25,26</sup>

Finally, there are patients for whom every test is normal and there is no symptom correlation to EAE. These patients are deemed as having functional heartburn and require a change in therapeutic approach. Psychological approaches, including low-dose antidepressants, biofeedback, and hypnotherapy, may help these patients.<sup>26</sup>

### Preventing NSAID-Related GI Effects

Nonsteroidal anti-inflammatory drugs are widely used for pain relief, and are associated with a dose-dependent risk of upper GI complications.<sup>27,28</sup> To prevent NSAID-related GI events, it is important to identify the clinical indicators of risk (Figure 8).<sup>28-30</sup> A history of upper GI bleeding and perforation (ie, complicated ulcer) greatly increases the risk of upper GI bleeding with NSAID use.<sup>28</sup> Other characteristics that increase the risk of adverse events include uncomplicated ulcer, use of multiple and/or high-dose NSAIDs, anticoagulant or oral corticosteroid therapy, and increasing age.<sup>29</sup>

In practical terms, a clinician recommending an agent for pain control must weigh the patient's background risk of an NSAID-related GI event against the cardiovascular



**Figure 8.**  
**Risk factors for NSAID-associated adverse events.**  
 Adapted from Garcia Rodriguez LA et al.<sup>28</sup>

(CV) risk indicating the need for aspirin.<sup>29</sup> A guide to NSAID therapy is shown in Table 3. For patients with low GI and CV risk who are not taking aspirin, an NSAID is appropriate. For patients with a low risk of GI complications but who are taking aspirin due to a higher risk of CV events, non-NSAID treatment for pain is advisable. An NSAID should be chosen with caution and with consideration of a gastroprotective agent. Patients in all other risk groups should be directed to a non-NSAID or to concomitant use of an NSAID with a gastroprotective agent.<sup>29</sup>

Agents indicated for prevention of NSAID-related GI effects are misoprostol, H<sub>2</sub>RAs, and PPIs. Misoprostol reduces the risk of gastric and duodenal ulcers, as well as ulcer complications.<sup>30</sup> However, the drug has a side effect profile (including diarrhea in >20% of patients) that many patients find intolerable and that may limit adherence to therapy.<sup>31,32</sup> Misoprostol is contraindicated in women of childbearing age.

Although H<sub>2</sub>RAs alleviate dyspeptic symptoms, they generally are less effective than PPIs, do not prevent gastric ulcers, and heal active ulcers only when NSAID use is discontinued.<sup>32</sup>

### Guide to NSAID Use by CV Risk

	No/Low NSAID GI Risk	NSAID GI Risk
No CV Risk (No Aspirin)	Traditional NSAID	Non-NSAID therapy or COX-2 inhibitor or Gastroprotective agent with traditional NSAID
CV Risk (Consider Aspirin)	Non-NSAID therapy or Traditional NSAID* + gastroprotective agent if GI risk warrants gastroprotection	Non-NSAID therapy or Gastroprotective agent with traditional NSAID

\*Ibuprofen should be used with caution by patients taking aspirin.

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PPIs are the agents of choice for preventing adverse GI events during NSAID use.<sup>32,33</sup> In addition to effectively alleviating dyspeptic symptoms, these agents, in contrast to H<sub>2</sub>RAs, can heal active ulcers even when NSAID therapy is continued.<sup>32</sup>

Guidance on preventing NSAID-associated GI events is available in an FDA consensus statement responding to concern over CV risks related to COX-2 inhibitors.<sup>34</sup> The FDA panel endorsed the use of an NSAID combined with a PPI rather than monotherapy with a COX-2 inhibitor and identified naproxen as the most favorable NSAID. Panel members urged caution in prescribing ibuprofen with aspirin and advised against aspirin and COX-2-selective agents in combination therapy. The panel urged cautious use of NSAIDs with concern for potential GI complications.<sup>34</sup>

### PPIs and GERD: The Long View

Acid-related disorders are both common and increasing in primary care practice. Left untreated, GERD can progress to erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Medical management of GERD is compensatory, not curative. Current medications do not address the underlying esophageal motor dysfunction, but prevent the symptoms and complications of reflux. Patients with GERD require long-term maintenance with medication.

Although the focus of GERD treatment has shifted from healing erosive esophagitis to controlling symptoms, PPIs are still the mainstay of therapy. Long-term data show that these agents generally are safe, although minor concerns exist with regard to their impact on osteoporosis<sup>33</sup> and an association with *Clostridium difficile* colitis. When patients are refractory to PPI treatment, clinicians should consider causes other than reflux disease, such as hypersensitivity of the esophagus or functional heartburn.

## CASE STUDY

### A 50-Year-Old Man With Heartburn 3 Times a Week

#### Presentation

The patient is a 50-year-old white man who experiences heartburn 3 days a week on average. Nocturnal GERD symptoms, including regurgitation and mild dysphagia, occasionally disrupt his sleep. The patient also has a chronic cough.

#### Physical Examination

- ➔ Vital signs: stable
- ➔ Height: 6 ft 2 in
- ➔ Weight: 280 lb, mild obesity
- ➔ Otherwise normal

#### Medical and Treatment History

- ➔ History includes hypertension, hypercholesterolemia, knee replacement surgery, and pulmonary embolism
- ➔ 4-week trial of over-the-counter (OTC) antacids and H<sub>2</sub>RAs
  - Mild improvement but significant breakthrough symptoms
- ➔ Other medications
  - Ibuprofen for knee pain 600 mg TID PRN
  - Hydrochlorothiazide
  - Potassium chloride
  - Atorvastatin
- ➔ No known drug allergies

#### Clinical Decision Point

##### *How would you manage this patient?*

- ➔ Empiric standard-dose PPI for 4 weeks
- ➔ Empiric PPI BID for 4 weeks
- ➔ Switch to standard dose PPI therapy and add OTC H<sub>2</sub>RA at bedtime
- ➔ Check for *Helicobacter pylori* infection

#### Comment

Most patients with clinical features similar to this patient's improve on standard-dose PPI treatment for 4 weeks. However, the triad of dysphagia, significant heartburn, and age 50 years may indicate more severe disease. The patient should be referred to a gastroenterologist, but the need for diagnostic testing does not preclude starting PPI therapy for his symptoms. Double-dose PPI therapy is not necessary and is warranted only in patients who have indications of more severe disease or after severe disease has been objectively diagnosed.

#### Clinical Decision Point

##### *Does this patient need diagnostic testing, and if so, which test?*

- ➔ No testing needed; just treatment
- ➔ *H pylori* testing
- ➔ Refer for endoscopy
- ➔ Upper GI series

#### Comment

The patient's symptom profile warrants endoscopy. Dysphagia and long-term, frequent heartburn combined with the patient's age (50 years) indicate screening for Barrett's esophagus.

Guidelines from the ACG state that an initial trial of empiric therapy is reasonable. However, diagnostic testing is warranted in patients with warning signs and those who do not respond to empiric therapy. The initial diagnostic test is most often endoscopy; depending on the results, patients may undergo esophageal pH monitoring.

Because the patient is taking ibuprofen for knee pain, antisecretory co-therapy should be considered. NSAIDs can irritate and damage the gastric mucosa. They deplete the mucosal defense mechanisms, which allows gastric juice to cause erosions. Among regular NSAID users, 15% to 30% develop ulcers whether or not they have symptoms. Ulcers often progress, and 1% to 2% of patients develop severe complications such as bleeding, perforation, and obstruction. Antisecretory co-therapy should be considered in patients with a history of ulcer; those >60 years of age; and those who take multiple NSAIDs, especially if the regimen includes aspirin, high-dose NSAID, an anti-coagulant, or oral steroids. Even CV disease by itself increases risk.

## QUESTIONS FROM SYMPOSIUM PARTICIPANTS

➔ **Q:** Do PPIs affect the absorption of vitamins and minerals?

**A:** Although PPIs are extremely potent, they do not suppress all stomach acid. Some foods and medicines require acid for absorption, and there has been concern that profound acid suppression might affect vitamin B<sub>12</sub> levels because acid is required to cleave this vitamin from food. However, the results of several meta-analyses show that this is not an important issue with PPIs. Again, because they do not completely suppress the production of stomach acid, PPIs have little potential to exacerbate iron deficiency.

➔ **Q:** What is the impact of long-term PPI therapy on osteoporosis risk?

**A:** Recent data showing an elevated risk (but a fairly low OR) for hip fracture associated with long-term use of PPIs may indicate decreased absorption of calcium.<sup>33</sup> Acid-suppressing agents dramatically improve quality of life, prevent esophageal erosions, and may prevent esophageal adenocarcinoma. An increased risk of hip fracture must be placed in context, and PPIs should not be discontinued in patients with good symptom resolution. Instead, there should be increased vigilance for osteoporosis, including lowering the threshold for osteoporosis screening and therapy and recommending vitamin D and calcium supplements. Overall, PPIs are safe, and safety concerns do not amount to a contraindication. PPIs should be used when indicated at the lowest effective dose.

➔ **Q:** Does *H pylori* infection have a role in GERD?

**A:** The interaction between GERD and *H pylori* is complicated and depends on the type of infection. Antral-predominant *H pylori* infection, which is the most common type in the United States, is associated with increased acid and duodenal ulcers and a 2- to 3-fold increased risk of adenocarcinoma. This type of *H pylori* can worsen reflux; treating it may improve reflux symptoms. In contrast, studies from Asia where body-predominant *H pylori* infection is prevalent show that it protects against Barrett's esophagus and adenocarcinoma. Currently, there are no data to support testing for *H pylori* in the management of GERD as eradication should not dramatically alter GERD severity in patients undergoing treatment. The clinical approach should be to test for *H pylori* if the patient presents with dyspepsia or has a documented peptic ulcer; serology usually is adequate. If *H pylori* is encountered it should be eradicated as it is the primary etiologic agent for gastric lymphoma and carries a 10% to 15% lifetime risk of peptic ulcer disease. Follow-up to confirm eradication usually is not needed, but in complicated cases, urea breath testing or stool antigen testing can confirm eradication.

➔ **Q:** Does hiatal hernia contribute to GERD?

**A:** The association between GERD and hiatal hernia is strong. Hiatal hernia is probably the most dramatic abnormality of the esophagogastric junction. It not only weakens the LES, but can also cause a pocket of acid to sit just beneath it, contributing to free reflux or re-reflux each time a person swallows. Patients with severe esophagitis and Barrett's esophagus usually have a severe hiatal hernia, and its presence is

an important predictor of reflux disease severity. Not all patients with hiatal hernia develop symptoms, but if a patient has a hiatal hernia and severe reflux disease, the hiatal hernia is probably an aggravating factor.

➔ **Q:** How often does endoscopy need to be repeated?

**A:** The frequency of repeat endoscopy depends on initial findings. In patients with NERD (ie, no erosions or Barrett's esophagus), repeat endoscopy is not necessary unless the patient develops a new symptom. Repeat endoscopy is needed in patients with Barrett's esophagus, although opinions differ on the interval. Recommendations are moving away from yearly endoscopy for all patients who have Barrett's esophagus. Instead, updated guidelines<sup>11</sup> recommend that patients who have only intestinal metaplasia (ie, no dysplasia) should undergo repeat endoscopy every 3 years, those with low-grade dysplasia should have endoscopy every 6 months, and those with high-grade dysplasia need endoscopic monitoring every 3 months after treatment with high-dose antisecretory therapy. Persistent high-grade dysplasia after treatment may indicate a need for esophagectomy, as 40% to 50% of such patients may have undetected adenocarcinoma.

➔ **Q:** When should surgery be considered to correct reflux?

**A:** Because PPIs are so effective, the need for fundoplication is uncommon. For surgery to be appropriate, there must be objective evidence of an abnormality such as a large hiatal hernia or Barrett's esophagus. A patient with a large hiatal hernia who has severe regurgitation affecting quality of life, despite heartburn control with a PPI, is a good candidate for surgery because there is no medical therapy to address this problem. Patients with GERD that is refractory because they cannot tolerate PPI therapy are also possible candidates. However, patients who continue to experience symptoms on a PPI but do not have an abnormal pH test are not good surgery candidates. About half of these patients have functional dyspepsia, and surgery can worsen the condition. If results of pH testing are abnormal or if impedance testing shows nonacid reflux, fundoplication may be reasonable, but it is important to confirm that the patient has PPI-refractory GERD and that failure to control symptoms is not due to lack of adherence to the medication. Finally, wanting to stop daily PPI therapy is not a good reason to have antireflux surgery. In the long term, more than 60% of patients who undergo surgery report continuing regular use of antireflux medications.<sup>35</sup>

➔ **Q:** How long should a patient continue PPI therapy?

**A:** If a patient with significant reflux disease discontinues PPI treatment, GERD will recur. This means that patients who need PPI therapy will do so for the rest of their lives. PPI treatment is compensatory, not curative, and will not correct the underlying mechanical causes of GERD, such as hiatal hernia or weak peristalsis. Surgery is the only technique that comes close to curing the condition, but more than 60% of patients who undergo surgery continue to require regular antireflux medications.<sup>35</sup> In addition, fundoplication is associated with complications, including

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dysphagia, bloating, and flatulence; if the procedure is performed correctly, the patient loses the ability to belch.

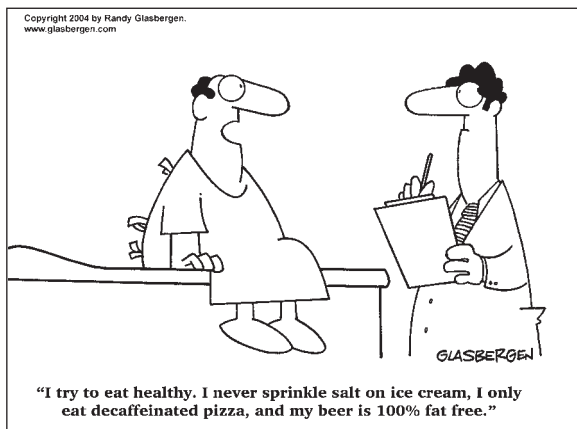
PPIs are safe medications, and long-term (10+ years) follow-up shows no increased risk for gastric adenocarcinoma in patients who use them.<sup>36</sup> There have been reports linking PPIs with community-acquired pneumonia and *C difficile* colitis. The study showing an association with pneumonias was methodologically flawed: reflux disease itself is associated with a higher rate of pneumonia, and the study did not control for PPI use as a covariate.<sup>37</sup> A 2005 study showed a 2.9 OR of *C difficile* colitis concurrent with PPI therapy,<sup>38</sup> but the absolute risk for the population is low.

➔ **Q:** Can pregnant women use acid-suppressive therapy?

**A:** It is best not to give systemic medication to a pregnant woman to avoid putting the fetus in jeopardy. However, heartburn is common in pregnancy, and treatment can be initiated with the safest medications: antacids. If antacids do not bring symptoms to a tolerable level, the next step is an H<sub>2</sub>RA. Although these drugs are not particularly effective, they can be effective enough to get a symptomatic woman through pregnancy. Ranitidine is the H<sub>2</sub>RA most studied in pregnancy. Should ranitidine fail, and the woman is not gaining weight or is vomiting, the fetus may be in jeopardy because the mother is not doing well. At this point, a PPI may be the next step—usually lansoprazole because it is category B and the PPI most studied in pregnancy. Omeprazole is the only PPI that is category C due to an association with cleft palate. Generally, the need for a PPI arises only later in pregnancy, if at all, so there is less risk to the fetus.

➔ **Q:** Is a PPI appropriate for a patient who is taking short-term (<2 weeks) NSAID therapy for an acute orthopedic problem if there are risk factors for ulcer (such as a history of uncomplicated ulcer) or no ulcer history, but the patient is also taking daily aspirin?

**A:** If the patient is taking daily aspirin and has other risk factors like previous ulcer history, a gastroprotective strategy is warranted even if the NSAID has only been prescribed for an acute problem. The risk for NSAID-associated ulcer is linear and does not change: as long as the patient is on the medication, he or she is at risk. In addition, in many cases the need for NSAID therapy recurs. PPI prophylaxis during a short NSAID course is prudent because the patient may develop a need for long-term NSAID treatment.



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