Acid suppression is the mainstay of therapy for GERD. Proton-pump inhibitors are indisputably the most effective acid suppression medications available and are the cornerstone of therapy for GERD. As GERD encompasses a heterogeneous patient group, treatment approaches should be individualized to the patient’s needs to achieve goals of GERD therapy. Despite advances in the management of GERD, there are several unmet needs in acid suppression in the areas of pharmacotherapy as well as therapeutic and diagnostic approaches. This review describes appropriate means for individualizing GERD therapy, areas for further investigation and algorithms offering a practical approach for primary care providers and specialists in treating GERD.
H. pylori, and the use of H2-RAs in control of nocturnal GERD, remain areas of controversy. Management of the patient with refractory GERD can be a challenge for practicing gastroenterologists. New and available diagnostic testing like impedance-pH testing (MII-pH) identifies patients with non-acid reflux with persisting symptoms on therapy, who will likely benefit from anti-reflux surgery. Failure to use this recent advance in diagnostic technology may result in patients with symptoms not due to GERD being referred for surgery without appropriate diagnostic evaluation.

This review examines the relative efficacies of available acid suppressing therapies and outlines evidence for the superiority of proton pump inhibitors over standard dose H2-antagonists in achieving goals of GERD therapy. The management strategies for initial and maintenance therapies are discussed comprehensively, including their cost effectiveness and the evidence for superiority of step-down and step-in approaches over the outdated step-up approach. An algorithm was constructed for primary care providers to provide a road map for approaching the majority of patients with typical symptoms of GERD. A second algorithm for specialist was constructed for evaluation of refractory GERD patients, incorporating newer diagnostic technologies like impedance-pH in addition to endoscopy. Also practical tips for optimal utilization of PPIs and essential means for achieving maximal acid suppression in refractory patients are provided. The devil is in the details, indeed!

**DEFINITION**

GERD is defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents either acidic or non-acidic into the esophagus. A broad definition of GERD includes symptoms without endoscopic findings, extra esophageal symptoms and symptoms due to non-acid reflux detected by MII-pH as opposed to conventional ambulatory pH testing.

GERD is a common condition with a complex pathophysiology. Defects in esophagogastric motility (transient LES relaxations, LES incompetence, poor esophageal clearance, and delayed gastric emptying) are central to the pathogenesis of GERD (1). Among them, the most important factor is inappropriate transient lower esophageal sphincter relaxation (TLESr). If this is the mechanism of reflux disease, why are we targeting therapy at suppression of physiologic amounts of gastric acid? Unfortunately none of the currently available promotility or other agents to decrease the frequency of TLESRs have the efficacy and favorable side-effect profile of acid suppressive therapy. Therefore, the medical management of GERD is directed at the control of gastric acidity. With the suppression of intragastric acidity, despite the continued reflux of gastric contents into the esophagus, the refluxate is rendered nonirritating to the esophageal mucosa. Acid-suppressive therapy is thus the best approach available for both the short-term and long-term management of this disease.

Gastric acid is pivotal in the pathogenesis of reflux symptoms with (erosive esophagitis) or without (non-erosive reflux disease) esophageal mucosal injury. Several randomized controlled trials (RCTs) have shown that healing of the esophagitis and symptom relief are strongly correlated with percent time the intragastric and intraesophageal pH is kept above 4, over a 24-hour period (2).

GERD has a heterogeneous presentation. For convenience, we can categorize GERD into several subgroups, although there is currently no established GERD classification:

1. **Typical GERD** presents with symptoms of heartburn and regurgitation severe enough to seek medical attention, and may be associated with erosive esophagitis on endoscopy.
2. **GERD and H. pylori**
3. **Complicated GERD** with Barrett’s metaplasia
4. **Refractory GERD**
5. **GERD with non-acid reflux** (using combined impedance-pH testing)

Above varieties of GERD presentations are discussed in the context of acid suppression with a focus on garden variety GERD with typical reflux symptoms, commonly seen by primary care physicians. The acid suppression in GERD centers around pharmacotherapy with proton pump inhibitors, the most potent inhibitors of acid secretion available. The following entities have either been covered before or will be discussed in detail in subsequent articles in this GERD series.

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6. GERD with supra esophageal manifestations like cough, asthma, hoarseness and throat clearing
7. GERD causing atypical chest pain
8. Endoscopy negative GERD
9. GERD with sensitive esophagus (positive symptom index with normal total acid exposure during pH testing)
10. Nocturnal GERD

For a disease with this degree of heterogeneity and unlike its counterpart acid peptic ulcer disease, one-size-fits-all therapy is not effective. Given such heterogeneity of presentation, with pharmacotherapy of GERD at its peak, refractory and complicated GERD are still common.

When posturing acid suppression therapy for GERD, identifying the goals of therapy is essential (Table 1). How effective is currently available acid suppressive therapy in achieving these goals of GERD therapy?

**Antacids:** Historically, antacids which neutralize gastric acid have been used since the time of the ancient Greeks, who used coral powder (containing calcium carbonate) to treat various digestive maladies. Unfortunately, the prompt fix obtained by short term neutralization of gastric acidity offers unsustained relief of heartburn limiting their use for treatment of mild episodic heartburn. The introduction of H2-RAs in mid 1970’s and PPIs in the late 1980’s has revolutionized the GERD therapy.

**H2-blockers in GERD therapy:** H2-blockers work by blocking the histamine stimulation of parietal cells, thereby reducing basal and, to a minor degree, postprandial acid production. The four available agents, cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), and ranitidine hydrochloride (Zantac), vary in potency at recommended doses but are clinically equivalent.

Advantages of H2-RAs:
1. Prompt relief of heartburn and more sustained effect than antacids.
2. Because of their rapid onset of action as compared to PPIs, can be used as needed to treat reflux symptoms with satisfactory responses.
3. Supplemental at bedtime for nocturnal gastric acid control in GERD patients taking PPI.

Disadvantages of H2-RAs:
1. Relatively short duration of action. Depending on the individual agent, they suppress acid for approximately 4–8 hours. Therefore, multiple daily doses of these agents are needed.
2. Incomplete inhibition of postprandial gastric acid secretion.
3. Development of tolerance to continuous administration of H2-RA when used in combination with PPI, although this is not a universal phenomenon (3–5).

**Proton pump inhibitors in GERD therapy:** The development of proton pump inhibitors signified a landmark step in the pharmacodynamics of acid control. PPIs act by irreversibly inhibiting the H+–K+ adenosine triphosphatase pump of the parietal cell which results in a marked decrease in gastric acidity as well as gastric volume. Several RCT’s have shown that they are the best available agents to strongly inhibit gastric acid secretion and control esophageal acid exposure in GERD. When compared to H2-receptor blockers (H2-RA) and prokinetic agents, they are more effective in achieving all the five goals in GERD treatment mentioned in Table 1(6–8). In contrast to H2-RAs, they control both basal and food stimulated acid secretion. They are remarkably safe and well tolerated for long periods of use. Hence, either used alone (once or twice a day) or in combination with H2-RA at bedtime, they have become the therapeutic agent of choice for any type of GERD.

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**Table 1**

**Treatment Goals in GERD**

1. Symptom relief
2. Heal esophagitis
3. Maintain remission
4. Improve quality of life
5. Prevent complications
Initial Approach to a Patient with Typical GERD (Algorithm 1)

When a patient with typical reflux symptoms presents to a physician, there is general consensus on initial treatment with acid suppressants without endoscopy assessment (also called PPI test) and reserving endoscopy to specific situations as mentioned below. Indeed this approach is suggested by the practice guidelines of ACG (1).

(continued on page 39)
Indications for Endoscopy in GERD
1. Alarm symptoms (eg: dysphagia, weight loss, GI bleeding)
2. Atypical symptoms
3. Refractory symptoms
4. Pre-operative assessment
5. Longstanding, frequent and troublesome symptoms
6. Chronic (>5 yrs) continuous maintenance medical therapy for symptom control
7. Age >40 yrs

Advantages of PPI test vs. initial endoscopy
1. PPI is readily available, safe and effective
2. Increases the role of PCP in the management of GERD
3. Decreases patient discomfort and invasiveness
4. Potential cost savings

Two therapeutic strategies have been used in the empiric initial treatment of GERD.

1. The “Step-up” Approach involves starting treatment with lifestyle modifications, antacids, and standard or over-the-counter doses of H2-receptor antagonists (H2-RAs). Then step-up to a proton pump inhibitor (PPI), if symptoms are not satisfactorily resolved. The best and perhaps the only argument for the step-up approach is cost. In the era of managed care, cost should be a consideration for any treatment. H2-RAs are cheaper than PPIs, and many insurance plans limit use of PPIs to short-term therapy (four to six weeks), or only after a failed trial of a H2-RA.

2. The “Step-down” Approach begins with the most effective regimen, a PPI given 15–30 minutes before breakfast, in addition to discussion of lifestyle modifications, gradually reducing the intensity of treatment to maintain the patient in remission. The Genval workshop recommendations endorse step-down therapy as the best medical strategy for patients with esophagitis (9). For most patients, once-daily PPI treatment adequately relieves symptoms and heals any existing erosive esophagitis. However, in unusual circumstances, the model provides for twice-daily (2nd dose given before the evening meal) or higher PPI doses, sometimes in combination with a bedtime H2-RA. The optimal duration of treatment is 4–8 weeks, although some patients may require a longer therapeutic trial. Because most patients presenting to a general practitioner with reflux symptoms are likely to have used self-medication throughout, early use of highly effective acid suppression PPI therapy in the initial management of GERD is a compelling argument. One problem with this approach however stems from PPIs effectiveness; patients are reluctant to step down to a less effective alternative for maintenance. Although PPIs are expensive when compared to H2-RAs, use of a PPI as initial therapy in a low-risk patient with moderate to severe reflux symptoms is probably less expensive than an initial trial of an H2-RA because a PPI provides better relief and thereby obviates the need for office visits and diagnostic studies (10). Therefore, the most effective initial therapy for GERD is also likely to be the most cost effective one, if treatment failure leads to higher utilization of medical resources and also a decrease in quality of life of patients (11).

References