For most patients, GERD is a chronic relapsing problem. Hence, long-term maintenance treatment with antisecretory therapy is crucial to assure quality of life and longer asymptomatic periods. Once the patient’s symptoms are well controlled with initial antisecretory therapy, often with a PPI, two pharmacological options are suited for maintenance therapy:

1. A step-wise reduction in treatment intensity down the hierarchy and attempted discontinuation of medications with continued lifestyle modifications. The decision to step-down should be individualized and takes into consideration the patient’s preference, their clinical status, the likelihood of complications, previous response to treatment, the likelihood of follow-up and overall costs. Many patients have episodic disease that recurs infrequently or not at all. This approach allows identifying these patients and avoiding unnecessary long-term prescription drug treatment. “On demand” therapy may be a reasonable approach in those with infrequent symptoms and mild esophagitis. Indeed, many GERD patients who are prescribed long-term medication only take it as needed, apparently content to experience some continuing symptoms (1). Differentiating patients who benefit from “on demand” use from those who require long-term antisecretory therapy is important. Should symptoms recur, after step down or discontinued therapy restart the initial effective regimen. Any patient who requires continuous maintenance medical therapy should undergo endoscopy at least once to rule out Barrett’s esophagus.
2. Continuation of whatever medication regimen that effectively controls symptoms, which is a PPI once or twice daily in most cases. Because moderate or severe esophagitis is more likely to relapse this approach is best in these patients (2,3). A controlled clinical trial in a primary care setting showed that this approach was more effective compared to a step-down or step-up approach in patients with heartburn (4). PPI’s have increasingly been accepted for maintenance therapy because of their long-term safety and efficacy profile. They have been used for over 15 years in the United States and much longer in Europe and it is becoming clear that the benefit of chronic PPI therapy in patients with chronic GERD outweighs any theoretical risk (5).

The responses of primary care physicians to a GERD questionnaire published recently showed that the inferior step-up approach (i.e., initiate treatment with H2RA) may have been largely abandoned and the step-in approach (i.e., begin and continue with a PPI) has increasingly been accepted by primary care doctors (6). In fact, the benefits of extended PPI therapy may extend beyond symptom control and maintenance of esophageal healing. In our institute’s esophageal laboratory, preliminary evidence suggests that prolonged acid suppression on maintenance therapy with BID PPI for an extended period of time improves peristaltic function in patients with GERD related ineffective esophageal motility (IEM) (7).

Once the decision is made to give a therapeutic trial with PPI, which PPI should be used? The five available PPIs, esomeprazole magnesium (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprazole (Aciphex), have similar pharmacologic activities at recommended doses. All are extremely effective and safe, and each is a reasonable choice for initial as well as maintenance therapy. There have been several physiologic studies suggesting modest benefits of one agent over another (1). Crossover studies comparing standard doses of different PPIs have shown that esomeprazole 40 mg, the S-isomer of omeprazole, produces a significantly greater amount of time at intragastric pH >4 on day 5 of treatment than standard doses of other proton pump inhibitors(8). It also produces greater 8 week healing rates in patients with erosive esophagitis than either omeprazole or lansoprazole (9,10). Although esophagel acid exposure should be the ideal marker for clinical efficacy, studies of acid suppressive medication have been based primarily on their effect on gastric acidity because reflux is an intermittent phenomenon leading to greater day to day and also greater inter-individual variability of esophageal acid exposure than gastric acidity (11).

Zegerid is an immediate release omeprazole suspension, a compound in which omeprazole powder is combined with sodium bicarbonate. There appears to be an advantage over traditional PPIs to bedtime administration of this agent in control of nocturnal acid. Also, because of its immediate release effect, it may be a PPI of choice for on demand use for prompt relief of symptoms followed by a sustained effect (12).

In practice the choice of PPI may be dictated by the patient’s drug plan and the cost of the drug. Whichever PPI the patient is started on, control of symptoms should determine continuation as a maintenance therapy. If symptom control is suboptimal switching to a different PPI before further diagnostic evaluation is worthwhile, as individual patient responses to different PPIs vary. When prescribing a PPI, educating the patient about optimal use is crucial. PPIs work best when given 15–30 minutes before meals, allowing an optimal blood level of PPI during meal-induced proton pump activation. Despite this 36% of PCPs (primary care physicians) attending a GERD conference, indicated in a survey that patients take a PPI with food, after food or that they provided no specific directions in this regard (6). Patients taking a second PPI appear more likely to take this dose after meals or at bedtime because either their physician did not reinforce the importance of taking PPI before meals or patients tend to forget to take their evening PPI before dinner more often than the one before breakfast. (Tips for optimal use of PPIs are provided in Table 1). The PCP questionnaire also revealed that there is considerable confusion among PCP’s regarding appropriate acid suppression therapy in patients with H. pylori infection or Barrett’s esophagus.

GERD, H. PYLORI AND ACID SUPPRESSION

Routine testing for Helicobacter pylori infection is unnecessary before starting GERD therapy. Eradica-
tion of *H. pylori* may be associated with mild worsening of GERD in patients with corpus-predominant gastritis and improvement in those with antral-predominant gastritis (13–15). Although *H. pylori* improves the ability of PPIs to suppress acid, the dose required to maintain remission of esophagitis is not affected (16,17). When the patient with GERD also has *H. pylori* infection, most authorities advocate eradication based upon a 10 percent lifetime risk of developing peptic ulcer disease and a two to three times higher incidence of gastric adenocarcinoma (18). The mild increase in reflux associated with eliminating corpus gastritis does not seem to outweigh these risks, and any worsening reflux can be managed by altering the medical regimen. This supports the maxim that “the only good *H. pylori* is a dead *H. pylori*.”

**ACID SUPPRESSION AND BARRETT’S ESOPHAGUS**

Although controversial, there is no definitive clinical evidence that aggressive antisecretory therapy or antireflux surgery modifies the underlying risk of adenocarcinoma in patients with Barrett’s metaplasia. Nevertheless, complete acid control for this complication of GERD may require a twice daily dose of PPI, even when patients are asymptomatic on lower doses (19,20). Some data suggests that complete acid suppression may have an effect on the length and area of Barrett’s esophagus (21–23). The ACG recommendation is to give PPI therapy for several weeks before EGD to identify Barrett’s esophagus, to allow healing of esophagitis before biopsies are performed. Hence we suggest an approach to Barrett’s esophagus that includes, titrating the antisecretory therapy to control reflux symptoms and heal esophagitis irrespective of the presence of Barrett’s metaplasia. Later, the treatment should be adjusted based on follow-up 24 hr pH monitoring to monitor the level of acid suppression and on-going reflux along with continued endoscopic surveillance for dysplasia (24).

**REFRACTORY GERD (ALGORITHM FOR REFRACTORY GERD)**

Patients with symptoms suggestive of reflux despite at least 4–8 weeks of acid suppression with PPI BID should be considered to have refractory GERD. This, however, does not necessarily mean severe or complicated GERD. Hence, they should not be referred for surgery before a further diagnostic work-up to determine whether or not their symptoms are truly secondary to reflux. Initial evaluation of these patients includes a careful history to ensure compliance with medication and optimal timing of the PPI (15–30 minutes before breakfast and dinner). Switching to another PPI is a reasonable approach at this point because individual responses to different PPIs vary. If EGD was not done prior to PPI, it should be done to rule out esophagitis. In those patients where ongoing acid reflux is suspected with or without esophagitis, the addition of nighttime H2RA to the PPI BID regimen should be considered. Bedtime H2RA decreases nighttime histamine stimulation that drives nocturnal acid breakthrough, a phenomenon observed in many patients on BID PPI. Although tolerance to continuous administration of H2RA therapy is of concern, it is still worth trying as this is not a universal phenomenon (25–27). Among refractory GERD patients surveyed at our clinic after the addition of a bedtime dose of H2RA to a twice-daily regimen of PPI, 72% of respondents reported improvement in overall symptoms, and only 13% discontinued treatment because of a perceived waning of clinical effect (28). Considering the low cost and safety profile of generic ranitidine, we recommend that addition of 150–300 mg at bedtime be used to aug-

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**Table 1**

**Tips for optimal use of PPIs**

1. Most effective when given 15–30 minutes before meals
2. For higher PPI dosages, divided doses are more effective than giving single higher doses
3. An occasional patient might need PPI three times a day
4. For maintenance therapy taper the PPI slowly to minimize rebound acid secretion
5. Remind patients to take the evening PPI 15–20 minutes before dinner
6. For patients with swallowing difficulties or with feeding tubes, the granules can be given in liquid
Acid Suppression Therapy for GERD

(continued from page 18)

ment the BID PPI (Tips for maximizing acid suppression are provided in Table 2). Patients on maximal acid suppression with persistent symptoms should be evaluated in a tertiary referral center for the possibility of non-acid reflux contributing to the symptoms. Detection of non-acid reflux is possible using combined MII-pH technology, which identifies refluxate bolus volume presence independent of the pH of the refluxate. This technique can identify a sub group of patients with refractory GERD who would benefit from anti-reflux surgery (29).

THE FUTURE IN ACID SUPPRESSION THERAPY

An optimal PPI inhibits acid secretion at the level needed for best clinical results. It should reach this level of inhibition rapidly and be able to sustain this high level of inhibition throughout the day and night predictably, regardless of host characteristics. Future investments might be focused on developing an optimal PPI with the above characteristics, by reformulation or modification of existing PPIs or by development of an effective potassium channel antagonist.

CONCLUSION

GERD is a common chronic relapsing esophageal disorder with associated significant morbidity. The most effective treatment option currently available for GERD is to minimize the effect of gastric acid on the esophagus. The proton pump inhibitor class of drugs are indisputably the most potent acid suppressing agents with favorable side effect profiles and long-term efficacy and safety. While consensus exists in regard to the current management of GERD with PPIs, there is little agreement as to the management of the associated mucosal metaplastic process. In this respect Barrett’s esophagus still presents a major biologic and management conundrum for physicians and scientists alike. Well conducted, large prospective studies utilizing the progression of intestinal metaplasia to dysplasia as end points are needed to address definitively the appropriate role of acid inhibition or other chemoprevention interventions. As our diagnostic and therapeutic technologies have advanced they have uncovered certain GERD mechanisms previously less clear, particularly non-acid reflux,
questioning the GERD dictum: No acid; no GERD. Future challenges include medical and endoscopic therapies to manage those volume (non-acid) refluxers who have symptomatic reflux despite neutralization of intragastric pH. This will be discussed in a subsequent article in this series. Although future research into refinement of the pharmacokinetic and acid control profiles of proton pump inhibitors may allow more effective acid control in GERD, more research to develop an effective prokinetic agent which targets the root cause of GERD is also desirable.

References