

Donald O. Castell, M.D., Series Editor

## Reflux Reduction Therapy: When PPIs Are Not Enough



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### INTRODUCTION

**P**roton pump inhibitors are well documented to be very effective in the management of gastroesophageal reflux disease (GERD). Healing rates for patients with esophagitis approach or exceed 90% after 4–8 weeks of therapy with a PPI. This observation underscores the importance of gastric acid as the instrument producing esophageal mucosal injury. On the other hand, up to 40% of patients with erosive esophagitis continue to have symptoms suspected to be due to GERD, often despite healing of esophagitis (1). In those patients with non-erosive reflux disease, so-called NERD patients, continued symptoms despite PPI therapy may occur in up to 60% of individuals (2). With the currently popular approach of using a trial of PPI therapy as a diagnostic step in the patient with suspected GERD symptoms, this group of patients with persistent symptoms despite PPI therapy has been unmasked with clinicians increasingly challenged to diagnose and treat the abnormality responsible for the symptoms.

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As the medical community has interacted with this newly-discovered group of “PPI Failures” the concept of “nonacid reflux” has become widespread. Of greater importance has been the evolving concept that GERD management includes two distinct parts; acid reduction therapy and reflux reduction therapy. The former predominately consist of PPI therapy with H<sub>2</sub>-RAs alone or in combination having an adjunct role (see previous 2 articles in this series). The latter includes all of those approaches that are directed at actually reducing the volume of refluxate, with major emphasis on the post-prandial period (Table 1).

Our approach to these patients has been to initially insure that GERD patients are receiving an appropriate dose and dosing schedule of their acid reducing therapy. Prior to further investigation, it is our belief that the patient should have failed a trial of 6–8 weeks of therapy with a PPI given twice daily, before breakfast and dinner, possibly with a single bedtime dose of a histamine 2 receptor antagonist (H<sub>2</sub>-RA) included. In the patient whose symptoms persist despite this regimen, three possibilities arise to explain the continuing symptoms; 1) perhaps the gastric acid is incompletely

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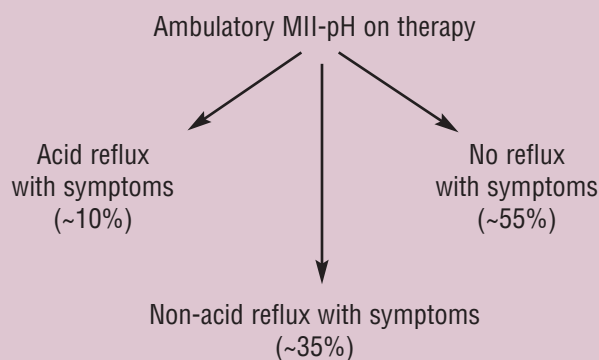
**Table 1**  
**Therapeutic Options for Symptomatic Non-Acid Reflux (Reflux Reduction Therapy)**

• Surgical	Laparoscopic Nissen fundoplication
• Endoscopic?	
• Medical	
Life-style modifications:	
	Stay upright for 3 hours after meals
	Sleep on left side
Decrease transient LES relaxations	Baclofen
Raised resting LES pressure	Bethanechol
Improved gastric emptying	Metoclopramide, Tegaserod
Foaming anti-refluxant	Alginic acid

suppressed and the patient is having continuing acid reflux with symptoms, 2) non-acid reflux is producing the symptoms, or 3) the residual symptoms are not related to any continuing reflux.

Over the past five years, studies using catheter based ambulatory monitoring to detect both electrical impedance and pH changes in the esophagus have demonstrated the ability to differentiate the three possible mechanisms of persistent symptoms described above (3). An example of continuing acid reflux and non-acid reflux is shown in Figure 1. Clinical testing at the Medical University of South Carolina performed

**Table 2**  
**Mechanisms of Persistent Symptoms on PPI bid**



on patients with persistent symptoms despite at least twice daily PPI as described above have revealed that the least likely explanation is continued acid reflux (about 10%). More likely, the patients continuing symptoms are temporally related (Table 2) to non-acid reflux (about 35%) or show no relation to reflux episodes (about 55%). Obviously, the approach to these different mechanisms of symptom production varies and is most reasonably pursued once the responsible mechanism has been elucidated. Using combined multi-channel intraluminal impedance and pH (MII-pH) monitoring in our Esophageal Laboratory has greatly expanded our ability to understand and manage this group of challenging patients.

**A DIRECTED THERAPEUTIC APPROACH TO REFLUX REDUCTION THERAPY**

Guided by the results of ambulatory MII-pH monitoring, patients with a continuing reflux etiology underlying their persistent symptoms are candidates for the reflux reduction approaches shown in Table 1. This diagnosis is based on the identification of a reflux episode by MII occurring within a 5 minute interval preceding the onset of the patient’s symptom with a frequency of 50% or greater of the symptom events. The reflux episodes may be either acid or non-acid as shown by the associated level of esophageal pH. An example of a non-acid reflux episode occurring before a cough symptom is shown in Figure 2.

**ANTI-REFLUX SURGERY**

Over the past decade, laparoscopic Nissen fundoplication (LNF) has evolved as the surgical option of choice for the management of chronic GERD. In the patient who has persistent symptomatic reflux despite good gastric acid control (i.e., non-acid reflux) a mechanical approach to stopping reflux is a reasonable option. We now have experience with greater than 20 patients in whom LNF was utilized as a treatment for their persistent symptomatic reflux. These patients have been followed for an average of greater than one year following surgery for a variety of reflux related symptoms, including regurgitation, heartburn, cough, throat clearing and hoarseness. Overall 90% of these patients are

asymptomatic and not requiring PPI therapy. The dramatic success of this initial follow-up suggests that surgery is a reasonable option in the patient who has failed PPI therapy once reflux is clearly documented as the mechanism of their continuing symptoms by the use of ambulatory MII-pH testing.

### ENDOSCOPIC THERAPY

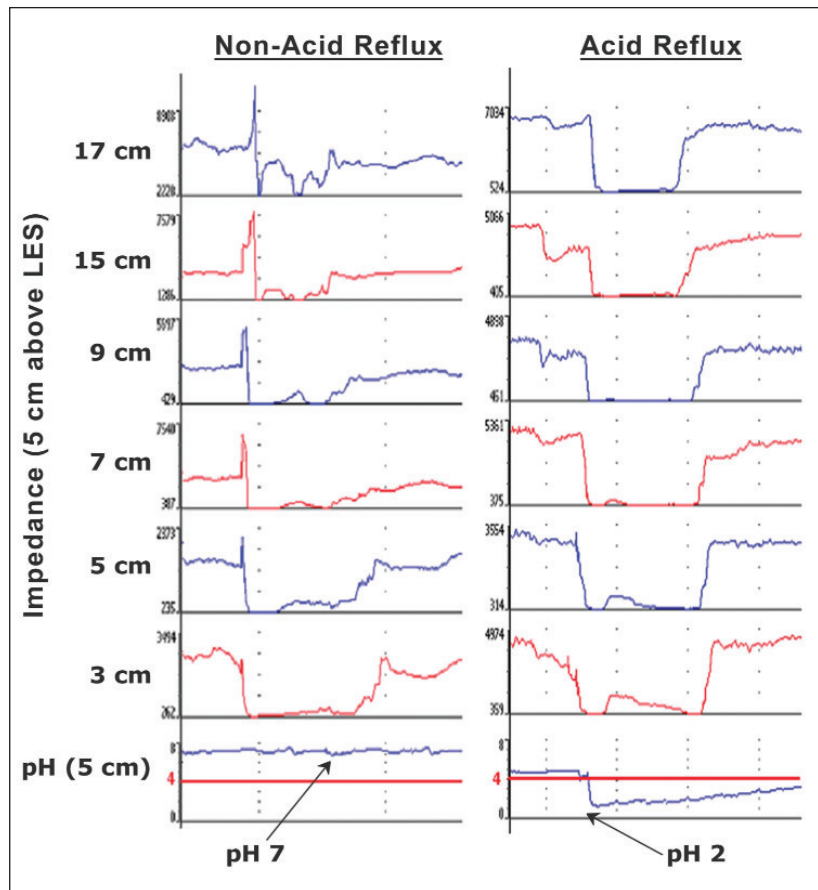
In this group of patients another mechanical approach to decreasing or stopping the continuing reflux may include an endoscopic antireflux procedure. In fact, these patients may well be ideal candidates for an effective procedure of this kind. At present, however, much controversy exists regarding the preferred endoscopic approach to symptomatic reflux or, even if one truly exists. There is currently no information on applying any of these endoscopic approaches to this specific group of patients.

### MEDICAL THERAPIES

The search for an effective medical therapy to correct the motility abnormality in GERD patients has been long and arduous. There are, however, approaches that can be used to supplement the PPI therapy in patients with documented persistent reflux symptoms.

Life-style modifications will decrease reflux, particularly those directed at improving a mechanical advantage while sleeping. When patients have difficulty sleeping with the head elevated, sleeping on the left side usually works. One of the best principles of GERD management is to stay upright for 3 hours after a meal.

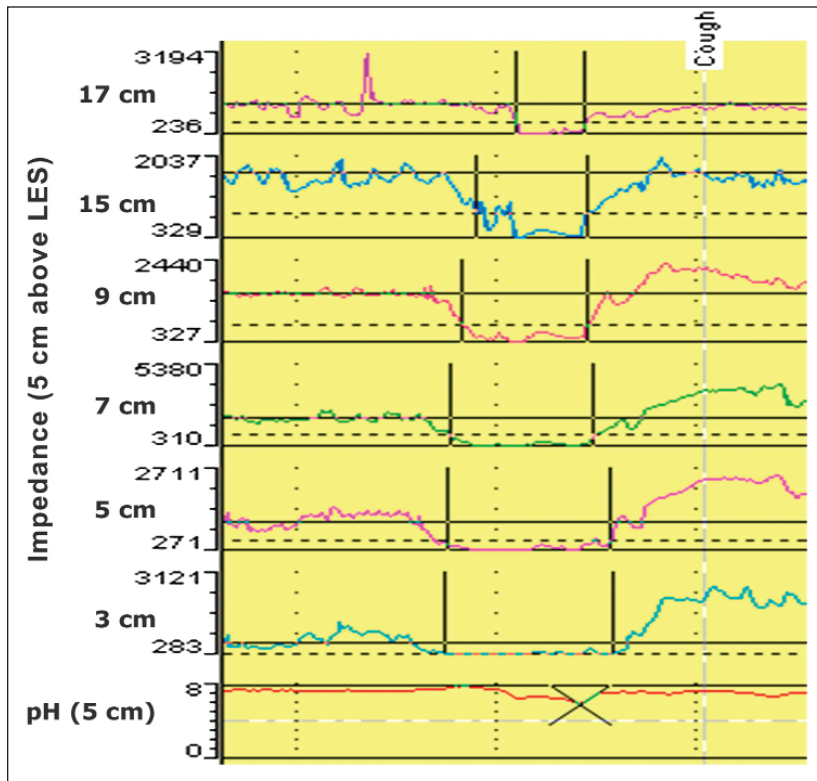
Baclofen is a GABA agonist that has been used over many years for the treatment of spastic disorders. It is being seriously considered as an addition to the therapeutic armamentarium of the gastroenterologist because of its well documented ability to decrease transient relaxations of the lower esophageal sphincter.



**Figure 1.** An example of non-acid and acid reflux episodes shown by MII reaching the proximal esophagus at 17 cm above the LES.

Such TLESRs are currently recognized as playing a major role in the pathogenesis of reflux episodes, particularly those occurring secondary to gastric distention post-prandially. Baclofen has been shown to effectively decrease post-prandial reflux of all types; acid, non-acid, and bile containing (4). It is our practice to initiate therapy with 5–10 mg taken before meals and to advance to a level of 20 mg before meals, watching for side effects, particularly drowsiness.

Bethanechol is a cholinergic agent that has been known for many years to have the ability to increase resting pressure of the lower esophageal sphincter. In a dose of 25 mg before meals and at bedtime, it has been shown to significantly improve reflux symptoms compared to placebo administration (5).



**Figure 2.** An example of a non-acid reflux episode into the proximal esophagus preceding the cough symptom.

Although the actual frequency has not been documented, some patients with non-acid reflux will have delayed gastric emptying as a potential etiologic factor. In these patient standard doses of currently available pro-motility agents such as metoclopramide and tegaserod should be considered.

Alginic acid incorporated into an antacid preparation (Gaviscon) provides an antireflux effect through mechanical blocking of reflux by the foaming antacid layer. Use of this preparation is recommended on an as-needed basis to help control symptoms of continuing acid or non-acid reflux in the patients discussed above.

### CONCLUSION

For the GERD patient in whom the antireflux motility mechanism is defective, it is likely that reflux episodes will continue despite suppression of gastric acid. The presence of such non-acid reflux and its ability to produce continuing symptoms has been well documented recently through the use of modern technology

incorporating multi-channel intraluminal impedance combined with pH. Documentation of such symptomatic non-acid reflux by MII-pH monitoring can lead to more effective management of this challenging group of patients using the reflux reducing therapies discussed above. ■

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