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EDUCATION PRACTICE

Persistent Heartburn in a Patient on Proton-Pump Inhibitor

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Clinical Scenario

A 36-year-old woman with 6-year history of heartburn was referred for further evaluation and management. Her symptoms occurred up to 3 times daily during "bad" months and about 3 times a week during the rest of the year. The patient describes a burning sensation behind the chest bone that travels to her neck. Symptoms occasionally awaken her from sleep during the night, primarily after having heavy meals in the evening. She has rarely experienced sour or bitter taste in the mouth. She denies dysphagia, odynophagia, chest pain, early satiety, epigastric pain or discomfort, bloating, nausea, or vomiting. Her appetite is good, and she has not lost any weight. She is a social worker, married, and has 2 toddlers at home. Both of her pregnancies were unremarkable. She considers her work and the need to juggle her family life at the same time to be very stressful. She denies smoking or drinking alcohol. However, she admits to occasional late-night business meals and a passion for Mexican food. Her physical examination is unremarkable except for borderline obesity. The patient was initially seen by her primary care physician, who suggested that she adopt lifestyle modifications, attempt to lose weight, and consider a less busy work schedule. She was also started on an H_2-receptor antagonist (H_2RA) twice daily. The patient stated that she felt no improvement in her symptoms despite 2 months of therapy with H_2RA. In addition, she was unable to lose weight or change her work schedule. Three months ago, she was initiated on proton-pump inhibitor (PPI) once daily half an hour before breakfast. She stated that the PPI appeared to help her during the first 2 weeks, but symptoms recurred, although with some lessened severity and frequency than before. She has been supplementing her PPI once daily with antacids, over-the-counter H_2RA, and occasionally by adding another PPI before bed time.

How should the patient's refractory heartburn be treated?

The Problem

Failure of PPI therapy in patients with typical or atypical/extraesophageal manifestations of gastroesophageal reflux disease (GERD) has become the most prevalent presentation of GERD in gastroenterology practice today. As primary care physicians, surgeons, and other subspecialists feel more comfortable prescribing PPIs for patients with GERD-related symptoms, not uncommonly in more than a standard dose, failure of PPI therapy has become an important indication for GERD-related referral to a gastroenterology clinic.

It has been estimated that between 10%–40% of the patients with GERD fail to respond symptomatically, either partially or completely, to a standard dose PPI. During a period of only 7 years (1997–2004), there was an increase by almost 50% in the usage of at least double-dose PPI in patients with GERD. It appears that less than 50% of the GERD patients are satisfied with their medical treatment, and only 58% of those receiving PPI report high level of satisfaction with their therapy.

In general, the proportion of nonerosive reflux disease (NERD) patients responding to a standard dose of PPI is approximately 20%–30% lower than what has been documented in patients with erosive esophagitis (EE). Given the fact that NERD accounts for the majority of GERD patients, then this group of patients is likely the main source for the PPI failure phenomenon.

Patients with NERD exhibit a direct relationship between response to PPI therapy and degree of esophageal acid exposure. The greater is the distal esophageal acid exposure, the higher is the proportion of NERD patients reporting symptom resolution. This is the opposite of what has been observed in patients with EE, in whom the greater is the esophageal inflammation, the lower is the response rate to PPI once daily. A partial explanation for the lower symptomatic response rate to PPI once daily of NERD as compared with EE patients is the common inclusion of functional heartburn subjects in therapeutic studies evaluating the NERD group. These patients with normal endoscopy and normal pH testing exhibit the lowest symptom response rate to PPI once daily when compared with the other NERD patients. In one study, only 45% of functional heartburn patients reported sufficient relief of heartburn symptoms when compared with other NERD patients. In addition, it appears that NERD patients with only mildly abnormal esophageal acid exposure, who account for a significant number of the NERD group, also exhibit a relatively lower symptomatic response rate to PPI once daily as compared with patients with EE.

Studies in patients with EE, treated with a PPI once daily, showed 85%–96% healing rates after 8 weeks of therapy, regardless of the brand of PPI that was used and the underlying severity of EE. Patients with more severe grades of EE have

Abbreviations used in this paper: DGER, duodenogastroesophageal reflux; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; H_2RA, H_2 receptor antagonist; MII, multichannel intraluminal impedance; NAB, nocturnal acid breakthrough; NERD, nonerosive reflux disease; PPI, proton-pump inhibitor; SAP, symptom association probability; SI, symptom index.

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Table 1. Putative Mechanisms for Failure of PPI Treatment

- Compliance
- Improper dosing time
- Weakly acidic reflux
- Duodenogastroesophageal/bile reflux
- Visceral hypersensitivity
- Delayed gastric emptying
- Psychological comorbidity
- Concomitant functional bowel disorder
- Reduced PPI bioavailability
- Rapid PPI metabolism
- PPI resistance
- Nocturnal reflux
- Helicobacter pylori infection status
- Eosinophilic esophagitis
- Others (unrelated to gastroesophageal reflux)

exhibited a higher PPI failure rate than those with less severe disease. In one study, the failure rates of patients with EE receiving either omeprazole 20 mg once daily or esomeprazole 40 mg once daily were 9.6% and 6.6% for Los Angeles grade A, 28.7% and 10.6% for grade B, 29.6% and 12.8% for grade C, and 36.2% and 20% for grade D, respectively. Because patients with severe EE (Los Angeles grades C and D) account for only 15%–30% of those with EE, their impact on the overall healing rate of this group of GERD patients is very limited.

Failure of PPI therapy in EE used to be determined by the persistence of esophageal inflammation despite a full course of PPI therapy. Subsequently, it was recognized that healing of EE might not be necessarily indicative of complete resolution of GERD-related symptoms. In fact, patients might continue to report GERD symptoms despite complete healing of the esophageal mucosa (up to 15%). The percentage of patients who report complete resolution of GERD symptoms despite the persistence of esophageal erosions while receiving PPIs is unknown. On the other hand, up to 50% of the patients with EE who relapse symptomatically while receiving a PPI once daily lack any evidence of concomitant relapse of esophageal inflammation.

Table 1 summarizes the different proposed underlying mechanisms for failure of PPI treatment in GERD patients. At present, much of the research that is conducted in this area focuses primarily on weakly acidic reflux and visceral hypersensitivity. However, it is highly likely that these 2 potential underlying mechanisms for PPI failure are related and might represent one underlying cause.

Weakly acidic gastroesophageal reflux is the reflux of gastric contents into the esophagus with a pH between 4 and 7. The recent introduction and usage of the multichannel intraluminal impedance (MII) with pH sensor allowed the detection of reflux of gastric contents into the esophagus without a concomitant drop in pH below 4. This recording assembly can also determine the characteristics of the gastric refluxate (gas, liquid, mixed gas and liquid). By using the MII with pH sensor, Vela et al demonstrated a shift in the reflux characteristics in patients who did not respond to PPI twice daily. Although there was no difference in the number of reflux events on PPI therapy compared with baseline, most of the reflux events detected were weakly acidic. The authors suggested that weakly acidic reflux was associated with classic GERD symptoms, although less so than acidic reflux. In addition, symptoms such as regurgitation and sour or bitter taste in the mouth were more associated with weakly acidic reflux than heartburn. In patients who failed PPI twice daily, 31% had positive symptom index (SI) with weakly acidic reflux, 11% with acidic reflux, and 58% had a negative SI. Interestingly, atypical symptoms are least likely to be preceded by a weakly acidic reflux event.

The role of visceral hypersensitivity has not been specifically studied in patients who failed PPI treatment. However, most patients who do not respond to PPI therapy have NERD. Many patients originate from the functional heartburn subgroup, which accounts for up to 50% of the NERD patients. In the functional heartburn group, those with a negative SI reported having heartburn at pH <4 only 12.7% of the time compared with 70.7% of the time in those with a positive SI, despite a similar mean number of heartburn episodes. Patients with functional heartburn, by using either esophageal balloon distention or electrical stimulation, have consistently exhibited a lower perception threshold for pain than patients with other presentations of GERD. Furthermore, objective neurophysiologic measures of esophageal-evoked potential latency revealed that functional heartburn patients achieve equivalent latency and amplitude esophageal-evoked potential responses with reduced afferent input, suggesting heightened esophageal sensitivity. In contrast, stimulus response functions to acid in patients with functional heartburn demonstrated a more mixed response, which resulted in higher mean value for time to heartburn symptoms and lower mean values for intensity and acid perfusion sensitivity score compared with patients with NERD and abnormal pH tests. A fourth of the patients had a negative acid perfusion test. This study further supports the hypothesis that functional heartburn is composed from a heterogeneous group of patients. However, a significant subset of these patients is unlikely to have gastroesophageal reflux as the underlying stimulus for their heartburn.

Last, studies evaluating patients who did not respond to PPI twice daily demonstrated that approximately 50%–60% have negative SI between symptoms and any type of gastroesophageal reflux.

Duodenogastroesophageal reflux (DGER) is the reflux of duodenal contents through the stomach and into the esophagus. A recent study demonstrated that DGER was significantly more common (64%) than acid reflux (37%) in patients who continued to have GERD-related symptoms on either standard-dose or double-dose PPI therapy. Patients with EE who did not respond to PPI treatment experienced a higher number of DGER episodes (35 vs 15.5) and longer exposure time to DGER (11.9% vs 6.3%) than NERD patients in whom PPI therapy failed.

Delayed gastric emptying has been shown to contribute to the failure of PPI therapy in patients with GERD. Thus far, there are very few studies that evaluated the frequency of gastric emptying in patients who did not respond to PPI therapy. Nevertheless, the rapidly growing number of patients with diabetes mellitus and those using narcotics for pain syndrome might soon make gastroparesis one of the leading causes of PPI failure.

Patients with poor symptom-reflux correlation exhibit significant psychosocial difference when compared with patients with positive symptom-reflux correlation. These patients display a high level of anxiety and hysteria. In addition, population-based studies have documented association between anxi-