Gastroesophageal Reflux Disease:
Endoscopy, Duration of Treatment, and Choice of PPI

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When is endoscopy indicated in the diagnosis and follow-up of Gastro-esophageal Reflux Disease (GERD)?

In the Montreal definition based on a consensus of experts, GERD was defined as "*a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications*."[1] It is important to note that the diagnosis may be symptom-based and made independent of endoscopy and other diagnostic testing. Patients diagnosed with GERD, therefore, will include patients with erosive esophagitis as well as those with **non-erosive reflux disease (NERD)**. Patients with NERD may account for two-thirds of all patients with GERD and, as they will appear normal endoscopically, the sensitivity of endoscopy for making the diagnosis of GERD is low.

Endoscopy does play a significant role in excluding other serious disorders such as esophageal or gastric cancer in a patient presenting with reflux-like symptoms. The concept of "alarm" signs or symptoms comes in to play here. Although not supported by literature, it is certainly appropriate to consider endoscopy in any patient presenting with reflux and dysphagia, odynophagia, weight loss, abdominal mass, GI bleeding or anemia.[2]

The issue of GERD, Barrett's esophagus and esophageal cancer remains controversial. Carcinoma of the esophagus is a clinically important disease. Worldwide esophageal cancer is diagnosed in almost a half a million people annually where it is the sixth leading cause of death in men (ninth leading in women). The incidence of adenocarcinoma of the esophagus is rising rapidly in the United States and other "Western" countries.[3] Over the period from 1976-1987, the incidence of adenocarcinoma of the esophagus in US white males increased more rapidly than that of any other cancer. With its incidence increasing almost 20% annually, adenocarcinoma has replaced squamous cell carcinoma as the most prevalent type of esophageal cancer in this population.[4]

The prognosis of esophageal adenocarcinoma is strongly associated with the stage at diagnosis. According to **Surveillance Epidemiology and End Results (SEER)** data from 2005, one-year survival in patients with local, regional, and distant (metastatic) disease were 68%, 54%, and 28%, respectively. The five-year survival for esophageal cancers confined to the mucosa (T1m, N0, M0) may approach 90%.[5] Therefore, there is great interest in identifying risk factors for esophageal cancer and focusing screening and surveillance efforts on populations at high risk for esophageal cancer. A large population-based Swedish study showed that the relative risk of esophageal cancer may be more than seven-fold greater in patients with recurrent reflux when compared to patients without reflux. The more frequent, more severe, and longer-lasting the symptoms of reflux, the greater the risk.[6] While this may make GERD patients appear to be a good target population for endoscopic esophageal cancer screening, enthusiasm for devoting limited health-care dollars on this effort is tempered by the realization that the majority of patients with adenocarcinoma of the esophagus do not report a history of reflux. Additionally, only a small percentage of all patients with reflux ever develop esophageal adenocarcinoma.

Like adenocarcinoma, GERD is a strongly associated with Barrett's esophagus. It is well accepted that Barrett's esophagus, defined as metaplasia of esophageal mucosa and presumably related to chronic exposure to acid, is a pre-malignant condition for adenocarcinoma of the esophagus. The risk estimated to be about 0.5% annually is substantially higher in patients with low or high grade dysplasia.[7] There are controversies in the diagnosis of Barrett's esophagus and dysplasia that are beyond the scope of this article. The American College of Gastroenterology has published guidelines addressing the management of patients with Barrett's esophagus.[8] In addition, a variety of exciting new ablative therapies and endoscopic mucosal resection techniques for Barrett's esophagus with dysplasia or early adenocarcinoma have been developed. These can eliminate dysplastic epithelium and, under acid suppression, permit restoration of squamous mucosa. The fact remains however, that at this time, no endoscopic screening protocol for Barrett's has been shown to improve survival by preventing deaths from esophageal cancer.

How long should daily drug treatment (for GERD) continue and how should it be stepped down?

As with all therapies, the decision as to choice and duration of therapy for GERD involves consideration of risks and benefits. In all patients with GERD, **Proton Pump Inhibitors (PPIs)** have been shown to be more efficacious in controlling acute symptoms and maintaining a symptom-free state than **Histamine 2 Receptor Antagonists (H2RA)** which have, in turn, proven to be more effective than placebo. PPIs are also the most effective agents for healing esophagitis. Regarding the dosing frequency, once daily dosing of PPIs has been used most often in studies, though for non-responders, a trial of twice daily dosing is certainly appropriate and supported by the pharmacodynamics of the drugs.[9]

Assuming the patient improves, how long should therapy continue? Without the benefit of maintenance therapy (typically one-half the dose of healing therapy), the recurrence of esophagitis is high, occurring in up to 80% of patients within 6 months of completing acute therapy. This potentially puts the patient at risk for complications including esophageal stricture. H2RA and placebo are less effective than PPIs in preventing recurrent esophagitis in a patient healed with PPIs. Similarly, on demand therapy with PPIs can not be recommended for patients with documented esophagitis as the recurrence rates are unacceptably high.[10]

The greater efficacy of PPIs must be weighed against the possible risks of therapy including bone fractures, inter-

ference with anti platelet therapy, and an increased risk of infections. In May 2010 the **Food and Drug Administration (FDA)** required a change in the labeling of prescription and over-the-counter PPIs to include information about a possible increased risk of fractures of the hip, wrist, and spine in patients treated with PPIs. This was based on a Drug Safety Communication that quoted seven of eight retrospective studies showing an increased risk of fractures in patients treated with one of these drugs.[11] Interestingly the eighth study which did not show an association between PPI and bone fractures was published this year by Tarownik, who previously reported an association using a different data base.[12] Three of the studies that showed an association between PPI and fractures did not document a change in bone mineral density in patients taking these medications. As with other retrospective studies, causation is unproven.

There is evidence that some PPIs may interfere with the action of clopidogrel (Plavix®). Clopidogrel is a pro-drug that is converted to the active form by the enzyme CYP2C19. The FDA has changed the labeling of clopidogrel to include a "Black Box warning" warning that 2-14% of people who, as a result of a variant of CYP2C19, are 'poor metabolizers' of clopidogrel. As a result, poor metabolizers are more likely than normal metabolizers to suffer from adverse cardiovascular events when treated with clopidogrel for acute coronary syndrome or percutaneous coronary intervention.[13] Omeprazole is an inhibitor of CYP2C19 thereby reducing by about 45% the *in vitro* efficacy of clopidogrel on platelets Although not mentioned in the "Black Box" warning, omeprazole's adverse effect on clopidogrel's metabolism is mentioned in the prescribing information with a recommendation that coadministration be avoided. Observational studies have indicated a possible increased of cardiovascular events in patients treated with clopidogrel and PPI in the setting of an acute coronary syndrome.[14] As with other observational studies, this may be subject to certain biases including confounding risk variables. Unfortunately, the only randomized trial, **The Clopidogrel and the Optimization of Gastrointestinal Events (COGENT)**, to study this interaction was stopped prematurely when the sponsoring company went bankrupt.

PPIs have also been associated with a slightly increased incidence of pneumonia, *Clostridium difficile* infection and bacterial gastroenteritis. The studies are all retrospective, and the risk modest.

For the larger population of patients with non-erosive disease who presumably do not carry the same risk of esophageal stricture, the cost and risk of therapy may play a more important role in decision making about maintenance therapy. Patients with NERD who improve on daily PPI are also more likely to remain asymptomatic when continued on PPI compared to those given H2RA or placebo.[15] The cost of therapies differs but in general, H2RA are less expensive than PPIs and have been shown to be a class of medications with a very favorable side-effect profile. Therefore a trial of step-down therapy is a reasonable approach in this setting. "On demand" PPI therapy for recurrent symptoms has been shown to improve the health-related quality of life and patient satisfaction but the comparison to daily maintenance therapy has not yet been published.

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Are there clinically significant differences among the proton pump inhibitors?

When reviewing the primary literature comparing the efficacy of PPIs in GERD it is important to make sure that the endpoints are not only clearly defined but clinically relevant. For example, a recently published article stated "significantly greater acid control" of one PPI over another because the authors demonstrated a greater percentage of time of gastric pH> 4 (45.7 vs. 36.8).[16] While this may have reached statistical significance at the p<0.0001 level, it is not at all clear that this minuscule change in gastric pH has any relationship to a better outcome for the patient.

Acid suppressive therapy is 'big business.' In 2000 the economic impact of GERD in the United States was estimated to be $9.3 billion dollars. More than 60% of that cost was attributed to anti-secretory therapy.[17] The potential influence of the pharmaceutical industry on the research of antisecretory therapy is clear when reading the conflict of interest statements of many authors in the field. The majority receive some support from the pharmaceutical industry. I think it is likely that many of the studies performed today regarding the treatment of GERD are adversely affected by the same influences that prompted a recently retired editor of the NEJM to conclude that:

> *Given the conflicts of interest that permeate the clinical research enterprise, it is not surprising that industry-sponsored research has consistently been shown to favor the sponsor's drug—partly because negative results are often not published partly because positive results are repeatedly published in slightly different forms, and partly because a positive spin is put on even negative results… Clinical research that is published is often biased, usually by designing the studies in ways that will almost inevitably yield favorable results for the sponsor.* [18]

The evidence supporting the superiority of one PPI over another is very limited, especially when one takes into account different doses and dosing schedules. In my own practice, I typically prescribe a generic PPI and patients are given a prescription that permits the pharmacist to substitute another PPI that is lowest cost to the patient. An exception to this is a patient requiring antiplatelet therapy with clopidogrel in whom a new prescription for omeprazole or esomeprazole may be eschewed in favor of another PPI such as pantoprazole that is metabolized through a different pathway. Otherwise, changes from one PPI to another are usually driven by the patient's report of side effects

though there are few data to support the efficacy of this practice. Changes in PPI driven by insurance company mandates may precipitate more severe symptoms and decreases patient satisfaction. [19]

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