Gastroesophageal Reflux, Barrett Esophagus, and Esophageal Cancer
Clinical Applications

Nicholas Shaheen, MD, MPH
David F. Ransohoff, MD

Gastroesophageal reflux disease (GERD), a condition commonly encountered in the primary care setting, is a risk factor for adenocarcinoma of the esophagus. Despite the ubiquity of the complaint, considerable uncertainty exists with respect to several basic questions, including when to perform endoscopy in patients with chronic reflux symptoms and how to address the cancer risk associated with GERD. These clinical vignettes illustrate common clinical questions encountered in caring for patients with GERD, especially as they relate to the issue of cancer risk. Applying data reviewed in the companion article, we propose practical answers to common clinical situations regarding care of patients with reflux. We also present an algorithm for treatment of patients with chronic GERD symptoms.


See also p 1972.

©2002 American Medical Association. All rights reserved.

Author Affiliations: Division of Digestive Diseases and Nutrition, the Center for Esophageal Diseases and Swallowing, and the Center For Gastrointestinal Biology and Disease, University of North Carolina, Chapel Hill. Corresponding Author and Reprints: Nicholas Shaheen, MD, MPH, CB#7080, UNC-CH, Chapel Hill, NC 27599-7080 (e-mail: nshaheen@med.unc.edu). Scientific Review and Clinical Applications Section Editor: Wendy Levinson, MD, Contributing Editor.
protectable metaplastic change of the lining of the esophagus so that some portion is lined with specialized columnar epithelium instead of the normal squamous epithelium (Figure 1). With respect to this patient’s cancer risk, several demographic and symptomatic features argue against further invasive measures to rule out esophageal adenocarcinoma or Barrett esophagus. Although symptom severity is not a reliable predictor of the presence of Barrett esophagus, the chronicity of symptoms is. Individuals who are symptomatic for more than 5 years are at increased risk compared with the general public and those with symptoms of shorter duration. Additionally, epidemiologic studies show that Barrett esophagus and adenocarcinoma of the esophagus are diseases most prevalent in white men. With respect to esophageal adenocarcinoma, the incidence in men is 4 times that in women and is approximately 8 times as likely in whites as in other races. The incidence of esophageal adenocarcinoma increases markedly with age, making a 36-year-old unlikely to be affected. Finally, and most important, the absolute risk of adenocarcinoma in patients with uncomplicated reflux symptoms is low, and screening endoscopy has not been demonstrated to further decrease this risk. For these reasons, the yield of endoscopic screening in this patient is low and may be outweighed by the small risk of complication from upper endoscopy.

Appropriate treatment for this patient consists of counseling about the pathophysiology of reflux and a review of conservative measures sometimes helpful in avoiding reflux symptoms. These conservative measures, listed in Box 1, may decrease distal esophageal acid exposures. Additionally, adding a pharmacologic intervention would be reasonable. Because the patient has had an incomplete symptomatic response to H2RAs, therapy with a proton pump inhibitor could be initiated at standard daily dosing. Alternatively, in this patient, increasing the dose of H2RA as an initial step is also acceptable. A discussion of the risk factors and demographics of esophageal adenocarcinoma and the risks and benefits of endoscopic screening should help the patient understand why this measure is not recommended in her situation. Finally, close follow-up to ensure response of symptoms to therapy and to allow the tapering of pharmacological therapy to the lowest dose at which the patient is symptom free should be arranged. Figure 2 demonstrates a suggested algorithm for the use of endoscopy and pharmacological therapy for patients with classic reflux symptoms. This figure demonstrates a step-down approach to pharmacological therapy, starting with a proton pump inhibitor and decreasing acid suppression to the lowest dosage of either proton pump inhibitor or, preferably, H2RA that keeps the subject symptom free. Step-up approaches, starting with H2RAs and intensifying therapy as necessary, are also acceptable in patients who have not tried H2RA before evaluation.

Patient 2

A 65-year-old white man visits your office for follow-up for chronic reflux symptoms. He had an endoscopy 3 years ago, at which time 5 cm of Barrett mucosa without dysplasia was discovered. He otherwise is well, with no weight loss or dysphagia. He has been receiving therapy with a proton pump inhibitor daily for the last 6 years and is worried about the long-term effects of these medications on his system.

Are There Adverse Effects of Long-term Proton Pump Inhibition? When omeprazole, the first proton pump inhibitor, was introduced into the US market, there was concern that the potency of the drug and the increase in serum gastrin levels associated with its use might lead to the development of gastrinomas. Now, despite the ubiquitous nature of these agents and more than 15 years of experience with them, no increased cancer risk associated with proton pump inhibitor use has been demonstrated. The drugs appear to be safe, even when taken long-term and at doses higher than those initially approved for the healing of erosive esophagitis. Routine monitoring of serum gastrin levels is not recommended and may, in fact, cause the physician and patient some distress if they are checked, because they are often elevated in those undergoing therapy.

What Is the Appropriate Follow-up for This Patient’s Barrett Esophagus? Because of the dearth of data supporting surveillance endoscopy in Barrett esophagus, any consideration of enrolling a patient in an endoscopic surveillance program should be preceded by a frank discussion of the risks and benefits of surveillance. At the end of this discussion, the patient should understand the rationale behind endoscopic surveillance.
surveillance (to detect cancer in a preclinical and potentially more curable stage), the absolute risk of esophageal adenocarcinoma (approximately 1 in 200-300 patient-years),\textsuperscript{30-32} the risk of serial upper endoscopy (1 major complication in approximately 1000 procedures),\textsuperscript{33} the treatment options if dysplasia occurs within the Barrett esophagus (esophagectomy, closer surveillance to detect early cancer,\textsuperscript{34} and enrollment in an experimental ablative protocol),\textsuperscript{35} and the lack of endoscopic-surveillance evidence showing a survival benefit in those with Barrett esophagus. If after this discussion the patient opts for enrollment in an endoscopic surveillance program, referral to a gastroenterologist or surgeon for upper endoscopy with biopsies is warranted.\textsuperscript{36}

**Patient 3**

A 36-year-old man presents for follow-up of 2 years of reflux disease. His condition, made manifest by substernal chest burning, is well controlled by twice-daily proton pump inhibitors, for which he pays out of pocket. He wonders how long he will have to take these medications and whether there are other treatment options for him. He has heard that cancer can be associated with reflux, and his neighbor recently underwent a surgical antireflux procedure. He wonders if this procedure would protect him from cancer.

**What Is the Natural History of Treated and Untreated Reflux Disease?** Longitudinal studies of reflux disease demonstrate that, for most patients, the condition is chronic.\textsuperscript{26,35,36} Furthermore, in most of those who develop erosive esophagitis, maintenance therapy will be necessary after healing to avoid recurrence of esophagitis.\textsuperscript{26,37} However, many patients requiring proton pump inhibitors to heal mucosal disease can continue taking H2RAs. Therefore, in individuals with erosive disease, an 8-week course of proton pump inhibitors to heal mucosal lesions may be followed by an attempt to continue giving the patient H2RAs. In reflux patients who again become symptomatic while receiving H2RAs, long-term maintenance therapy with proton pump inhibitors may be initiated. In addition to good relief of symptoms and high healing rates of erosive esophagitis, proton pump inhibitor treatment effectively delays the

---

**Figure 2. Algorithm for Initial Evaluation and Treatment of Patients With Gastroesophageal Reflux Disease Symptoms**

This diagram illustrates a step-down approach, initiating therapy with a proton pump inhibitor, as might be used for patient 1. Initial therapy with H$_2$ receptor antagonists in patients not previously receiving these medications is also acceptable (a step-up approach).
development of peptic strictures in patients with a history of strictures.\textsuperscript{7,38} However, medical therapy has not been demonstrated to avert the development of Barrett esophagus or decrease the risk of cancer in individuals with long-term reflux symptoms.

**Does a Surgical Antireflux Procedure Decrease the Risk of Cancer in Individuals With Long-term Reflux Symptoms?** Although a surgical antireflux procedure is a safe and effective treatment for GERD in appropriately selected patients, it should not be pursued to decrease the risk of cancer in patients with reflux symptoms. Although the risk of mortality from a laparoscopic antireflux procedure is low (approximately 0.2%),\textsuperscript{39-41} it is still likely higher than the lifetime risk of death from adenocarcinoma in patients with chronic reflux disease because of the rareness of this cancer in the GERD population. Also, although it is intuitive to expect that decreasing exposure of the esophagus to gastric acid might halt the development of neoplasia, no data suggest that surgical antireflux procedures decrease the already low risk of esophageal adenocarcinoma among patients with GERD. The limited data that do exist suggest that surgical antireflux procedures do not decrease the cancer risk in subjects with GERD.\textsuperscript{8,42,43} Whether surgical antireflux procedures decrease the incidence of cancer in the subgroup with Barrett esophagus is a debated and unsettled issue. However, for patients with typical reflux symptoms, cancer prevention should not be the impetus for a surgical antireflux procedure.

**CONCLUSIONS**

Despite the commonness of GERD, it is often undiagnosed or undertreated in practice. In patients with classic substernal chest burning, further diagnostic testing is usually unnecessary, and empirical therapy with antisecretory medications may be instituted. Testing is appropriate for individuals who display alarm symptoms and those who do not respond as expected to therapy. The cancer risk in patients with GERD is low, and screening endoscopy has not been demonstrated to be effective in decreasing cancer incidence or increasing life expectancy. Potent anti-acid medications, such as proton pump inhibitors, make total relief of symptoms attainable in most patients. Long-term therapy with proton pump inhibitors may be necessary and, given the available evidence, appears safe and well tolerated. Surgical antireflux procedures are effective in appropriately chosen patients but should not be pursued solely in an attempt to decrease the already low risk of esophageal cancer in those with reflux.

Several other resources for physicians and patients to learn more about the evaluation and management of gastroesophageal reflux disease are available on the Internet (Box 2).

**Funding/Support:** This research was supported in part by the National Institutes of Health grant K23DK99311-01.

**REFERENCES**


15. Fass R, Ofman JJ, Sampliner RE, Camargo L, Wendt C, Fenerty MB. The omeprazole test is as sensitive as 24-h oesophageal pH monitoring in diagnosing gastro-oesophageal reflux disease in symptomatic...


---

I am certain of nothing but the holiness of the Heart’s affections, the truth of Imagination. What the Imagination sees as of Love: they are all, in their sublime, creative of essential Beauty.

—John Keats (1795-1821)