

Esophageal Complications of Gastroesophageal Reflux Disease: Presentation, Diagnosis, Management, and Outcomes

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The esophageal complications of gastroesophageal reflux disease include peptic esophageal erosion and ulceration, peptic esophageal strictures, and Barrett's esophagus. Endoscopy is the diagnostic procedure of choice for the initial evaluation of lesions. For most patients, symptoms can be controlled with proton pump inhibitor (PPI) therapy. PPIs are also highly effective for healing esophageal erosions and ulcerations and for preventing recurrence of peptic esophageal strictures. Because Barrett's esophagus predisposes individuals to esophageal adenocarcinoma, these patients are advised to have regular endoscopic surveillance to detect early, curable neoplasms. Clinical Cornerstone® Vol. 5, No. 4. Copyright © 2003 Excerpta Medica, Inc.

PATHOPHYSIOLOGY

Refluxed gastric juice can injure and inflame the stratified squamous epithelium that normally lines the distal esophagus (1). Peptic esophageal erosions and ulcerations occur when squamous epithelial cells succumb to the caustic effects of refluxed acid and pepsin. If peptic ulceration penetrates the blood vessels that supply the esophagus, esophageal hemorrhage may ensue. Peptic ulceration also can stimulate the deposition of fibrous tissue in the wall of the esophagus, resulting in a peptic esophageal stricture. Healing of peptic esophageal ulcerations usually involves the regeneration of more stratified squamous epithelium. In some individuals, however, healing occurs through a metaplastic process in which an intestinal-type columnar epithelium replaces the reflux-damaged squamous lining. This condition is called Barrett's esophagus, and the intestinal metaplasia of Barrett's

esophagus predisposes patients to esophageal adenocarcinoma.

The frequency of the esophageal complications of gastroesophageal reflux disease (GERD) varies substantially among different ethnic groups. Studies from the Far East have suggested that complicated GERD is rare in Asians (2). For decades it has been known that Barrett's esophagus and esophageal adenocarcinoma are predominantly disorders of whites (3). Peptic esophageal ulcerations and strictures have been found more commonly in whites than in blacks in the United States (4). In one recent study, investigators reviewed endoscopy reports and medical records for data on race and GERD complications in 2477 consecutive patients seen in the general endoscopy unit of a Boston hospital (5). One or more esophageal complications of GERD were observed in 267 of 2174 white patients (12.3%), but in only 7 of 249 black patients (2.8%)

and 1 of 54 Asian patients (1.9%). All 50 patients with peptic esophageal strictures were white, as were 61 of the 62 patients with peptic esophageal ulcerations. This study suggests that all esophageal complications of GERD have a strong predilection for whites and are uncommon in blacks and Asians. One important implication of this observation is that clinicians should be especially cautious about attributing esophageal ulcerations and strictures to GERD in black and Asian patients. Other etiologies (eg, cancer, infection) must be strongly considered and pursued vigorously in these patients.

KEY POINT

A recent study suggests that all esophageal complications of GERD have a strong predilection for whites and are uncommon in blacks and Asians.

PEPTIC ESOPHAGEAL EROSION AND ULCERATION

Histologically, erosions are defined as superficial necrotic defects that do not penetrate the muscularis mucosae, whereas ulcerations are deeper defects that extend through the muscularis mucosae into the submucosa (6). Clinically, peptic esophageal ulcers are identified on the basis of their gross endoscopic or radiographic features, and clinicians seldom have histologic confirmation that the lesions they call “esophageal ulcers” in fact have breached the muscularis mucosae. Thus, the distinction between an esophageal ulceration and an erosion usually is based on a subjective assessment of the depth of the necrotic lesion.

One current method for grading the severity of reflux esophagitis, called the Los Angeles Classification System, avoids the problem of distinguishing erosions from ulcerations by referring to both as “mucosal breaks” (7). A mucosal break is defined as “an area of slough or erythema with a discrete line of demarcation from the adjacent, more normal-looking mucosa.” The Los Angeles Classification System grades esophagitis on a scale

of A to D, depending on the length and circumferential extent of the mucosal breaks. Los Angeles grades C and D represent severe reflux esophagitis.

Odynophagia (pain with swallowing) is the symptom usually attributed to esophageal erosions and ulcerations. Ulcerative esophagitis can also cause dysphagia even in the absence of a mechanical obstruction such as a peptic esophageal stricture (8). However, heartburn may be the only esophageal symptom noted by many patients with severe reflux esophagitis, and some patients with verified esophageal ulcerations on endoscopic examination may have no esophageal symptoms whatsoever. Endoscopy is the diagnostic procedure of choice to document esophageal erosions and ulcerations. Although these lesions can be identified by a barium swallow, the sensitivity of radiography for detecting reflux esophagitis is ~70% (using endoscopy as the diagnostic gold standard) (9). Furthermore, lesions identified radiographically generally require an endoscopic evaluation and a biopsy sampling for confirmation. Endoscopy is consequently preferred over radiography for the initial evaluation of patients who have symptoms suggestive of esophageal ulceration.

Uncommonly, esophageal erosions and ulcerations can erode into blood vessels and cause acute hemorrhage. In a series of patients hospitalized for acute upper gastrointestinal bleeding, <5% of cases were due to esophagitis (10). However, cases have been reported of peptic esophageal ulcers that have perforated into the mediastinum or penetrated into the airway, resulting in esophago-tracheal or esophagobronchial fistulae (11,12).

Only 2 forms of therapy are effective for the healing of ulcerative esophagitis: proton pump inhibitors (PPIs) and antireflux surgery (13). Histamine₂-receptor antagonists (H₂RAs) are not reliable agents for patients with such severe reflux disease. PPIs are almost always effective for healing severe reflux esophagitis, provided they are administered in sufficient dosage (14). Although antireflux surgery can heal esophageal ulcerations, surgical treatment is seldom necessary solely to effect esophageal healing. Furthermore, recent studies have raised questions regarding the long-term efficacy of antireflux operations (15).

KEY POINT

Endoscopy is the diagnostic procedure of choice to document esophageal erosions and ulcerations.

PEPTIC ESOPHAGEAL STRICTURES

Deep esophageal ulcerations can stimulate fibrous tissue production and collagen deposition, thereby resulting in an esophageal stricture. The precise pathogenetic mechanisms involved in stricture formation are not known, however, and it is conceivable that some peptic strictures may develop as a result of chronic esophageal inflammation without mucosal ulceration. It has been estimated that in the United States 60% to 70% of all benign esophageal strictures are caused by reflux esophagitis, with the remainder due largely to caustic ingestions, radiation, and infectious esophagitis (16). It is the opinion of some esophagologists that the frequency of peptic esophageal strictures has decreased since 1989 when the first PPI was approved for clinical use in the United States, but definitive data to prove this contention are not available.

Patients with esophageal strictures typically complain of dysphagia for solid foods that progresses slowly (over months to years) in severity. Most patients have no problem swallowing liquids, and they usually experience little or no weight loss. Endoscopy is the diagnostic procedure of choice if a peptic esophageal stricture is suspected. Radiography is not required in most cases, but if esophageal strictures are unusually long or tight, a barium swallow can be helpful to delineate the anatomy and to guide the choice among dilators for therapy.

In the era before PPIs, medical therapy had little role in the management of peptic esophageal strictures. Clinical trials comparing H₂RAs with placebo in the treatment of patients with peptic esophageal stenoses showed no reduction in the need for stricture dilation (17,18). Thus, peptic

strictures were regarded as fixed fibrotic lesions that would respond only to dilation therapy aimed at stretching or tearing the fibrous tissue. However, recent studies have shown that PPIs both improve dysphagia and decrease the need for subsequent esophageal dilations in patients with peptic esophageal strictures (19). This observation indicates that a reversible component of reflux esophagitis contributes to dysphagia in some patients with peptic esophageal strictures (20).

Patients with peptic esophageal strictures who have dysphagia despite treatment with PPIs are treated with esophageal dilation. Three types of esophageal dilating devices are commonly used: mercury-filled bougies that are passed blindly through the mouth (eg, Maloney dilators); polyvinyl bougies that can be passed over a guidewire positioned within the stricture using either fluoroscopic or endoscopic guidance (eg, Savary dilators); and balloon dilators that are passed either over a guidewire or through the endoscope. Guidewires are used if the stricture is unusually long or tight. If bougies are chosen, the physician passes a series of dilators of increasing diameter to gradually stretch the peptic stricture. If a balloon is chosen, it is simply inflated to its maximal diameter. Most patients experience substantial relief of dysphagia when the esophagus is stretched to a diameter between 12 mm and 18 mm. No study has established the superiority of one type of dilator over another, and serious complications such as perforation and bleeding occur in ~0.5% of all esophageal dilation procedures (21).

BARRETT'S ESOPHAGUS

In Barrett's esophagus an abnormal columnar epithelium, called specialized intestinal metaplasia, replaces esophageal squamous epithelium that has been damaged by GERD (22). Specialized intestinal metaplasia usually shows evidence of DNA damage (23), and most esophageal adenocarcinomas appear to arise from this metaplastic mucosa (24). GERD and Barrett's esophagus are the major recognized risk factors for esophageal adenocarcinoma, a tumor whose frequency has increased profoundly over the past few decades in Western countries (25).

Symptoms and Cancer Risk

Barrett's esophagus per se causes no symptoms. The condition usually is discovered when endoscopy is performed to evaluate GERD symptoms. The Practice Parameters Committee of the American College of Gastroenterology has recommended the following guideline on initial evaluation for patients with GERD (8): "If the patient's history is typical for uncomplicated GERD, an initial trial of empirical therapy (including lifestyle modification) is appropriate. Patients in whom empiric therapy is unsuccessful or who have symptoms suggesting complicated disease should have further diagnostic testing (ie, endoscopy)." Symptoms that might suggest complicated disease requiring early endoscopic evaluation include anorexia, weight loss, dysphagia, odynophagia, bleeding, and signs of systemic illness. In another publication specifically addressing Barrett's esophagus (26), the Practice Parameters Committee states, "Patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo upper endoscopy." It is important to appreciate that these guidelines are merely committee recommendations whose efficacy has not been verified by clinical studies. Indeed, some authorities believe there is insufficient evidence to support the practice of rou-

KEY POINT

Endoscopy with random biopsy sampling for dysplasia remains the clinical standard for managing patients with Barrett's esophagus.

tine endoscopic screening of patients with chronic GERD symptoms (27).

Endoscopists recognize Barrett's esophagus because specialized intestinal metaplasia has a dull reddish color that contrasts sharply with the pale, glossy appearance of the normal squamous lining. This finding is not specific, however, and therefore the diagnosis of Barrett's esophagus requires the demonstration of specialized intestinal metaplasia

in esophageal biopsy specimens. If specialized intestinal metaplasia extends ≥ 3 cm above the gastroesophageal junction, the condition is called long-segment Barrett's esophagus; < 3 cm of esophageal metaplasia is called short-segment Barrett's esophagus (28). In patients who undergo endoscopy because of GERD symptoms, 3% to 5% are found to have long-segment Barrett's esophagus, and 10% to 15% are found to have the short-segment condition (22). Although it is not clear that long- and short-segment Barrett's esophagus have the same pathogenesis and risk for malignancy, the 2 conditions presently are managed similarly.

Published estimates on the annual risk of cancer in patients with Barrett's esophagus have ranged from 0.2% to 2.9% (29,30). However, a recent report has provided compelling evidence that the cancer risk in Barrett's esophagus has been overestimated for years because of publication bias—the selective reporting of studies that have positive or extreme results (30). Current studies suggest that patients with Barrett's esophagus develop esophageal cancer at the rate of $\sim 0.5\%$ per year. Endoscopic surveillance is recommended to identify neoplasms that are in an early curable stage.

No definitive studies (ie, randomized controlled trials) prove that regular endoscopic surveillance decreases cancer mortality for patients with Barrett's esophagus. Observational studies have documented that endoscopic surveillance can detect curable neoplasms in Barrett's esophagus, and that cancers discovered during surveillance are less advanced than those found in patients who present with cancer symptoms such as dysphagia and weight loss (31). Those studies however are subject to a number of biases that might inflate the value of surveillance (32). Computer models also have suggested that screening and surveillance for Barrett's esophagus can prolong life provided certain assumptions are met (33–35). For example, in one Markov model of 50-year-old patients who had an assumed annual cancer incidence rate of 0.4%, endoscopic surveillance every 5 years was found to be the preferred strategy, costing \$98,000 per quality-adjusted life-year gained (35). Such computer models incorporate numerous layers of

questionable assumptions, which limit their clinical utility.

Dysplasia

Cancers in Barrett's esophagus evolve through a sequence of genetic (DNA) alterations that endow the affected cells with growth advantages and produce morphological changes in the tissue (**Figure**) (36). When the genetic damage is sufficient to cause neoplasia, the accompanying morphological changes may be recognized histologically as dysplasia. Thus, dysplasia is the morphological expression of early neoplasia, and dysplastic cells are predisposed to malignancy. Pathologists categorize dysplasia as low- or high-grade, depending on the extent of cytological and architectural changes in the tissue.

Unfortunately, dysplasia is an imperfect marker for malignancy in Barrett's esophagus for several reasons. Among experienced pathologists, interobserver agreement for the diagnosis of low-grade dysplasia in Barrett's esophagus is <50% (37,38). Furthermore, cancers can be detected in the resected esophagus of approximately one third of patients who have undergone esophagectomy because of the finding of high-grade dysplasia; presumably, these cancers are missed preoperatively

because of biopsy sampling error. Published estimates of the 5-year cumulative esophageal cancer incidence for patients with high-grade dysplasia range widely, from 9% to 59% (38–41). Alternative markers for cancer risk are being studied (eg, abnormalities in p53 expression and flow cytometry), as are endoscopic techniques that enable identification of abnormal tissue for biopsy sampling (eg, chromoendoscopy, endosonography, and fluorescence spectroscopy). Despite the many problems with dysplasia as a biomarker for malignancy, endoscopy with random biopsy sampling for dysplasia remains the clinical standard for managing patients with Barrett's esophagus.

Patients with high-grade dysplasia in Barrett's esophagus have 3 major management options: esophagectomy, endoscopic ablative therapy, or intensive surveillance. Esophagectomy is the only therapy that clearly can prevent the progression from dysplasia to cancer. However, esophagectomy has an operative mortality rate of 3% to 12%, and a 30% to 50% rate of serious operative complications (42). Endoscopic ablative therapies use thermal or photochemical energy to destroy the abnormal epithelium, or localized lesions can be resected using a technique called endoscopic mucosal resection that is similar to

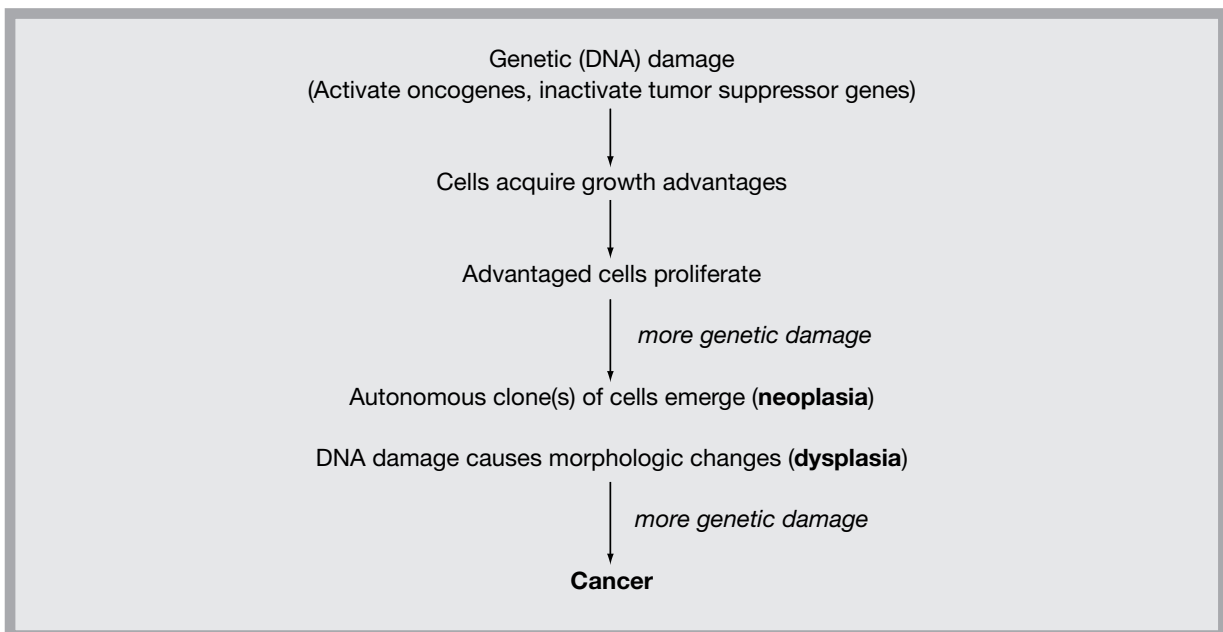


Figure. Carcinogenesis in Barrett's esophagus.

colonoscopic polypectomy (43,44). Serious side effects (eg, esophageal stricture formation) occur frequently with these treatments, and no study yet has demonstrated that ablative therapy decreases the long-term risk for cancer development in Barrett's esophagus. Intensive surveillance for high-grade dysplasia involves endoscopic examinations every 3 to 6 months, and invasive therapies are withheld until biopsy specimens show adenocarcinoma. Few published data directly support the safety and efficacy of this practice, and published reports suggest that ~3% to 10% of cancers discovered in this fashion may be incurable (41,45,46).

KEY POINT

Clinicians may consider the use of experimental ablative therapies for high-grade dysplasia provided the therapy is administered as part of an established, approved research protocol.

Management of Barrett's Esophagus

No management strategy for patients with Barrett's esophagus has been proved to prolong life. Nevertheless, the management strategy endorsed by the American College of Gastroenterology, and which can be considered the present standard of care, is as follows (26):

- Patients with Barrett's esophagus should have regular surveillance endoscopy to obtain esophageal biopsy specimens. GERD should be treated prior to surveillance to minimize confusion caused by inflammation in the interpretation of dysplasia.
- For patients who have had 2 consecutive endoscopies that show no dysplasia, surveillance endoscopy is recommended at an interval of every 3 years.
- If dysplasia is noted, the finding should be verified by consultation with another expert pathologist.
- For patients with verified low-grade dysplasia

after extensive biopsy sampling, yearly surveillance endoscopy is recommended.

- For patients found to have high-grade dysplasia, another endoscopy should be performed with extensive biopsy sampling (especially from areas with mucosal irregularity) to look for invasive cancer, and the histology slides should be interpreted by an expert pathologist. If the finding is focal high-grade dysplasia (defined as high-grade dysplastic changes involving fewer than 5 crypts), the condition may be followed with endoscopic surveillance performed at 3-month intervals. If the determination is verified to be multifocal high-grade dysplasia, intervention (eg, esophagectomy) may be considered.

Although not specifically recommended in the practice guidelines, clinicians may consider the use of experimental ablative therapies such as photodynamic therapy for their patients with high-grade dysplasia in Barrett's esophagus, *provided the therapy is administered as part of an established, approved research protocol*. The use of ablative therapies outside research protocols cannot be condoned at this time.

SUMMARY

Esophageal complications of GERD include peptic esophageal erosion and ulceration, peptic esophageal strictures, and Barrett's esophagus. Frequency of these complications varies substantially among different ethnic groups. Results of a recent study suggest that all esophageal complications of GERD have a strong predilection for whites and are uncommon in blacks and Asians. For these groups, other etiologies such as cancer and infection must be strongly considered and pursued. Endoscopy is the diagnostic procedure of choice to document esophageal erosions and ulcerations. Of the 2 forms of effective therapy for healing severe reflux esophagitis, PPIs, if administered in sufficient dosage, are almost always effective. For managing patients with Barrett's esophagus, surveillance endoscopy with random biopsy sampling for dysplasia remains the clinical standard.

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REFERENCES

- Spechler SJ. A 59-year-old woman with gastroesophageal reflux disease and Barrett esophagus. *JAMA*. 2003;289:466–475.
- Ho KY, Kang JY, Seow A. Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. *Am J Gastroenterol*. 1998;93:1816–1822.
- Cameron AJ. Epidemiology of columnar-lined esophagus and adenocarcinoma. *Gastroenterol Clin N Am*. 1997;26:487–494.
- Sonnenberg A, Massey BT, Jacobsen SJ. Hospital discharges resulting from esophagitis among medicare beneficiaries. *Dig Dis Sci*. 1994;39:183–188.
- Spechler SJ, Jain SK, Tendler DA, Parker RA. Racial differences in the frequency of symptoms and complications of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2002;16:1795–1800.
- Grossman MI, ed. *Peptic Ulcer: A Guide for the Practicing Physician*. Chicago: Year Book Medical Publishers, Inc; 1981.
- Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut*. 1999;45:172–180.
- Triadafilopoulos G. Nonobstructive dysphagia in reflux esophagitis. *Am J Gastroenterol*. 1989;84:614–618.
- Ott DJ. Gastroesophageal reflux disease. *Radiol Clin North Am*. 1994;32:1147–1166.
- Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. *Am J Gastroenterol*. 1995;90:206–210.
- Cappell MS, Sciales C, Biempica L. Esophageal perforation at a Barrett's ulcer. *J Clin Gastroenterol*. 1989;11:663–666.
- Diehl JT, Thomas L, Bloom MB, et al. Tracheoesophageal fistula associated with Barrett's ulcer: the importance of reflux control. *Ann Thorac Surg*. 1988;45:449–450.
- DeVault KR, Castell DO, and The Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol*. 1999;94:1434–1442.
- Klinkenberg-Knol EC, Nelis F, Dent J, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology*. 2000;118:661–669.
- Spechler SJ, Lee E, Ahnen D. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease. Follow-up of a randomized controlled trial. *JAMA*. 2001;285:2331–2338.
- Marks RD, Shukla M. Diagnosis and management of peptic esophageal strictures. *Gastroenterologist*. 1996;4:223–237.
- Ferguson R, Dronfield MW, Atkinson M. Cimetidine in treatment of reflux oesophagitis with peptic stricture. *Br Med J*. 1979;2:472–474.
- Farup PG, Modalsli B, Tholfsen JK. Long-term treatment with 300 mg ranitidine once daily after dilatation of peptic oesophageal strictures. *Scand J Gastroenterol*. 1992;27:594–598.
- Smith PM, Kerr GD, Cockel R, et al, for the Restore Investigator Group. A comparison of omeprazole and ranitidine in the prevention of recurrence of benign esophageal stricture. *Gastroenterology*. 1994;107:1312–1318.
- Dakkak M, Hoare RC, Maslin SC, Bennett JR. Oesophagitis is as important as oesophageal stricture diameter in determining dysphagia. *Gut*. 1993;34:152–155.
- Spechler SJ. AGA technical review on treatment of patients with dysphagia caused by benign disorders of the distal esophagus. *Gastroenterology*. 1999;117:233–254.
- Spechler SJ. Barrett's esophagus. *N Engl J Med*. 2002;346:836–842.
- Wong DJ, Paulson TG, Prevo LJ, et al. p16 (INK4a) lesions are common, early abnormalities that undergo clonal expansion in Barrett's metaplastic epithelium. *Cancer Res*. 2001;61:8284–8289.
- Theisen J, Stein HJ, Dittler HJ, et al. Preoperative chemotherapy unmasks underlying Barrett's mucosa in patients with adenocarcinoma of the distal esophagus. *Surg Endosc*. 2002;16:671–673.
- Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am*. 2002;11:235–256.
- Sampliner RE and The Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. *Am J Gastroenterol*. 2002;97:1888–1895.
- Shaheen N, Ransohoff DF. Gastroesophageal reflux, Barrett esophagus, and esophageal cancer: scientific review. *JAMA*. 2002;287:1972–1981.
- Sharma P, Morales TG, Sampliner RE. Short segment Barrett's esophagus—the need for standardization of the definition and of endoscopic criteria. *Am J Gastroenterol*. 1998;93:1033–1036.
- Drewitz DJ, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. *Am J Gastroenterol*. 1997;92:212–215.
- Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology*. 2000;119:333–338.

31. Corley DA, Levin TR, Habel LA, et al. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. *Gastroenterology*. 2002;122:633–640.
32. Shaheen NJ, Provenzale D, Sandler RS. Upper endoscopy as a screening and surveillance tool in esophageal adenocarcinoma: a review of the evidence. *Am J Gastroenterol*. 2002;97:1319–1327.
33. Inadomi JM, Sampliner R, Lagergren J, et al. Screening and surveillance for Barrett esophagus in high-risk groups: a cost-utility analysis. *Ann Intern Med*. 2003;138:176–186.
34. Soni A, Sampliner RE, Sonnenberg A. Screening for high-grade dysplasia in gastroesophageal reflux disease: is it cost-effective? *Am J Gastroenterol*. 2000;95:2086–2093.
35. Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. *Am J Gastroenterol*. 1999;94:2043–2053.
36. Morales CP, Souza RF, Spechler SJ. Hallmarks of cancer progression in Barrett's oesophagus. *Lancet*. 2002;360:1587–1589.
37. Skacel M, Petras RE, Gramlich TL, et al. The diagnosis of low-grade dysplasia in Barrett's esophagus and its implications for disease progression. *Am J Gastroenterol*. 2000;95:3383–3387.
38. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. *Hum Pathol*. 2001;32:368–378.
39. Reid BJ, Levine DS, Longton G, et al. Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. *Am J Gastroenterol*. 2000;95:1669–1676.
40. Buttar NS, Wang KK, Sebo TJ, et al. Extent of high grade dysplasia in Barrett's esophagus correlates with risk of adenocarcinoma. *Gastroenterology*. 2001;120:1630–1639.
41. Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology*. 2001;120:1607–1619.
42. Swisher SG, DeFord L, Merriman KW, et al. Effect of operative volume on morbidity, mortality, and hospital use after esophagectomy for cancer. *J Thorac Cardiovasc Surg*. 2000;119:1126–1132.
43. Van den Boogert J, van Hillegersberg R, Siersema PD, et al. Endoscopic ablation therapy for Barrett's esophagus with high-grade dysplasia: a review. *Am J Gastroenterol*. 1999;94:1153–1160.
44. May A, Gossner L, Pech O, et al. Intraepithelial high-grade neoplasia and early adenocarcinoma in short-segment Barrett's esophagus (SSBE): curative treatment using local endoscopic treatment techniques. *Endoscopy*. 2002;34:604–610.
45. Reid BJ, Blount PL, Feng Z, Levine DS. Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. *Am J Gastroenterol*. 2000;95:3089–3096.
46. Weston AP, Sharma P, Topalovski M, et al. Long-term follow-up of Barrett's high-grade dysplasia. *Am J Gastroenterol*. 2000;95:1888–1893.

Dialogue Box

EDITORIAL BOARD

Do esophageal complications occur in patients with mild GERD, ie, patients with occasional symptoms, typically after meals, adequately controlled with over-the-counter antacids or H₂-blockers?

SPECHLER

Esophageal complications (esophageal ulcerations, stricture, Barrett's esophagus) occur almost exclusively in patients who have severe reflux esophagitis. However, the severity of symptoms does not reflect the severity of esophagitis. Patients with mild symptoms may have severe esophagitis and patients who do not have severe esophagitis may have severe symptoms.

EDITORIAL BOARD

Should clinicians have a higher threshold for ordering upper gastrointestinal (UGI) endoscopy in black and Asian GERD patients? Also, what are the differences in adenocarcinoma of the esophagus in these groups?

SPECHLER

In answer to the first part, no. Indications for this procedure are the same among different ethnic groups. The SEER program publishes data about the frequency of adenocarcinoma of the esophagus in whites and African Americans, but I do not think that data on Asians are readily available. Adenocarcinoma of the esophagus is predominantly a disease of white men. Furthermore, data from the Far East suggest that adenocarcinoma of the esophagus is rare in Asians.

EDITORIAL BOARD

To what extent does adenocarcinoma of the cardia show gender and racial differences?

SPECHLER

The epidemiology of adenocarcinoma of the cardia is very similar to that of adenocarcinoma of the esophagus, including gender and racial differences. However, many of the so-called adenocarcinomas of the cardia are really adenocarcinomas of the esophagus that have grown down into the stomach. From the data available, it is not possible to know whether the epidemiology of "true" adenocarcinomas of the cardia (ie, cancers that truly originate in the proximal stomach and not the distal esophagus) differs substantially from that for adenocarcinoma of the esophagus.

EDITORIAL BOARD

Other than odynophagia, are there any other symptoms that would be predictive of esophageal complications?

SPECHLER

Dysphagia for solid foods suggests the possibility of an esophageal stricture. The combination of dysphagia and weight loss suggests the presence of esophageal cancer.

EDITORIAL BOARD

For patients with severe reflux esophagitis, what dosage of PPIs should be prescribed and for how long?

SPECHLER

The conventional dosages for reflux esophagitis are as follows:

esomeprazole (Nexium [®])	20 mg QD or 40 mg QD
lansoprazole (Prevacid [®])	30 mg QD
omeprazole (Prilosec [®])	20 mg QD
pantoprazole (Protonix [®])	40 mg QD
rabeprazole (Aciphex [®])	20 mg QD

Physicians often increase the dosages to BID or higher as necessary for patients who do not respond to the conventional dosages.

Dialogue Box

EDITORIAL BOARD

What is the pathophysiologic mechanism for the favorable impact of PPIs on the “reversible component” of the dysphagia seen in GERD patients with strictures?

SPECHLER

The mechanism is not entirely clear. Reflux esophagitis causes swelling of the mucosa within the stricture, which further narrows the lumen of the esophagus. PPIs cause healing of the reflux esophagitis and, presumably, this opens the lumen and improves dysphagia.

EDITORIAL BOARD

Why has the incidence of esophageal adenocarcinoma increased in Western countries despite the availability and growing use of PPI therapy?

SPECHLER

The answer to this question is not known. Some authorities speculate that the declining frequency of *H pylori* infection in Western populations has predisposed to more severe GERD. Others have proposed that the increased use of nitrate-based fertilizers in Western countries after World War II has resulted in increased exposure of the distal esophagus to genotoxic levels of nitric oxide. Further studies are needed to resolve this important issue.

EDITORIAL BOARD

What are the risk factors for the development of Barrett’s esophagus?

SPECHLER

Risk factors for Barrett’s esophagus in patients with GERD include male gender, white ethnicity, advanced age, and long duration of symptoms.

EDITORIAL BOARD

Since the cost benefit of screening for Barrett’s is difficult to justify in an unselected group, would it be easier to justify in white males >50 years with prolonged reflux symptoms?

SPECHLER

Middle-aged white males clearly are the group most at risk for esophageal adenocarcinoma, and the cost-efficacy of screening has not been established even in this group. Presently, however, no medical society recommends that endoscopic surveillance should be limited only to certain ethnic groups.

EDITORIAL BOARD

The drastic increases in GER and adenocarcinoma of the esophagus seem to parallel the increase in obesity. Is there a reason not to include increasing obesity along with declining *H pylori* and nitric oxide exposure among the probable causes for epidemic GERD?

SPECHLER

Obesity has been established as a risk factor for esophageal adenocarcinoma, and the increase in obesity certainly could be contributing to the increased frequency of the tumor.