An Overview of Gastroesophageal Reflux Disease

Based on a presentation by M. Michael Wolfe, MD

Presentation Summary

Gastroesophageal reflux disease (GERD) is a chronic acid-peptic disorder that is the combined result of several factors: 1) the lack of gastrointestinal motility coordination, 2) the failure of the lower esophageal sphincter to prevent reflux, and 3) the caustic nature of the gastric refluxate. Although GERD is very common, only a small fraction of sufferers consult a physician regarding their problem. This disease has a tremendous impact on both quality of life and overall health. If untreated, GERD can result in many serious complications, including erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. Because the caustic nature of the refluxate is a direct cause of esophageal damage, the cornerstone of GERD therapy is gastric acid suppression.

Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal disorder in the western world.[1] Heartburn with or without regurgitation of gastric contents,[2] which is GERD's most prominent symptom, has been estimated to affect 10% of the US adult population on a daily basis.[1] GERD can also be manifested by atypical symptoms such as laryngitis, hoarseness, chronic cough, wheezing, and asthma.[3-6] These symptoms are thought to be the result of physical contact of the oropharynx/respiratory tract with the gastric refluxate and the microaspiration of gastric acid.[6] It has also been hypothesized that the presence of gastric acid in the lower esophagus may induce a reflex mechanism from the vagus nerve to produce bronchospasm, which is manifested by cough, wheezing, and asthma symptoms.[6] Some GERD patients experience noncardiac chest pains, thus, cardiac disease must be excluded in these patients before an evaluation can be performed to identify the upper gastrointestinal source of the symptom.[2,6] Dental erosion caused by the regurgitation of gastric acid recently has been recognized as another atypical symptom of GERD.[7]

Etiology of GERD

Gastroesophageal reflux disease has been described as a disorder that is secondary to mechanical events. As a result, an important contributing factor to this disease is a breakdown

of peristaltic coordination because of a failure of the pylorus to relax in the presence of increased gastric volume and delayed clearance of stomach contents.[8] Reflux also may be further facilitated by the proximity of gastric contents to the gastroesophageal junction, which can occur as a result of recumbancy or an increase in gastric pressure because of obesity, pregnancy, ascites, or other factors.[8]

Dysfunction in the lower esophageal sphincter (LES) as a result of inappropriate smooth muscle relaxation and the loss of muscle tone is the major factor contributing to the occurrence of gastric reflux. Agents that can contribute to smooth muscle relaxation include oral β-2 agonists, anticholinergics, theophylline, nitrates, and calcium channel blockers.[8] Certain foods, such as peppermints, coffee, chocolates, and fatty foods, can also cause smooth muscles, such as the LES, to relax (Table).[8] Fatty foods are thought to relax the sphincter muscle by inducing the production of cholecystokinin. In pregnancy, elevated levels of estrogen and progesterone may induce smooth muscle relaxation.[9] Scleroderma-like diseases also can have a detrimental effect on the LES as well as on the esophageal body.[8]

Esophageal injury occurs as a result of direct contact between the esophagus and refluxed material. As a result, high concentrations of gastric acid that are refluxed into the esophagus can lead to significant mucosal damage. Acid also catalyzes the conversion of the proenzyme pepsinogen to its active form, pepsin, which can cause further injuries.[10,11]

Table. Treatment of GERD: Lifestyle Modifications

- Remove precipitating factors
  - Food: mints, fatty foods, chocolate
  - Drugs: anticholinergics, nitrates, theophylline, Ca^{2+} channel blockers, oral β–2agonists
- Addition of barriers to gastric reflux
  - Elevate head of bed 6 inches with bricks or blocks or elevate the entire thorax with a firm wedge
  - Decrease gastric pressure (weight loss, avoiding tight clothes, etc)
- Other modifications
  - Avoid eating before bed
  - Chew gum (increases level of salivary HCO_3)

Diagnosis of GERD

The diagnosis of GERD can be difficult because this disease is not easily characterized. The presence of GERD is suggested by patient history,[8] however, determining the existence of this condition based on the presence of its classic symptoms (eg, heartburn and regurgitation) alone can be misleading because not all GERD patients experience these symptoms.[2] Moreover, serious disorders, such as achalasia and coronary heart disease, can mimic GERD symptoms. Symptoms that can signal the presence of a more serious disease include chest pain, odynophagia, dysphagia, weight loss, anemia, gastrointestinal bleeding, and refractoriness to GERD treatment. Urgent endoscopy is usually indicated for patients with such symptoms.

However, use of endoscopy alone in the diagnosis of GERD can also be problematic because most patients with classic GERD symptoms do not exhibit esophageal injury on endoscopic examination, and esophagitis experienced by asymptomatic patients may have etiologies other than GERD.[2] An objective approach to defining GERD is to measure the amount of esophageal exposure to gastric acid. Although 24-hour monitoring of esophageal pH can yield an accurate assessment, it is impractical as a routine method.[10] Currently, one practical method for the identification of esophagitis is to establish the presence of classic symptoms and at least one piece of objective evidence (ie, endoscopic esophagitis, biopsy results, or histology results). Alternatively, asymptomatic patients or

those with atypical symptoms may require more sources of objective evidence for an accurate diagnosis to be made such as a response to empiric treatment with a proton pump inhibitor (PPI).[10]

It is estimated that physicians see only a small fraction of GERD sufferers. Whereas a minority of patients present with chronic heartburn, dysphagia, hoarseness, and other GERD symptoms, a larger number report recurrent heartburn episodes but no other symptoms. The vast majority of GERD sufferers who may experience intermittent heartburn do not consult a physician about their problem.[10]

Complications of GERD

Untreated GERD can result in complications, including esophagitis, a condition characterized by endoscopically visible mucosal injury in the form of erythema friability, bleeding, superficial linear ulcers, and exudates.[8] After a patient has been diagnosed with erosive esophagitis, it demonstrates that GERD has resulted in mucosal damage. Esophagitis can lead to peptic strictures, hemorrhage, and the loss of esophageal glands.[12] For erosive esophagitis to heal, the pH of the esophagus must be maintained above 4.0. Untreated esophagitis or progression of ongoing healing/injury cycles can result in the development of more serious diseases such as Barrett's esophagus and esophageal adenocarcinoma.

Barrett's esophagus is a disease in which the squamous mucosa that normally lines the distal esophagus is replaced by columnar epithelium similar to that of the stomach and intestines.[13] Data suggest that the risk of developing Barrett's esophagus increases with the duration of GERD (Figure 1).[14] Although Barrett's esophagus can affect both sexes and all age groups, the typical patient is a 55-year-old Caucasian male.[13] Most patients are seen initially by the physician because of heartburn, regurgitation, and/or dysphagia.[13]

The prevalence of Barrett's esophagus in the general population is currently unknown because many cases are asymptomatic. Approximately 8% to 20% of patients undergoing endoscopy for the assessment of esophagitis and 44% of patients with chronic peptic strictures of the esophagus have this disease.[13] A study of unselected autopsies suggests that the frequency of Barrett's esophagus in the general population may be approximately 1%.[15] Taken together, these studies suggest that a majority of Barrett's esophagus cases go unrecognized. The development of this condition can lead to serious consequences. Several studies indicate a link between Barrett's esophagus and the development of esophageal adenocarcinoma.[16-19] In most cases, adenocarcinoma has arisen from intestinal metaplasia associated with Barrett's esophagus.

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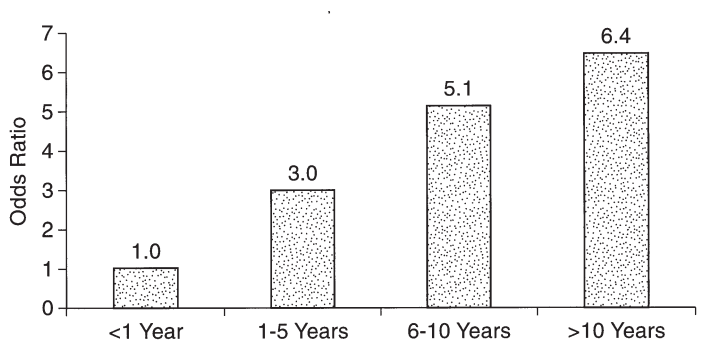
Current recommendations for the treatment of Barrett's esophagus include reducing the severity of esophageal damage by suppressing the effects of gastric refluxate.[13] Endoscopic surveillance for disease progression is also recommended.[20] If dysplasia is absent, the patient should be monitored endoscopically every 2 years. Low-grade dysplasia, confirmed by pathology findings, should be monitored endoscopically every 6

months. In addition, patients with low-grade dysplasia should receive intensive medical treatment for reflux disease.[13] High-grade dysplasia generally requires esophageal resection.

Esophageal adenocarcinoma is a relatively rare disease that has been increasing in prevalence in recent years (Figure 2).[21] Its increase has not been attributed to improvements in detection, and it is particularly striking when contrasted with a decline in the historically more prevalent squamous cell carcinoma.[21]

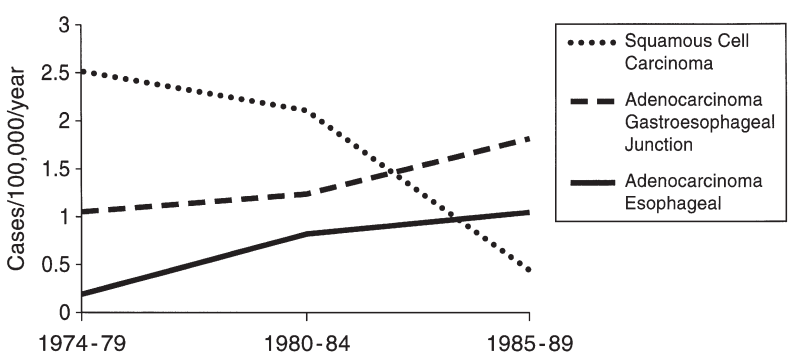
The reason for the rise in GERD-associated complications (eg, Barrett's esophagus and esophageal adenocarcinoma) is unclear. However, in 1998, Vicari and associates[22] made an interesting hypothesis. They suggested that certain strains of the bacteria *Helicobacter pylori* offer a protective effect against GERD and its complications. The basis for their hypothesis lies in the observation that the eradication of *H pylori* has become increasingly common because of its link to the development of gastrointestinal diseases such as peptic ulcer disease, stomach cancer, and gastric lymphoma. In studying the relationship between *H pylori* and GERD, Vicari and associates noted that the prevalence of infection did not differ significantly between those who have GERD and those who do not. However, the incidence of infection by cagA$^+$ strains of *H pylori* decreased progressively with an increase in the severity of GERD complications (Figure 3). Furthermore, patients with cagA$^+$ strains of *H pylori* were 3 times less likely to have a more serious form of GERD than patients with cagA$^-$ strains. The odds of having Barrett's esophagus complicated by dysplasia or metaplasia decreased more than 2-fold in those patients compared with those with cagA$^-$ strains or those without *H pylori* infection. Several hypotheses have been formulated to explain these observations. First, infection by cagA$^+$ *H pylori* can potentially induce fundic gastritis that is sufficiently severe to morbidly decrease the production of gastric acid. Alternatively, cagA$^+$ *H pylori* may be more effective in neutralizing gastric acid than cagA$^-$ strains because it generates greater quantities of ammonia.

Figure 1. Correlation of the Duration of GERD and the Risk of Barrett's Esophagus



Source: Reference 14.

Figure 2. Prevalence of Cancer of the Esophagus



Source: Reference 21.

The relationship between GERD and the development of esophageal adenocarcinoma was addressed in a recent study that concluded that increases in GERD frequency, severity, and duration are correlated with increases in the risk for esophageal adenocarcinoma.[23] The risk is 8 times greater in individuals who have weekly reflux symptoms and is approximately 11 times greater in those with nighttime symptoms compared with those without GERD symptoms.[23]

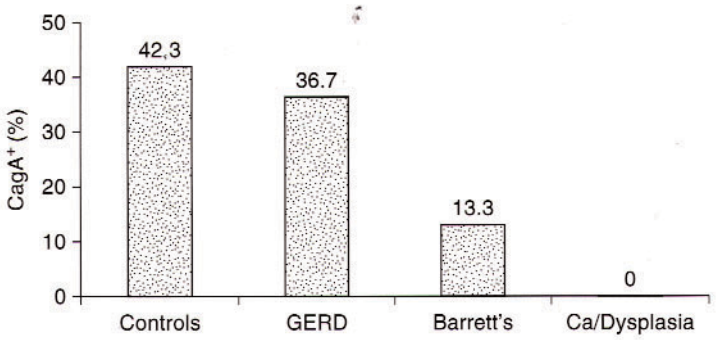
GERD and Quality of Life

In addition to its effect on overall health, GERD also has a significant negative impact on quality of life.[24] Nighttime GERD symptoms can be especially troublesome because they may interfere with sleep. A 1999 study concluded that GERD has a greater negative impact on the sense of well-being than hypertension, congestive heart failure, menopause, angina, and duodenal ulcer (Figure 4).[24] In fact, the only illness that has a greater effect on quality of life is psychiatric disease.[24]

GERD Treatment

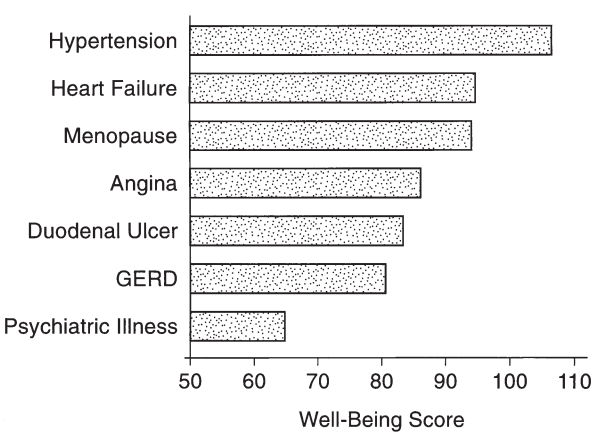
The initial treatment for GERD symptoms should include lifestyle modifications, as noted earlier.[2,8] If these modifications fail, medical management of the disease becomes necessary. The ideal therapy for any disease is the reversal of its pathophysiology. In GERD, this entails increasing gastric/esophageal motility, decreasing gastric pressure, and restoring LES tone. In the absence of a motility agent that can effectively prevent the occurrence of reflux without the risk of serious adverse events, the cornerstone of GERD treatment is acid suppression. Although acid suppression does not eliminate the underlying motor abnormalities that cause the disease, it does provide symptom relief, promote healing of esophageal injuries, and prevent relapse, which can lead to more serious complications. Many patients may initially opt for self-treatment with an increasingly large choice of over-the-counter medications such as antacids and histamine$_2$ receptor antagonists.[10] Often, a patient will consult a physician only after taking large doses of over-the-counter drugs.[10] For those patients, a

Figure 3. Incidence of Infection by CagA$^+$ Strains of *H pylori* Associated With Severity of GERD



Source: Reference 22.

Figure 4. GERD and Quality of Life



Source: Reference 24.

more potent GERD therapy, such as a PPI, should be considered.

···REFERENCES ···

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