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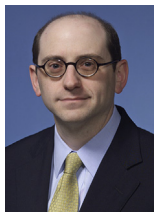
GASTROESOPHAGEAL REFLUX DISEASE

Presentation and Epidemiology of Gastroesophageal Reflux Disease



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Gastroesophageal reflux disease (GERD) is the most prevalent gastrointestinal disorder in the United States, and leads to substantial morbidity, though associated mortality is rare. The prevalence of GERD symptoms appeared to increase until 1999. Risk factors for complications of GERD include advanced age, male sex, white race, abdominal obesity, and tobacco use. Most patients with GERD present with heartburn and effortless regurgitation. Coexistent dysphagia is considered an alarm symptom, prompting evaluation. There is substantial overlap between symptoms of GERD and those of eosinophilic esophagitis, functional dyspepsia, and gastroparesis, posing a challenge for patient management.

Keywords: Erosive Esophagitis; Barrett's Esophagus; Esophageal Stricture.

By consensus, gastroesophageal reflux disease (GERD) has been defined as the effortless movement of stomach contents into the esophagus or mouth causing troublesome symptoms or complications.[1] We review the clinical presentation and epidemiology of GERD. The cardinal symptoms of GERD are heartburn and regurgitation. GERD is exceedingly common, ranking as the most frequent gastrointestinal diagnosis associated with outpatient clinic visits in the United States (US), with nearly 9 million visits in 2009.[2] Although complications such as bleeding erosive esophagitis or peptic stricture are becoming less common, individuals with GERD symptoms have a decrement in their quality of life that is similar to patients with inflammatory bowel disease.[2] To accurately diagnose and manage GERD, it is important to recognize the epidemiologic risk factors for GERD, the variety of presenting symptoms and their relative likelihood of representing pathological reflux, and the potential for overlap with other gastrointestinal disorders.

Clinical Presentation

Heartburn and acid regurgitation are the classic symptoms of GERD. Patients generally report a burning feeling in the retrosternal area, raising into the chest and radiating toward the neck, throat, and occasionally the back.[1] It occurs post-prandially, particularly after large fatty meals or the ingestion of spicy foods, citrus products, fats, chocolates, or alcohol. The supine position and bending over may exacerbate heartburn. Nighttime heartburn may cause sleeping difficulties and impair next-day function.[3] Sleep deprivation as well as psychological or auditory stress may lower the threshold for symptom perception.[4] GERD can be diagnosed based on symptoms, such as the occurrence of heartburn 2 or more days a week, although symptoms can be less frequent if they are troublesome and have adverse effects on well-being.[1] The frequency and severity of heartburn does not associate with degree of esophageal damage.

Regurgitation has been more inconsistently described in clinical trials and epidemiologic studies on GERD. Per the Montreal consensus statement, regurgitation is defined as the "perception of flow of refluxed gastric contents into the mouth or hypopharynx."[1] Among patients with daily regurgitation, lower esophageal sphincter pressure is often low; many patients have associated gastroparesis, and esophagitis is common, making this symptom more difficult to treat medically than classic heartburn.[5]

The lack of a standard for the diagnosis of GERD has made it difficult to define the accuracy of the typical reflux syndrome of troubling heartburn and/or regurgitation. The

Abbreviations used in this paper: **EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; PPI-REE, PPI-responsive esophageal eosinophilia.**

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Diamond Study from the United Kingdom attempted to address this question in patients presenting to family practitioners with complaints of upper gastrointestinal symptoms.[6] GERD was present in 203 of 308 patients (66%), based on endoscopic esophagitis and/or abnormal acid exposure or a positive symptom association probability from 24-hour pH tests. Only 49% of patients with GERD selected either heartburn or regurgitation as their most troublesome symptom, followed by dyspepsia, bloating, regurgitation, and abdominal pain or discomfort that was not characterized as dyspepsia. Sensitivity and specificity values for symptom-based diagnosis of GERD were 63% and 63% by family practitioners and 67% and 70% by gastroenterologists, respectively. Questionnaires about reflux symptoms did not perform any better; they identified patients with GERD with only 62% sensitivity and 67% specificity. Nor could response of symptoms to treatment with the proton pump inhibitor (PPI) esomeprazole (40 mg for 2 weeks) increase diagnostic precision (a positive response to the PPI test was observed in 69% of patients with GERD and 51% of patients without GERD).[7] Similarly, a well-performed meta-analysis cast doubt on the diagnostic accuracy of the PPI trial, finding that it identified patients with GERD with 78% sensitivity and 54% specificity.[8]

Less-common symptoms of GERD include dysphagia, chest pain, water brash, odynophagia, burping, hiccups, nausea, and vomiting. Dysphagia is considered an alarm symptom in patients with GERD that warrants upper endoscopy.[9] Dysphagia usually occurs in patients with long-standing heartburn with slowly progressive dysphagia for solids. Weight loss is uncommon because patients have good appetites. The most common causes are peptic stricture and severe inflammation, but dysphagia can be the first symptom of Barrett's esophagus with esophageal cancer. The chest pain associated with GERD can be indistinguishable from that of ischemic cardiac pain. GERD is a more frequent cause of non-cardiac chest pain than esophageal motor disorders.[1] The most problematic and controversial symptoms associated with GERD are chronic cough, chronic laryngitis (including hoarseness, globus sensation, and throat clearing), and asthma. Although potential mechanisms of pathogenesis have been identified, trials of medical and surgical anti-reflux treatments have produced uncertain and inconsistent results.[1]

Some patients with GERD are asymptomatic. This is particularly true in older patients, perhaps because of decreased acidity of the reflux material or decreased pain perception. Many older patients present first with complications of GERD because of long-standing disease with minimal symptoms. This is a particular problem for patients with Barrett's esophagus. European population studies found that 44%–46% of patients did not report symptoms of GERD.[10,11]

Overlap With Other Disorders

GERD symptoms overlap with those of other syndromes. This poses a challenge to diagnosis and can alter medical and surgical treatments.

Eosinophilic Esophagitis

The issue of how to differentiate eosinophilic esophagitis (EoE) from GERD has confounded clinicians and researchers since the recognition of the disease. This diagnostic dilemma began with a pathology study of pediatric patients in 1982, which found that eosinophils in the esophageal squamous epithelium could be a manifestation of GERD, documented by 24-hour pH tests.[12] Pathologists rapidly accepted the concept, and it became common clinical practice to attribute esophageal eosinophilia to GERD. The first report describing EoE as a unique syndrome, characterized by solid food dysphagia and distinct from GERD by esophageal tests, was published in 1993.[13] Subsequently, EoE was considered a chronic immune- or antigen-mediated esophageal disease. However, many cases still overlapped with GERD, so the PPI trial became the most logical and convenient means to differentiate GERD from EoE. This practice was based on the assumption that the only major effect of PPIs is to inhibit gastric acid production. Accordingly, in 2007, the American Gastroenterological Association's consensus report defined EoE as a primary disorder characterized by esophageal symptoms, esophageal biopsies with more than 15 eosinophils per high-powered field, and the "absence" of pathologic GERD, evidenced either by normal results from pH tests or lack of response to PPIs.[14]

This mutually exclusive paradigm began to fall apart as editorials raised the possibilities of a complex interaction between GERD and EoE. These raised questions such as: does EoE cause GERD? Does GERD cause EoE? Or do these merely co-exist, because GERD is such a common disease?[15] Subsequently, Ngo et al[16] described 3 patients with EoE and significant mucosal eosinophilia who improved, based on clinical and histologic features, after 2 months of PPI therapy. Several years later, Molina-Infante et al[17] published findings from 35 patients with mucosal eosinophilia (more than 15 eosinophils per high-powered field); 75% responded to rabeprazole (20 mg, twice daily) for 2 months. All 17 of the patients with GERD profile and objective acid reflux, based on endoscopy or pH tests, responded to this treatment. However, 50% of the patients with an EoE-like profile and normal pH test results also responded to the rabeprazole.

The recognition of this condition, which was termed PPI-responsive esophageal eosinophilia (PPI-REE), caused further confusion. Studies documented that 23% to 61% of patients with symptomatic esophageal eosinophilia respond to PPI treatment.[18] Furthermore, the clinical, endoscopic, histologic, and even esophageal gene-expression features of PPI-REE and EoE are virtually identical.[19] Therefore, PPI-REE resembles EoE far more than it resembles GERD.

An exciting discovery around this controversy has been the recognition that EoE and GERD could each arise via cytokine-mediated esophageal injury. In contrast to the model in which refluxed acid causes a chemical injury that destroys esophageal cells, studies from patients and animal models indicated that the esophageal damage found in patients with GERD was caused by inflammatory cells that are attracted to the esophagus by cytokines produced by esophageal epithelial cells following exposure to refluxed