Gastroesophageal Reflux Disease: Treating Wisely

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Gastroesophageal reflux disease (GERD) is commonly managed in both primary and secondary care settings, as this condition occurs in patients of all ages and has a wide variety of clinical presentations. However, evidence suggests that GERD is commonly overdiagnosed and overtreated. Adherence to guidelines may help reduce the harms of overdiagnosis.

Gastroesophageal reflux disease (GERD) is one of the most frequently encountered and managed diseases in the primary care setting. In the United States, 18.1%–27.8% of the population report weekly symptoms of GERD, and up to 40% of people report occasional symptoms [1]. Most patients respond completely to a relatively short course of pharmacotherapy and do not require endoscopy; however, GERD is often overdiagnosed and overtreated [2, 3]. Guidelines for diagnosis and treatment of GERD and screening for Barrett's esophagus (BE) are available from the American College of Gastroenterology (ACG), the Society of American Gastrointestinal Endoscopic Surgeons (SAGES), and the University of Michigan Health System [2, 4]. Understanding the indications and recommendations regarding the diagnosis and treatment of GERD will help clinicians identify those in need of endoscopy, minimize the risks of pharmacotherapy, and reduce costs.

Diagnosis

The diagnosis of GERD in adults can usually be made clinically. Heartburn and regurgitation are the most reliable symptoms in establishing the diagnosis, identifying up to 70% of patients with GERD [5]. Chest pain is also indicative of GERD once a cardiac cause has been ruled out. In patients with atypical symptoms—such as dyspepsia, epigastric pain, nausea, bloating, and eructation—a good clinical response to a proton pump inhibitor (PPI) may help establish GERD as the diagnosis but should not be considered definitive [2].

Endoscopy should be reserved for patients with alarm symptoms, including dysphagia, unintentional weight loss, and anemia; those with risks for BE; and those whose symptoms have been unresponsive to adequate PPI therapy [2]. Barium swallow studies, esophageal biopsy, and esophageal manometry are not helpful for diagnosis of GERD but may help to evaluate the patient for complications, such as an esophageal stricture or ring, or to rule out other diagnoses such as achalasia [4]. Ambulatory reflux monitoring has the benefit of determining esophageal acid exposure, reflux frequency, and correlation of reflux to reported symptoms. Thus, its use is justified when the diagnosis of GERD is uncertain, when symptoms are refractory, or when surgical management is being considered in the absence of other objective evidence of GERD [2, 4].

Extraesophageal symptoms such as chronic cough, asthma, dental erosions, sinusitis, and laryngitis have been attributed to GERD; however, multiple studies have failed to conclusively demonstrate causality. Indeed, trials in which patients with extraesophageal symptoms are empirically treated with PPIs have no, poor, or mixed evidence for improvement of those symptoms, even in patients with objective evidence of GERD on endoscopy or reflux monitoring [2].

In children aged 1–5 years, presenting symptoms of GERD are more likely to include regurgitation, vomiting, abdominal pain, and cough. Severe symptoms and anorexia or feed refusal should raise clinical suspicion for erosive esophagitis [6, 7]. In infants, normal gastroesophageal reflux may result in spitting up 4 or more times per day. GERD is only diagnosed when gastroesophageal reflux symptoms become troublesome—including spitting, vomiting, back arching, feeding difficulties, and cough—or when they lead to complications. Barium swallow testing, pH probe testing, and upper gastrointestinal endoscopy have poor evidence for establishing GERD as a cause of these symptoms [8].

Treatment

Lifestyle Modification

Lifestyle modification is often recommended for the treatment of GERD symptoms. For nocturnal symptoms, elevating the head of the bed and avoiding meals 2–3 hours prior to bedtime may be helpful. For patients with a body mass index above 25 kg/m^2 or patients with a normal body mass index but recent weight gain, weight loss may result in

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significant improvement of symptoms [9]. Other commonly touted lifestyle recommendations such as avoidance of caffeine, carbonated beverages, alcohol, spicy foods, and fatty foods have no evidence to support them [2].

H2RAs

For patients with intermittent, mild, and nonerosive reflux disease, histamine$_2$ receptor antagonists (H2RAs) may provide adequate symptom relief [9]. H2RAs may also be used in addition to daytime PPI therapy in patients with significant nighttime symptoms, although H2RAs may be associated with tachyphylaxis after several weeks of daily usage [2].

PPIs

PPIs are more effective than H2RAs and may be more cost effective than step-up therapy. Most PPIs should be dosed 30–60 minutes prior to a meal; the exception is dexlansoprazole, which may be dosed irrespective of meal timing [5]. For patients with typical symptoms, noncardiac chest pain, or erosive disease, an 8-week trial of a PPI is indicated. For patients with atypical symptoms or extraesophageal symptoms, further diagnostic work-up is indicated unless typical GERD symptoms are also present [2, 4]. Despite the fact that no particular PPI has been demonstrated to be more effective than another, switching to another PPI in patients with a partial response may improve symptoms. Alternatively, escalating to twice-daily dosing may improve symptoms. Endoscopy is indicated for nonresponders [2, 4, 5, 9]. Maintenance therapy with a PPI is indicated for patients with complications of GERD, such as BE or erosive esophagitis, and for patients who develop recurrence of symptoms with cessation of the PPI [2]. In the latter group, periodic trials off medication should be attempted to minimize costs and potential adverse effects [4].

Adjunctive Treatments

Baclofen, a gamma-aminobutyric acid (B) receptor agonist, inhibits transient lower esophageal sphincter relaxation and may reduce GERD symptoms that are refractory to PPI therapy [9]. Prokinetic agents, such as metoclopramide and domperidone, increase the lower esophageal sphincter pressure and may provide additional relief in combination with a PPI in patients suffering from GERD with comorbid gastroparesis [2]. Use of these agents is not approved by the US Food and Drug Administration (FDA) for the treatment of GERD, and they should only be used with specialist consultation and objective evidence of GERD [4].

Surgical Treatments

Surgical management of patients with chronic or refractory symptoms is indicated only when there is objective evidence of GERD. In patients without evidence of erosive esophagitis on endoscopy, preoperative ambulatory reflux monitoring is indicated [4]. Surgical interventions are most likely to benefit patients who have typical symptoms, patients with atypical symptoms that correlate well with ambulatory reflux monitoring, and those with at least a partial response to PPI therapy [10].

Special Groups

As opposed to the general adult population, pregnant women should typically receive step-up therapy, beginning with sucralfate and antacids without bicarbonate. These first-line treatments can be used on an as-needed basis. H2RAs (category B) may then be added if needed. If the patient has still not obtained adequate relief, PPIs may be used [9]. (PPIs are classified as category B for use during pregnancy, with the exception of omeprazole, which is category C.)

In children, both H2RAs and PPIs are considered safe. Management is similar to that of adults, with a bigger emphasis on lifestyle modification in younger children [7]. In infants, nonpharmacologic management should be employed whenever possible. Positioning after feeds, thickening of feeds, changes of formula (particularly to hypoallergenic formulas), and modification of feed volume and frequency may improve gastroesophageal reflux symptoms [7, 8]. Medication should be reserved for those with true GERD and generally requires a gastroenterology consultation. The American Academy of Pediatrics Choosing Wisely campaign advises against acid-suppressive therapy in any patient who is a "happy spitter"—that is, an infant with gastroesophageal reflux that is effortless, painless, and not affecting growth [11].

Screening for Barrett's Esophagus

GERD is a well-established risk factor for the development of esophageal adenocarcinoma. BE, a common precursor to esophageal adenocarcinoma, develops in 10%–15% of GERD patients [12, 13]. Patients with esophageal adenocarcinoma diagnosed during screening have a longer life expectancy than patients diagnosed once they become symptomatic, which suggests that early detection and surveillance of BE may be beneficial [12]. However, identifying patients with BE who are at high risk for progression to esophageal adenocarcinoma is difficult. Forty percent of patients with esophageal adenocarcinoma do not experience frequent GERD symptoms prior to diagnosis [14]. Furthermore, the absolute risk for progression of BE to esophageal adenocarcinoma is low—0.2%–0.5% per year for nondysplastic BE, 0.7% for low-grade dysplasia, and 7% for high-grade dysplasia—and 90% of BE patients die from causes other than esophageal adenocarcinoma [13]. Additionally, data to support specific endoscopic screening and surveillance guidelines are lacking [14].

While there is no consensus on screening for or surveillance of BE, multiple organizations have overlapping guide-

lines that focus on risk factors and alarm symptoms. The ACG notes that risk factors for BE including male sex, GERD symptoms for more than 5 years, tobacco use, age greater than 50 years, central obesity, and a first-degree relative with BE. SAGES also includes hiatal hernia as a risk factor [4].

The ACG, the American Society for Gastrointestinal Endoscopy (ASGE), the American College of Physicians (ACP), and the American Gastroenterological Association (AGA) all recommend that clinicians perform an endoscopy to screen for BE in patients with GERD and persistent symptoms despite PPI therapy. For patients with GERD and multiple risk factors, the strength of the recommendation varies, but each organization recommends that clinicians at least consider endoscopy [15]. Screening is not recommended for the general population or for women with chronic GERD symptoms without multiple risk factors [13].

For surveillance of BE without dysplasia, the ACG, ACP, AGA, and ASGE recommend endoscopic surveillance every 3–5 years. For low-grade dysplasia, the ACG recommends endoscopic surveillance at 6 months and 12 months, then annually until there are 2 negative consecutive tests. The AGA recommends screening every 6–12 months, and the ASGE recommends both 6-month and 12-month screenings, followed by annual screening. Each organization recommends screening patients with high-grade dysplasia every 3 months [4, 15].

Adverse Effects of PPIs

PPIs are among the most commonly prescribed medications in both primary care and secondary care settings [3]. Their low cost, high efficacy, and perceived low toxicity all contribute to the overprescription and inappropriate continuation of PPIs. As their use escalates, however, PPIs are increasingly being associated with adverse effects, which is fueling increased scrutiny on appropriate prescribing practices and adherence to guidelines.

Kidney Disease

The use of PPIs has been associated with both acute and chronic kidney disease. In a population-based study involving nearly 300,000 people, acute kidney injury and acute interstitial nephritis were 2.5–3-fold more common in adults older than 66 years who used PPIs [16]. In another study, a 20%–50% increase in the risk of development of chronic kidney disease was observed in PPI users; this observational cohort study followed more than 10,000 patients for nearly 14 years [17]. It is hypothesized that recurrent acute kidney injury or PPI-related hypomagnesemia may be responsible for this finding. Thus, routine monitoring of creatinine levels is advised in patients who require long-term PPI therapy.

Hypomagnesemia

Prolonged PPI use is associated with hypomagnesemia, which, in turn, is associated with an increased risk for kidney disease. Low serum magnesium levels in the setting of PPI use may not respond to supplementation unless the PPI is discontinued [18]. Routine monitoring of magnesium levels in patients on maintenance PPI therapy is likely warranted, particularly for patients on high doses of PPIs.

Dementia

In a prospective cohort study involving more than 73,000 people aged 75 years or older who were followed for 7 years, there was a 44% increased risk of incident dementia among regular PPI users. Rates of dementia were similar in patients receiving omeprazole, pantoprazole, and esomeprazole, the 3 most commonly prescribed PPIs evaluated in the study [19].

Infection

Reduced gastric pH and increased bacterial colonization of the stomach are thought to increase the risk of certain infections. PPI use is associated with a 74% higher risk of *Clostridium difficile* infection and a 2.5-fold risk of recurrent *C. difficile* infection. Community-acquired pneumonia, but not hospital-acquired pneumonia, is 34% higher among PPI users compared with nonusers [18].

Fractures

Multiple observational studies have associated PPI use with increased risk of hip, spine, and any-site fractures (26%, 58%, and 33% higher risk, respectively). Even use of a PPI for less than 1 year conferred risk. Reduction of intestinal calcium absorption in PPI users may play a role in decreasing bone density [18].

Conclusions

GERD is a common disease, but it is also overdiagnosed and overtreated. Most patients with GERD should respond to an 8-week course of PPI therapy. Only patients with alarm symptoms, those with multiple risk factors for BE, those with an unclear diagnosis, or patients who are unable to wean from a PPI should undergo endoscopy. As evidence grows linking PPIs to adverse effects, adherence to treatment guidelines may minimize risks, reduce costs, and identify those in need of endoscopy. NCMJ

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