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Gastroesophageal Reflux Disease

Pathophysiology, Diagnosis, and Treatment

ABSTRACT

Gastroesophageal reflux disease (GERD) is a common chronic disorder in industrialized countries. Gastroesophageal reflux disease is one of the most frequent diseases encountered by primary care providers. The primary symptoms of GERD include heartburn, regurgitation, globus sensation, dysphagia, chest pain, and belching. If symptoms are left untreated, a major concern is complications and the potential risk of esophageal adenocarcinoma associated with GERD. With the increasing prevalence and incidence of GERD and the increasing cost of this disease, there is a need for advanced practice registered nurses to understand the nature of GERD including its pathophysiology, signs and symptoms, and treatment options to address the disease.

Gastroesophageal reflux disease (GERD) is defined by the American College of Gastroenterology as "chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus" (Dent et al., 1999). Heartburn is one of the most common symptoms of GERD; it is estimated that between 20% and 40% of patients with heartburn will have a diagnosis of GERD (Patrick, 2011). Other symptoms of GERD include regurgitation, globus sensation, sore throat, cough, chest pain, and dysphagia. Gastroesophageal reflux disease also includes the diagnosis of nonerosive esophageal reflux disease and the complications of GERD that include esophagitis, esophageal ulcer and/or stricture, Barrett's esophagus, and esophageal adenocarcinoma (Vakil et al., 2006).

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Background

In the United States, GERD is a common disease among all age groups and accounts for about 4% of office visits in primary care practice (Dent, El-Serag, Wallander, & Johansson, 2005). The prevalence of GERD is estimated between 18.1% and 27.8%, and the incidence of GERD is approximately five per 1,000 person-years in the U.S. populations (El-Serag, Sweet,Winchester, & Dent, 2013). The goal of antireflux treatment is to effectively control GERD symptoms, prevent complications of GERD, and improve quality of life (Dickman, Maradey-Romero, Gingold-Belfer, & Fass, 2015). Currently, proton pump inhibitors (PPIs) and histamine Type 2 receptor antagonists (H2RAs) are the mainstay of therapy for GERD. The introduction of PPIs revolutionized the management of acid reflux, as demonstrated by the profound inhibitory effect on gastric acid secretion with high rates of esophageal mucosal healing and effective control of GERD symptoms (Gralnek, Dulai, Fennerty, & Spiegel, 2006). Although many patients' GERD symptoms respond to standard medical treatment, diagnosis and management of patients who do not respond to PPI therapy can be challenging.

One of the most common complications of GERD is esophagitis, which is the inflammation of the esophagus. Esophagitis may lead to esophageal bleeding, erosions, and scarring. Formation of scarring may cause narrowing of the esophageal sphincter and resulting dysphagia. With long-term uncontrolled acid

reflux, Barrett's esophagus may develop as squamous cells that normally line the gastroesophageal junction are replaced by columnar intestinal cells. In patients with GERD, the esophagus is constantly exposed to excessive amounts of gastric acid by long-standing reflux; the intestinal cells are more resistant to acid than normal squamous esophageal cells. Barrett's esophagus is a strong risk factor of developing esophageal adenocarcinoma. A recent meta-analysis reported that the incidence rate of esophageal adenocarcinoma among patients with Barrett's esophagus is 0.54% annually (Singh et al., 2014). Uncontrolled GERD may also cause extraesophageal manifestations such as hoarseness, asthma, subglottic stenosis, and sinusitis.

With the increasing prevalence and incidence of GERD and the increasing cost of this disease, there is a need for advanced practice registered nurses (APRN) to understand the nature of GERD including its pathophysiology, signs and symptoms, and knowing the treatment options to address the disease.

Pathophysiology of GERD

Some acid reflux is normal physiologic gastroesophageal reflux (GER), and the esophagus clears that refluxed acid with peristaltic action. Normal functioning of the lower esophageal sphincter (LES) acts as an antireflux barrier protecting the esophagus from the acidic gastric content. For the LES to function properly, the gastroesophageal junction must be in the abdomen so that the diaphragmatic crura can assist the LES by acting as an external sphincter (Patrick, 2011).

Protective mechanisms in GER include (1), gravity, upright posture allows gravity to augment esophageal acid emptying; (2), peristalsis, acid clearance begins with peristalsis that empties the refluxed content from the esophagus; and (3), saliva, the final phase of esophageal acid clearance depends on the swallowed saliva, which has a neutralizing pH around 6.0. The factors contributing to GERD may include LES dysfunction, hiatal hernia, increased numbers of transient lower esophageal sphincter relaxations (TLESR), ineffective esophageal clearance, the presence of an acid pocket, and delayed gastric emptying.

LES Dysfunction

The LES is closed at rest, with an average pressure of about 20 mmHg, which prevents gastric content from refluxing into the esophagus. The most common trigger of acid reflux is spontaneous relaxation of the LES, usually triggered by gastric distention after meals. Acid reflux occurs when the basal LES pressure is within 1–4 mmHg of the intragastric pressure (Mittal, Holloway, Penagini, Blackshaw, & Dent, 1995). Studies have shown that the basal LES pressure is a less relevant pathophysiological factor for GERD, because only a minority of patients with GERD have a constantly low LES pressure. Factors modulating LES pressure can be multifactorial including lifestyle such as exercise, high-fat food intake, or consumption of chocolate, caffeine, peppermint, and alcohol (Katz, Gerson, & Vela, 2013). Low LES pressure and GERD can also be related to certain diseases such as scleroderma, which damages the muscle and excitatory cholinergic innervation (Lahcene et al., 2011).

Transient Lower Esophageal Sphincter Relaxation

The LES is located at the distal end of the esophagus, which closes at rest and opens with swallowing. Transient lower esophageal sphincter relaxation (relaxation without swallowing) is the main mechanism of acidic and nonacidic reflux in both healthy individuals and patients with GERD. These TLESRs are vagal nerve–mediated reflexes and are believed to play an important role in the pathophysiology of GERD, as many studies show that most reflux episodes occur during TLESRs (Dent, Holloway, Toouli & Dodds, 1988; Singhal & Khaitan, 2014).

Transient lower esophageal sphincter relaxations occur largely in the postprandial period and in the upright position. They are rare at night. Transient lower esophageal sphincter relaxations are triggered by gastric distention and serve to vent gas from the stomach after meals (Mittal et al., 1995). They are more frequent with delayed gastric emptying, high-fat meals, and diets high in indigestible carbohydrates due to colonic fermentation (glucagon-like peptide-1) (Piche, des Varannes, Sacher-Huvelin, Holst, Cuber, & Galmiche, 2003). In GERD patients, TLESRs are two times more likely to be associated with the acid reflux (Mittal et al., 1995). Proton pump inhibitors reduce the acidity of the gastric refluxate entering the esophagus, but they have no effect on the function of the LES basal pressure or TLESRs and frequency of reflux episodes (Lv & Qiu, 2015).

Acid Pocket

Fletcher, Wirz, Young, Vallance, and McColl (2001) first introduced the concept of the acid pocket in 2001, hypothesizing that the acid pocket was formed as a result of meal-stimulated acid mixing poorly with the chyme in the proximal stomach. They confirmed that the acid pocket occurred after meals as the esophageal refluxate was frequently more acidic than the contents of the body of the stomach. They named the phenomena the "acid pocket" at the esophagogastric junction due to low buffering from the meals in this region (Fletcher et al., 2001). Since the description of the acid pocket, numerous studies have confirmed its existence. Importantly, the proximal margin of the acid pocket

may extend into or cross the LES, and the acid pocket correlates with the presence and size of a hiatal hernia (Pandolfino et al., 2007).

Subsequent studies have shown that the acid pocket is significantly larger in patients with GERD, and its size and location are greatly influenced by the presence of a hiatal hernia (Beaumont, Bennink, de Jong, & Boeckxstaens, 2010). Hiatal hernias are involved in the pathogenesis of GERD, affecting both LES function and esophageal clearance, therefore, increasing acid exposure in the esophagus (Pandolfino et al., 2007). For the development of GERD, the presence of hiatal hernia may influence acid reflux by effecting the size and position of the acid pocket. The position of the acid pocket is more important than its length. When the acid pocket was located above the diaphragm, 74%–85% of all TLESRs resulted in acidic reflux. In contrast, when the acid pocket was located below the diaphragm, only 7%–20% of the TLESRs had acid reflux (Beaumont et al., 2010).

Risk Factors of Acid Reflux

Acid reflux symptoms are often triggered by lifestyle factors such as exercise, heavy lifting, specific foods, including a high-fat diet (delayed gastric emptying), foods that lower LES pressure (alcohol, chocolate, peppermint, caffeine, and onion), and acidic foods (citrus, tomato products, and carbonated beverages). These may trigger reflux symptoms (Katz et al., 2013). Other lifestyle factors include overeating, eating immediately before bedtime, and sleeping in a supine position; these may be linked to nocturnal reflux symptoms. Central obesity is a very important factor for acid reflux (Richter, 2012). Obesity may lead to GERD through chronically increased intra-abdominal pressure and increased frequency of TLESRs (Singhal & Khaitan, 2014). Other risk factors include smoking, pregnancy, and medications such as anticholinergics, selective serotonin reuptake inhibitor antidepressants, birth control pills, and inhaled bronchodilators (Table 1).

TABLE 1. Risk Factors of Acid Reflux

Lifestyle	Foods	Medications
Exercise Heavy lifting Overeating Eating before bedtime Sleeping in supine position	High-fat diet Citrus Tomato products Carbonated beverages Alcohol Chocolate Peppermint Onion Caffeine	Anticholinergics SSRI antidepressant Inhaled bronchodilators Birth control pills

Note. SSRI = selective serotonin reuptake inhibitor.

Manifestations of GERD

Typical symptoms of GERD are heartburn and regurgitation. Heartburn is a retrosternal burning sensation that can extend to the neck and the throat. It occurs 30–60 minutes after eating, especially a large meal or acidic foods. Symptom can be relieved after taking an antacid or drinking water. Acid regurgitation is the reflux of the gastric content into the oral cavity, or a sense of fluid moving up and down in the chest. Atypical symptoms of GERD include noncardiac chest pain, chronic cough, globus sensation, hoarseness, frequent throat clearing, and sleep disturbances. Alarm symptoms suggesting complications of GERD include dysphagia, odynophagia, weight loss, hematemesis, and melena (Vakil et al., 2006). Typical and atypical clinical presentations of GERD are outlined in Table 2.

Diagnosis of GERD

The first step in GERD diagnosis is a careful clinical history; identifying the characteristic symptoms and their duration, intensity, and relationship to food, posture, and exercise; and the impact of these symptoms on the quality of life (Katz et al., 2013). If symptoms are present, an empirical trial of acid suppression therapy should be provided, with resolution of acid reflux symptoms considered clinically suggestive of GERD. If symptoms are not resolved with acid suppression therapy, objective tools such as esophagogastroduodenoscopy should be considered to identify secondary complications of mucosal injury and esophagitis (Richter, 1994).

Upper Endoscopy

Patients who fail a PPI once daily and/or who have alarm symptoms (dysphagia, odynophagia, melena,

TABLE 2. Manifestations of Gastroesophageal Reflux Disease

Typical Symptoms	Atypical Symptoms	Alarm Symptoms	Complications
Heartburn Regurgitation	Chronic cough Hoarseness Noncardiac chest pain Globus Throat irritation Sleeping disturbance	Dysphagia Odynophagia Weight loss Melena Hematemesis	Esophagitis Esophageal ulcers Peptic stricture Barrett's esophagus Adenocarcinoma

hematemesis, abnormal weight loss) should undergo upper endoscopy to determine whether they have a complication of acid reflux such as esophagitis, ulcers, strictures, or Barrett's esophagus.

Esophageal pH Monitoring

Ambulatory 24-hour pH study is done to objectively measure the severity of the patient's acid reflux. In the traditional pH test, a transnasal pH catheter is placed 5 cm above proximal border of the LES and data collected for 24 hours. This study is indicated in patients for whom acid suppression medications lack effectiveness, those with atypical symptoms, those who experience side effects from medications, and those being evaluated for an antireflux surgery (Singhal & Khaitan, 2014). Ambulatory 24-hour esophageal pH monitoring is considered the gold standard for diagnosing GERD (Streets & DeMeester, 2003). The pH test can be performed in patients without typical symptoms while off PPI and H_2-receptor blockers to determine whether their symptoms are due to acid reflux and the severity of reflux or while on treatment together with impedance pH testing to see whether there is continued pathological acid or nonacid exposure despite acid suppression. In this test, the acid reflux symptom correlation is particularly important (Katz et al., 2013).

Bravo pH monitoring is a wireless pH monitoring system. The pH sensor is placed endoscopically 6 cm above the GE junction and pH monitored continuously for 48 hours. No catheters are required. The Bravo pH sensor contains a radio frequency transmitter, which sends the pH data to a recorder worn on the patient's waist. After the study is complete, the pH data are downloaded from the recorder to a computer for interpretation. An event marker is pushed by the patient to indicate symptomatic episodes, supine periods, and meals allowing correlation of these events with episodes of acid reflux (Figure 1). This study is considered to be more accurate as patients can go about their normal activities without a catheter in place. One of the most important pieces of information from this study is the symptom correlation (correlation of symptoms with episodes of acid reflux), because this can help the clinician make a decision about the role of acid reflux in the patient's symptoms and on the need for antireflux surgery (Singhal & Khaitan, 2014).

Esophageal Manometry

Esophageal manometry is an esophageal function study, which evaluates peristalsis, contraction amplitudes, and LES pressure, relaxation, and length. This test provides information on esophageal motility, the strength of peristaltic contractions, and the function of the LES (Figure 2). It helps providers to distinguish motility disorders (such as achalasia or diffuse spasms) from GERD and to adjust GERD treatment. Esophageal manometry should be performed for patients with suspected achalasia and in all patients being evaluated for surgery to treat GERD (Alzubaidi & Gabbard, 2015; Singhal & Khaitan, 2014).

Treatments for GERD

Lifestyle Modifications

For all GERD patients, lifestyle modifications are the recommended first-line therapy. Modifications include elevation of the head of the bed, weight loss, and avoidance of alcohol, tobacco, caffeine, chocolate, spicy foods, acidic foods, and fatty foods. Studies show that weight loss and head of bed elevation are effective for

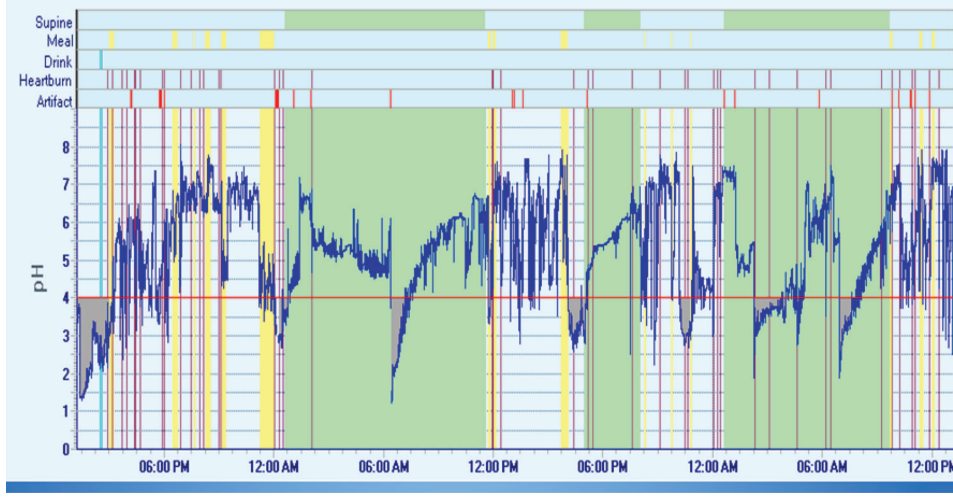

FIGURE 1. Forty-eight-hour Bravo pH study. Severe acid reflux disease with both abnormal upright/supine acid reflux. Reflux episodes are indicated by a drop in pH to <4. Supine periods are shaded.

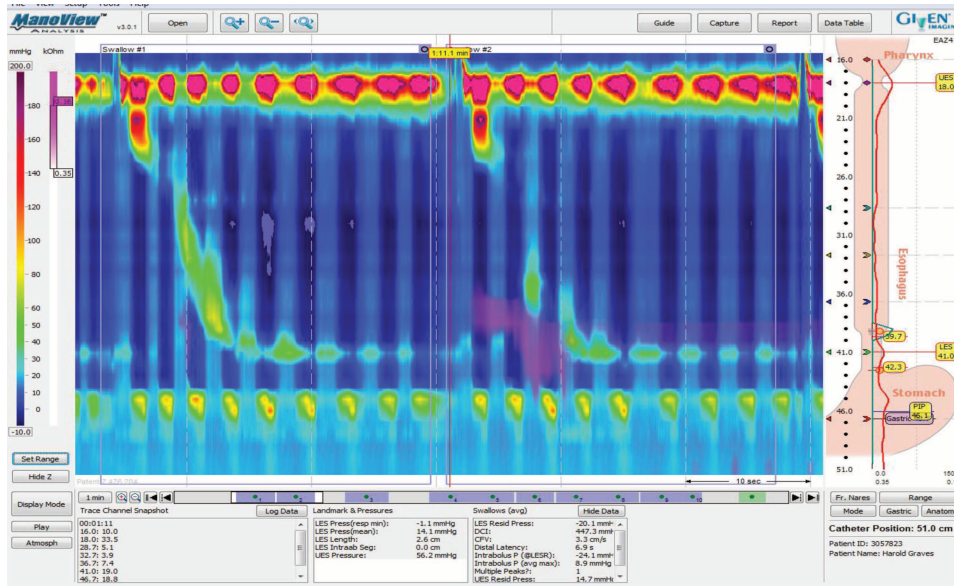

FIGURE 2. Esophageal manometry. Weak peristalsis and hiatal hernia on a patient with gastroesophageal reflux disease.

reflux control; in addition, smoking cessation significantly improves GERD symptoms in patients with a normal body mass index (Kaltehbach, Crockett, & Gerson, 2006; Ness-Jensen, Lindam, Lagergren, & Hveen, 2014). The algorithm for management of GERD is outlined in Figure 3.

Medical Treatment

Depending on the severity of GERD, pharmacologic management includes antacids, H2RAs, and PPIs.

Antacid and Alginate

Antacids are basic compounds primarily used as needed for episodic acid reflux symptoms. They work by neutralizing acid in the esophagus (Collings, Rodriguez-Stanley, Proskin, Robinson, & Miner, 2002). Antacids provide rapid but transient relief from episodes of acid reflux but do not contribute to healing of erosive esophagitis (Fletcher et al., 2001). Antacids include sodium bicarbonate, aluminum hydroxide, magnesium hydroxide, and calcium carbonate.

Alginate-based formulations are used to control heartburn; Gaviscon is one of these medications. After taking alginate-based medication, a foamy raft is created above the gastric fluid pool. The alginate raft acts as an antireflux barrier, which can move up into the esophagus to prevent acidic gastric contents from refluxing into the esophagus (Rohof, Bennink, Smout, Thomas, & Boeckxstaens, 2013).

Histamine-2 Receptor Antagonists

The H2RAs are commonly used for the treatment of GERD and include ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid), and cimetidine (Tagamet). The H2RAs can reduce gastric acid by inhibiting histamine at H_2-receptors on parietal cells and decrease

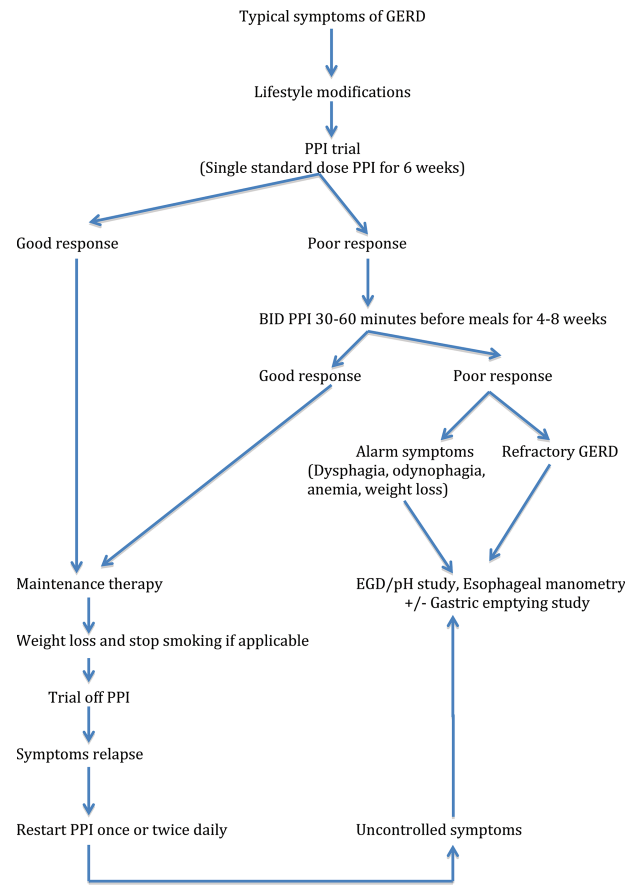

FIGURE 3. Algorithm for initial management of GERD. BID = twice daily; EGD = esophagogastroduodenoscopy; GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor.

pepsin output through an unknown mechanism (Schubert & Peura, 2008). The H2RAs can increase postprandial gastric pH rapidly and may be used for prophylaxis against postprandial acid reflux. The effects of these drugs on nighttime histamine gastric acid secretion have led to the use of H2RAs at bedtime to help patients with nighttime reflux symptoms despite optimal PPI use (Fackler, Ours, Vaezi, & Richter, 2002). However, tachyphylaxis can occur quickly with H2RAs after starting therapy, which limits their regular use in GERD management (McRorie, Kirby, & Miner, 2014). For GERD in pregnancy, ranitidine is the only H2RAs with documented efficacy in controlling acid reflux symptoms (Richter, 2005).

Proton Pump Inhibitors

There are seven available PPIs including four that do not require a prescription (lansoprazole, omeprazole, esomeprazole, and omeprazole–sodium bicarbonate) and three more available by prescription only (pantoprazole, rabeprazole, and dexlansoprazole). Proton pump inhibitors are the most potent gastric acid suppressants because they work on the final pathway of gastric acid secretion to inhibit the proton pump, H^+, K^+-ATPase (Zajac, Holbrock, Super, & Vogt, 2013). Proton pump inhibitors are the most successful agents for controlling acid reflux symptoms, induce mucosal healing, and provide better results than H2RAs (Chiba, De Gara, Wilkinson, & Hunt, 1997). In practice, all PPIs appear to be similar in terms of symptom control (Gralnek et al., 2006). Most PPIs should be taken at least 30 minutes before meals except omeprazole–sodium bicarbonate and dexlansoprazole, which can be taken before or after meals.

Proton pump inhibitors are widely used in the treatment of GERD. Studies using PPIs and H2RAs in the treatment of esophagitis in patients with GERD find that about four in five patients experienced recurrent symptoms within 1 year after discontinuation of therapy, especially, patients with Grade C and D esophagitis (one or more mucosal break that involves about 75% of the esophageal circumference) (Sami & Ragunath, 2013). Proton pump inhibitors are generally safe; however, there are potential adverse effects due to long-term use.

Safety Concerns of PPIs

There are numerous reports of harmful associations with prolonged PPI use, which are receiving considerable attention and alarming patients. The clinical benefits and risks of using PPIs should be evaluated for each patient individually. For patients needing continued long-term PPI therapy, the clinical effects should be reviewed periodically and treatment adjusted as needed. The lowest dose of a PPI that controls symptoms should be used.

Osteoporosis

In 2010, the U.S. Food and Drug Administration (FDA) issued a safety communication regarding the possible increased risk for hip, wrist, and spine fracture in chronic PPI users (FDA, 2010). A recent large prospective population-based cohort study (N = 9,423) with 10-year follow-up monitored the incidence of nontraumatic fractures and PPI use. The results revealed an association between PPI use and increased risk of osteoporosis-related fractures (hazard ratio [HR] =1.4, 95% confidence interval [CI] = 1.11–1.77, p = . 004) (Fraser, Leslie, Targownik, Papaioannou, & Adachi, 2012). However, the American College of Gastroenterology guidelines recommend that patients with known osteoporosis can remain on PPI therapy, and concern for hip fracture and osteoporosis should not affect the decision to use PPI long term except on patients with other risk factors for hip fracture (Katz et al., 2013).

To minimize the risk of osteoporosis related to PPI use, the options include the following: (1), reduce the dose of PPI to the lowest dose that prevents GERD symptoms; (2), use H_2 blockers on a as needed basis for patients with infrequent symptoms (<3 times weekly); (3) add calcium and vitamin D supplementation for those on long-term PPI, and exercise regularly; and (4), stop smoking. In addition, monitoring bone density is beneficial for those on long-term treatment with PPIs. A recent prospective study found that treatment with a PPI results in a significant reduction in bone density (Ozdil et al., 2013).

Community-Acquired Pneumonia

Chronic PPI therapy and the risk for community-acquired pneumonia cannot be clearly connected. Multiple studies have investigated the potential correlation, with evidence suggesting that short-term but not long-term PPI use may be associated with an increased risk of community-acquired pneumonia (Giuliano, Wilhelm, & Kale-Pradhan, 2012; Hermos et al., 2011). A recent systemic review and meta-analysis concluded that outpatient PPI use is associated with a 1.5-fold increased risk of community-acquired pneumonia, and the highest risk is within the first 30 days after initiation of treatment (Lambert et al., 2015). Current guidelines suggest that short-term PPI usage may increase the risk of community-acquired pneumonia, but the risk does not apply to long-term users (Katz et al., 2013).

Clostridium difficile Infection

In theory, PPIs increase the ability of *C. difficile* to change to the vegetative (spore) state and to survive in the gastrointestinal tract, increasing the risk of *C. difficile* infection. Clinical research and systematic reviews have suggested that PPIs increase the risk of developing

C. difficile infection, and patients with continuous PPI use remain at elevated risk of recurrence of *C. difficile* infection (Bavishi & Dupont, 2011; McDonald, Milligan, Frenette, & Lee, 2015). The American College of Gastroenterology guidelines recommend that PPIs should be used with care in patients at risk (Katz et al., 2013).

Interaction With Clopidogrel

Clopidogrel is used to treat acute coronary syndrome by reducing the risk of new ischemic events. Clopidogrel requires metabolic activation by the hepatic cytochrome P450 isoenzyme cytochrome 2C19 (CYP2C19). Proton pump inhibitors are also metabolized by the CYP2C19 isoenzymes (Drepper, Spahr, & Frossard, 2012). There was a concern about decreased clopidogrel antiplatelet activity when administered with PPI. However, large prospective studies did not observe an increased risk for adverse cardiovascular events in patients receiving clopidogrel and PPI treatment at the same time (Drepper et al., 2012; Gerson, 2013). Therefore, PPI therapy does not need to be altered in concomitant clopidogrel users (Katz et al., 2013).

Kidney Disease due to PPI

Proton pump inhibitor–induced kidney disease is an uncommon side effect. A nested case-control study found that renal disease was positively associated with PPI use (odds ratio: 1.72, 95% CI: 1.27–2.23, $p < .001$), and patients with a renal disease diagnosis were twice as likely to have taken a PPI in the past (Klepser, Collier, & Cochran, 2013). In a second study, investigators conducted a population-based cohort study with the conclusion that PPI use is associated with a higher risk of incident chronic kidney disease (Lazarus et al., 2016). Although these studies show an association of PPI use with renal disease, they do not prove causation. The alternative explanation is that patients with underlying renal disease have a higher incidence of gastrointestinal disorders requiring PPI use. Prospective studies will be required to resolve this issue.

Dementia and PPI

A recent prospective cohort study using observational data from 2004 to 2011 concluded that patients taking regular PPIs (n = 2,950, mean [*SD*] age, 83.8 [5.4] years) had a significantly increased risk of incident dementia compared with patients not taking PPI (n = 70,729, mean [*SD*] age, 83 [5.6] years) (HR: 1.44 [95% CI: 1.36–1.52]; $p < .001$). Again, this study shows an association but does not prove causality. The finding is supported by a mouse model in which the use of PPIs increased the levels of β-amyloid in the brains of mice (Gomm et al., 2016).

Surgical Interventions for GERD

If patients decide to proceed with a surgical procedure to control their acid reflux, there are several options available that include Nissen fundoplication, LINX (magnetic sphincter augmentation), and transoral incisionless fundoplication. It should be remembered that GERD patients with no response to PPIs are less likely to do better after antireflux surgery (Jobe et al., 2013). Esophageal/Bravo pH monitoring to ensure that symptoms are due to GERD and esophageal manometry to confirm normal peristalsis are mandatory prior to surgical therapy.

Conclusion

Gastroesophageal reflux disease is a common medical condition and its diagnosis and management can be difficult particularly if symptoms are atypical. Gastroesophageal reflux disease can present with a variety of symptoms including typical heartburn and regurgitation, as well as atypical symptoms such as chest pain, hoarseness, and chronic cough. A PPI therapeutic trial is a safe diagnostic tool for patients having typical GERD symptoms. If symptoms persist despite medical therapy, further testing with endoscopy, pH monitoring, and esophageal manometry should be considered. Special attention should focus on reducing the rate of refractory GERD and complications from GERD such as Barrett's esophagus and adenocarcinoma. Gastroesophageal reflux disease can significantly affect quality of life. Proton pump inhibitors are safe and well tolerated but they may be associated with side effects such as community-acquired pneumonia, *C. difficile* infection, and chronic kidney disease. Patients should be assessed individually regarding GERD symptoms and diagnostic testing recommended accordingly. Treatment should be tailored for optimal management of GERD and minimization of side effects. ✪

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