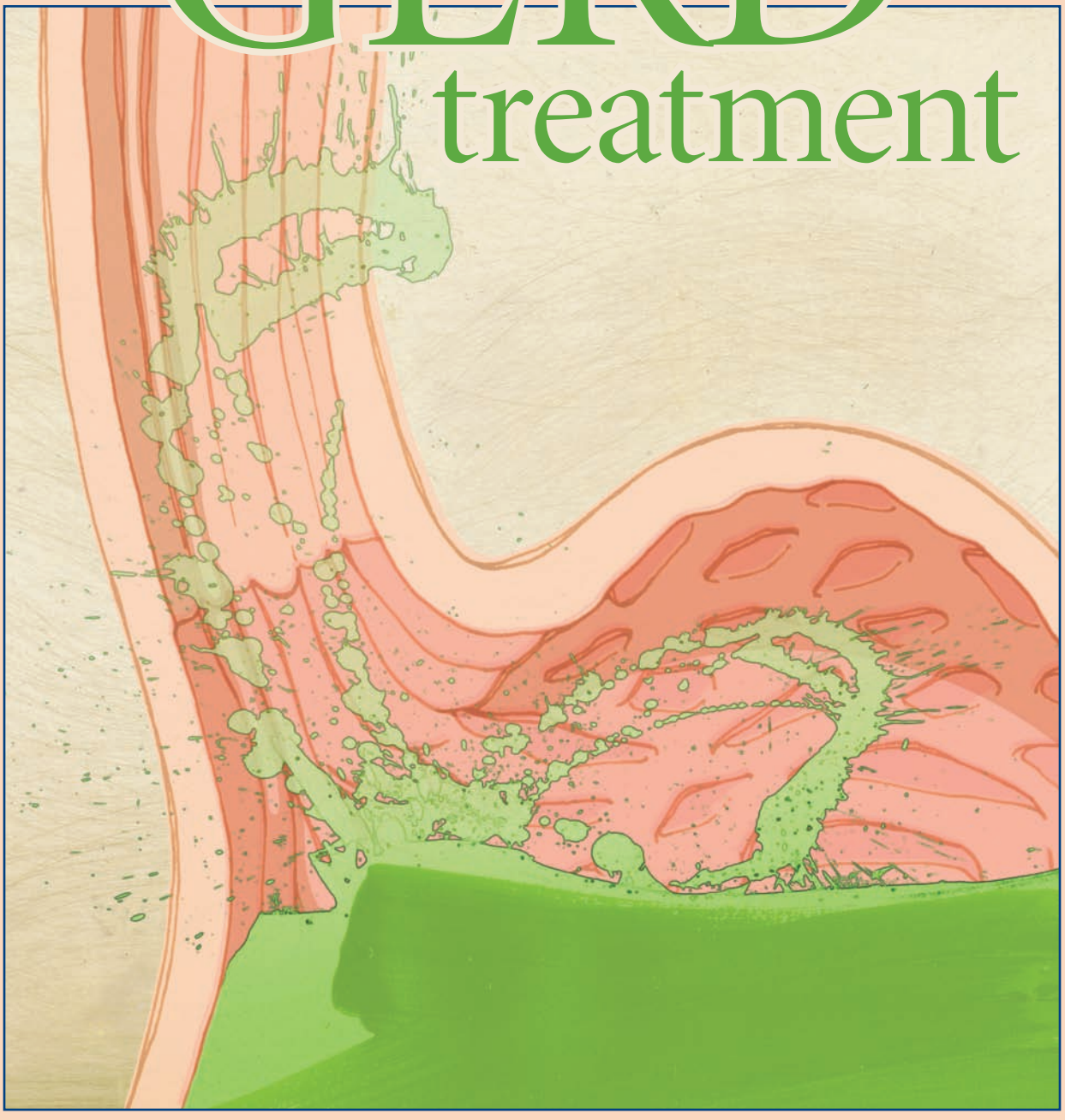
Evidence-based recommendations for GERD treatment



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Abstract: Gastroesophageal reflux disease (GERD) is a common presentation in primary care. New research findings have implications for the diagnosis and management of GERD. The purpose of this article is to synthesize current research related to the diagnosis and management of GERD in adults and to make practice recommendations.

By Ann Marie Hart, PhD, FNP

Gastroesophageal reflux disease (GERD) is a painful condition many adults experience. Recent research findings have important implications for the management of GERD. It is critical for nurse practitioners (NPs) to stay abreast of current management and safety issues related to GERD. The purpose of this review is to synthesize current research related to the diagnosis and management of GERD in adults and to make recommendations for NP practice.

Epidemiology

Although its prevalence varies worldwide, GERD is the most common outpatient gastrointestinal diagnosis in the United States.[1] A systematic review found prevalence rates of 15% to 20% in the United States, 10.1% to 15% in the United Kingdom and Sweden, 5.1% to 10% in Spain, and 0.1% to 5% in China. Similar rates were found between males and females, and higher rates were found in individuals with a body mass index (BMI) greater than 25.[2] The relationship between aging and GERD was less clear, with one study in the review finding GERD rates increased until age 69 and then decreased.[3]

Co-occurring conditions associated with GERD include irritable bowel syndrome, peptic ulcer disease, asthma, chronic obstructive pulmonary disease, and angina.[2] The relationship between GERD and *Helicobacter pylori* (*H. pylori*) infection is complex, with some studies suggesting that eradication of *H. pylori* can result in a mild worsening or improvement of GERD depending upon the location of the infection. However, a Cochrane review of 17 trials found that patients presenting with concomitant GERD and *H. Pylori* infection typically experience improvement in GERD symptoms with *H. pylori* eradication.[4]

Several behavioral factors have been associated with GERD, including tobacco use, coffee drinking, and alcohol consumption. GERD is more prevalent in individuals taking anticholinergics, nitrates, and oral corticosteroids. Despite previous beliefs, the prevalence of GERD has not been shown to be higher in individuals taking benzodiazepines, calcium antagonists, or aspirin.[2] In addition, rates of GERD are inversely associated with the use of oral contraceptives and hormone replacement therapy.[2]

Pathophysiology

GERD results when the stomach's acidic contents cause troublesome symptoms or damage to the esophagus.[5] Normal gastric acid has a pH of 1.5 to 3.5 (similar to lemon juice) and is secreted by the stomach's parietal cells in response to histamine, acetylcholine, and gastrin. All three of these substances coordinate hydrogen ion generation; however, histamine represents the dominant route and plays an important role in current GERD management strategies.[6]

GERD is primarily believed to stem from an alteration in the lower esophageal sphincter (LES), located at the juncture of the stomach and the esophagus. When the LES is lax, acid contents can easily reflux into the esophagus

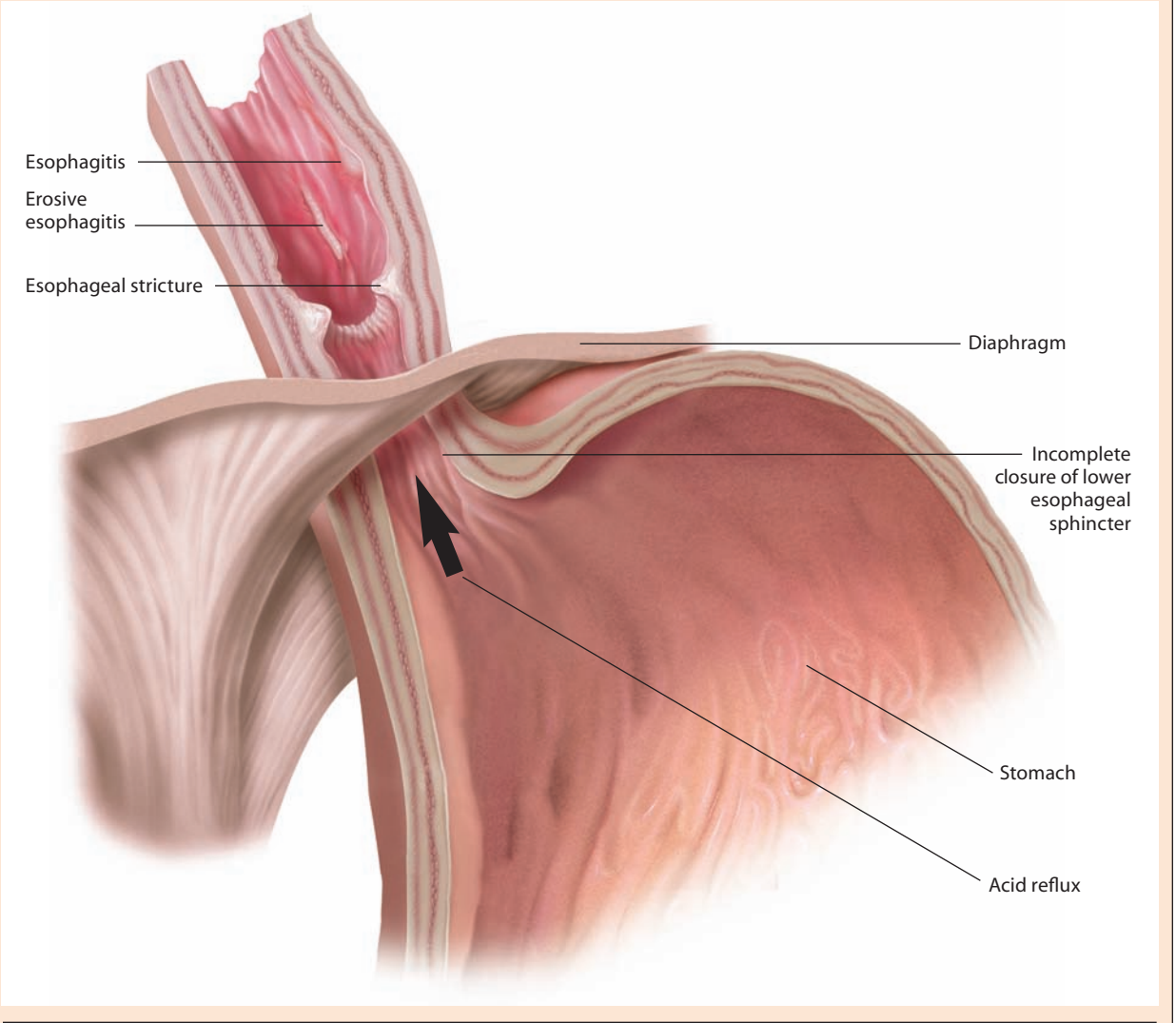
Key words: gastroesophageal reflux disease; GERD; proton pump inhibitors

(see *Gastroesophageal reflux*). Alterations in LES tone result from a variety of factors, including transient LES relaxations (similar to prolonged belches), a hypotensive LES, and anatomic disruption of the gastroesophageal junction (that is, hiatal hernia, obesity, and shortened abdominal length).[7]

Other factors possibly contributing to the development of GERD include altered esophageal peristalsis, delayed gastric emptying, hyposalivation, gastrinomas, and hypersensitivity to gastric acid.[1,7] In fact, there is evidence to suggest that hypersensitivity may play a larger role in GERD than excessive gastric acid exposure; two classic studies evaluated this in the 1990s. Trimble and colleagues[8] evaluated 128 subjects with GERD with 24-hour pH monitoring: 70 had confirmed normal gastric acid exposure in their esophagi, and 58 had confirmed excessive acid exposure. Over the next 4 to 6 years, 87% of those in the normal acid exposure group and 79% of those in the elevated acid group continued to have GERD. Additionally, Rodriguez-Stanley and colleagues[9] examined 152 subjects who were experiencing chronic heartburn with both endoscopy and 24-hour pH monitoring and found normal acid exposure and normal LES pressure in 43% and 64% of the subjects, respectively. Clearly, there is more to GERD pathophysiology than decreased LES pressure and increased gastric acid exposure.

In addition to being a bothersome condition, GERD is associated with several moderate-to-severe complications ranging from dental erosion, pharyngeal ulcerations, and

Gastroesophageal reflux



Source: Anatomical Chart Company. *Atlas of Pathophysiology.* 3rd ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2010:183.

laryngeal damage, to esophageal ulcerations, strictures, and adenocarcinoma.[10] GERD is also a major cause of altered sleep[11] and can result in pulmonary complications, including aspiration, asthma, and pneumonia.[10] Interestingly, 50% to 85% of individuals experiencing GERD have nonerosive reflux disease (that is, no evidence of esophageal damage on endoscopy).[12] However, 10% of individuals with chronic GERD have Barrett esophagus,[13] a condition where reflux causes the stratified squamous epithelium that normally lines the distal esophagus to be replaced by metaplastic columnar epithelium, a risk factor for developing esophageal adenocarcinoma.[10]

Clinical presentation and diagnosis

The diagnosis of GERD is based primarily on the presence of typical esophageal and extraesophageal symptoms. Typical esophageal symptoms include burning sensation in the retrosternal area (pyrosis), and regurgitation into the mouth. Extraesophageal symptoms include bronchospasm, laryngitis, and chronic cough. Less typical symptoms include chest pain, water brash (regurgitation of sour fluid into the mouth), globus sensation (a lump feeling in the throat), and nausea.[10] The presence of less typical symptoms and/or alarm symptoms (that is, bleeding, anemia, odynophagia, dysphagia, and weight loss) requires further investigation.

Differential diagnoses to consider and exclude when evaluating all patients with GERD symptoms (regardless of typical or atypical nature) include but are not limited to the following: infectious esophagitis, eosinophilic esophagitis, pill-induced esophagitis, peptic ulcer disease, biliary tract disease, esophageal motor disorders, esophageal cancer, Barrett esophagus, Zollinger-Ellison syndrome, and coronary artery disease.[10]

Beyond a thorough history and physical exam focused on ruling out the differential diagnoses, further diagnostic workup is rarely indicated. However, a 2008 analysis of endoscopic procedures found that esophagogastroduodenoscopy (EGD) was second only to colonoscopy. Although EGD was most commonly performed for the diagnosis of GERD,[14] it was rarely indicated. This finding is concerning due to costs and safety. Although EGD is a relatively low-risk procedure with complication rates of 1-in-1000 to 1-in-10,000, the risks are serious and include perforation, aspiration pneumonia, respiratory failure, hypotension, anesthesia reactions, dysrhythmia, other cardiovascular events, and death.[15] To help guide clinicians, the American College of Physicians (2012) recently published "Best Practice Advice" regarding EGD for GERD[15] (see *American College of Physician's best practice advice for EGD in adults with GERD symptoms*).

American College of Physician's best practice advice for EGD in adults with GERD symptoms

Best practice advice 1
Upper endoscopy is indicated in men and women with heartburn and alarm symptoms (dysphagia, bleeding, anemia, weight loss, and recurrent vomiting).

Best practice advice 2
Upper endoscopy is indicated in men and women with:
- Typical GERD symptoms that persist despite a therapeutic trial of 4 to 8 weeks of twice-daily PPI therapy.
- Severe erosive esophagitis after a 2-month course of PPI therapy to assess healing and rule out Barrett esophagus. Recurrent endoscopy after this follow-up exam is not indicated in the absence of Barrett esophagus.
- History of esophageal stricture who have recurrent symptoms of dysphagia.

Best practice advice 3
Upper endoscopy may be indicated:
- In men older than 50 years with chronic GERD symptoms (symptoms for more than 5 years) and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated BMI, tobacco use, and intra-abdominal distribution of fat) to detect esophageal adenocarcinoma and Barrett esophagus.
- For surveillance evaluation in men and women with a history of Barrett esophagus. In men and women with Barrett esophagus and no dysplasia, surveillance exams should occur at intervals no more frequently than 3 to 5 years. More frequent intervals are indicated in patients with Barrett esophagus and dysplasia.

Source: Shaheen NJ, Weinberg DS, Denberg TD, et al. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the clinical guidelines committee of the American College of Physicians. *Ann Intern Med.* 2012;157(11):812. Reprinted with permission.

Management

There are two general management strategies to GERD: "step-up" and "step-down" approaches. The "step-up" approach begins with lifestyle management and dietary measures, gradually "stepping up" to medications (including types and doses) as needed. Conversely, the "step-down" approach begins with potent acid-suppressive agents (that is, proton pump inhibitors) to achieve rapid symptom relief, then gradually decreases until the minimal therapy is found for managing the individual's symptoms. Either approach is considered acceptable; thus, symptom severity and patient preferences should guide initial management choice.[16]

Lifestyle management

A variety of lifestyle measures have been proposed for the management of GERD and anecdotally have received much support: dietary limitations (avoiding citrus, tomatoes, coffee, peppermint, fatty foods, carbonation, and chocolate),

smoking cessation, weight loss, avoiding alcohol, avoiding restrictive clothing around the waist, eating smaller, more frequent meals, avoiding lying down for two hours after eating, and raising the head of the bed. Although these measures are considered safe, there are limited research data to support them. A systematic review found evidence that exposure to tobacco, alcohol, chocolate, and high-fat meals decreased LES pressure.[17] However, it found no published studies regarding the effectiveness of avoidance-type dietary measures (for example, avoiding chocolate), and a few studies showed no difference in esophageal pH or symptoms with tobacco or alcohol cessation. The only lifestyle measures with supportive research evidence were weight loss and elevating the head of the bed by 6 to 8 in (15.2 to 20.3 cm); however, this review[17] was severely limited by the small number of published studies.

Pharmacologic management

Pharmacologic management of esophageal reflux is classified into five major categories: acid neutralizing medications (for example, calcium carbonate and sodium bicarbonate), alginate-based barriers, sucralfate, adjunctive therapies (prokinetic agents and reflux inhibitors [bethanechol, as off-label use]), and acid-suppressive medications (H_2-receptor antagonists and proton pump inhibitors). Acid-suppressive medications target GERD symptoms by decreasing gastric acid production (goal of increasing gastric pH to greater than 4).[18] These medications are the mainstay of pharmacologic GERD management and are the focus of this section.

H_2-receptor antagonists

H_2-receptor antagonists (H2RAs) work by blocking histamine (the dominant hormone in gastric acid production) and reducing pepsin output and gastric acid volume. Developed in the 1970s, H2RAs were the first class of acid-suppressive medications. Although H2RAs are not as effective as proton pump inhibitors (PPIs), two Cochrane systematic reviews concluded H2RAs are effective in the management of GERD with and without esophagitis.[19,20]

There are currently four H2RAs, all of which are available over-the-counter (OTC): cimetidine, famotidine, nizatidine, and ranitidine. All four agents are considered equivalent when administered in equipotent doses. They are more effective on basal acid secretion than postprandial secretion and should be taken 30 to 60 minutes prior to eating.[18]

Although the H2RAs are generally well-tolerated, they have been shown to increase the risk of drowsiness and falls in those 65 years and older, especially when combined with severe illness, cognitive impairment, or in those who are taking other anticholinergic medications.[21] NPs should be aware that all of the H2RAs are listed on the 2012 Beers criteria for potentially inappropriate medications for older adults, and cimetidine should be avoided in those 65 and older due to increased risk for delirium.[22] In addition, H2RAs are eliminated by the renal route and should be avoided or dose reduced in those with CrCl less than 50 mL/minute.[21]

PPIs

PPIs have been the mainstay of GERD management since omeprazole was introduced 1989 and continue to be one of the top selling medication classes. PPIs suppress gastric acid by inhibiting the H^+-K^+-ATPase (proton pump) in the gastric parietal cells and have been shown to provide better GERD symptom resolution and esophageal healing than the H2RAs.[19,20] PPIs work quickly and are most effective on basal versus postprandial acid secretion. However, more proton pumps are present after a prolonged fast; thus, PPIs are most effective when administered 1 hour prior to the first meal of the day. In addition, not all of the parietal cell's proton pumps are active at the same time, so it often takes several days of PPI dosing to obtain maximal proton pump inhibition. Due to the marked reduction in their acid inhibitory effects, PPIs and H2RAs should not be given concomitantly; however, they can be given at opposite ends of the day (for example, PPI in the morning and H2RA at bedtime).[23]

There are currently five PPIs: omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole; the former two are available OTC. A Cochrane systematic review found no differences in these PPIs for the treatment of GERD,[19] so it is reasonable to base initial PPI choice on cost and insurance coverage. PPIs should be dosed at the lowest effective dose, and a discontinuation trial should be considered after 3 months; however, some individuals experience "rebound reflux" after abrupt PPI discontinuation.[24] It is reasonable to advise gradual PPI discontinuation, especially in individuals taking moderate-to-high doses of PPIs.[25]

Despite the superiority of PPIs over the H2RAs, questions continue regarding their safety. These concerns primarily relate to PPI use and cancer, infections, fractures, and vitamin malabsorption, as well as interactions with clopidogrel and bisphosphonates.

Cancer. Concerns regarding PPI use and increased rates of cancer originated early in the history of PPIs but have essentially been shown to be unfounded. Gastric acid suppression can result in hypergastrinemia and trophic mutations in the stomach mucosa, changes that have been associated with gastric polyps, gastric cancer, gastric carcinoids, and colorectal cancer in animal studies. However, similar data in species with gastrin physiology more similar to humans have not been supported,[26] and a population-based case control study of 450,000 persons found no

increase in colorectal cancer rates among individuals with a history of long-term PPI use.[27]

Infections. Gastric acid has a protective effect against enteric infections[6]; therefore, gastric acid suppression can permit pathogens to more readily colonize in the upper gastrointestinal tract and predispose individuals to infections, such as pneumonia and *Clostridium difficile* associated diarrhea (CDAD). In fact, there is evidence that even short-term (1 week) PPI use increases the risk of infection.[28] A meta-analysis of 31 studies found that individuals who were taking PPIs (OR = 1.27, 95% CI, 1.11 to 1.46) or H2RAs (OR = 1.22, 95% CI, 1.09 to 1.36) were at a slight increased risk for pneumonia.[29] Unfortunately, the risk of CDAD appears stronger. In a review of 28 observational studies, the U.S. FDA found a higher risk of CDAD with PPI use in 23 studies. The strength of the association varied among the studies with ORs ranging from 1.4 to 2.75 among individuals who were exposed to PPIs versus those who were not exposed. Because of this, the FDA has recommended that clinicians consider and test for *C. difficile* in patients who have a recent history of PPI use and diarrhea that does not improve.[30]

Fracture risk. Several systematic reviews have demonstrated an association between prolonged PPI use (greater than 1 year) and a moderately increased risk of hip (20% to 62%) and vertebral (40% to 60%) fractures in both men and women.[31-34] The acidic environment in the stomach facilitates dissolution and absorption of calcium; therefore, reduced calcium absorption and a resultant decrease in bone density have been hypothesized to explain the association between prolonged PPI use and increased fracture risk. However, current data have not shown an association between PPI use and lower bone mineral density, and several shorter (30 days) studies have shown that dietary calcium absorption is not affected by omeprazole[35]; the mechanism by which prolonged PPI use affects fracture risk is unclear.

Vitamin and mineral malabsorption. There is some evidence that prolonged PPI use may impact vitamin B12, iron, and magnesium absorption. It is well known that gastric acid facilitates the absorption of both vitamin B12 and non-heme iron[6]; however, the impact of PPIs on absorption is not clear. Several small studies have shown an association between PPI use and both decreased vitamin B12 levels and vitamin B12 deficiency[36,37]; other studies have not supported this association.[38,39]

The impact of PPIs on iron absorption is also controversial, and the data regarding this are limited. A 2010 systematic review of four studies found conflicting evidence regarding iron absorption with prolonged (greater than 1 year) PPI use.[40] Adding to the controversy, a study of seven patients with hereditary hemochromatosis who took PPIs for 1 year found a significant reduction in the volume of blood phlebotomized to maintain appropriate iron stores.[41] Moreover, a 2012 retrospective study of 50 patients with iron deficiency anemia taking omeprazole and ferrous sulfate found decreased response to iron therapy.[42]

Over the past 6 years, there have been a growing number of case reports linking PPI use to hypomagnesemia, a dangerous, potentially fatal condition. Hess and colleagues[43] recently conducted a systematic review of case studies to examine the PPI-induced hypomagnesemia. Ultimately, 18 cases were reviewed representing 36 patients, ranging in age from 30 to 83 years (mean of 67.4 years). Length of time on PPIs ranged from 14 days to 13 years (median of 5.5 years).

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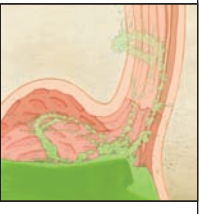

Hypomagnesemia reversed 4 days after discontinuing PPIs and recurred after resuming them. Interestingly, substituting an H2RA for a PPI did not result in hypomagnesemia. To explore the association PPI-induced hypomagnesemia, Danziger and colleagues[44] conducted a large retrospective review of 11,490 adults admitted to an ICU, 23% and 6% had been taking PPIs and H2RAs, respectively. Compared to non-PPI use, PPI use was associated with 0.012 mg/dL lower adjusted serum magnesium level; however, this effect was limited to patients taking diuretics. Among patients taking diuretics, PPI use was associated with a significant increase in hypomagnesemia (OR = 1.54; 95% CI, 1.22 to 1.95) and 0.028 mg/dL lower serum magnesium levels. This effect was seen regardless of diuretic type but was strongest with loop diuretics (for example, furosemide, bumetanide). Among patients not taking diuretics, PPI use was not associated with lower serum magnesium levels. Furthermore, H2RA users did not experience lower serum magnesium levels, regardless of concomitant diuretic use.

Clopidogrel interaction. Clopidogrel is a prodrug metabolized in the liver to an active form that inhibits platelet aggregation. Cytochrome CYP2C19, an enzyme involved in this activation process, is inhibited by PPIs, a phenomenon that can decrease antiplatelet response and increase risk for cardiovascular events.[45] However, studies of the cardiovascular outcomes associated with combination PPI and clopidogrel have been mixed. Several randomized controlled trials found no effect on cardiovascular outcomes when

Summary of evidence-based management recommendations for adults with GERD

Management strategies and recommendations with citations

Lifestyle changes:

- A trial of lifestyle changes (dietary limitations [avoiding citrus, tomatoes, coffee, peppermint, fatty foods, carbonation, and chocolate], smoking cessation, weight loss, avoiding alcohol, avoiding restrictive clothing around the waist, eating smaller, more frequent meals, avoiding lying down for two hours after eating, and raising the head of the bed) should be considered in all adults experiencing GERD, regardless of "step up" or "step down" approach.*

* All of these measures are considered safe and anecdotally have been reported to be effective. Evidence supporting lifestyle measures is limited. A systematic review[17] found evidence that weight loss and elevating the head of the bed by 6 to 8 in (15.2 to 20.3 cm) were moderately effective in reducing GERD symptoms; however, this review was severely restricted by the small number of published studies.

H2RAs:

- H2RAs are effective[19,20] and should be considered as part of a "step up" regimen after a trial of lifestyle changes and prior to initiation of PPIs or as part of a "step down" regimen after weaning off of PPIs[16]
- Available H2RAs are considered equivalent when administered in equipotent doses.[23]
- H2RAs should be used cautiously in patients with severe illness, cognitive impairment, or in those who are using other anticholinergic medications.[22]
- H2RAs should be avoided or used cautiously in patients ≥ 65 years[21,22]
- Cimetidine should be avoided in patients ≥ 65 years[21,22]
- H2RAs should be avoided or the dose-reduced in patients with CrCl < 50mL/minute[22]
- For best results, H2RAs should be taken 30 to 60 minutes prior to eating[18]
- PPIs and H2RAs should not be taken simultaneously but may be given at opposite ends of the day (PPI in the AM and H2RA in the PM)[23]

PPIs:

- PPIs should be considered as part of a "step up" regimen after a trial of H2RAs and should be used initially as part of a "step down" regimen[16]
- The available PPIs are considered equally effective.[19] Base initial PPI choice on cost and insurance preference.
- To avoid "rebound reflux," PPIs should be gradually discontinued over a few weeks (halving the dose every week, until on lowest dose, then taking lowest dose for 1 week)[24]
- For best results, PPIs should be dosed in the morning, 1 hour prior to eating[23]
- PPIs and H2RAs should not be taken simultaneously but may be given at opposite ends of the day (PPI in the AM and H2RA in the PM)[23]
- PPIs should be avoided in those taking Clopidogrel[45,48,49,51]
- PPIs should be used cautiously in patients with a history of vitamin B12 deficiency, and serum levels should be monitored periodically[36,37]
- PPIs should be used cautiously in patients with a history of iron deficiency anemia and/or who are taking oral iron supplements, and serum levels should be checked periodically[40,42]
- PPIs should be used cautiously in patients who are concomitantly taking diuretics, and serum magnesium levels should be monitored periodically[44]
- PPI should be used cautiously in patients at increased risk for fractures[31-34]
- All patients on PPIs who develop persistent diarrhea should be tested for *C. difficile*[30]

clopidogrel and PPIs were combined.[46,47] Other retrospective observational studies suggest that the combination results in higher cardiovascular deaths with more than a 30% increase in the risk of poor cardiovascular outcomes.[48,49] A recent nested case-control study of 43,159 clopidogrel users, 35.7% of whom had taken a PPI at any time during the study, found an increased rate for all-cause mortality in concomitant PPI users (OR = 1.40; 95% CI, 1.29 to 1.53) but not for major cardiovascular events.[50] In addition, the interaction with clopidogrel may not apply to all PPIs. Although lansoprazole and pantoprazole interact with clopidogrel in vitro, they do not appear to inhibit CYP2C19 in vivo.[49] Clopidogrel's package insert currently advises against administration with omeprazole and esomeprazole.[51] However, there is no known interaction between PPIs and other oral antiplatelet agents (for example, ticagrelor, prasugrel, and ticlopidine).[52-54]

Bisphosphonate interaction. There is also some evidence that PPI use might decrease the ability of bisphosphonates (for example, alendronate and risedronate) to protect against fractures. To date, a cohort study[55] and a case-control study[56] both found an increased risk of hip fracture in patients who take PPIs with bisphosphonates. However, more data are needed, and no formal recommendations have been made regarding the use of PPIs and bisphosphonates concurrently.

Refractory GERD

Despite a trial of daily PPI use, 10% to 40% of patients will continue to have symptoms of reflux.[57] In the event of failed response to a PPI trial, it is important to both reconfirm the diagnosis of GERD (focusing on ruling out alarm symptoms) and ensure proper administration of PPIs 30 minutes prior to breakfast. Although the management of refractory GERD is beyond the scope of this article, readers are encouraged to review Herschcovici and Fass' recommendations.[57]

Implications for advanced practice nursing

With up to 20% of the adults in the United States experiencing GERD, primary care NPs will see patients presenting with GERD on a regular

basis. Although the diagnosis and management of GERD are not difficult, incorrectly diagnosing and/or improperly managing GERD can have serious consequences; therefore, it is imperative for practicing NPs to be meticulous in their approach to patients with GERD or suspected GERD and to remain aware of current research findings related to GERD (see *Summary of evidence-based management recommendations for adults with GERD*).

When assessing a new patient with suspected GERD, the NP should ascertain for the presence of alarm signs/symptoms and should consider and rule out competing differential diagnoses. Although EGD should not routinely be part of the diagnostic workup for or follow-up of GERD, there are several situations where it is indicated.

Recommendations for Treatment for GERD can follow a "step up" or a "step down" approach depending on patient preference and severity of symptoms. Although there is limited research to support the effectiveness of lifestyle measures for GERD, anecdotally, many patients report improvement with them, so it is reasonable to consider discussing lifestyle measures with patients.

H2RAs are effective acid-suppressive medications and are available OTC. They should be used cautiously in those 65 and older and in those with CrCl less than 50 mL/minute. PPIs have been shown to be more effective than H2RAs and are currently the mainstay of GERD management; however, several PPI-related safety concerns need to be considered, particularly in patients with a history of iron-deficiency anemia, pernicious anemia, who are taking clopidogrel or diuretics, or who are at an increased risk for fractures.

REFERENCES

1. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. *Am J Gastroenterol*. 2006;101(9):2128-2138.
2. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2005;54(5):710-717.
3. Ruigómez A, García Rodríguez LA, Wallander MA, Johansson S, Graffner H, Dent J. Natural history of gastro-oesophageal reflux disease diagnosed in general practice. *Aliment Pharmacol Ther*. 2004;20(7):751-760.
4. Moayyedi P, Soo S, Deeks J, et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. *Cochrane Database Syst Rev*. 2006;(2):CD002096.
5. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006;101(8):1900-1920.
6. Feldman M. J. Edward Berk Distinguished lecture: Gastric acid secretion: still relevant? *Am J Gastroenterol*. 2013;108(3):347-352.
7. Hoshino M, Sundaram A, Mittal SK. Role of the lower esophageal sphincter on acid exposure revisited with high-resolution manometry. *J Am Coll Surg*. 2011;213(6):743-750.
8. Trimble KC, Douglas S, Pryde A, Heading RC. Clinical characteristics and natural history of symptomatic but not excess gastroesophageal reflux. *Dig Dis Sci*. 1995;40(5):1098-1104.
9. Rodriguez-Stanley S, Robinson M, Earnest DL, Greenwood-Van Meerveld B, Miner PB Jr. Esophageal hypersensitivity may be a major cause of heartburn. *Am J Gastroenterol*. 1999;94(3):628-631.
10. Kahrilas PJ, Hirano I. Chapter 292. Diseases of the esophagus. In: Fauci AS, Kasper DL, Jameson JL, Longo DL, Hauser SL, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012.
11. Fujiwara Y, Arakawa T, Fass R. Gastroesophageal reflux disease and sleep disturbances. *J Gastroenterol*. 2012;47(7):760-769.
12. Dent J. Microscopic esophageal mucosal injury in nonerosive reflux disease. *Clin Gastroenterol Hepatol*. 2007;5(1):4-16.
13. Taylor JB, Rubenstein JH. Meta-analyses of the effect of symptoms of gastroesophageal reflux on the risk of Barrett's esophagus. *Am J Gastroenterol*. 2010;105(8):1729-1737
14. Sonnenberg A, Amorosi SL, Lacey MJ, Lieberman DA. Patterns of endoscopy in the United States: analysis of data from the Centers for Medicare and Medicaid Services and the National Endoscopic Database. *Gastrointest Endosc*. 2008;67(3):489-496.
15. Shaheen NJ, Weinberg DS, Denberg TD, et al. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the clinical guidelines committee of the American College of Physicians. *Ann Intern Med*. 2012;157(11):808-816.
16. Kahrilas PJ. Medical management of gastroesophageal reflux disease in adults. In: Talley NJ, Grover S, eds. UpToDate; 2013.
17. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? an evidence-based approach. *Arch Intern Med*. 2006;166(9):965-971.
18. Hershcovici T, Fass R. Pharmacological management of GERD: where does it stand now? *Trends Pharmacol Sci*. 2011;32(4):258-264.
19. Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. *Cochrane Database Syst Rev*. 2007;(2):CD003244.
20. van Pinxteren B, Sigterman KE, Bonis P, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev*. 2010;(11):CD002095.
21. PL Detail-Document. H2-blockers in the elderly. *Pharmacist's Letter/Prescriber's Letter*. 2012.
22. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60(4):616-631.
23. Proton pump inhibitors: appropriate use and safety concerns. *Pharmacist's Letter/Prescriber's Letter*. 2010;26(7):260705.
24. Lødrup AB, Reimer C, Bytzer P. Systematic review: symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. *Scand J Gastroenterol*. 2013;48(5):515-522.
25. Niv Y. Gradual cessation of proton pump inhibitor (PPI) treatment may prevent rebound acid secretion, measured by the alkaline tide method, in dyspepsia and reflux patients. *Med Hypotheses*. 2011;77(3):451-452.
26. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci*. 2011;56(4):931-950.
27. van Soest EM, van Rossum LG, Dieleman JP, et al. Proton pump inhibitors and the risk of colorectal cancer. *Am J Gastroenterol*. 2008;103(4):966-973.
28. Vakil N. Acid inhibition and infections outside the gastrointestinal tract. *Am J Gastroenterol*. 2009;104(suppl 2):S17-S20.
29. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ*. 2011;183(3):310-319.
30. U.S. Food and Drug Administration. FDA Drug Safety Communication: *Clostridium difficile*-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs). 2012. http://www.fda.gov/drugs/drugsafety/ucm290510.htm.
31. Lau YT, Ahmed NN. Fracture risk and bone mineral density reduction associated with proton pump inhibitors. *Pharmacotherapy*. 2012;32(1):67-79.
32. Eom CS, Park SM, Myung SK, Yun JM, Ahn JS. Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies. *Ann Fam Med*. 2011;9(3):257-67.
33. Kwok CS, Yeong JK, Loke YK. Meta-analysis: risk of fractures with acid-suppressing medication. *Bone*. 2011;48(4):768-776.
34. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. *Am J Gastroenterol*. 2011;106(7):1209-1218.
35. Hansen KE, Jones AN, Lindstrom MJ, et al. Do proton pump inhibitors decrease calcium absorption? *J Bone Miner Res*. 2010;25(12):2786-2795.
36. Rozgony NR, Fang C, Kuczmarski MF, Bob H. Vitamin B(12) deficiency is linked with long-term use of proton pump inhibitors in institutionalized older adults: could a cyanocobalamin nasal spray be beneficial? *J Nutr Elder*. 2010,29(1):87-99.

37. Dharmarajan TS, Kanagala MR, Murakonda P, Lebelt AS, Norkus EP. Do acid-lowering agents affect vitamin B12 status in older adults? *J Am Med Dir Assoc*. 2008;9(3):162-167.

38. den Elzen WP, Groeneveld Y, de Ruijter W, et al. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. *Aliment Pharmacol Ther.* 2008,27(6):491-497.

39. Hirschowitz BI, Worthington J, Mohnen J. Vitamin B12 deficiency in hypersecretors during long-term acid suppression with proton pump inhibitors. *Aliment Pharmacol Ther.* 2008;27(11):1110-1121.

40. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. *Curr Gastroenterol Rep*. 2010;12(6):448-457.

41. Hutchinson C, Geissler CA, Powell JJ, Bomford A. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis. *Gut.* 2007;56(9):1291-1295.

42. Ajmera AV, Shastri GS, Gajera MJ, Judge TA. Suboptimal response to ferrous sulfate in iron-deficient patients taking omeprazole. *Am J Ther.* 2012;19(3):185-189.

43. Hess MW, Hoenderop JG, Bindels RJ, Drenth JP. Systematic review: hypomagnesaemia induced by proton pump inhibition. *Aliment Pharmacol Ther*. 2012;36(5):405-413.

44. Danziger J, William JH, Scott DJ, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. *Kidney Int*. 2013;83(4):692-699.

45. Proton pump inhibitor and Plavix interaction: does it exist? *Pharmacist's Letter/Prescriber's Letter*. 2009;25:250419.

46. Zairis MN, Tsiaousis GZ, Patsourakos NG, et al. The impact of treatment with omeprazole on the effectiveness of clopidogrel drug therapy during the first year after successful coronary stenting. *Can J Cardiol.* 2010;26(2):e54-e57.

47. Cuisset T, Frere C, Quilici J, et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. *J Am Coll Cardiol.* 2009;54(13):1149-1153.

48. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*. 2009;301(9):937-944

49. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ.* 2009;180(7):713-718.

50. Mahabaleshwarkar RK, Yang Y, Datar MV, et al. Risk of adverse cardiovascular outcomes and all-cause mortality associated with concomitant use of clopidogrel and proton pump inhibitors in elderly patients. *Curr Med Res Opin*. 2013;29(4):315-323.

51. Plavix [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2011. 2013. http://packageinserts.bms.com/pi/pi_plavix.pdf.

52. Effient [package insert]. Indianapolis, IN: Daiichi Sankyo, Inc. and Eli Lilly and Company; 2009, 2012. 2013. http://pi.lilly.com/us/effient.pdf.

53. Brilinta [package insert]. Willmington, DE: AstraZeneca LP; 2010, 2012, 2013. 2013. http://www1.astrazeneca-us.com/pi/brilinta.pdf.

54. Ticlid [package insert]. Toronto, ON, Canada: GenPharm ULC; 2008. 2013. http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8668.

55. Abrahamsen B, Eiken P, Eastell R. Proton pump inhibitor use and the antifracture efficacy of alendronate. *Arch Intern Med*. 2011;171(11):998-1004.

56. Lee J, Youn K, Choi NK, et al. A population-based case-control study: proton pump inhibition and risk of hip fracture by use of bisphosphonate. *J Gastroenterol.* [e-pub Jan. 11, 2013]

57. Hershcovici T, Fass R. An algorithm for diagnosis and treatment of refractory GERD. *Best Pract Res Clin Gastroenterol.* 2010;24(6):923-936.

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