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Updates in the Management of Erosive Esophagitis

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TARGET AUDIENCE

This activity is intended for gastroenterologists, primary care physicians, nurse practitioners, physician assistants, and pharmacists.

GOAL STATEMENT

The goal of this activity is for learners to be better able to select evidence-based treatments for patients with gastroesophageal reflux disease (GERD) and erosive esophagitis (EE).

LEARNING OBJECTIVES

Upon completion of this activity, participants will:
Have increased knowledge regarding the
- Mechanistic differences between proton pump inhibitors (PPIs) and potassium-competitive acid blockers (PCABs)
- Evidence comparing PPIs with PCABs for the treatment of GERD and EE

Have greater competence related to
- Selecting evidence-based treatments for EE

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Chapter 1: Best Practices in the Diagnosis and Management of Gastroesophageal Reflux Disease and Erosive Esophagitis

INTRODUCTION

Gastroesophageal reflux disease (GERD) encompasses various syndromes and complications associated with abnormal movement of gastric refluxate from the stomach into the esophagus, and even into the oral pharynx, lungs, and throat.[1] It can be divided into nonerosive reflux disease (NERD) and erosive esophagitis (EE). Several treatment options are available for patients who present with GERD-like symptoms, including antacids for on-demand symptom relief, histamine H_2-receptor antagonists (H_2RAs), and proton pump inhibitors (PPIs).[2,3] The potassium-competitive acid blocker (PCAB) vonoprazan has been approved (together with either amoxicillin plus clarithromycin or amoxicillin alone) for the treatment of *Helicobacter pylori* infection in adults,[4] and PCABs are now being developed for the treatment of EE. The most appropriate treatment approach depends on various individual factors, including the underlying cause of the patient's symptoms and the severity of their underlying disease.[2,3]

DIAGNOSIS AND ASSESSMENT OF GERD

Guidelines recommend that a presumptive diagnosis of GERD can be made when patients present with classic symptoms—heartburn and regurgitation—without alarm symptoms (ie, dysphagia, weight loss, bleeding, anemia, nausea, vomiting). An 8-week trial of an empiric PPI once daily before a meal can be considered and, when GERD symptoms respond to this trial, efforts should be made to discontinue treatment.[2]

Endoscopy can distinguish with certainty between NERD and EE and is recommended for patients with alarm symptoms, patients whose symptoms do not respond to a PPI trial, and patients whose symptoms return after discontinuation of treatment.[2] The Los Angeles (LA) classification is the widely accepted standard for assessing the severity of GERD esophagitis. It has been well validated in terms of its internal and external consistency, so that if different clinicians are shown the same pictures they will usually grade them similarly (**FIGURE 1**).[2,5,6]

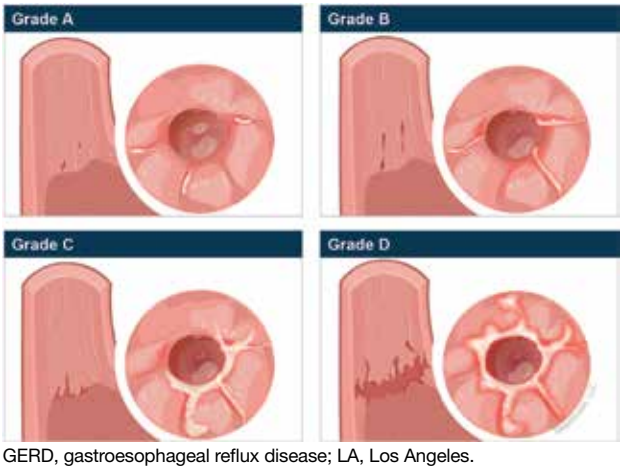
There is a clear correlation of acid exposure severity and increasing LA grade classification, which is supported by extensive clinical data.[2,3,6] Therefore, if a patient has LA stage B, C, or D esophagitis, it is possible to say with confidence that they have GERD and that their symptoms are the result of abnormalities associated with the movement of the gastric fluid into the esophagus. Approximately 50% to 75% of patients who present with classic GERD symptoms—such as heartburn, esophageal chest pain, and regurgitation—have no ulcerations or lesions that can be seen on endoscopy.[7] So, although they have esophagitis in the context of typical GERD-like symptoms, it is not possible to make a definitive diagnosis of GERD without additional testing.

In this scenario, the patient should be sent for reflux testing, which can be done using wireless pH testing over 96 hours or pH impedance over 24 hours. If reflux testing reveals an abnormal reflux burden or findings consistent with GERD, it is appropriate to conclude that the patient has NERD. Patients who present with symptoms of GERD but who are negative on both endoscopy and reflux testing do not have GERD; their symptoms generally result from an alternative cause, such as a functional or motility disorder.[2]

Detailed recommendations for the diagnosis and management of GERD are provided by the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA), which are mostly consistent with each other.[2,3] For many patients experiencing heartburn and/or regurgitation with sufficient frequency or intensity to impair their quality of life (QoL), the diagnostic process can be initiated with an 8-week trial of a PPI, taken once daily before a meal. If their symptoms resolve, they likely have GERD. If they do not achieve complete symptom relief on a PPI, or if their symptoms recur after discontinuing the PPI, they should undergo endoscopy (**FIGURE 2**). Patients should also undergo endoscopy if they present with any so-called "alarm symptoms," including dysphagia, weight loss, gastrointestinal (GI) bleeding, vomiting, anemia, multiple risk factors for Barrett's esophagus, or chest pain not resulting from heart disease.[2]

It is also advisable to perform endoscopy in patients older than age 60 years with the new-onset GERD symptoms, not necessarily to diagnose reflux, but to rule out other serious conditions that are more common in older

FIGURE 1. Endoscopic Assessment of GERD Using the LA Classification System[6]



GERD, gastroesophageal reflux disease; LA, Los Angeles.

Reprinted from Gastrointestinal Endoscopy, 60(2), Nayar DS, et al. Classifications of esophagitis: who needs them? pp. 253-257, Copyright (2004), with permission from Elsevier.

adults, such as cancer. Endoscopy is also recommended in patients who have been on long-term GERD treatment to ensure they have not developed Barrett's esophagus or other complications. In addition to endoscopy, patients should be offered reflux testing when long-term PPI therapy is planned and a diagnosis has not been confirmed by endoscopy.[3] Generally speaking, if a patient is going to be prescribed a PPI indefinitely, clinicians should obtain objective evidence of GERD via endoscopy or reflux testing.

Once the patient's symptoms have resolved, repeat endoscopy in patients with LA grade C and D esophagitis is necessary while on PPI therapy to confirm that the erosions have healed and to ensure the patient has not developed Barrett's esophagus in the meantime.[2] Before conducting a *first-time* endoscopy, however, the patient should stop taking their PPI for at least 2 to 4 weeks.[2] This is because, by partially controlling acid production, the PPI can mask the severity of the patient's esophagitis and the degree of erosion. Therefore, studying patients while they are off medication allows clinicians to assess their level of symptoms and quantify their degree of acid-related erosion more accurately.[2] Similarly, patients with a negative endoscopy who are undergoing reflux testing to confirm a diagnosis of GERD should also stop their PPI for 1 to 2 weeks to assess their baseline reflux burden.

IMPORTANCE OF LIFESTYLE MANAGEMENT IN EE

Although PPIs are firmly established as the first-line treatment of patients with GERD symptoms, the benefits of lifestyle management in this setting should not be overlooked. The ACG and AGA guidelines both highlight the importance of lifestyle modification in addition to pharmacologic therapy. When provided together with PPI therapy, aggressive lifestyle modifications and weight management often bring about meaningful symptom improvement in patients with mild to moderate GERD.[2,3]

Various foods have been associated with exacerbation of GERD symptoms in some individuals. In clinical practice, however, it can be counterproductive to ask patients to avoid all foods that could be associated with reflux because it can cause them to become overly focused on restriction, and their QoL actually deteriorates. Furthermore, the evidence for most foods significantly impacting GERD symptoms is relatively weak.[2] It is more helpful to counsel patients to be alert to specific foods that trigger their symptoms. Smoking may also contribute to GERD symptoms, which is one of many reasons why patients who smoke should be encouraged to quit.[2]

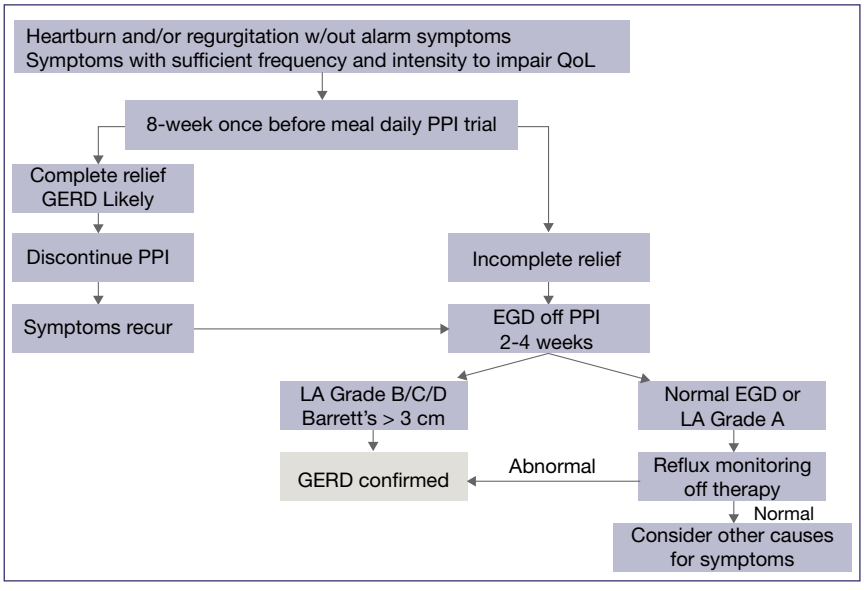
There are experimental data showing that psychological stress exerts a variety of effects on GI pathophysiology and can promote gastroesophageal reflux symptoms.[8] Although stress is unlikely to cause GERD in a person who does not already have reflux, it may exacerbate their symptoms. Patients can also develop hypervigilance and visceral anxiety about their symptoms, which can increase symptom severity. Treatments such as neuromodulators, cognitive behavioral therapy, and hypnosis can help some patients with reflux exacerbated by stress and visceral anxiety.[9]

INITIATING PPI TREATMENT FOR EE

Among the PPIs, there are some notable differences. Omeprazole is a good starting option for the treatment of EE because it is available over the counter (OTC) as a generic preparation and is covered by most formularies. Many patients with EE will require a daily dose of 40 mg, which is twice the US Food and Drug Administration (FDA)-approved dose for GERD. While this dose is recommended by the latest guidelines,[2,3] it is not FDA approved. Pantoprazole appears to be the least potent PPI for acid suppression, whereas rabeprazole is highly potent and the only PPI not metabolized primarily by CYP2C19.[10,11] Therefore, rabeprazole is a good option for patients who do not respond sufficiently to omeprazole.

Suboptimal PPI response is often the result of poor adherence. These medications are usually most effective when taken 30 to 60 minutes before a meal. However, approximately 40% to 50% of patients do not take PPIs appropriately—some individuals take them with meals, whereas others take them at bedtime because they experience nighttime symptoms.[12,13] Dexlansoprazole can sometimes be helpful in patients who do not respond to other PPIs because it is available as an

FIGURE 2. ACG Algorithm for the Diagnosis of GERD[2]



EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; LA, Los Angeles; QoL, quality of life; PPI, proton pump inhibitor.

Katz, PO, et al. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. The American Journal of Gastroenterology, 117(1):27-56. doi:10.14309/ajg.0000000000001538.

extended-release formulation and its effectiveness is therefore less affected by timing.[2]

After a course of PPI treatment, patients with NERD or LA grade A esophagitis should be tapered to the lowest effective dose or even to on-demand therapy with either a PPI or an H_2RA. Those with more severe EE (LA grade C or D) usually experience recurrence when maintenance therapy is discontinued. These patients should, therefore, be maintained on lifelong acid-suppressing therapy.[2] Even grade B esophagitis is a sign of significant acid exposure and may require permanent maintenance therapy to prevent the recurrence of erosions (**FIGURE 3**).[2,3]

Overall, PPIs are safe medications with good tolerability and low rates of adverse effects. Nevertheless, suppressing acid production can alter bacterial growth in the gastrointestinal tract. Because bacteria are able to survive only within specific pH ranges, acid in the stomach kills the majority of bacteria. Therefore, when patients are taking a PPI, there is the potential for bacterial overgrowth.[12,13]

In addition, some vitamins and minerals require acid for optimal absorption. Individuals who follow certain diets, such as vegans, can be susceptible to deficiencies in vitamin B12 and magnesium when taking a PPI. Reported increases in the risk for more serious side effects with PPIs, such as cardiovascular disease, dementia, osteoporosis, and kidney disease, have not been demonstrated in well-designed prospective studies.[14]

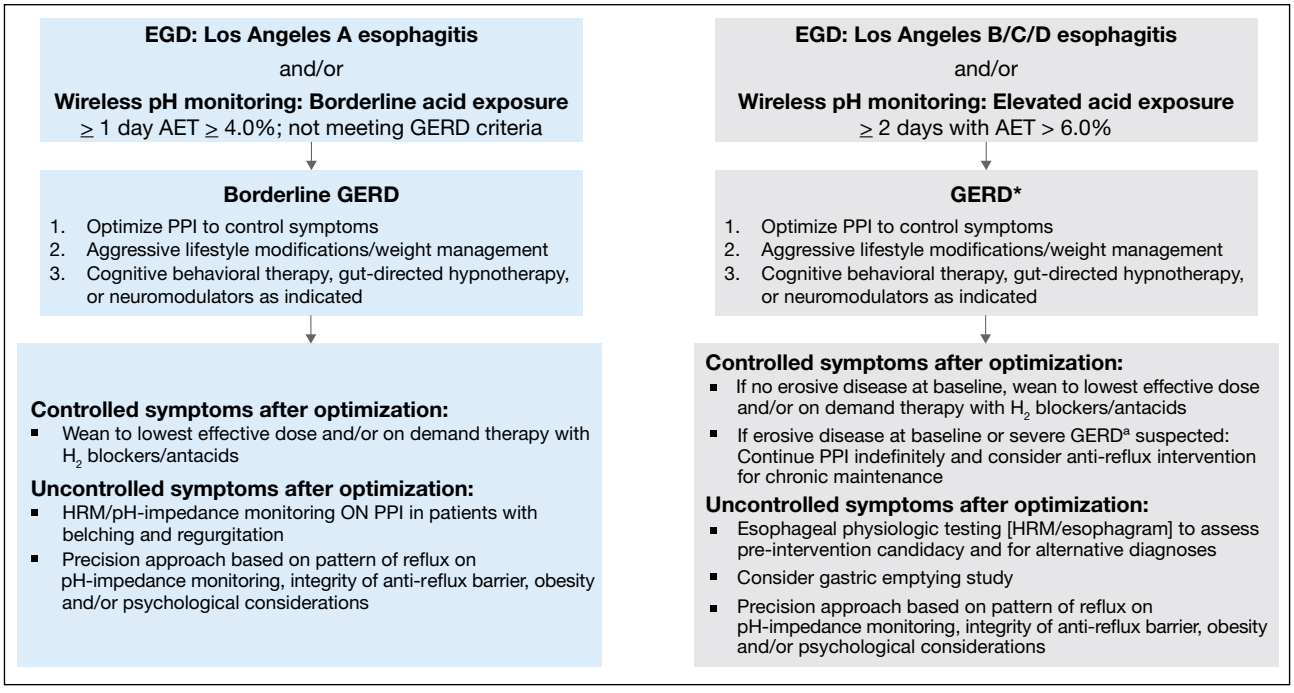
LIMITATIONS OF CURRENT TREATMENTS FOR EE

Despite their overall safety and effectiveness in most individuals, PPIs do have some important limitations:

- Many patients do not take them appropriately at the correct time.[12,13]
- The full acid-suppressing effect is not achieved for several days.[4]
- Almost 40% of patients do not achieve adequate control of nighttime symptoms even with twice-daily PPI therapy.[13]
- They are sometimes ineffective—lack of healing of EE with 8 weeks of PPI therapy can be expected in 5% to 20% of patients, with rates up to 30% reported in patients with more severe esophagitis.[7]
- Even after erosions have healed, 10% to 45% of patients, most commonly those with more severe disease at diagnosis, experience recurrence within 12 months despite PPI therapy.[7]

Patients who do not achieve healing of erosions on a PPI may benefit from augmentation with an H_2RA. However, long-term use of these medications is limited by tachyphylaxis.[3] Many patients with GERD/EE could benefit from a therapy that does not require premeal dosing, provides more rapid acid suppression, and more effectively heals erosions. PCABs appear to overcome many of these limitations and are discussed in greater detail in Chapter 2.

FIGURE 3. AGA Algorithm for Management of GERD[3]



AET, acid exposure time; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; HRM, high-resolution esophageal manometry; PPI, proton pump inhibitor.

[a]The presence of LA grade C or D esophagitis, bipositional reflux, extreme levels of acid exposure (AET > 12% or DeMeester score > 50), and/or a large hiatal hernia may indicate a more severe GERD phenotype.

MULTIDISCIPLINARY TEAM APPROACH TO MANAGING GERD

The majority of patients with GERD do not need to see a gastroenterologist; rather, their symptoms can usually be managed effectively by primary care clinicians, including family physicians, physician assistants, and nurse practitioners. Referral to a gastroenterologist is indicated when endoscopy and reflux testing are necessary, such as when patients are experiencing severe symptoms or alarm symptoms, or they are not getting adequate relief with OTC medications. Pharmacists are important as part of the care team, particularly for explaining to patients how to take their PPI. Some patients have difficulty taking medications as tablets or capsules. Pharmacists can let those patients know which PPI capsules can be opened and mixed with water or juice. Dieticians can help patients identify and avoid foods that trigger symptoms. Finally, some patients with GERD symptoms exacerbated by stress or anxiety can benefit from referral to a psychologist for cognitive behavioral therapy.

SUMMARY

Although GERD is generally viewed as a straightforward disease that is usually resolved by treatment with PPIs, it involves complex pathophysiologic alterations that can be challenging to address. A thorough patient history and methodical evaluation of changes in the patient's anatomy and physiology, including endoscopy and reflux testing when appropriate, allows the healthcare team to provide a personalized treatment approach that offers effective, sustained disease control and optimizes QoL.

The next chapter will review new data in the management of EE, including studies evaluating the efficacy and safety of PCABs. ●

CHAPTER 2: New Data in the Management of Erosive Esophagitis

INTRODUCTION

In 1989, omeprazole was the first PPI to be approved by the FDA for the treatment of acid-related disorders.[13] A number of other PPIs have been approved since then and, until recently, PPIs were the only available drugs that could reliably heal EE. Consequently, PPIs have been the mainstay of treatment for EE for the past 3 decades.[13] Despite their overall efficacy, PPIs have some drawbacks.[13] For example, a substantial minority of patients, particularly those with severe grades of EE, may not achieve complete healing of erosive lesions when given PPIs in conventional dosages.[4]

Potassium-competitive acid blockers (PCABs) have several features that might offer advantages over PPIs for healing severe EE, including a more rapid onset of action, more effective and longer-lasting acid suppression, and better control of nocturnal acidity.[15] Several PCABs have either already been developed or are being studied as alternatives to PPIs.[4] Studies on PCABs have been conducted primarily in Asia; revaprazan, vonoprazan, tegoprazan, fexuprazan, and keverprazan have been approved for clinical use in some Asian countries.[4,15-17] In May 2022, vonoprazan, used with either amoxicillin plus clarithromycin or amoxicillin alone, became the first new acid-suppressing agent in more than 30 years to receive FDA approval for the treatment of *Helicobacter pylori* infection in adults.[4] Vonoprazan is currently awaiting FDA approval for the treatment of EE. However, at the time of this writing, the release of vonoprazan has been delayed while awaiting resolution of concerns regarding nitrosamine impurities in its preparations.[18]

HOW PPI AND PCAB MECHANISMS OF ACTION DIFFER

PPIs block the final step in gastric acid secretion by binding covalently and irreversibly to H^+/K^+-ATPase, the "proton pump" enzyme in gastric parietal cells that pumps hydrogen ions (protons) out of the cell and into the lumen in exchange for potassium ions. PCABs also inhibit H^+/K^+-ATPase, but they do so by binding ionically to the proton pump, thereby competing with the binding of potassium and preventing the exchange of potassium ions for hydrogen ions.

Several features of PPIs limit their speed of onset or their efficacy for acid inhibition; PCABs do not share these features.[4]

Degradation. Because PPIs are vulnerable to degradation by acid in the stomach, they require an enteric coating, which protects them from gastric acid but also delays their absorption. PCABs are acid stable and, therefore, do not require an enteric coating.

Activation. Available PPIs are all prodrugs that must be activated by acid produced by gastric parietal cells to bind covalently to the proton pumps. Because acid is required to activate the PPIs, only parietal cells that are actively secreting acid will be affected by the PPIs. In the fasting state, only about 5% of proton pumps in the stomach are actively secreting acid; when stimulated by a meal, the proportion of proton pumps that are actively secreting acid increases to 60% to 70%. For this reason, patients are advised to take PPIs 30 to 60 minutes before a meal.[2] Conversely, PCABs are active drugs, not prodrugs; therefore, they do not require acid activation—they form an ionic bond with both active and inactive proton pumps, so there is no need to time dosing around meals.

Duration of effect. PPIs have a relatively short plasma half-life—only 1 to 3 hours—and the stomach is constantly making new proton pumps. Consequently, some 3 to 5 days of treatment are required before steady-state inhibition is reached. PCABs, on the other hand, achieve maximal suppression of gastric acid production within hours of administra-

tion and have a longer plasma half-life (eg, 6 to 9 hours for vonoprazan).

Cytochrome P450 metabolism. PPIs are metabolized primarily by the cytochrome P450 enzyme CYP2C19, and there is considerable variability among individual patients in how rapidly they metabolize PPIs. PCABs are metabolized primarily by other enzymes, such as CYP3A4, and are therefore not affected by CYP2C19 polymorphisms.[4]

SAFETY OF ACID-REDUCING THERAPIES

In general, PPIs have an excellent track record for safety.[2] Established PPI adverse effects, such as headache, diarrhea, constipation, and abdominal discomfort, are uncommon, typically minor, and easily managed. However, a number of more serious putative PPI adverse effects have been identified through weak associations found in observational studies.[19,20] The putative adverse effects include the following:

Cancer. There have been concerns that PPIs might increase the risk for developing certain types of cancer. As a result of gastric acid inhibition, PPI usage commonly results in elevated serum levels of gastrin, a hormone that has trophic effects on certain tissues; in patients with untreated *H pylori* infection, PPIs have been observed to accelerate the development of gastric atrophy that might predispose patients to gastric cancer.

Infections. Gastric acid plays a role in killing ingested microorganisms, and it has been proposed that inhibiting acid production with PPIs might increase the risk for developing a variety of infections, including community-acquired pneumonia, enteric infections, *Clostridioides difficile* colitis, and spontaneous bacterial peritonitis in patients with cirrhosis.

Vitamin absorption. There are proposed risks related to the effects of PPIs on the absorption and metabolism of vitamins and minerals. For example, PPIs can interfere with the absorption of calcium and vitamin B12, and some studies have found an association between PPI usage and increased risk for bone fractures and hypomagnesemia.

Drug metabolism. PPIs can have potentially adverse effects on the metabolism of certain drugs, such as clopidogrel and methotrexate.

Miscellaneous. A number of other issues have been linked to PPIs, including interstitial nephritis, chronic kidney disease, microscopic colitis, food allergy, celiac disease, myocardial infarction, stroke, dementia, and even early death. Most of these issues appear to be unrelated to PPI effects on gastric acid, and proposed underlying mechanisms are either unknown or not well established.

The aforementioned putative PPI adverse effects have been identified largely in observational studies that are notoriously unreliable for identifying true risks and that cannot establish cause-and-effect relationships.[20] A large, placebo-controlled, randomized trial, published in 2019, clarified the issue of PPI safety considerably.[14] In this study, 17,598 patients with cardiovascular or peripheral artery disease were randomized to receive pantoprazole or placebo. Data were collected over a 3-year period to identify potential PPI adverse effects, including pneumonia, *C difficile* infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, dementia, cardiovascular disease, cancer, and all-cause mortality. The use of pantoprazole for 3 years was not significantly associated with any adverse event other than enteric infections (for which the risk was only modestly elevated), and the authors concluded that the associations between PPIs and adverse events found in observational studies are unlikely to represent cause-and-effect relationships.[14] Nevertheless, it is important to consider that the trial had a maximum follow-up of only 5 years, which might not be sufficient time for some adverse events to develop, and the nature of statistics is such that a small risk for any of these putative adverse effects can never be excluded no matter how large the study sample size.

The H_2RAs, including cimetidine, famotidine, and nizatidine, are still very safe and useful agents for treating GERD that is not associated with severe reflux esophagitis, and have been reported to be beneficial for eliminating nocturnal acid breakthrough in patients on PPIs.[21] Unlike PPIs, H_2RAs do not result in reliable healing of EE,[2,22] and their acid-reducing effect tends to diminish over time.[23]

Data from clinical trials with PCABs indicate that these drugs are also very safe, at least for short-term use. Approval of vonoprazan in the United States for the treatment of *H pylori* infection was based on data from the phase 3 PHALCON-HP trial, which compared vonoprazan-based regimens with lansoprazole triple therapy in 1046 patients.[24] Adverse events, which included low rates of diarrhea, dysgeusia, vulvovaginal candidiasis, abdominal pain, headache, hypertension, and nasopharyngitis, were comparable for the 2 treatments.[24] Similar rates of adverse events were seen in a phase 3 trial conducted in Japan in patients with NERD and recurrent acid reflux symptoms.[25] Vonoprazan has now been used in Japan for 8 years, and no new safety concerns were identified during a 1-year, real-world, postmarketing surveillance study.[26] However, long-

TABLE 1. Efficacy Outcomes for Vonoprazan vs Lansoprazole in EE: 8-Week Healing Phase[7]

Efficacy Endpoint	% of Patients Who Achieved Endpoint	
	Vonoprazan 20 mg (n = 514)	Lansoprazole 30 mg (n = 510)
Healing by week 8	92.9	84.6
24-h heartburn-free days, mean (SD)	66.8 (34.6)	64.1 (35.5)
Healing at week 2 in LA grade C/D	70.2	52.6
Onset of sustained resolution of heartburn by day 3	34.4	32.2
Healing by week 8 in LA grade C/D	91.7	72.0
Healing at week 2	74.3	68.2

EE, erosive esophagitis; LA, Los Angeles; SD, standard deviation.

term data on the use of PCABs are limited, and relatively few data are available on the use of PCABs in Western populations. In a phase 3 trial conducted in South Korea, adverse effects observed with fexuprazan, which is also being developed for use in the United States, were shown to be comparable to those observed with esomeprazole.[27]

COMPARING THE EFFECTIVENESS OF PPIS AND PCABS IN EE

The efficacy of vonoprazan in EE recently was assessed in a large, noninferiority study conducted in the United States and Europe involving 1024 patients who were randomized to once-daily treatment with either vonoprazan 20 mg or lansoprazole 30 mg.[7] After 8 weeks, patients who achieved healing were rerandomized to receive maintenance therapy with once-daily vonoprazan 10 mg or 20 mg or lansoprazole 15 mg for an additional 24 weeks.[7]

During the initial 8-week healing phase, vonoprazan was noninferior to lansoprazole for the primary endpoint of the percentage of participants with healing by week 8, which

TABLE 2. Studies Evaluating PCABs in Asian Patients With EE[27,29-35]

PCAB	Patient Population	Treatment Regimens	Key Findings
Vonoprazan	732 Japanese patients with EE[29]	• Vonoprazan (5 mg, 10 mg, 20 mg, or 40 mg once daily) vs lansoprazole (30 mg once daily) for 8 weeks	• Vonoprazan at all doses was effective and noninferior to lansoprazole in healing EE • Vonoprazan 20 mg or higher was highly efficacious for severe EE (LA grades C/D)
	607 Japanese patients with EE who achieved healing on vonoprazan (20 mg once daily) for up to 8 weeks[30]	• Maintenance therapy with vonoprazan (10 mg or 20 mg once daily) or lansoprazole (15 mg once daily) for 24 weeks	• Both doses of vonoprazan were noninferior to lansoprazole as maintenance therapy • In a *post hoc* analysis, EE recurrence was significantly lower for both doses of vonoprazan than for lansoprazole
	24 Japanese patients with PPI-resistant reflux esophagitis[31]	• Vonoprazan (20 mg once daily) for 4 weeks • Patients whose esophagitis was healed at 4 weeks were treated for an additional 4 weeks with vonoprazan (10 mg once daily) maintenance therapy • Patients whose esophagitis remained healed at 8 weeks continued vonoprazan maintenance therapy up to 52 weeks	• Vonoprazan 20 mg effectively healed esophageal mucosal breaks in 21/24 patients (87.5%) within 4 weeks • Long-term maintenance therapy with vonoprazan 10 mg was effective in preventing relapse for up to 52 weeks
	238 patients with EE in several countries in Asia[32]	• Vonoprazan (20 mg once daily) vs lansoprazole (30 mg once daily) for up to 8 weeks	• Vonoprazan was noninferior to lansoprazole for healing EE at 8 weeks • In patients with severe baseline EE (LA grades C/D), healing rates at 2 weeks, 4 weeks, and 8 weeks were higher with vonoprazan than with lansoprazole
	401 Japanese patients with EE[33]	• Vonoprazan (20 mg once daily) vs lansoprazole (30 mg once daily) for up to 8 weeks • Patients whose esophagitis remained healed at 8 weeks were rerandomized to vonoprazan 10 mg once daily or 20 mg once daily up to 52 weeks	• Vonoprazan was noninferior to lansoprazole for healing EE at 8 weeks • There were few recurrences (< 10%) of EE in patients treated with vonoprazan 10 or 20 mg for up to 52 weeks
Tegoprazan	302 Korean patients with EE[34]	• Tegoprazan (50 mg or 100 mg once daily) vs esomeprazole (40 mg once daily) for 4 or 8 weeks	• Both doses of tegoprazan were noninferior to esomeprazole
Fexuprazan	263 Korean adults with EE[27]	• Fexuprazan (40 mg once daily) vs esomeprazole (40 mg once daily) for 8 weeks	• Fexuprazan was noninferior to esomeprazole in healing EE at 8 weeks
Keverprazan	238 Chinese patients with EE[35]	• Keverprazan (20 mg once daily) vs lansoprazole (30 mg once daily) for 4 to 8 weeks	• Keverprazan was noninferior to lansoprazole in treating EE

EE, erosive esophagitis; LA, Los Angeles; PCAB, potassium competitive acid blocker; PPI, proton pump inhibitor.

was 92.9% for vonoprazan, compared to 84.6% for lansoprazole (difference 8.3%; 95% CI: 4.5%, 12.2%) (**TABLE 1**). A secondary analysis showed that vonoprazan was superior to lansoprazole for this endpoint and with respect to the percentage of participants with LA grade C or D erosions who achieved healing at week 2 (70.2% vs 52.6%, respectively).[7]

Vonoprazan at either the 20-mg or 10-mg dose was also shown to be noninferior to lansoprazole with respect to the overall percentage of participants who maintained healing at week 24, the percentage of participants with LA grade C or D erosions who maintained healing at week 24, and the percentage of heartburn-free days. Both doses of vonoprazan resulted in significantly more patients maintaining healing at week 24, regardless of esophagitis severity.[7]

Several additional studies evaluating the efficacy of PCABs for EE have been conducted in Asia. Acid production in the stomach, and some aspects of CYPC219 metabolism in Asian individuals, can differ from those in White participants.[28] Nevertheless, these studies were consistent with the United States/European study in showing that PCABs were at least as effective as the comparator PPI at recommended dosages, with no significant differences in adverse effect rates (**TABLE 2**).[27,29-35] Changes in gastrin levels were also generally comparable for PCABs and PPIs.

SUMMARY

For patients with EE, PPIs are likely to continue to be used extensively for the foreseeable future. If PCABs are approved for EE in the United States, they could represent another treatment option and may be especially useful for patients with LA grade C/D EE. Available data indicate that vonoprazan has efficacy superior to that of PPIs given in FDA-approved dosages in this population. Further, PCABs can provide potent inhibition of acid production within a couple of hours, as opposed to the 5 days needed for steady-state inhibition of acid production for PPIs.

Treatment of patients with EE can involve various healthcare professionals, including primary care physicians, gastroenterologists, physician assistants, nurse practitioners, and nurses in primary care and gastroenterology practices. Pharmacists are also well positioned to guide patients on the management of GERD using over-the-counter therapies, including PPIs. It will be important for all members of the care team to understand how PCABs differ from PPIs, the clinical implications of those differences—for example, timing of doses and time to achieve suppression of acid production—as well as situations in which PCABs may offer greater benefit than do current standard-of-care options.

The next chapter will put the information presented in chapters 1 and 2 into clinical context using patient cases to illustrate the management of EE in clinical practice. ●

CHAPTER 3: Case Studies in the Clinical Management of Erosive Esophagitis

INTRODUCTION

As described in the 2 previous chapters, PPIs are well established as the standard of care for the treatment of GERD. However, there remains a need to individualize treatment based on disease severity and response to therapy. The following cases highlight important considerations in the management of patients who have recent onset of GERD symptoms and patients with EE who did not achieve an adequate response with PPI treatment.

CASE 1: PATIENT WITH RECENT-ONSET GERD SYMPTOMS

Barry is a 30-year-old man with a body mass index (BMI) of 29 who has been experiencing persistent heartburn and regurgitation 2 to 3 times a week for several months. He has tried an OTC antacid and an H_2RA, but his heartburn is getting worse, particularly at night.

This is a common presentation of patients with GERD symptoms who are routinely seen in both primary care and gastroenterology clinics. According to the Montreal classification, Barry's symptoms would be considered troubling because they occur 2 or more times a week, or at least once a week at night.[1] If the patient does not have alarm symptoms—dysphagia, weight loss, bleeding, anemia, nausea, vomiting—both the ACG and AGA guidelines recommend starting empiric treatment with a PPI.[2,3]

Some patients are reluctant to start a PPI, particularly if they have kidney dysfunction. Older women are commonly concerned about an increased risk of osteoporosis, and older patients in general are sometimes concerned about dementia, which has been reported with PPI therapy.[20] It is, therefore, important to counsel patients on the overall safety of PPIs in line with the current guidelines. It is common for patients to consult a pharmacist if they have questions about taking a PPI, especially as they often do not recall their physician explaining some important aspects of PPI use, as shown in a recent European study.[36] Pharmacists have a valuable role in successful GERD treatment by offering clear and accurate information about PPIs and how to take them.

When treating GERD, the patient's weight and any changes in their weight, particularly recent weight gain, can be important information. In this case, the patient is overweight, with a BMI of 29, and should be counseled about the benefits of weight loss with respect to his GERD symptoms.[2,3] It could also be worth referring him to a weight management program where healthcare professionals can have a more expert discussion about diet, weight-reducing medications, or even surgery. It would also be valuable to explore whether the patient is hypervigilant and anxious about his symptoms. Regard-

less of whether his symptoms are caused by GERD, if there is anxiety surrounding the symptoms it needs to be addressed. The most effective approach to identifying and managing any anxiety involves integrated interprofessional care.[37]

CASE (CONT'D)

After an 8-week trial of omeprazole 20 mg once daily, Barry reports some improvement; he says that his heartburn is getting better, but there has been no reduction in regurgitation.

This scenario is very common—acid suppression with PPIs is more effective for improving heartburn symptoms, but the regurgitation does not tend to respond to the same extent. At this point, an upper endoscopy should be done. Wireless reflux monitoring to measure the percentage of time spent at pH of 4.0 or less would also be valuable.[3] Recently published studies have shown that an acid exposure time (AET) of greater than 6% is highly consistent with GERD, whereas an AET of less than 4% essentially excludes GERD, and a result between 4% and 6% is inconclusive.[3] When empiric PPI therapy has been tried and it is still not clear whether the patient has GERD, the best course of action would be to pause the PPI for 2 to 4 weeks and then simultaneously perform endoscopy and wireless reflux monitoring.[2,3]

CASE (CONT'D)

Endoscopy results show Barry has LA grade A EE and a 2-cm hiatal hernia but no Barrett's esophagus. Wireless reflux monitoring finds an AET of 6.5%, predominantly when in the supine position.

A finding of LA grade A EE does not always mean the patient has GERD. In this case, however, because we also have an AET of 6.5%, we can conclude that the patient has GERD. The next step would be to optimize his PPI regimen. The current ACG and AGA guidelines recommend doubling the PPI dose, in this case from omeprazole 20 mg once daily to either 20 mg twice daily or 40 mg once daily.[2,3] Although this dose is not FDA approved, a substantial portion of patients are only able to achieve maximal symptom control with the higher dose.[2,3]

It is also important to make sure the patient is taking the PPI before meals; if PPIs are not taken before meals, their effectiveness is significantly reduced. Up to 54% of patients take PPIs incorrectly.[38] Setting appropriate expectations is also very important. The patient should understand that the treatment goal is to reduce symptoms to a tolerable level and optimize QoL, while realizing that complete symptom resolution is rarely achieved if no completely reversible cause for his symptoms is found.

CASE (CONT'D)

8 weeks after Barry started taking omeprazole 20 mg twice daily, he reports a reduction in symptoms of greater than 50%. He has also lost 7 lbs on a weight management program.

It would now be reasonable to attempt tapering Barry's PPI to a lower dose. As he is now taking the omeprazole twice daily, he could be instructed to go back to taking it just once daily for 2 weeks. If his symptoms do not worsen, he could try taking omeprazole 20 mg every other day for 1 to 2 weeks and then stopping it altogether. There is no specific formula for tapering PPIs. If Barry's current dose is the only one that controls his symptoms, it can be resumed. However, it would be preferable for him to be on a lower dose if possible or, ideally, to wean off the medication altogether. Realistically, patients with GERD usually need on-demand acid control from time to time. PPIs fall short in this regard because they do not produce immediate acid suppression. Among the existing FDA-approved options for heartburn, patients can use either an H_2RA or an OTC antacid for on-demand acid suppression.

CASE CONCLUSION

Over the course of the next 4 weeks, Barry is able to successfully reduce his PPI dosage; he now takes an H_2RA as needed to control nighttime symptoms.

CASE 2: PATIENT WITH PERSISTENT GERD SYMPTOMS THAT ARE NOT CONTROLLED BY PPI TREATMENT

Sylvia is a 65-year-old woman who was diagnosed with GERD approximately 1 year ago. She underwent an upper endoscopy at that time but does not remember the results. Her physician prescribed omeprazole 20 mg once daily, which was increased to 20 mg twice daily to improve symptom control. However, Sylvia reports that she is still experiencing little or no reduction in symptoms. She was referred to your office for a GI consultation.

Up to 40% of patients treated with a PPI report persistent symptoms of heartburn and regurgitation, which are accompanied by negative impacts on their QoL.[2] The most pressing question with this patient is whether she does in fact have GERD. If not, she may have hypersensitivity, anxiety, eosinophilic esophagitis (EoE), or another disorder that is causing her symptoms. If she does have GERD, her refractory symptoms could be caused by various pathologies, including a hiatal hernia, a hypotensive lower esophageal sphincter, or poor esophageal motility that prevents her from effectively clearing the reflux from her esophagus back down into her stomach (**TABLE 3**).[2]

Given that the cause of this patient's symptoms is not clear, it would be essential to obtain further information before recommending a treatment course. Her age increases the probability that she is taking medication for other conditions; therefore, it would also be important to consider whether polypharmacy might be at work. Because it is not possible to be certain the patient has GERD, the ACG guidelines recommend that an upper endoscopy be performed when off PPI therapy, as shown in **FIGURE 4**.[2]

CASE (CONT'D)

Endoscopy results show that Sylvia has LA grade C EE and a hiatal hernia greater than 3 cm.

TABLE 3. When Symptoms Suspected to Be Caused by GERD Are Refractory to PPI Therapy, Consider These Disorders[2]

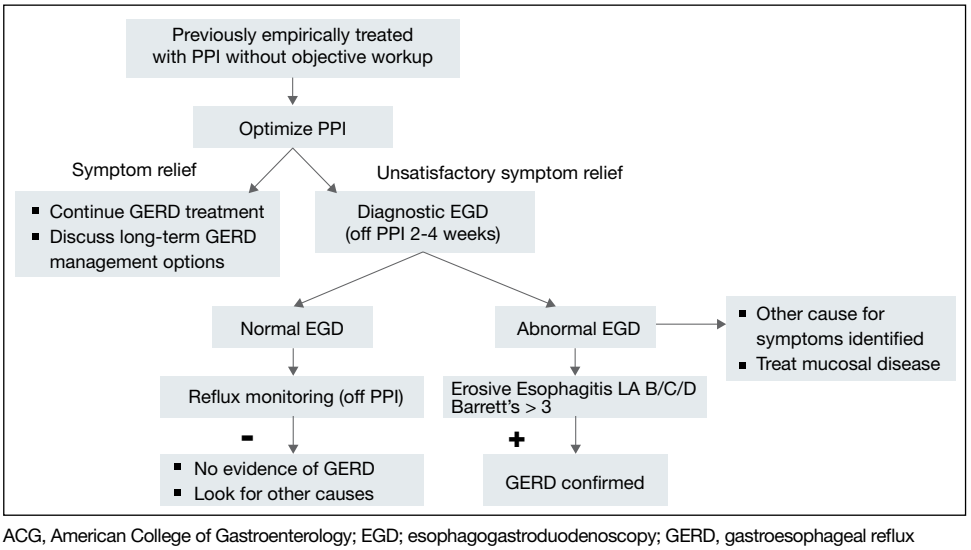
Reflux hypersensitivity, a condition in which PPIs have normalized esophageal acid exposure, but "physiologic" reflux episodes (acidic or nonacidic) nevertheless are strongly associated with and evoke symptoms
Esophageal disorders other than GERD, including EoE and achalasia
Nonesophageal disorders, such as gastroparesis, rumination, and heart disease
Functional GI disorders in which the symptoms are not due to GERD or any other identifiable histopathologic, motility, or structural abnormality

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

When patients with EE have symptoms that are refractory to initial PPI therapy, guidelines recommend optimizing the PPI dosage.[2,3] This patient's daily omeprazole dose has already been increased to 40 mg, so alternative treatment approaches need to be considered at this time.

PPIs are metabolized primarily in the cytochrome P450 pathway by CYP2C19. Studies examining the influence of CYP2C19 polymorphism on response to PPI treatment have identified a CYP2C19 rapid-metabolizer genotype, which increases patients' risk of being refractory to PPIs.[39] When patients do not respond to PPI therapy as expected it may be because they are a CYP2C19 rapid metabolizer. PPIs vary with respect to their dependence on CYP2C19 metabolism. A reasonable course of action for a patient such as Sylvia, who has refractory symptoms on optimization of initial PPI treatment, would be to switch to a PPI that is less dependent on CYP2C19, such as rabeprazole.[2,11] PCABs are not metabolized primarily by CYP2C19; therefore, if approved for use in EE, these agents could be an alternative to PPIs in these situations.[28]

FIGURE 4. ACG Algorithm for Management of Suspected GERD That Is Refractory to PPI Treatment[2]



ACG, American College of Gastroenterology; EGD; esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; LA, Los Angeles; PPI, proton pump inhibitor.

Katz, PO, et al. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. The American Journal of Gastroenterology, 117(1):27-56. doi:10.14309/ajg.0000000000001538. ©2022 American College of Gastroenterology.

CASE (CONT'D)

8 weeks after switching to rabeprazole 20 mg twice daily, Sylvia reports little improvement in her symptoms. A repeat endoscopy shows ongoing EE.

The treatment options for this patient are limited at the moment, and a personalized treatment plan is recommended. Augmentation of the PPI treatment based on the pattern of symptoms can be helpful; adjunctive therapies include nighttime H_2RAs for nocturnal symptoms, alginate antacids for breakthrough symptoms, baclofen for regurgitation or belch-predominant symptoms, and prokinetic agents (such as metoclopramide and erythromycin) for coexistent gastroparesis.[3,40] In patients with more severe EE, studies suggest that vonoprazan is more effective than PPIs.[7] However, as noted in an earlier chapter, the FDA approval of vonoprazan has been delayed while awaiting resolution of concerns regarding nitrosamine impurities in its preparations.[18] If vonoprazan is approved for EE, it could be beneficial in patients with LA grade C or D erosions who do not have an adequate response to PPIs.

This patient's hiatal hernia is likely contributing to her refractory disease. Although hiatal hernias do not always require treatment, surgical repair of the hernia, together with an antireflux procedure such as fundoplication, would likely be recommended in this case. Many patients are reluctant to undergo surgery; however, in the absence of a more effective medication, it may be the best option for this patient. Even though the surgeon will typically discuss relevant surgical approaches with the patient, additional GI testing may be required to help clarify the most appropriate option; for example, manometry would be performed before fundoplication to ensure there is no achalasia.

Regardless of the treatment course, this patient will require follow-up endoscopy to assess whether the erosions have healed and to confirm that she does not have Barrett's esophagus. Esophageal cancer is an aggressive disease and a major cause of death in the United States.[41] Endoscopic monitoring is an important tool for preventing the development of esophageal cancer and late-stage diagnosis.[42]

CASE CONCLUSION

Sylvia was referred to a surgeon and agreed to undergo

laparoscopic fundoplication. Follow-up endoscopy 12 weeks later showed significant improvement in her EE and confirmed the absence of Barrett's esophagus.

SUMMARY

These case examples are meant to demonstrate the importance of optimizing PPI therapy in patients with GERD and EE, obtaining adequate diagnostic information by endoscopy and/or acid exposure testing, and considering nonpharmacologic interventions, particularly weight management and surgery, as appropriate. For patients who do not achieve or maintain an adequate response to PPIs, there is a need for alternative pharmacologic options to PPIs that are not metabolized primarily by CYP2C19, do not have to be timed around meals, and provide more effective control of acid secretion. ●

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