



A guide to GERD, *H pylori* infection, and Barrett esophagus

How long should you treat GERD with a PPI? When should you order an endoscopy or test for *Helicobacter pylori*? How might *H pylori* treatment choices vary with a patient's antibiotic history?

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PRACTICE RECOMMENDATIONS

- ▶ Recommend endoscopy for patients with gastroesophageal reflux disease (GERD) and red flag symptoms: dysphagia, unintentional weight loss, or bleeding. (B)
- ▶ Recommend long-term use of a proton pump inhibitor at the lowest tolerated dose in patients with esophagitis or Barrett esophagus. (C)
- ▶ Test for *Helicobacter pylori* in patients with peptic ulcer disease, in those with past ulcers not investigated for *H pylori*, and in those starting chronic nonsteroidal anti-inflammatory drug therapy. (A)
- ▶ Use a urea breath test, stool antigen study, or endoscopically obtained biopsy to test for *H pylori*. (A)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Three conditions seen in primary care—gastroesophageal reflux disease (GERD), *Helicobacter pylori* (*H pylori*) infection, and Barrett esophagus (BE)—evolve in a gastric acid environment and are treated in part through gastric acid suppression. While GERD is a risk factor for the development of BE, *H pylori* is not associated with BE.¹ Patients with *H pylori* are actually less likely to have GERD symptoms.^{2,3} In this article, we describe similarities and differences in patient presentations, diagnostic testing, and management, and review screening recommendations.

Gastroesophageal reflux disease

GERD is a clinical diagnosis based on symptoms of regurgitation and heartburn or the presence of one of its known complications (esophagitis, peptic strictures, or BE).^{2,4} Chest pain is also common. Atypical symptoms are dysphagia, bleeding, chronic cough, asthma, chronic laryngitis, hoarseness, wheezing, teeth erosions, belching, and bloating.^{2,5-7}

The worldwide prevalence of gastroesophageal reflux symptoms in adults is 14.8%.⁸ When using a stringent definition of GERD—weekly symptoms occurring for at least 3 months—prevalence drops to 9.4%.⁹ GERD symptoms vary markedly by geographic location; the highest rates are in Central America (19.6%) and the lowest rates are in Southeast Asia (7.4%).⁸ TABLE 1^{2,9-11} lists risk factors for GERD.

GERD results from dysfunction of the esophagogastric junction that permits regurgitation of acidic gastric contents into the esophagus. Normally, the lower esophageal sphincter (LES) relaxes temporarily with gastric distention; when this relaxation is frequent and prolonged, it causes GERD.^{2,12} Several medications, particularly those with anticholinergic effects (eg, tricyclic antidepressants) can decrease LES tone and contribute to symptoms. Nonsteroidal anti-inflammatory

TABLE 1

Risk factors for GERD, *H pylori* infection, and Barrett esophagus^{2,9-11}

Condition	Risk factors
GERD	Obesity, smoking, genetic predisposition
<i>H pylori</i> infection	Low socioeconomic status; immigrant to North America; increasing number of siblings or a parent infected with <i>H pylori</i> ; certain ethnicities, including: African American, Hispanic, Native American, Alaskan Native, and Canadian First Nation
BE	Men with chronic or frequent GERD symptoms and ≥ 2 other risk factors: age > 50 years, Caucasian race, central obesity, history of smoking, or family history of BE or esophageal adenocarcinoma

BE, Barrett esophagus; GERD, gastroesophageal reflux disease; *H pylori*, *Helicobacter pylori*.

drugs (NSAIDs) are often linked to dyspepsia and gastritis and should be avoided in patients who have symptoms of GERD. Pathologic reflux can also occur in conditions that increase intra-abdominal pressure, such as obesity and pregnancy, and with esophageal dysmotility, hiatal hernia, and delayed gastric emptying.⁵ When gastric contents travel proximally, this contributes to extraesophageal symptoms, such as chronic cough, asthma, laryngitis, dyspepsia, bloating, and belching.^{2,4}

Treatment

Proton pump inhibitors (PPIs) are the most effective treatment for GERD, but lifestyle modifications are also recommended for all patients.^{2,6,13-16} Consider selective elimination of beverages and foods that are commonly associated with heartburn (eg, alcohol, caffeine, chocolate, citrus, and spicy foods) if patients note a correlation to symptoms.^{5,6,13} Also, advise weight loss and smoking cessation, as appropriate, and suggest that the patient elevate the head of their bed when sleeping.

■ **All PPIs are equally effective** in suppressing acid when given at equivalent doses (TABLE 2¹⁷), so they can be used interchangeably.¹⁷ Treat uncomplicated GERD with a once-daily PPI 30 to 60 minutes prior to a meal for 4 to 8 weeks. If treatment is effective, you'll want to try to reduce or stop the medication after the 4- to 8-week period. (It's worth noting that the benefits of treatment for those with extraesophageal GERD are less predictable than for those with heartburn or esophagitis symptoms.⁵)

If GERD symptoms reemerge after the PPI is stopped, the medication can be restarted but should be limited to the least potent

effective dose, no matter if it is taken daily or only as needed.^{2,6,17} In patients with esophagitis, you may need to continue PPI treatment indefinitely at the lowest possible dose given the increased risk of recurrent esophagitis.^{2,13,16}

Keep in mind that the safety of long-term PPI use has not been fully established. While observational studies have shown that long-term PPI use may be associated with adverse events, including kidney damage, *Clostridioides difficile* infection, osteoporosis, and gastric cancer, subsequent prospective studies have not shown any significant risks with long-term PPI use.^{2,13,14,16,18,19} If a decision is made to discontinue PPIs after long-term use, the patient should be advised that rebound acid hypersecretion may occur, although this possibility can be mitigated by gradually tapering the PPI dose.

■ **Another maintenance therapy option.** Histamine-2 receptor antagonists (H2RAs) are a reasonable alternative to PPIs as maintenance therapy, but they are ineffective in healing esophagitis^{6,13} and may be best used as adjunctive therapy at bedtime for breakthrough symptoms while a patient is on maintenance PPIs.^{6,19} Antacids (eg, calcium carbonate, aluminum hydroxide, or magnesium hydroxide) and alginate may provide some symptomatic relief, as well.

■ **When PPIs don't work.** If initial lifestyle changes and PPI treatment do not provide adequate relief, consider the possibility of nonadherence with medication or lifestyle directives. If nonadherence does not appear to be an issue, twice-daily PPI dosing is also an option. Recognize, though, that PPI treatment failure occurs in as many as 40% of patients and is much more common in those with atypical symptoms.⁶

TABLE 2

Potency of PPIs, based on omeprazole equivalents¹⁷

Medication at lowest available dose, mg	Omeprazole equivalent, mg	Relative potency
Rabeprazole, 20	36	Most potent ↓ Least potent
Esomeprazole, 20	32	
Omeprazole, 20	20	
Lansoprazole, 15	13.5	
Pantoprazole, 20	4.5	

PPIs, proton pump inhibitors.

Adapted from Graham DY, Tansel A. *Clin Gastroenterol Hepatol*. 2018.¹⁷

Consider upper gastrointestinal (GI) endoscopy—and perhaps esophageal manometry or pH testing—if a patient does not respond to empiric treatment with a PPI for 4 to 8 weeks at a standard, once-daily dose.^{2,4,13} (Alternative diagnoses may also need to be considered.) Upper endoscopy is also appropriate for patients who have symptoms concerning for malignancy (progressive dysphagia, unintentional weight loss, or bleeding).

Esophagitis detected on endoscopy confirms GERD, although it is seen in only 18% to 25% of patients with GERD symptoms.^{2,4} (The absence of esophagitis only indicates a lack of mucosal injury and not the absence of GERD.⁴) Acid exposure can cause fibrotic scarring and, in turn, strictures visible on endoscopy.² BE, the precursor to esophageal adenocarcinoma, is also a complication of GERD and is defined by columnar metaplasia replacing the normal squamous cell esophageal epithelium; it is detected on pathology review of biopsies.²

GERD confirmed but PPIs aren't working? Laparoscopic fundoplication is an effective treatment for GERD. However, due to its adverse effects (dysphagia, bloating, flatulence) and risk of treatment failure or breakdown within 5 to 10 years, it should be reserved for those poorly managed with PPIs.^{2,13,19}

Considerations in pregnancy. GERD is reported by 40% to 85% of pregnant women,^{20,21} and its clinical presentation, diagnosis, and treatment are similar to that of nonpregnant adults.²¹ If lifestyle modification is not effective, pharmacologic therapy may be considered. Often, lifestyle modifications and antacids followed by the addition

of sucralfate will be used first given the lack of systemic effects. H2RAs can be used next based on long-term historical use and reported safety.²¹ As with nonpregnant patients, PPIs are more effective than other medical therapies. If PPIs are used, dexlansoprazole, lansoprazole, pantoprazole, and rabeprazole are preferred. Omeprazole and esomeprazole are typically avoided due to findings of embryonic and fetal mortality in early animal studies, although subsequent human studies have noted no teratogenicity.^{2,20,21}

Considerations in children. As with adults, findings in the history and exam are sufficient to diagnose and initiate treatment of GERD in children, provided there are no warning signs (eg, bilious vomiting, GI bleeding, consistent forceful vomiting, fever, lethargy, hepatosplenomegaly, bulging fontanelle, macro- or microcephaly, seizures, abdominal tenderness/distention, or genetic/metabolic syndromes). Lifestyle changes are first-line treatment, followed by medication. Acid suppressants are preferred, with PPIs showing superior efficacy compared with H2RAs.¹⁵ Some PPIs (omeprazole, lansoprazole, and esomeprazole) have US Food and Drug Administration (FDA) approval beginning at age 1 year, while rabeprazole has FDA approval beginning at age 12.²² As in adults, if PPIs are ineffective, consider alternative diagnoses.^{15,22}

Helicobacter pylori infection

H pylori is a gram-negative spiral-shaped bacterium found in the stomach of humans and other mammals. It survives the acidic environment by metabolizing urea into alkaline ammonia and carbon dioxide. *H pylori* infec-

➤ Consider endoscopy for patients with GERD symptoms unresponsive to empiric treatment with a proton pump inhibitor.

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tion increases the risk of peptic ulcer disease, gastric cancer, iron deficiency anemia, and immune thrombocytopenia. It may be associated with dyspepsia, increased ulcer risk with use of an NSAID, and chronic gastritis.⁹ Infection with *H pylori* can decrease the risk of GERD.² The bacterial infection causes atrophic gastritis and subsequent hypochlorhydria, which then diminishes the acidity of the reflux contents.¹⁹ There is no link between *H pylori* infection and BE.¹

TABLE 1^{2,9-11} shows those at highest risk of *H pylori*. The estimated prevalence of infection is 40% to 48%²³ worldwide but lower in North America, at 32% to 42%.²⁴ *H pylori* is often acquired in childhood, and risk of infection is more likely if the parents (particularly mothers) are infected.⁹

Whom to test, and how

Test for *H pylori* in those with active peptic ulcer disease or a history of peptic ulcer disease that was not investigated for *H pylori*. Also test individuals who have gastric mucosa-associated lymphoid tissue lymphoma, have a history of gastric cancer or family history of gastric cancer, are scheduled for endoscopic evaluation for dyspepsia, or are starting chronic NSAID therapy. Patients with typical GERD symptoms do not need to be tested for *H pylori*.^{9,25}

■ **Means of testing** for *H pylori* include the urea breath test, stool antigen studies, endoscopically obtained biopsies, or serum antibody tests. Antibody testing is discouraged because it has a lower diagnostic utility and cannot determine if the patient's infection is current or past. Before undergoing urea breath tests, stool antigen tests, or biopsies for *H pylori* identification, patients should have abstained from taking the following agents for the time periods indicated: PPIs, 1 to 2 weeks; H2RAs, at least 1 day and preferably 2 weeks; and antibiotics, 4 weeks.⁹

The urea breath test and endoscopically obtained biopsies have the greatest diagnostic utility and, where available, should be the first-line tests. Stool antigen studies are useful for ruling out *H pylori* infection (very low negative likelihood ratio), but a positive test result is not as useful for confirming an infection, as false-positives do occur (moderate

positive likelihood ratio).^{9,26,27} Stool antigen testing is less expensive and, in many cases, more convenient and readily available for patients than urea breath testing and endoscopic biopsies.

Treatment

Offer treatment to all patients who test positive for *H pylori*. Eradication rates range from 70% to 91% using first-line treatment options.⁹ Treatment regimens consist of acid suppression and 2 to 3 antibiotics in combination (TABLE 3^{9,28}). The single greatest predictive factor for treatment failure is antibiotic resistance, so a detailed antibiotic history is essential. In particular, ask about macrolide antibiotic usage and penicillin allergies.

People living in areas with population macrolide resistance $\geq 15\%$ should avoid clarithromycin-based regimens unless bacterial sensitivity testing has been done and shows sensitivity to these agents.^{9,28,29} For cases that do not resolve with a first-line treatment program, choose an alternative regimen with different antibiotics.^{9,29}

Additionally, adequate acid suppression is directly related to successful eradication. Thus, the likelihood of treatment success can be improved by using higher doses of PPIs and avoiding ones that are more likely to be metabolized quickly in some patients (lansoprazole, omeprazole). Patient adherence to the treatment regimen is an important determinant of effectiveness.^{9,29} Adding vitamin C 400 to 1000 mg/d, vitamin E 100 to 400 mg/d, and probiotics may improve the effectiveness of treatment.^{9,30}

Duration of treatment is directly related to treatment effectiveness. Whenever possible, opt for 14 days of treatment instead of just 7.⁹

■ **Test of cure.** Patients treated for *H pylori* should be re-tested no sooner than 4 weeks after completion of therapy. Urea breath testing, stool antigen testing, and endoscopic biopsies (if endoscopy is indicated for some other reason) can all be used post treatment for test of cure.⁹

Barrett esophagus

Chronic reflux can lead to BE, in which metaplastic columnar epithelium replaces the

TABLE 3

Recommended treatment for *Helicobacter pylori* infection^{9,28}

Macrolide exposure	PCN allergy	Recommended treatment options
No	No	<p><i>First-line:</i></p> <ul style="list-style-type: none"> • Bismuth quadruple^a for 14 d <p>or</p> <ul style="list-style-type: none"> • Rifabutin triple^b for 14 d <p><i>Second-line:</i></p> <ul style="list-style-type: none"> • Clarithromycin triple^c with amoxicillin for 14 d <p>or</p> <ul style="list-style-type: none"> • Concomitant therapy^c for 14 d
No	Yes	<p><i>First-line:</i></p> <ul style="list-style-type: none"> • Bismuth quadruple for 14 d <p><i>Second-line:</i></p> <ul style="list-style-type: none"> • Clarithromycin triple with metronidazole for 14 d
Yes	No	<p><i>First-line:</i></p> <ul style="list-style-type: none"> • Bismuth quadruple for 14 d <p>or</p> <ul style="list-style-type: none"> • Rifabutin triple for 14 d <p><i>Second-line:</i></p> <ul style="list-style-type: none"> • Levofloxacin triple^d for 14 d <p>or</p> <ul style="list-style-type: none"> • Levofloxacin sequential^e for 14 d
Yes	Yes	<ul style="list-style-type: none"> • Bismuth quadruple for 14 d

PCN, penicillin.

^a **Bismuth quadruple:** Proton pump inhibitor (PPI) bid standard dose; bismuth subcitrate 120-300 mg or subsalicylate 300 mg qid; tetracycline 500 mg qid; metronidazole 250 mg qid or 500 mg tid or qid. *Note: The combination of bismuth subcitrate, metronidazole, and tetracycline is available in a pill (Pylera), but it comes in only a 10-day supply, which is inadequate for full treatment.*

^b **Rifabutin triple:** High-dose PPI tid; amoxicillin 1 g tid; rifabutin 50 mg tid. *Note: Combination is available in a pill (Talcia).*

^c **Clarithromycin triple with amoxicillin or metronidazole:** PPI standard or double dose bid; clarithromycin 500 mg bid; and metronidazole 500 mg tid or amoxicillin 1 g bid. Concomitant: PPI standard dose bid; clarithromycin 500 mg bid; amoxicillin 1 g bid; and metronidazole 500 mg bid.

^d **Levofloxacin triple:** PPI standard dose bid; levofloxacin 500 mg/d; amoxicillin 1 g bid.

^e **Levofloxacin sequential:** *First 7 days,* PPI standard or double dose bid; amoxicillin 1 g bid. *Second 7 days,* PPI standard or double dose bid; amoxicillin 1 g bid; levofloxacin 500 mg/d; metronidazole 500 mg bid.

normal squamous epithelium lining the distal esophagus. BE is linked to dysplasia and esophageal adenocarcinoma (EAC).¹¹ Endoscopic examination with biopsy is used to diagnosis BE. The global prevalence of histology-confirmed BE in people with GERD symptoms is 7.2%.¹⁰ Similar to GERD and *H pylori* infections, the prevalence of BE var-

ies significantly with geographic location (14% in North America; 3% in the Middle East).¹⁰ BE is twice as likely to occur in men as in women, and it is rare in children.¹⁰

Whom to screen

The American College of Gastroenterology recommends consideration of screening with

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Not everyone with Barrett esophagus (BE) experiences GERD symptoms; sometimes BE may be diagnosed incidentally on upper endoscopy performed for unrelated symptoms.

upper endoscopy for men with chronic GERD (> 5 years) or frequent GERD symptoms (once weekly or more often), plus 2 or more of the following risk factors: age > 50 years, Caucasian race, central obesity, smoking (current or past), or a family history of BE or EAC (TABLE 1^{2,9-11}). Screening for BE in women is not routinely recommended but can be considered in individuals with several of the risk factors just described.

Not everyone with BE experiences GERD symptoms; sometimes BE may be diagnosed incidentally on upper endoscopy performed for unrelated symptoms.¹¹ GERD patients who are currently asymptomatic and had a normal prior upper endoscopy do not require surveillance.

Diagnosis and management

BE is diagnosed based on specific endoscopic and histologic findings. The presence of dysplasia (either low grade or high grade) or its absence has important treatment implications. When histology is indefinite for dysplasia, treat reflux and, following acid suppression with PPIs for 3 to 6 months, repeat endoscopy (since reactive changes with reflux may obscure results).¹¹

Nondysplastic BE has a risk of progressing to cancer in only 0.2% to 0.5% of affected patients per year.¹¹ Guidelines for BE without dysplasia advise repeating surveillance endoscopy every 3 to 5 years after appropriate counseling regarding overall low risk of cancer progression.^{11,31} Surveillance endoscopy recommendations exist despite the lack of prospective randomized trials that demonstrate benefit. The rationale for surveillance is that survival in EAC is stage dependent and often EAC metastasizes prior to the development of symptoms from the tumor. Observational cohort studies in BE have demonstrated that surveillance endoscopy programs find EAC at earlier stages with improved survival; however, lead and length time bias may attenuate or eliminate these surveillance benefits.^{11,32}

Risk for neoplastic progression increases with degree of dysplasia. BE with low-grade dysplasia and high-grade dysplasia have a risk of cancer progression of 0.7% per year and 7% per year, respectively.¹¹

■ **Historically, esophagectomy** was the preferred treatment for BE with dysplasia. Now, endoscopic eradication therapies, including radiofrequency ablation and endoscopic mucosal resection for nodular BE, are the usual treatment for either low- or high-grade dysplasia.¹¹

■ **Chemoprophylaxis with PPIs.** Most patients with BE have symptoms of GERD or reflux esophagitis, so treatment with a PPI is indicated for symptom control. In patients with BE without GERD, PPI use may still be indicated, although this is controversial. Current guidelines recommend once-daily PPI therapy for BE (twice daily only if needed for symptom control) to reduce reflux-associated inflammation and recommend against routine prescription of aspirin or NSAIDs for BE.¹¹ In vitro and observational studies support PPI use to prevent progression to EAC^{11,33}; however, data from randomized controlled trials to support their use are limited.^{34,35}

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