

Acid suppression therapy: taking the heartburn out of the evidence



Balanced data about medications

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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

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Introduction

Symptoms related to gastrointestinal acid production are among the most common in medicine. Approximately 25% of adults regularly experience heartburn.¹ Such symptoms are usually just an occasional nuisance, but for some people they may be debilitating, or a sign of a more serious problem.

Histamine-2 receptor antagonists (H₂ blockers) revolutionized the care of acid-related disease when they were first introduced in the 1970s, and are now available over-the-counter and in generic forms. Proton pump inhibitors (PPIs) are currently among the most widely used and heavily advertised medications in the world. More than 113 million prescriptions for PPIs are filled each year, making this class of drugs, at \$14 billion in sales, the third highest seller in the United States.² These medications are effective for the treatment of gastroesophageal reflux disease (GERD), prevention of ulcers induced by non-steroidal anti-inflammatory drugs (NSAIDs), the healing of peptic ulcers, and as part of a regimen for *Helicobacter pylori* eradication, erosive esophagitis, Barrett's esophagus, and Zollinger-Ellison syndrome. However, these indications do not account for the number of prescriptions written, and 50% - 70% of PPI prescriptions may be for inappropriate indications.²

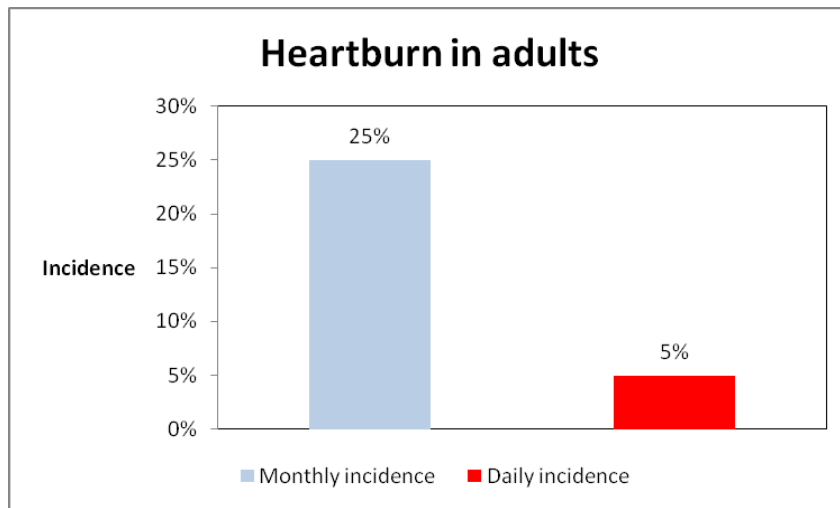
Over the past several years, some PPIs have become available over-the-counter, which has led to even wider advertising of PPIs. Clinicians now face difficult challenges when considering acid suppression options for their patients including deciding when to prescribe acid-suppressive medications, whether to choose a PPI or another agent, and how long to continue therapy. Considerations of patient costs, medication adherence, and uncertainty about what patients may be purchasing over-the-counter compound the complexity of these prescribing decisions, as do recent studies suggesting previously unrecognized risks associated with PPI treatment.²⁻⁵

This document presents an evidence-based approach for the evaluation and management of several common gastrointestinal complaints, including GERD, NSAID-induced dyspepsia, peptic ulcer disease (including NSAID-induced ulcers), and non-ulcer dyspepsia.

Common causes of dyspepsia

The term dyspepsia includes a constellation of symptoms such as upper abdominal discomfort, heartburn, retrosternal pain, nausea, early satiety (sensation of fullness), acid regurgitation, and excessive belching.⁶ It is very common.¹

Figure 1. Incidence of heartburn



The three major causes of dyspepsia are GERD, peptic ulcer disease, and non-ulcer dyspepsia. The prevalence of the 3 conditions are 14-20%, 0.5-5%, and 2% respectively, although the figures are only approximations as GERD has a somewhat nebulous definition and non-ulcer dyspepsia is a diagnosis of exclusion.^{7, 8} Symptoms mistaken for dyspepsia may also result from other conditions such as coronary artery disease, pericarditis, aortic dissection, pulmonary embolism, gallstones, and pancreatitis.

Gastroesophageal reflux disease

Definition

The American Gastroenterological Association defines GERD as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.”⁹ GERD may involve esophageal injury (esophagitis).⁹

Pathogenesis

The primary underlying mechanism is thought to be impaired lower esophageal sphincter (LES) function. The LES normally relaxes in response to esophageal peristalsis to allow the passage of food, liquid or saliva into the stomach. There are brief periods where the LES relaxes when there is no swallowing or esophageal peristalsis, known as transient LES relaxations (TLESRs). These are normal, and expose the esophagus to a small amount of acid after meals. Patients with GERD have an increased frequency of TLESRs, exposing the esophagus to acid for longer periods. This increases the risk of symptoms and esophageal damage. A minority of patients have a permanent defect in the LES leading to a constant decrease in resting tone. These patients usually have severe esophagitis and/or complications such as esophageal stricture ^{10, 11}

Epidemiology and risk factors

Gastroesophageal reflux disease is the most common gastrointestinal diagnosis recorded in outpatient clinics.⁷ Risk factors for GERD include:

- smoking
- alcohol use
- obesity
- hiatal hernia
- pregnancy
- asthma
- diabetes
- reduced gastric motility
- rarer conditions including scleroderma and Zollinger-Ellison syndrome

Peptic ulcer disease

Definition

In peptic ulcer disease, there is a break in the mucosal lining of the stomach and/or proximal duodenum. Less commonly, ulcers can also occur in the lower esophagus, the distal duodenum, or the jejunum in gastric acid hypersecretory states such as Zollinger-Ellison syndrome.¹² Ulcers smaller than 5mm or without obvious depth are known as erosions.

Pathophysiology

Peptic ulcers result from an imbalance between factors that damage the gastroduodenal mucosal lining and defense mechanisms that limit the injury. Normal mucosal defense involves a mucus bicarbonate layer which forms a viscous gel over the gastric mucosa.

H. pylori infection in the gastric antrum stimulates the release of gastrin, which stimulates excess acid secretion from the proximal acid-secreting mucosa in the fundus. The increased acid load damages the duodenal mucosa, causing ulceration and gastric metaplasia. The metaplastic mucosa can then become colonized by *H. pylori*.⁸ Chronic *H. pylori* infection and inflammation throughout the stomach causes degradation of the mucus layer and death of gastric epithelial cells.⁸

NSAIDs cause gastric ulcers by direct topical injury, and indirectly by inhibiting the synthesis of prostaglandins needed for maintaining the integrity of the gastric mucosa. NSAIDs also increase bleeding risk through their antiplatelet activity.

In Zollinger-Ellison syndrome, a gastrin-secreting neuroendocrine tumor stimulates high levels of gastric acid secretion and subsequent peptic ulcer disease.

Epidemiology

Lifetime prevalence of peptic ulcer in the U.S. is about 10%, and about 500,000 persons develop peptic ulcer disease in the U.S. each year.^{12, 13} In about 70% of patients it occurs between the ages of 25 and 64 years. The annual direct and indirect health care costs of the disease are estimated at about \$10 billion. However, the incidence of peptic ulcers is declining, possibly as a result of the increasing use of PPIs and decreasing rates of *H. pylori* infection.¹²

Risk factors

H. pylori infection and the use of aspirin and other NSAIDs are the major causes of peptic ulcer disease in the United States.^{8, 12} Critical illness, surgery, or hypovolemia leading to splanchnic hypoperfusion may result in gastroduodenal erosions or ulcers (stress ulcers); these may be silent or manifest with bleeding or perforation. Other risk factors for peptic ulcer disease include older age, low socio-economic status, smoking, a family history of ulcers, and excessive alcohol intake.⁸ Smoking also increases the risk of ulcer recurrence and slows healing.¹²

Approximately 70% of gastric ulcers are due to *H. pylori* infection, and 30% due to NSAIDs. About 90% of duodenal ulcers are due to *H. pylori* infection.¹⁴ Non-NSAID, non-*H. pylori* peptic ulcers can also occur, and usually heal with PPI therapy. NSAIDs and *H. pylori* independently increase the risk of peptic ulcer bleeding (see table below).¹⁵

Table 1. Risk factors for ulcer bleeding

Risk factor	Increase in risk of ulcer bleeding
NSAIDs	2 times
<i>H. pylori</i>	5 times
NSAIDs and <i>H. pylori</i>	6 times (compared with patients who have neither risk factor)

Non-ulcer dyspepsia

Non-ulcer dyspepsia is a term given to persistent dyspepsia when other diagnoses have been excluded and no other specific cause can be identified. After GERD, non-ulcer dyspepsia is the second-most common cause of upper GI symptoms and is the most frequent diagnosis reached after endoscopy. The cause of non-ulcer dyspepsia is not known, but is likely to be multifactorial.¹⁶

Other causes

Dyspepsia is a common adverse effect of many medications, including aspirin, NSAIDs, COX-2 inhibitors, diuretics, antibiotics, antihypertensives, corticosteroids, and bisphosphonates. NSAIDs and COX-2 inhibitors can cause dyspepsia without peptic ulceration, but the mechanism by which these agents cause dyspepsia is not well defined.¹⁷

Assessment of patient presenting with dyspepsia

An organized approach to the assessment and management of patients presenting with dyspepsia can make it easier to choose appropriate medical therapy, to understand when to stop therapy, and to communicate effectively with patients about these management decisions. The first steps are to:

1. **Characterize the dyspepsia.** Location of discomfort/pain, onset, timing, radiation, aggravating factors, alleviating factors, associated symptoms, duration, and intensity.
2. **Look for precipitating medications.** Identify whether the patient is taking medications that may cause or exacerbate dyspepsia, in particular aspirin, other NSAIDs, anticholinergic agents, theophylline, dopaminergic agents, oral bisphosphonates, corticosteroids, and calcium channel blockers.¹⁸
3. **Exclude serious non-GI causes of symptoms that may present as dyspepsia** such as coronary artery disease, pericarditis, aortic dissection, and pulmonary embolism. Discomfort/pain that worsens with exertion or deep inspiration, or that radiates to the shoulders or arms, may reflect a cardiac or vascular cause.
4. **Assess presence of alarm symptoms/signs** suggesting cancer, stricture or severe ulceration:

<ul style="list-style-type: none">• Dysphagia• hematemesis• gastrointestinal bleeding• change in bowel habit• anemia• odynophagia• previous GI malignancy or ulcer	<ul style="list-style-type: none">• recurrent vomiting• anorexia• unexplained weight loss• early satiety• abdominal mass• hepatomegaly• lymphadenopathy
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Alarm symptoms are relatively uncommon and occur in only a minority of patients. If any of these alarm symptoms are present, refer for prompt upper endoscopy and possible biopsy. Additional diagnostic testing beyond esophagogastroduodenoscopy (EGD) such as endoscopic ultrasonography or 24-hour esophageal pH testing has a low yield in the initial assessment of dyspepsia in primary care.¹⁹

5. **Consider testing for *H. pylori*** in patients ≤ 55 years without alarm symptoms see page 20).

Patients with predominant or frequent (more than once a week) heartburn or acid regurgitation should be considered to have GERD until proven otherwise.^{19, 20} Peptic ulcer disease may present with gnawing or burning, non-radiating, epigastric pain that is relieved by antacids, food, or milk. However, symptoms from different upper

gastrointestinal problems have significant overlap, making it difficult to clinically distinguish between conditions in the patient first presenting with dyspepsia.^{19 21}

Diagnosis of GERD

GERD can present with a wide variety of clinical symptoms,¹¹ but its cardinal symptoms are heartburn (a burning feeling in the epigastrium or central chest rising toward the neck) or acid regurgitation (a sour or bitter taste in the mouth).^{19, 20}

Most patients with GERD will not require endoscopy, but for the subset of patients with GERD who also have alarm symptoms, the American Gastroenterological Association 2008 guidelines for the management of GERD recommend endoscopy with biopsy.⁹ GERD may involve esophagitis in a minority of people and it is important to identify these patients, since a diagnosis of esophagitis has long-term treatment implications.

Diagnosis of peptic ulcer disease

The most specific symptoms that help rule in a diagnosis of peptic ulcer are:¹²

- episodic gnawing or burning epigastric pain
- pain occurring two to five hours after meals or on an empty stomach
- nighttime awakening because of abdominal pain, with relief on eating
- pain relieved by food intake, antacids, or antisecretory agents

Less common symptoms include indigestion, vomiting, loss of appetite, intolerance of fatty foods, and heartburn. The physical examination is usually unremarkable. Abdominal pain is absent in $\geq 30\%$ of older patients with peptic ulcers. Postprandial epigastric pain is more likely to be relieved by food or antacids in patients with duodenal ulcers than in those with gastric ulcers. Weight loss precipitated by avoidance of food intake is characteristic of gastric ulcers.¹²

Prompt endoscopy is recommended for patients with symptoms highly suspicious for peptic ulcers who have alarm symptoms or symptoms that do not respond to treatment. Some gastroenterologists also recommend endoscopy in all patients > age 55 with suspected ulcer symptoms, regardless of alarm symptoms. Endoscopy is the gold standard for diagnosis.¹²

Diagnosis of non-ulcer dyspepsia

Non-ulcer dyspepsia is a common diagnosis of exclusion, assigned to patients with persistent dyspepsia who have no evidence of structural disease (including at endoscopy) that is likely to explain their symptoms.

Bottom line: Exclude non-GI causes of dyspepsia, consider if symptoms may be drug-induced (especially NSAIDs), assess for alarm symptoms, and consider testing for *H. pylori* or referral for endoscopy.

Management of GERD

Lifestyle interventions

Lifestyle modification can be very effective, are the foundation of GERD treatment, and may help avoid or reduce the need for medications. Lifestyle interventions include:^{7, 9, 22}

- **avoiding foods that worsen reflux, especially those that lower the tone of the lower esophageal sphincter or precipitate symptoms in a give patient** (e.g., coffee, tea, other caffeinated drinks, chocolate, fatty or fried foods)
- **avoiding acidic foods** that may precipitate heartburn (e.g., citrus, carbonated drinks, onions, tomatoes, spicy foods)
- **encouraging lifestyle modification** including:
 - weight loss for patients who are overweight (BMI 25.0–29.9) or obese (BMI ≥ 30.0),
 - smoking cessation,
 - discourage lying down for 2–3 hours after meals,
 - avoid excessive alcohol;
 - discourage use of clothing that constricts the waist;
 - encourage smaller and more frequent meals.
- **elevating the head of the bed** for patients troubled with heartburn or regurgitation when lying down.

Medications

Antacids

Aluminium hydroxide, calcium carbonate and magnesium salts are inexpensive and provide quick relief. They may be used alone or in combination with other acid-suppressive drugs. Despite their time-honored place in therapy, evidence of efficacy from controlled clinical trials is lacking, perhaps because they are generally available over-the-counter, and came into widespread use before a time when randomized trials were required for marketing.

Acid-suppressive medications

Acid suppression therapy should be initiated for GERD if lifestyle interventions fail to adequately control symptoms. It is recommended for patients with GERD with or without esophagitis. A short course or as-needed use of acid suppression therapy is appropriate in patients with GERD without esophagitis when symptom control is the primary objective.⁹ PPIs (or H₂-receptor antagonists) in higher than standard doses (see table below) are not recommended in GERD without esophagitis, although twice-daily dosing of PPIs may improve symptom relief in patients with an inadequate response to once-daily dosing.⁹ Because PPIs require an acidic environment to act, using them concurrently with a H₂-receptor antagonist can paradoxically decrease symptom control. There is no evidence of improved symptom relief with adding a night-time H₂-receptor antagonists to twice-daily PPI therapy.^{9, 23}

Table 2. Standard doses of PPIs and H₂-receptor antagonists

PPI	H ₂ -receptor antagonist
esomeprazole 20 mg once daily	cimetidine 800mg once daily
lansoprazole 30mg once daily	famotidine 40mg once daily
omeprazole 20mg once daily	nizatidine 300mg once daily
pantoprazole 40 mg once daily	ranitidine 300mg once daily
rabeprazole 20 mg once daily	

An important limitation of PPI therapy is that these agents take longer to provide symptom relief than H₂-receptor antagonists or antacids; **over 24 hours are required for PPIs to fully suppress acid production, while antacids relieve symptoms within minutes and H₂-receptor antagonists relieve symptoms within an hour.** In one study of GERD patients randomized to PPI therapy, the median time to first symptom relief was 2 days and the median time to sustained symptom relief was > 10 days.²⁴ Therefore, antacids and H₂-receptor antagonists generally provide quicker symptom relief than PPIs (see also comparative effectiveness of PPIs on page 26).

Although PPI's take longer to begin working, once they do so they are likely to be more effective than other acid suppressive drugs. A recent comprehensive Cochrane review examined the effect of short-term treatment with medications for heartburn symptoms. It found that in the empirical treatment of GERD, the risk reductions for heartburn remission were as follows:¹

Table 3. Heartburn remission in GERD

Drug therapy	Relative risk reduction compared to placebo
PPIs	63%
H ₂ -receptor antagonists	23%
Prokinetic agents	Not significant

In a direct comparison, PPIs were 34% more effective than H₂-receptor antagonists (relative risk, 0.66; 95% CI, 0.60 to 0.73) and 47% more effective than prokinetic agents (relative risk 0.53; 95% CI 0.32 to 0.87).¹

Medication therapy for patients with esophagitis

PPIs are also more effective than H₂-receptor antagonists for healing esophagitis. A Cochrane review found that the healing rate of esophagitis after 4-8 weeks of treatment with standard dose PPI was 84% compared to 19% with placebo.¹⁰ The number needed to treat was 1.7 (95% CI, 1.5 to 2.1), a very small number for benefit. Higher doses of PPIs were more effective than standard doses in healing esophagitis.

Patients with esophagitis have high rates of recurrence of erosive disease if they do not continue acid suppression therapy.⁹ Several clinical trials have shown that:⁹

- recurrence of erosive esophagitis is dramatically reduced with daily PPI treatment compared to placebo;
- patients taking H₂-receptor antagonists are almost twice as likely to have recurrent erosive disease compared with patients taking PPIs; and
- patients with erosive esophagitis who are healed with PPI therapy have higher recurrence rates of erosive disease if they are continued with on-demand compared with continuous therapy.

Before committing patient to long-term PPI treatment, a diagnosis of esophagitis should be confirmed by endoscopy.⁹ Once confirmed, long-term PPI therapy should be used for such patients.⁹ Long-term daily therapy should be titrated down to the lowest effective dose based on symptom control.⁹ Less than daily dosing of PPI maintenance therapy in patients with GERD who have previously had erosive esophagitis is not recommended.⁹

For further data on the efficacy of acid-suppressive medications see Appendix 1.

Maintenance therapy

Many patients who do not have erosive esophagitis or other indications for long-term PPI therapy (e.g. Zollinger-Ellison syndrome) can tolerate lowering the dose or discontinuing PPI therapy after a sufficient course.^{9, 25} Patients on long-term PPI treatment produce very high levels of gastrin in response to the lower acidity of the stomach, and when PPIs are removed the level of gastric acid secretion can be very high. Because of this, some patients will develop significant symptoms of "rebound" acid hypersecretion. However, even when symptoms occur, their duration is generally brief.²⁶ For many patients, a tapering regimen including the use of H₂-receptor antagonists and antacids can control rebound symptoms and provide the best chance of successfully stopping PPIs. A suggested tapering regimen is provided in the figure below (and as a tear-off pad for patients).

Figure 2. Tapering down PPIs

<p style="text-align: center;">Three steps to reduce dependence on your acid-lowering drug ("PPI")</p> <p style="text-align: center;">Aciphex(rabeprazole); Nexium(esomeprazole); Prevacid(lansoprazole); Prilosec (omeprazole); Protonix (pantoprazole);</p>
<p>1. For the first 2 weeks: _____ to _____ Reduce your dose by half.</p> <p><input type="checkbox"/> If you were taking one pill a day, take one pill every other day.</p> <p><input type="checkbox"/> If you were taking two pills a day:</p> <ul style="list-style-type: none">• take one pill a day for a week,• then take one pill every other day for the following week
<p>2. For the next 2 weeks: _____ to _____ Stop the PPI.</p> <p>If you still have abdominal symptoms:</p> <p><input type="checkbox"/> For immediate relief, take an antacid such as Maalox, Mylanta, or Tums.</p> <p><input type="checkbox"/> You can also take a H₂-receptor antagonist such as ranitidine (Zantac), famotidine (Pepcid), or cimetidine (Tagamet). These are available OTC and as \$4 generics (the \$4 generics are usually cheaper than OTC).</p>
<p>3. Over the next 2 weeks: _____ to _____</p> <p>Slowly decrease the dose of H₂-receptor antagonist or antacid to the lowest amounts needed to control your symptoms.</p> <p><input type="checkbox"/> Contact your doctor if symptoms persist.</p>

Role of *H. pylori* eradication

Routine testing for *H. pylori* is not recommended in GERD, but testing may be considered in patients receiving long-term maintenance treatment with PPIs (because long-term acid suppression may cause atrophic gastritis, and *H. pylori* eradication slows its progression).¹⁵ This approach is controversial and is recommended by European but not American guidelines.^{9, 15}

Despite previous thought to the contrary, eradication of *H. pylori* infection does not cause or exacerbate GERD, improve symptoms, or affect the outcome of PPI therapy.^{15, 27, 28} Therefore, although routine testing is not suggested, treatment of *H. pylori* infection should not be withheld in patients with GERD.²⁸

See page 20 for further details on tests used to detect *H. pylori* and recommended eradication regimens.

Follow-up

The American Gastroenterological Association 2008 guidelines for the follow up of patient after initial treatment of GERD recommend:⁹

- Assess and reinforce lifestyle modification (see above). Endoscopy to evaluate patients who have not responded to an empirical trial of twice-daily PPI therapy.
- Manometry to evaluate patients who have not responded to an empirical trial of twice-daily PPI therapy and have normal findings on endoscopy.
- Ambulatory impedance-pH, catheter pH, or wireless pH monitoring (PPI therapy withheld for 7 days) to evaluate patients who have not responded to an empirical trial of PPI therapy, have normal findings on endoscopy, and have no major abnormality on manometry.

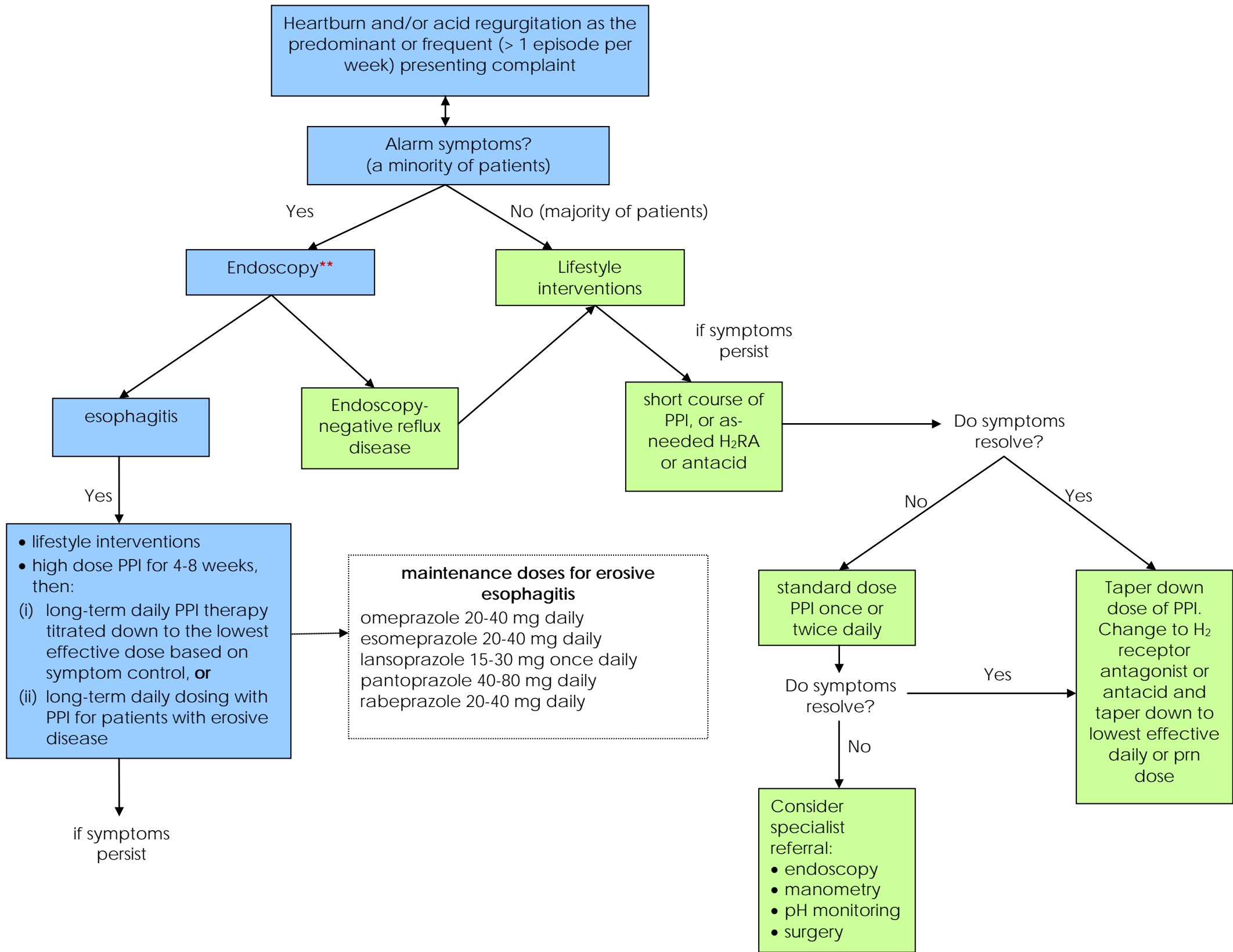
There is insufficient evidence to recommend for or against combined impedance-pH, catheter pH, or wireless pH esophageal monitoring studies performed while taking PPIs. Routine endoscopy to assess disease progression is not recommended.⁹

Bottom line: If lifestyle measures inadequately control symptoms in patients without esophagitis, use either (i) a short course of a PPI, or (ii) as needed antacid and/or H₂-receptor antagonist. Patients with proven esophagitis should be treated with long-term daily PPI therapy titrated down to the lowest effective dose based on symptom control. Patients with erosive esophagitis should receive long-term daily PPI maintenance therapy (see algorithm below).

Management algorithm

A management algorithm for GERD is provided in the next figure.

Figure 3. Algorithm for the management of GERD^{9, 19, 20}



** patients with an abnormal endoscopy should be managed according to findings.

all patients who test positive for *H. pylori* should be offered eradication therapy.

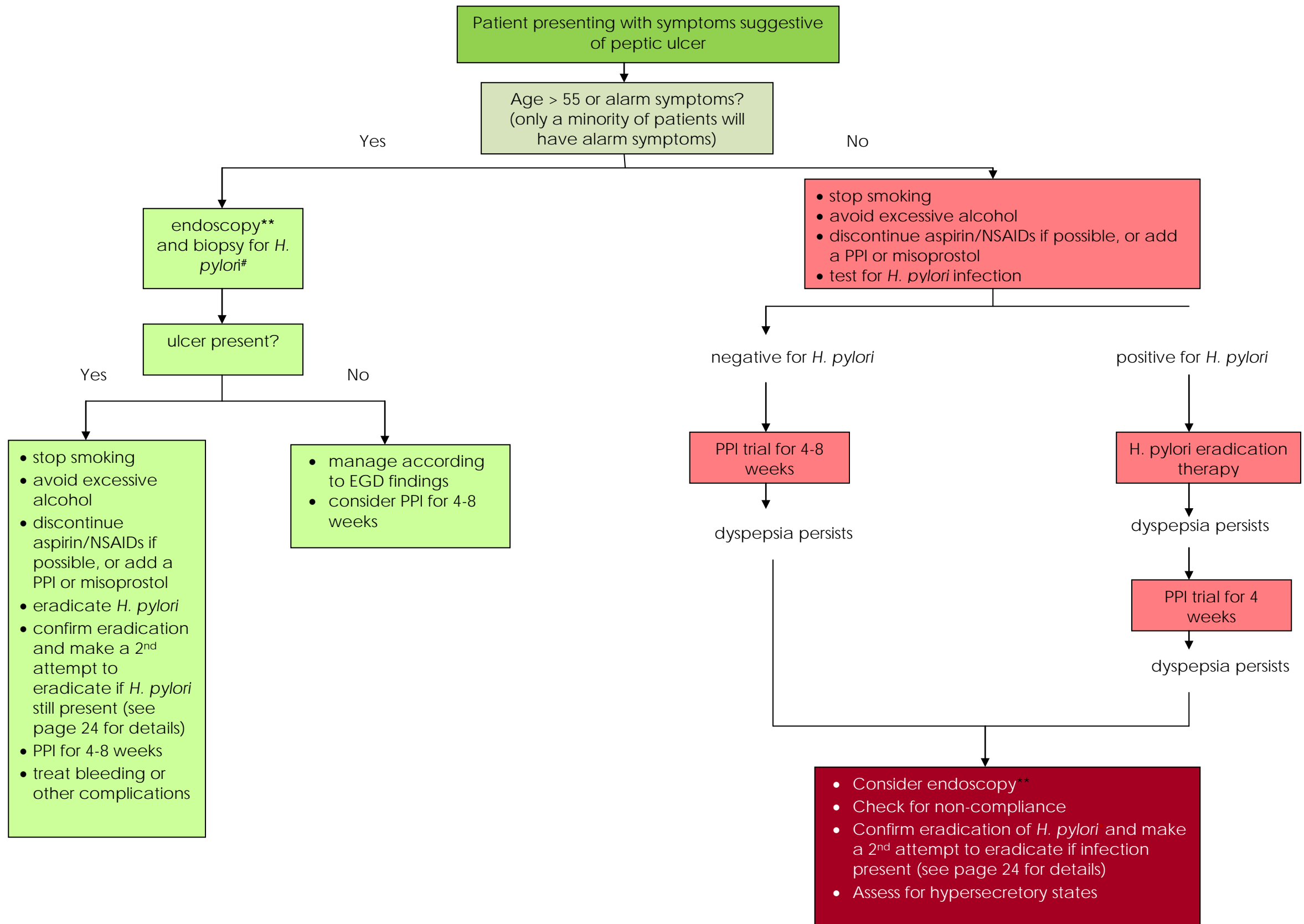
Management of peptic ulcer disease

Key recommendations for the treatment of peptic ulcers are as follows:¹²

- Patients should be advised to stop smoking and avoid excessive alcohol.
- Discontinue aspirin and NSAIDs if possible; if these agents need to be continued, consider adding a PPI or misoprostol.
- If *H. pylori* is present, eradicate it to assist in healing and reduce the risk of ulcer recurrence.
- PPIs provide healing rates and symptom relief superior to other acid suppression therapies.

An algorithm for the management of peptic ulcers in primary care is provided in the figure below.

Figure 4. Algorithm for treatment of peptic ulcer disease



**patients with an abnormal endoscopy should be managed according to findings.

#all patients who test positive for *H. pylori* should be offered eradication therapy.

Bleeding ulcer

Upper GI bleeding occurs in 15-20% of patients with peptic ulcer disease. In older persons, 20% of bleeding episodes result from asymptomatic ulcers. Patients may present with hematemesis (bright red or “coffee ground”), melena, anemia, orthostasis, or syncope.¹²

In stable patients with GI bleeding, ulcer-causing medications should be discontinued and a PPI initiated.¹² For patients hospitalized with a bleeding ulcer, intravenous PPIs can reduce transfusion requirements, need for surgery, and duration of hospitalization.¹² EGD should be performed as soon as possible. Start oral PPIs as soon the patient can resume oral intake.¹²

A meta-analysis of 1157 patients from 7 clinical trials examined the effectiveness of high-dose PPIs vs. standard/low-dose PPIs in patients with bleeding peptic ulcer, to assess the effect on re-bleeding, surgical intervention, and mortality. High-dose PPIs and standard/low-dose PPIs did not significantly differ in their effects on these outcomes.²⁹

H. pylori testing should be performed and eradication therapy prescribed if infection is present. Treatment of *H. pylori* infection is more effective than acid suppression therapy without eradication for preventing recurrent bleeding.³⁰ Surgery may be required in continued or recurrent bleeding.

If continued administration of aspirin or NSAIDs is required, add concurrent misoprostol or proton pump inhibitor.¹²

Role of acid suppression therapy for primary and secondary prevention of NSAID-induced ulcers

A detailed discussion of reducing the risk of NSAID-induced ulcers is provided in the IDIS evidence document on pain management, available at www.RxFacts.org. In summary:

- NSAIDs (alone or in combination with aspirin) significantly increase the risk of upper GI complications.
- To reduce NSAID-associated GI complications, use the lowest NSAID dose for the shortest possible time, and/or add a PPI or misoprostol to the regimen.
- COX-2 inhibitors have significantly less risk of GI complications than non-selective NSAIDs, but concomitant use of aspirin with a COX-2 inhibitor produces an ulcer risk that is the same as a non-selective NSAID.
- PPIs are superior to regular-dose H₂-receptor antagonists in the primary and secondary prevention of NSAID- or aspirin-associated ulcers, but PPIs are equivalent to double-dose H₂-receptor antagonists for primary prevention.

- Non-selective NSAID + PPI is as effective as a COX-2 inhibitor for primary and secondary prevention of GI complications. A COX-2 inhibitor +PPI reduces recurrent ulcer risk more than a COX-2 inhibitor alone.
- Concomitant use of steroids or anticoagulants increases the risk of GI complications.

Role of *H. pylori* testing/eradication in preventing NSAID-induced ulcers

A recent report of The European Helicobacter Study Group found that:¹⁵

- In naive NSAID users, *H. pylori* eradication reduces the risk of peptic ulcer and bleeding, but does not completely prevent NSAID related ulcer disease in chronic NSAID users.
- For chronic NSAID users with peptic ulcer and/or ulcer bleeding, PPI maintenance treatment is more effective than *H. pylori* eradication in preventing ulcer recurrence and/or bleeding.
- Patients who have a GI bleed while receiving long-term aspirin should be tested for *H. pylori* and, if positive, receive eradication therapy.

Eradication of *H. pylori* infection can provide a long-term cure of ulcers in patients with ulcers that are not associated with the use of NSAIDs.⁸ Regardless of whether or not a patient is taking an NSAID, all patients with a peptic ulcer should be tested for *H. pylori* and treated with eradication therapy if infected (see Figure 4 on page 17).²⁸

Bottom line: Most peptic ulcers are caused by *H. pylori* and/or NSAIDs. Treat confirmed peptic ulcers by discontinuing NSAIDs, testing/eradicating *H. pylori*, and 4-8 weeks of PPI therapy; test to confirm eradication of *H. pylori* (see page 20). Options for the prevention of NSAID-induced ulcers include stopping the NSAID, switching to a COX-2 or a different class of analgesic, or adding a PPI, double-dose H₂-receptor antagonist, or misoprostol.

Management of non-ulcer dyspepsia

Lifestyle interventions

Lifestyle interventions for non-ulcer dyspepsia have not been well studied and specific recommendations cannot be made.

Acid suppression therapy

A Cochrane review found that H₂-receptor antagonists and PPIs were significantly more effective than placebo for the treatment of non-ulcer dyspepsia (relative risk reductions of 23% and 13% respectively), while sucralfate and antacids were not.³¹ PPIs were not significantly more effective than H₂-receptor antagonists in a direct comparison of the 2 medication classes (relative risk of symptom response 0.93; 95% CI, 0.84-1.02). There appears to be no statistically significant difference between low- and standard-dose PPI therapy in these patients (relative risk of persisting symptoms on standard-dose PPI compared to low-dose PPI, 0.98; 95% CI, 0.92-1.04).³¹

H. pylori eradication

Eradication of *H. pylori* can cure non-ulcer dyspepsia, with a number needed to treat of 12-15 patients.^{15, 32, 33} A Cochrane review found that eradication of *H. pylori* infection in non-ulcer dyspepsia had a statistically significant clinical benefit (therapeutic gain of eradication over placebo = 8%, , relative risk of remaining symptomatic, 0.91; 95% CI, 0.86–0.95; number needed to treat = 15).³⁴ This compares favorably with other available treatments for non-ulcer dyspepsia.¹⁵

A Cochrane review examined 3 trials that compared *H. pylori* eradication with other pharmacological therapies.³² *H. pylori* eradication was associated with a significant reduction in symptom scores compared to H₂-receptor antagonist or sucralfate therapy, and a non-significant reduction compared to metoclopramide.

Other options

The management of non-ulcer dyspepsia is difficult if initial acid suppression therapy and *H. pylori* eradication fails.¹⁹ Prokinetic agents, antidepressant therapy, or psychological treatments (psychotherapy, cognitive behavioral therapy, relaxation therapy and hypnosis) are sometimes tried, although their benefits are not well established.^{19, 20, 31, 35}

Bottom line: Non-ulcer dyspepsia is a diagnosis of exclusion. Acid suppression therapy and *H. pylori* eradication can be helpful.

Helicobacter pylori infection

Epidemiology

H. pylori infection is usually contracted in the first few years of life and persists life-long unless treated.⁸ Approximately 30–40% of the U.S. population is infected with *H.*

pylori.²⁸ Infection rates in children are decreasing, and it is likely that the prevalence of *H. pylori* in the United States will continue to fall in coming years.²⁸

Disease states associated with *H. pylori* infection

Infection is associated with a number of disease states, as shown in the figure below. Duodenal or gastric ulcers occur in 1-10% of infected patients, gastric cancer in 0.1-3%, and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma in <0.01%.⁸ However, the vast majority of patients with *H. pylori* infection do not have any related clinical disease, and routine testing is not recommended.⁸

Figure 5. Disease states associated with *H. pylori* infection¹⁴

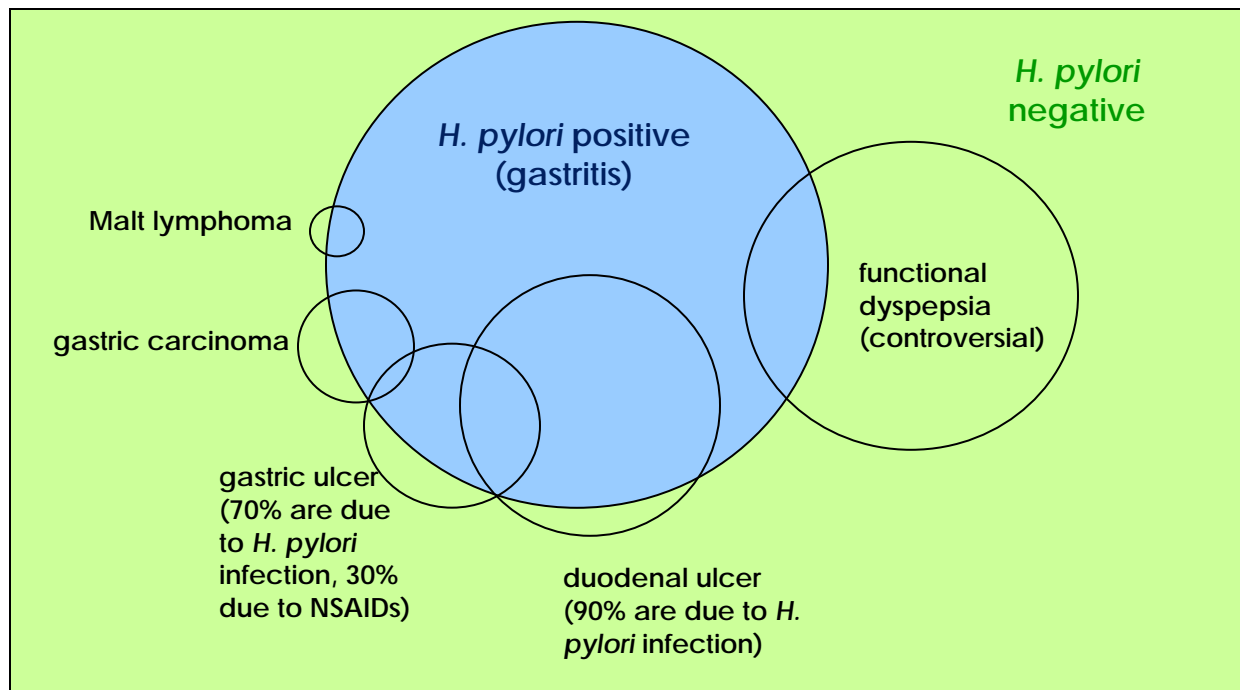


Figure adapted from Marshall BJ. JAMA 1995;274:1064-1066

Whom to test

Diagnosing and treating *H. pylori* infection can cure some patients with peptic ulcer disease and may eliminate the need for lifelong drug therapy.³⁰ The American College of Gastroenterology recommends that testing for *H. pylori* should be performed in patients with a number of conditions, including:²⁸

- an active gastric or duodenal ulcer
- a history of active gastric or duodenal ulcer not previously treated for *H. pylori* infection
- uninvestigated dyspepsia in adults under 55 years without alarm symptoms (the 'test-and-treat' strategy)

Bottom line: *H. pylori* infection is associated with a number of disease states, including peptic ulcer disease. Testing for *H. pylori* is indicated in a number of clinical circumstances, but the majority of patients with *H. pylori* infection do not have any related clinical disease, and routine screening is not recommended.

Diagnostic testing

When endoscopy is not indicated, non-invasive testing can be performed with the urea breath test, fecal antigen test, or antibody testing (serology).⁸ The urea breath test (UBT) and fecal antigen test (FAT) are the most accurate non-invasive diagnostic tools, each having a sensitivity and specificity of about 95%.^{8, 19, 28} For both the breath test and the fecal antigen test, the patient should stop their PPI 2 weeks before testing, stop their H₂-receptor antagonists for 24 hours before testing, and should avoid taking antibiotics for 4 weeks before testing.^{8, 28} All these medications can suppress the infection and cause false negatives. These requirements make the UBT and FAT more difficult to use in routine practice.

Biopsy is the diagnostic test of choice for diagnosing *H. pylori* for patients who undergo endoscopy.²⁸ Options for *H. pylori* testing with biopsy include the rapid urease test, histology, bacterial culture, and polymerase chain reaction.²⁸

Serum antibody testing has lower sensitivity (85%) and specificity (79%) than UBT or FAT.^{8, 19, 28} The positive predictive value (PPV) of antibody testing varies significantly with *H. pylori* prevalence; in areas with a *H. pylori* prevalence less than 20%, the PPV of antibody testing is about 50%.²⁸ The negative predictive value (NPV) of IgG antibody testing has been reported as 94% - 100% (depending on the test and cut-off values used).³⁶ The low PPV of antibody testing means that there may be some overuse of antibiotic based eradication regimens, but antibody testing is often the most practical option in primary care settings, where UBT or FAT may not be immediately available, or if patients have difficulty stopping their PPI for 2 weeks. The UBT and FAT have high positive (and negative) predictive values irrespective of *H. pylori* prevalence.²⁸

Bottom line: Non-invasive tests for *H. pylori* used in primary care include the urea breath test, stool antigen test, and antibody testing. PPIs should be stopped for at least 2 weeks before the UBT and FAT. Although antibody testing is less accurate than the UBT and FAT, it does not require cessation of acid suppressive therapy and is often a practical option.

Eradication therapy

Various drug regimens are used to treat *H. pylori* infection. The most commonly recommended first-line regimen for eradicating *H. pylori* is triple therapy for 10-14 days as shown below:^{8, 19, 28}

Figure 6. Triple therapy for eradication of *H. pylori*

PPI, standard dose twice daily,* **with**
 amoxicillin 1000 mg twice daily, **and**
 clarithromycin 500 mg twice daily

Single-script triple therapy (Prevpac) is available

Metronidazole (500 mg twice daily) may be substituted for
 amoxicillin in penicillin-allergic patients

*A meta-analysis found that the various PPIs have similar efficacies for *H. pylori* eradication in triple therapy.³⁷ Standard doses of PPIs are provided in Table 2 on page 11.

An alternative first-line treatment is bismuth-based quadruple therapy, and 2 regimens are shown below. Both involve four-times-daily dosing.^{8, 28}

Figure 7. Quadruple therapies for eradication of *H. pylori*

<p>H₂-receptor antagonist# with:</p> <ul style="list-style-type: none"> • bismuth subsalicylate 525 mg • metronidazole 250 mg • tetracycline 500 mg <p>available as single script: Helidac; one dose taken four times daily for 14 days</p>	<p>standard dose PPI twice daily with:</p> <ul style="list-style-type: none"> • bismuth subcitrate potassium 140 mg • metronidazole 125 mg • tetracycline 125 mg <p>available as single script: Pylera; 3 capsules taken 4 times daily for 10 days</p>
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#Ranitidine 150 mg, or cimetidine 400 mg, or famotidine 20 mg; twice daily

Continuation of acid suppression therapy after treatment of infection is not necessary unless symptoms persist.

Comparative efficacy and cost of eradication therapies

Eradication rates reported with 5 medication regimens are shown in the table below.^{8, 28, 38-40} A clinical trial comparing the efficacy of triple therapy with bismuth-based quadruple therapy found no significant difference for eradication rates between the 2 therapies (83% vs. 88% respectively; p = 0.29). Although eradication rates are similar with different regimens, there are substantial differences in cost. Prevpac, Helidac, and Pylera are single script therapies that may be simpler to use than multiple individual medications, but are much more expensive.

Table 4. Comparative efficacy and cost of eradication therapies

Drug regimen	Eradication rates	Duration of therapy	Approximate cost of single-script therapy* (brand name)	Approximate cost using individual scripts and generics
Triple therapy (with amoxicillin)	70-94%	14 days	\$760 (Prevpac)	\$150
Triple therapy (with metronidazole)	70-85%	14 days	Not available	\$135
Quadruple therapy (bismuth subsalicylate-based)	75-90%	14 days	\$530 (Helidac)	\$50
Quadruple therapy (bismuth subcitrate potassium-based)	88-93%	10 days	\$450 (Pylera)	Not available [^]
Sequential therapy [#]	84-93%	10 days	Not available	\$160

Prices from www.epocrates.com and www.drugs.com June 2011. Prices may vary with discounts.

*Costs of Helidac and Pylera include the price of acid-suppression medication.

[#] PPI plus amoxicillin 1000mg twice daily for 5 days, followed by PPI plus clarithromycin 500mg twice daily and tinidazole 500mg twice daily for 5 more days. Efficacy needs to be validated in the US before it can be recommended as a first-line therapy.^{8, 28}

[^]Bismuth subcitrate potassium is not available in the US.

Confirming eradication

American College of Gastroenterology guidelines suggest that eradication of infection should be confirmed in patients with a peptic ulcer and those with persistent dyspepsia following the test-and-treat strategy for uninvestigated dyspepsia.²⁸ However, data from clinical trials are lacking to guide management of patients whose symptoms persist after completion of *H. pylori* eradication therapy for uninvestigated dyspepsia, and other valid management options are a 4 week trial of PPI therapy or endoscopy.⁸

Non-invasive tests (UBT or FAT) can be used to confirm eradication, unless repeat endoscopy is indicated e.g., in patients with gastric ulcer. *H. pylori* eradication should be confirmed **no sooner than 4 weeks after the completion of eradication therapy** to avoid false negative results due to temporary suppression of *H. pylori*.^{8, 15, 28} Antibody testing is not suitable to confirm eradication, because antibody titers can remain elevated for many months following successful eradication of *H. pylori*.^{8, 28}

Managing persistent infection

Failure to eradicate *H. pylori* infection may be due to poor adherence and/or resistance to clarithromycin and/or metronidazole. The choice of treatment following failure of eradication is guided by the initial therapy, and 2 options are as follows:^{8, 28}

- If initial therapy did not include a bismuth salt: bismuth-based quadruple therapy for 14 days; or
- if initial therapy was with PPI/amoxicillin/clarithromycin: PPI with metronidazole and either amoxicillin or tetracycline

Patients in whom *H. pylori* infection persists after a second course of treatment should be referred to a specialist for biopsy, culturing, and antibiotic sensitivity testing.

Bottom line: Triple therapy with PPI/amoxicillin/clarithromycin is effective at eradicating *H. pylori* infection. Eradication should be confirmed no sooner than 4 weeks after the completion of eradication therapy in patients with a peptic ulcer and/or persistent dyspepsia.

Management of dyspepsia: test-and-treat vs. empirical acid suppression

Primary care physicians are often required to treat patients with uninvestigated dyspepsia. A "test-and-treat" strategy for *H. pylori* or empirical acid suppression therapy is recommended by both the American College of Gastroenterology and the American Gastroenterological Association for the management of uninvestigated dyspepsia in adults under 55 years without alarm symptoms.^{19, 20}

The test-and-treat option is preferred in populations with a moderate to high prevalence of *H. pylori* infection ($\geq 10\%$), especially recent immigrants from developing countries. The overall prevalence of *H. pylori* infection in the U.S. is about 30-40%.^{19, 28} If symptoms persist despite successful eradication, a 4 week trial of PPIs may be tried. If that fails, endoscopy is a reasonable option.¹⁹

In areas of low *H. pylori* prevalence ($< 10\%$), empirical PPI therapy for 4-8 weeks is a reasonable approach, followed by tapering of PPI.¹⁹ If initial acid suppression treatment fails to manage symptoms after 2-4 wks, one can change drug class or increase the dose. If the patient fails to respond or relapses rapidly after stopping acid suppression therapy, then the test-and-treat strategy should be tried before considering EGD.¹⁹

Bottom line: Testing and treating for *H. pylori* or empirical acid suppression is a reasonable strategy for many patients for the initial management of dyspepsia. If the first choice fails to adequately control symptoms, the alternate strategy may be tried.

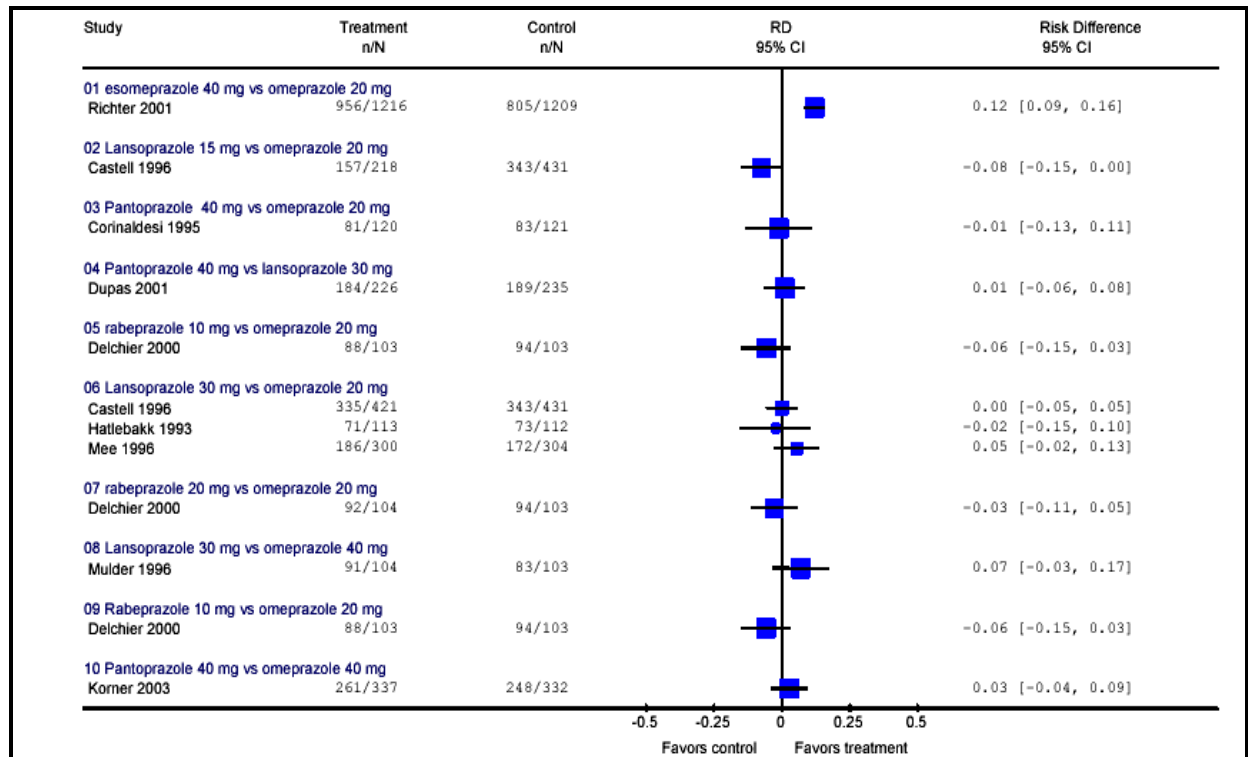
Comparative effectiveness and safety

Comparative effectiveness of PPIs

A number of studies have demonstrated that the different PPIs have similar efficacies in the treatment of GERD, peptic ulcers, *H. pylori* eradication, non-ulcer dyspepsia, or Zollinger-Ellison syndrome.⁴¹⁻⁴⁵ There are no clinically meaningful differences between most of the PPIs in efficacy, pharmacokinetics, pharmacodynamics, interactions with food, and potential for drug interactions. Therefore, the choice of one PPI over another will rarely depend on clinical differences.⁴⁶ More important considerations may be the patient's insurance coverage, cost, and whether a PPI is necessary at all (and for how long).

A comparison of the effectiveness of PPIs in patients with esophagitis illustrates their clinical equivalence in 4-week healing rates:⁴⁷

Figure 8. Healing rates of PPIs



Omeprazole is a mixture of its 2 optical isomers, S-omeprazole (esomeprazole) and R-omeprazole. Esomeprazole reaches higher plasma concentrations than omeprazole after equivalent doses.^{48, 49}

Esomeprazole at a high dose of 40 mg once daily is more effective than other PPIs at standard doses (omeprazole 20mg or lansoprazole 30mg once daily) for healing esophagitis,⁵⁰⁻⁵² but the benefit is small and has not been demonstrated in all studies.⁵³

A number of studies have compared esomeprazole with other PPIs, and although differences favoring esomeprazole have been reported, their magnitude has been variable and is of uncertain clinical significance.⁵⁴ There is no conclusive evidence that esomeprazole is more effective than other PPIs for patients with GERD who do not have esophagitis, particularly if equivalent doses are used. A recent clinical trial found that in patients with uninvestigated GERD, rabeprazole 20 mg once daily was non-inferior to esomeprazole 40 mg once daily for the relief of regurgitation and heartburn.⁵⁵

Bottom line: PPIs have similar clinical efficacy in the treatment of gastrointestinal diseases when acid suppression is indicated. Although esomeprazole has been shown to be more effective than other PPIs in some (but not all) trials, the benefit is of uncertain clinical significance.

Serious adverse effects of PPIs

A review of the literature supported by the federal Agency for Healthcare Quality and Research concluded that while PPIs are more effective in managing conditions in which total acid suppression is necessary, the PPIs also caused a substantially higher incidence of side effects than H₂-receptor antagonists.⁵⁶ The most commonly cited side effects were headache, diarrhea, and abdominal pain. Reducing PPI dose may help overcome some side effects; switching to another PPI is sometimes attempted, but is not well studied. Other important PPI side effects are discussed below.

Clostridium difficile-associated diarrhea

A case-control study found that patients taking PPIs had nearly 3 times the risk of *Clostridium difficile*-associated disease compared to patients not taking acid suppression therapy, and those taking H₂-receptor antagonists had approximately 2 times the risk.⁵⁷ The study raised important concerns about the relationship between gastric acid suppression and the incidence of this sometimes-serious complication. Several (but not all) observational studies of this relationship have also reported an increased risk of *C. difficile*-associated disease with PPI use.⁵⁸⁻⁶⁶

A recent cohort study examined acid suppression therapy in >100,000 patients discharged from hospital during a 5-year period.³ After adjustment for confounders such as comorbid conditions, age, and antibiotics, the risk of nosocomial *C. difficile* infection increased with increasing levels of acid suppression, as shown below.

Table 5. Risk of *C. difficile* infection with acid suppression

Patient group	Relative risk of <i>C. difficile</i> infection
No acid suppression	1.0 (baseline)
H ₂ -receptor antagonist only	1.53 (95% CI, 1.12-2.10)
PPI therapy (once daily)	1.74 (95% CI, 1.39-2.18)
PPI therapy (more than once daily)	2.36 (95% CI, 1.79-3.11)

A retrospective cohort study of > 1000 patients found that PPI use during the treatment of *C. Difficile* infection was associated with a 42% increased risk of recurrence compared to non-use (HR 1.42; 95% CI, 1.11-1.82).⁴

Interstitial nephritis

One systematic review found 60 cases of PPI-associated acute interstitial nephritis with PPI use (59 confirmed by renal biopsy).⁶⁷ The mean treatment duration before diagnosis was 13 weeks, and the average recovery time was 35 weeks. One patient required permanent dialysis, and there were no deaths. The review concluded that PPI-related interstitial nephritis is rare, idiosyncratic, and unpredictable.⁶⁷ All PPIs have been associated with interstitial nephritis (indicating a class effect) and PPIs may now be the most common cause of drug-induced acute interstitial nephritis.^{68, 69}

Pneumonia

Several case-control studies have reported an increase in the risk of community- and hospital-acquired pneumonia associated with PPIs and H₂-receptor antagonists, although the association may be confounded by the underlying indications for the drug.⁷⁰⁻⁷⁶ A recent meta-analysis found an increased risk of community acquired pneumonia associated with PPI use (odds ratio 1.36; 95% CI, 1.12-1.65), but significant heterogeneity existed among the 6 studies included.⁷⁷

Osteoporosis and fractures

PPIs may decrease calcium absorption, but it is unclear if an association exists between PPI use and fractures. A systematic review of observational studies found an association between PPI use and increased risk of hip and vertebral fractures, but could not establish a causal relationship.⁷⁸

One recent study examined the effect of PPI use on fracture in a prospective analysis of > 130,000 postmenopausal women without a history of hip fracture, enrolled in the Women's Health Initiative studies.⁷⁹ Bone mineral density (BMD) measurements at baseline were not significantly different between PPI users and non-users. Use of PPIs was associated with a small negative effect on 3-year BMD change at the hip ($P=.05$). However, this association was not present after examining a longer follow-up of up to 6 years, or at other body sites. The hazard ratios (HR) for fractures with PPI use were:

- hip fracture: HR 1.00; 95% CI, 0.71-1.40
- clinical vertebral fracture: HR 1.47; 95% CI, 1.18-1.82
- forearm or wrist fracture: HR 1.26; 95% CI, 1.05-1.51
- total fractures: HR 1.25; 95% CI, 1.15-1.36

There is insufficient evidence to recommend calcium supplementation or bone density studies solely because of PPI use.⁹ However, a prudent strategy in older adults who require long-term PPI therapy would be to use the lowest effective dose, assess dietary calcium intake, and add calcium and Vitamin D supplements when necessary.

Reduced efficacy of clopidogrel

There has been some concern that the concomitant use of a PPI might decrease the platelet inhibitory effect of clopidogrel (Plavix), because both drugs are metabolized by CYP 2C19.⁸⁰ Two retrospective studies have found rates of re-hospitalization for acute coronary syndrome in patients treated with clopidogrel and a PPI to be increased by about 25%, compared to those treated with clopidogrel alone.^{81, 82} Of note, the subgroup of patients in one of these studies who received pantoprazole, which does not inhibit CYP 2C19, did not have a higher rate of adverse cardiovascular events.⁸² By contrast, one prospective study showed that PPIs did not affect clinical response to clopidogrel.⁸³ A large retrospective study found a slightly increased risk of MI or death in older patients initiating both clopidogrel and a PPI, although the risk was unlikely to be of major clinical relevance.⁸⁴

The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) examined the effect of omeprazole on dual antiplatelet therapy with clopidogrel and

aspirin.⁸⁵ The primary gastrointestinal end point was a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, revascularization, or stroke. The trial was terminated prematurely due to loss of funding. Results were as follows:

Table 6. Results of the COGENT trial

Outcome	Rate in placebo group	Rate in omeprazole group	Relative risk reduction	Hazard ratio
Composite of GI events	2.9%	1.1%	66%	0.34; 95% CI, 0.18 to 0.63; P<0.001)
Overt upper GI bleed	1.2%	0.2%	87%	0.13; 95% CI, 0.03 to 0.56; P=0.001
Composite of cardiovascular events	5.7%	4.9%	Not significant	0.99; 95% CI, 0.68 to 1.44; P=0.96

The two groups did not differ significantly in the rate of serious adverse events.

The COGENT study demonstrated a clear G.I benefit to PPI use with clopidogrel/aspirin, and did not provide any evidence for an increased cardiovascular risk, though it could not completely exclude it.⁸⁵⁻⁸⁷ The clinical significance of a PPI-clopidogrel interaction remains somewhat controversial.⁸⁷ For clinicians concerned about this possible risk, one strategy while awaiting more definitive data would be to limit the use of PPIs to those clopidogrel-treated patients at higher risk of adverse gastrointestinal events, and/or use a PPI that is not metabolized by the CYP enzyme (e.g. pantoprazole).

Bottom line: While PPIs are more effective than H₂-receptor antagonists, they also have more side effects, the most common of which are headache, diarrhea, and abdominal pain. PPIs also appear to cause a higher risk of serious adverse effects such as *C. difficile*-associated disease, interstitial nephritis, and pneumonia. The clinical significance of a PPI-clopidogrel interaction remains unclear.

Compliance and adverse drug reactions

Patients taking multiple medications are more likely to have problems with compliance and adverse drug reactions. They may also be less able to afford the cost

of their drug regimens. Prescribing unnecessary acid-suppressive drugs can put patients at increased risk of omitting other drugs that are essential for treating chronic conditions.⁸⁸ Complex drug regimens can also make older patients confused about their medication schedules. A review of risk factors for adverse drug reactions (ADRs) in elderly patients found that the absolute number of concurrently used medications was the most important independent predictor for ADRs.⁸⁹ This is one more reason to try to discontinue unnecessary PPI therapy if possible.

Costs and comparative value of acid-suppressive drugs

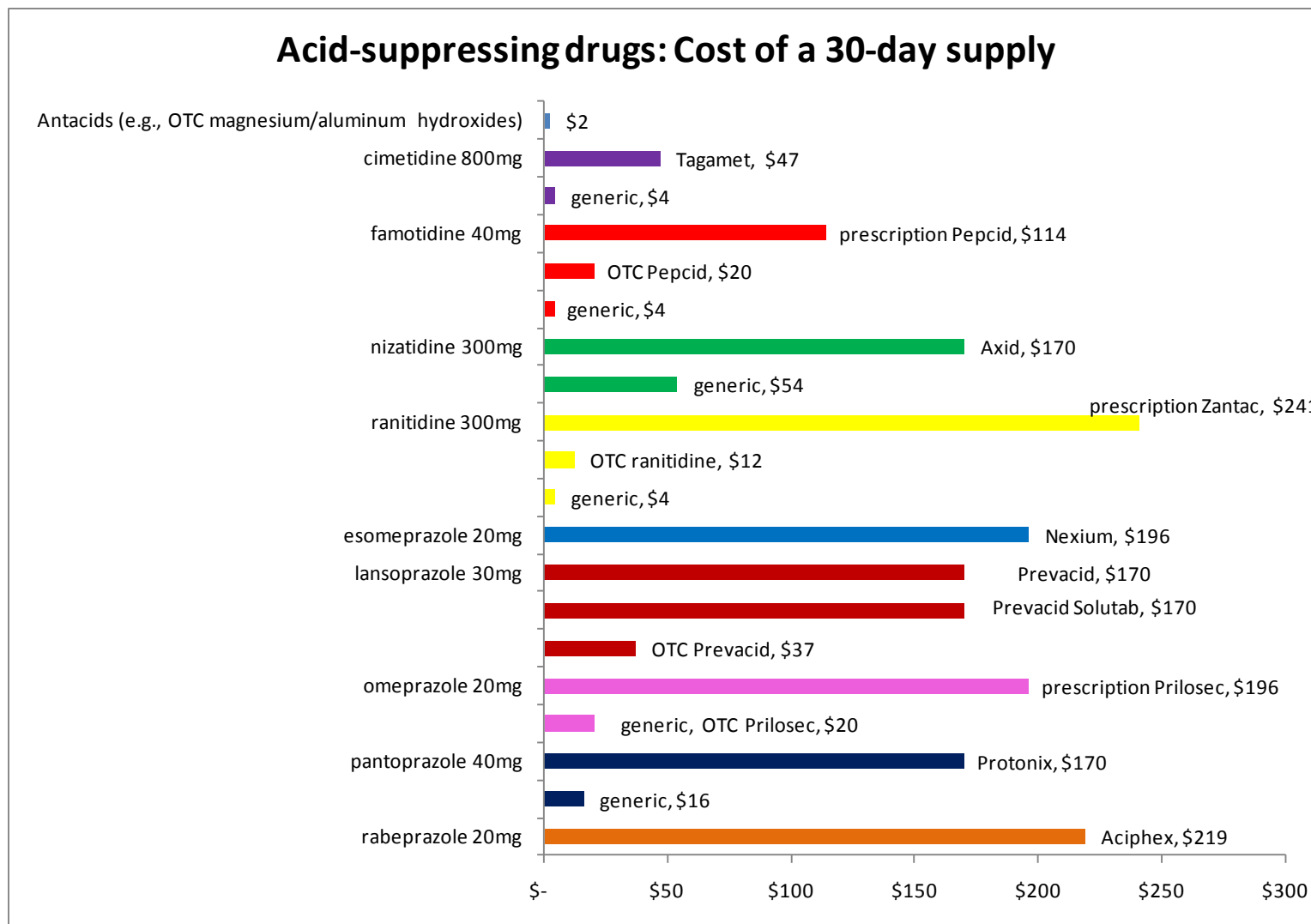
Table 7 below shows therapeutic options for several conditions. Cost of medications can be a barrier to patient adherence and persistence, and the price of acid-suppressive drugs varies widely. Several (but not all) PPIs and all H₂-receptor antagonists are available as prescription generics and/or over-the-counter. The costs of a 30-day supply of commonly used daily doses of acid-suppressive medications are provided in Figure 9. A comparison of the efficacy, safety and cost of acid-suppressive drugs for GERD is provided in Figure 10.

Table 7. Choice of acid-suppressive medications

GERD (without esophagitis)	GERD (with esophagitis)	Non-ulcer dyspepsia	NSAID-induced ulcers
Standard dose PPI more effective than H ₂ RA for resolution of heartburn.	PPI better than H ₂ RA for healing esophagitis.	PPI or H ₂ RA.	Options include:
Twice daily PPI if once daily PPI ineffective.	PPI better than H ₂ RA for resolution of heartburn.	Antacid no better than placebo.	<ul style="list-style-type: none"> • use the lowest NSAID dose for the shortest possible time • stop NSAID • change to COX-2 • change to analgesic from another drug class • add PPI or double dose H₂RA • add misoprostol
Antacids and H ₂ RAs may provide quicker symptom relief than PPIs.	High dose PPI better than standard dose PPI for healing esophagitis.		
Titrate down to lowest effective dose of PPI, and consider switching to H ₂ RA and/or antacid.	Daily PPI better than H ₂ RA or prn PPI for preventing recurrence of erosive disease.		

H₂RA = H₂-receptor antagonist

Figure 9. Cost of acid-suppressive medications



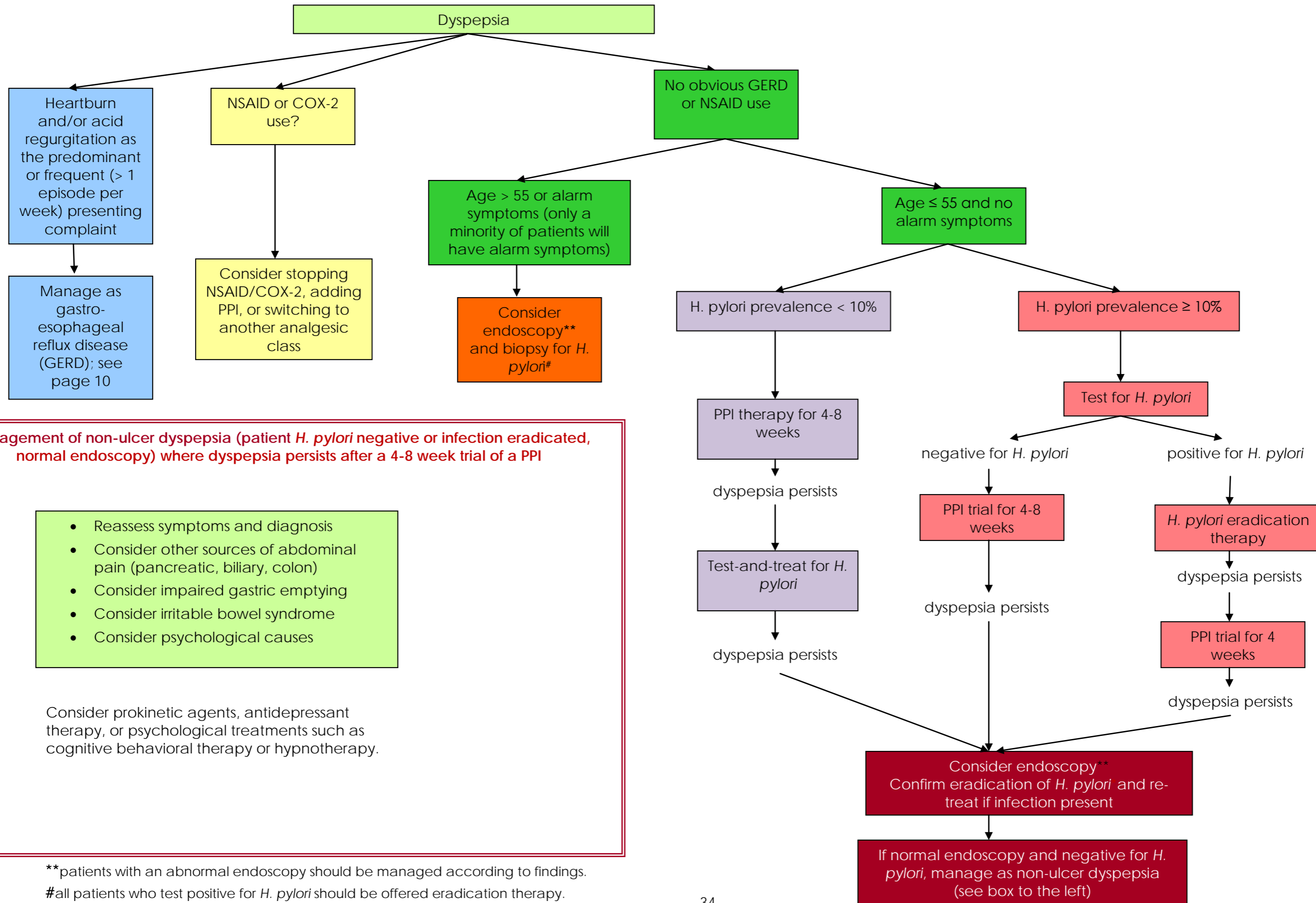
Prices from www.drugstore.com, www.epocrates.com, and several dispensing pharmacies, June 2011. Prices may vary with discounts.

Figure 10. Comparative efficacy, safety and cost of acid-neutralizing/suppressive drugs for GERD

Therapy	Efficacy	Adverse effect profile	Cost	Overall value
Antacids				
H₂-receptor antagonists				
cimetidine (generics, Tagamet)				
famotidine (generics, Pepcid)				
nizatidine (generics, Axid)				
ranitidine (generics, Zantac)				
Proton pump inhibitors				
esomeprazole (Nexium)				
lansoprazole (generics, Prevacid)				
omeprazole (generics, Prilosec)				
pantoprazole (generics, Protonix)				
rabeprazole (Aciphex)				
Unknown or no effect	Best outcome	Intermediate	Problem	

Putting it all together: managing the patient with dyspepsia

Figure 11. Assessing and managing dyspepsia^{8, 19, 20, 28}



Glossary of terms

Antacid	a medication that neutralizes gastric acid
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
COX	cyclooxygenase
EGD	esophagogastroduodenoscopy
Dyspepsia	a term that embraces a constellation of symptoms, including upper abdominal discomfort, heartburn, retrosternal pain, epigastric pain, nausea, early satiety (sensation of fullness), acid regurgitation, excessive belching, and water brash (patient's mouth suddenly fills with saliva)
Non-ulcer dyspepsia	a term given to a persistent dyspepsia where other diagnoses have been excluded and where an organic cause cannot be identified
GERD	Gastro-esophageal reflux disease; reflux of stomach contents into the esophagus
H ₂ -receptor antagonists	histamine receptor antagonists; a class of acid-suppressive drugs
<i>H. pylori</i>	Helicobacter pylori bacterium which colonizes the upper GI tract and can cause a number of diseases including peptic ulcers, MALT lymphoma, and gastric cancer
MALT lymphoma	gastric mucosa-associated lymphoid-tissue lymphoma
NSAID	Non-steroidal anti-inflammatory drug
PPIs	proton pump inhibitors; a class of acid-suppressive drugs
PPV	Positive predictive value; the probability that a positive test result is true
PUD	peptic ulcer disease – ulceration of the gastric or duodenal mucosa
Zollinger-Ellison syndrome	a gastric secreting tumor causing hypersecretion of gastric acid

Appendix 1. Efficacy of acid-suppressive medications in GERD

The following figure summarizes data from clinical trials and meta-analyses relating to the efficacy of acid-suppressive medications used to treat GERD.⁷

Treatment Data on the Use of PPIs and H ₂ -receptor antagonists (H ₂ RA) for GERD*
<p>Healing of esophagitis</p> <p>Proton-pump inhibitor</p> <ul style="list-style-type: none"> Superior to placebo (83% vs. 18%) at 8 wk; NNT, 1.7 Superior to H₂RA (83% vs. 18%); relative risk, 0.51 Superior to H₂RA (84% vs. 52%); relative risk, 0.51 Significant dose-response effect at 4 wk <ul style="list-style-type: none"> Low dose vs. standard dose once daily: NNT, 10 Standard dose vs. high dose once daily: NNT, 25 <p>H₂RA</p> <ul style="list-style-type: none"> Superior to placebo (41% vs. 20%) at 6 wk; NNT, 5 No significant dose-response effect (standard dose vs. high dose twice daily)
<p>Resolution of heartburn†</p> <p><i>Patients with esophagitis</i></p> <ul style="list-style-type: none"> Proton-pump inhibitor superior to placebo (56% vs. 8%) at 4 wk; NNT, 2 to 3 Proton-pump inhibitor superior to H₂RA (77% vs. 48%) at 4 to 12 wk H₂RA superior to placebo (56% vs. 45%) at 12 wk No significant dose-response effect for proton-pump inhibitor at 4 wk <ul style="list-style-type: none"> Low dose vs. standard dose once daily: 75% vs. 79% Standard dose vs. high dose once daily: 73% vs. 76% <p><i>Patients without known esophagitis</i></p> <ul style="list-style-type: none"> Proton-pump inhibitor superior to placebo (36.7% vs. 9.5%); NNT, 3 to 4 Proton-pump inhibitor superior to H₂RA (61% vs. 40%); NNT, 5 H₂RA superior to placebo (relative risk, 0.77; 95% CI, 0.60 to 0.99) No significant dose-response effect for H₂RA at 8 wk <ul style="list-style-type: none"> Standard dose vs. high dose twice daily: 45.8% vs. 44.8%
<p>Maintenance therapy‡</p> <p><i>Remission of esophagitis</i></p> <ul style="list-style-type: none"> Proton-pump inhibitor superior to placebo (93% vs. 29%) Low dose of proton-pump inhibitor effective in 35% to 95% of patients <p><i>Remission of heartburn (without esophagitis)</i></p> <ul style="list-style-type: none"> Acceptable symptom control with low-dose, intermittent therapy with Proton-pump inhibitor in 83% to 92% of patients

*Relative risk refers to the probability of treatment failure in the active-treatment group. NNT denotes number of patients needed to treat to benefit one patient.

† Resolution of heartburn is generally defined as no symptoms for 7 days.

‡ The duration of maintenance therapy was 6 to 12 months.

Figure adapted with permission from: Kahrilas PJ. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med.* Oct 16 2008;359(16):1700-1707.

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