Gastrointestinal Disorders: Dyspepsia and Peptic Ulcer Disease

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Dyspepsia, defined as pain or discomfort in the upper abdomen, is one of the most common complaints bringing patients to consult their family physician. These patients may also complain of nausea, fullness, early satiety, bloating or regurgitation.[1]

Dyspepsia occurs in about 25% of the North American population. Five to 15% of patients with chronic dyspepsia have esophagitis due to gastroesophageal reflux disease (GERD), 15–25% have peptic ulcer disease (PUD), <2% have gastric or esophageal cancer and about 60% have normal endoscopy (functional or idiopathic dyspepsia). Lifestyle factors such as smoking, excess alcohol intake, stress and a high fat diet could precipitate dyspeptic symptoms. Non-ulcer dyspepsia (NUD) and non-erosive reflux disease (NERD) are types of functional dyspepsia with PUD-like and GERD-like symptoms respectively (Figure 1 - Classification of Dyspepsia and its Causes). Unlike PUD and GERD, NUD and NERD are not associated with erosive mucosal findings when investigated by esophagogastroduodenoscopy (EGD). The severity of dyspeptic symptoms is not useful in predicting what the result of the EGD might be.

Lifetime prevalence of peptic ulcers is about 10% in North Americans. Chronic PUD is most commonly caused by *Helicobacter pylori* (*H. pylori*) infections and use of nonsteroidal anti-inflammatory drugs (NSAIDs) or ASA. The resulting gastric ulcer (GU) or duodenal ulcer (DU) is usually detected visually by EGD. However, 5–20% of patients with GU/DU have no evidence of either *H. pylori* or ASA/NSAID use. PUD may present with epigastric tenderness upon examination with other typical symptoms including nausea, vomiting, dyspepsia, bloating or burning epigastric pain which may be relieved by food or antacids.

This chapter considers the management of:

1. Uninvestigated dyspepsia
2. Dyspepsia with normal endoscopy (functional dyspepsia)
3. Treatment of PUD due to *H. pylori* infection
4. Prevention of PUD in ASA/NSAID users
5. Treatment of PUD in ASA/NSAID users

GERD is addressed in Gastrointestinal Disorders: Gastroesophageal Reflux Disease

Goals of Therapy

- Relieve symptoms of dyspepsia and peptic ulcer disease
- Prevent recurrence of symptoms
- Heal the ulcer if it exists
- Prevent recurrence of ulcer if it existed
- Prevent complications, e.g., bleeding, perforation

Investigations

- History and physical examination
  - exclude nongastrointestinal sources of pain or discomfort in the upper abdomen, e.g., ischemic heart disease
  - "red flags" such as age >50 years, abdominal mass, vomiting, bleeding, dysphagia, anemia or weight loss occurring with symptoms may be associated with rare but serious causes such as esophageal or gastric cancer. However, the stage of these malignancies is usually so far advanced when the patient presents that empirical treatment of dyspepsia for 4–8 weeks does not make the bad prognosis worse
  - identify those with predominant reflux-like symptoms because they are more likely to respond to empiric proton pump inhibitor (PPI) therapy.
  - take a drug history for NSAID/ASA use, including low-dose ASA for cardioprotection, as well as other medications that may cause or aggravate dyspepsia, e.g., bisphosphonates, tetracyclines, calcium channel blockers
  - physical examination will usually be normal. Epigastric tenderness is a common but nonspecific finding

- Investigations for *H. pylori* infection
  - *H. pylori* infection may cause or worsen dyspepsia and its complications. About 25% of Canadians have an *H. pylori* infection in the stomach, but <25% of them exhibit symptoms that respond to eradication therapy
  - a ^{13}C or ^{14}C urea breath test (UBT) is required to determine the presence of *H. pylori* infection if the uninvestigated dyspepsia (UD) does not respond to lifestyle changes, avoidance of ASA/NSAIDs or a 4–8 week course of a PPI (Figure 2 - Management of Dyspepsia and *H. pylori* Infections[2]).[2], [3] Ensure patients are off antibiotics and bismuth for 1 month and PPIs or histamine H_2-receptor antagonists (H_2RA) for at least 1 week prior to the UBT. These drugs may suppress growth of the *H. pylori* sufficiently to produce a false negative result
  - IgG serology is appropriate if there is no access to UBT or endoscopy. If the serology is negative, the patient is truly *H. pylori*-negative. A 20% decline in IgG serology titer over 6 months correlates with successful eradication of *H. pylori*. The necessary wait of 6 months' duration prior to repeat testing and the need to save and compare the sera have removed the utility of serology testing

- Investigations for dyspepsia
  - although *prompt* endoscopy is the most sensitive and specific means to diagnose the cause of dyspepsia, it is most appropriate in dyspeptic patients with 1 or more of the following red flags: age >50 years, alarm signs and symptoms (vomiting, bleeding, anemia, weight loss, dysphagia), GU detected on an upper GI series (to obtain biopsies to exclude gastric cancer)
  - in all other dyspeptics, initial endoscopy or test-and-treat for *H. pylori* infection does not produce better outcomes (e.g., improvement of symptoms or quality of life) than empirical PPI therapy. However, if PPI therapy is ineffective, the clinician may consider a UBT, endoscopy or referral. Long-term health care costs are estimated to be approximately the same regardless of which investigative approach is followed
  - although empiric antisecretory therapy is relatively simple and non-invasive, endoscopy permits the diagnosis of dyspepsia causes such as erosive esophagitis, Barrett's epithelium, GU or DU, gastric or duodenal erosions, *H. pylori* infection and gastric or esophageal cancer. Normal EGD results are reassuring to both patient and physician

- the disadvantages of EGD include:
  - scarcity of gastroenterologists to perform the procedure (the average waiting time to arrange for an endoscopy is 2–6 months)
  - relatively higher cost
  - time lost from work
  - risk of complications such as aspiration or perforation (about 1/5000 procedures)
- the use of EGD to confirm healing of GU has fallen out of favour and can likely be skipped unless there is a strong suspicion that an ulcer is malignant (large size or ongoing symptoms despite *H. pylori* eradication or PPI therapy)
- upper GI barium study has an approximately 20% false-positive and false-negative rate for detection of ulcer disease and is generally not recommended, especially in those with red flags (see above).[2] However, barium studies are often more readily available than UBT or endoscopy and are still used to reassure the physician that nothing serious has been missed as a cause of the dyspepsia
- do not perform an upper GI series in a patient with bleeding from the upper GI tract because this may obscure the diagnosis when endoscopy is performed
- about a third of persons with dyspepsia may have lower abdominal complaints suggestive of irritable bowel syndrome (IBS). Treatment of IBS may reduce the severity of the reflux symptoms and enhance the person's quality of life

Uninvestigated Dyspepsia (UD)

Therapeutic Choices
Nonpharmacologic Choices
Pharmacologic Choices

Therapeutic Choices

Nonpharmacologic Choices

General lifestyle modification is the first approach for the management of UD:

- Recommend moderation if a food or beverage (e.g., coffee, orange juice, spicy foods, fatty foods, large meals or eating on the run) worsens dyspepsia.
- Recommend a diet and exercise program to help sufferers achieve a normal body mass index (BMI) to help separate dyspepsia from GERD.
- Encourage smoking cessation; it may indirectly benefit dyspeptic symptoms by improving ulcer healing and reducing recurrence of ulcers not related to *H. pylori* infection. (See Psychiatric Disorders: Smoking Cessation.)
- Advise patients with prominent heartburn or regurgitation to eat slowly, take small, non-fatty meals and not to lie down or bend forward for at least 2 hours after a meal.
- Recommend 4 inch (10 cm) elevation of the head of the bed if nighttime symptoms or sleep disturbances are bothersome.
- Consider the contribution of medications that relax smooth muscles (e.g., calcium channel blockers, nitrates) on lowering esophageal sphincter pressure sufficiently to cause or worsen dyspeptic symptoms.

Pharmacologic Choices

- Treat UD empirically with *standard dose* **PPIs** for up to 4 weeks.
- Continued and standard dose PPIs are more efficacious than **H_2RAs** or *half-dose* **PPIs** for improvement of GERD and dyspeptic symptoms.[4]
- Approximately 20% of patients with UD will remain asymptomatic for up to 6 months after a successful initial course of therapy with PPI or H_2RA.
- If dyspepsia symptoms persist, or if there are frequent recurrences, investigate for *H. pylori* infection with a UBT or with prompt endoscopy. UBT for *H. pylori* is safe, effective, more comfortable and less distressing for the patient than endoscopy.[5]
- The *test-and-treat* approach assumes that a DU/GU (if present) is responsible for the dyspeptic symptoms and is caused by *H. pylori*. Treat patients with positive test results with *H. pylori* eradication therapy (Table 1). About 90% of patients with DU and 70% of those with GU may be *H. pylori*-positive, although the association may be less striking in community practice, or in patients with a past history of an ulcer complicated by bleeding. In patients with *H. pylori* infection or normal EGD the benefit of eradication is small (7–15% symptom resolution).[6, 7, 8]
- The advantage of the *test-and-treat* strategy is that the investigations needed to diagnose *H. pylori* can be readily used by the family physician, when available in the community, and produce rapid results. The disadvantage is that serology and UBT are not universally available in Canada, and the cost of these tests may not be covered by provincial health care plans.

Dyspepsia with Normal Endoscopy (Functional Dyspepsia)

Therapeutic Choices
Nonpharmacologic Choices
Pharmacologic Choices

Therapeutic Choices

Nonpharmacologic Choices

- Reassure and educate patients about the benign nature of this condition.[9]

- Reassure and educate patients about the benign nature of this condition.[2]
- Avoiding high fat meals/foods which exacerbate symptoms and eating frequent smaller meals may be helpful.[9]

Pharmacologic Choices

Symptomatic management of functional dyspepsia is challenging and is often unsuccessful. Reconsider diagnosis in patients with resistant symptoms.

- Empiric treatment with a **PPI** or **H_2RA** for 4–8 weeks is reasonable. Antisecretory agents may be most beneficial for those with reflux- or ulcer-like symptoms.[9] , [10]
- The majority of patients with functional dyspepsia do not derive symptomatic benefit from *H. pylori* eradication.[9]
- Prokinetic agents such as **metoclopramide** and **domperidone** may be more likely to produce symptomatic improvement compared with placebo.[11] , [12] , [13]
- Tricyclic antidepressants (e.g., **amitriptyline**, **desipramine**, **nortriptyline**) may offer some symptomatic benefit but convincing evidence is lacking.[9]

Useful Info?

Treatment of Peptic Ulcer Disease Due to *Helicobacter pylori* Infection

Pharmacologic Choices

Pharmacologic Choices

The treatment of PUD caused by an *H. pylori* infection requires acid inhibition and eradication of *H. pylori.*

Acid Inhibition

- A **PPI** is included as part of a 7-day *H. pylori* eradication therapy.[14]
- Consider the need for PPI maintenance therapy on an individual basis.
- **H_2RAs** may relieve mild pain symptoms but are much less effective for pain relief and ulcer healing than PPIs.
- Disadvantages of using H_2RAs include twice daily dosing, relatively longer treatment period required (4–8 weeks for DU and 8–12 weeks for GU) and the development of tachyphylaxis.

Eradication of *Helicobacter pylori*

- First-line *triple* therapy consists of any **PPI** plus 2 antibiotics (**clarithromycin** and either **amoxicillin** or **metronidazole**) administered BID for 1 week (Table 1).
- *Quadruple* therapy consisting of any **PPI** taken BID combined with **bismuth subsalicylate**, **metronidazole** and **tetracycline** taken QID for 1 week is also considered to be a first-line treatment (Table 1) and may be used for triple therapy failures or if patient is intolerant of macrolide antibiotics.[16]
- If one triple-therapy regimen fails to eradicate *H. pylori*, re-treat the patient with a different antibiotic combination, for 2 weeks rather than 1, or with quadruple therapy rather than triple therapy.[17]
- The above regimens are approved by the Canadian Helicobacter Study Group and achieve a minimum eradication rate (on an intention-to-treat basis) of at least 80%.[16]
- After successful *H. pylori* eradication, the risk of re-infection is about 1% per year.
- *H. pylori* eradication has benefits beyond the relief of the dyspepsia. These benefits include the removal of the approximately 15% lifetime risk of PUD, and 1% risk of developing gastric cancer or mucosa-associated lymphoid tissue (MALT) lymphoma if the infection is left untreated.
- The prevalence of metronidazole-resistant *H. pylori* in Canada is about 20% and resistance to amoxicillin is <1%,[16] thus use of amoxicillin-containing regimens is increasing.
- With increasing resistance of *H. pylori* to metronidazole or clarithromycin, the choice of antibiotic combinations depends on local resistance patterns. Generalized treatment guidelines may not be appropriate if they are not supported by local sensitivity results.[18]
- To ensure eradication of *H. pylori*, UBT or endoscopic biopsy may be repeated at least 30 days after completion of eradication therapy. Retesting may be particularly important if the patient experienced complicated ulcers (bleeding or perforation). It may also be necessary to prove that eradication has occurred before looking for new causes of dyspepsia in the occasional patient who experiences recurrent dyspepsia after the use of an approved eradication regimen.
- Continued treatment with a PPI after a course of *H. pylori* eradication therapy does not produce higher ulcer healing rates than eradication therapy alone in infected patients with uncomplicated DU.[19] This does not apply to GU.[19]

Table 1: *Helicobacter pylori* Eradication Regimens

Regimen	Dose	Treatment Period	Cost[a]
Triple Therapy			
PPI *clarithromycin* *amoxicillin* Hp-PAC, Losec 1-2-3 A, Nexium 1-2-3 A	BID 500 mg BID 1 g BID	7 days	$$$
PPI	BID	7 days	$$$

clarithromycin[b] *metronidazole* Losec 1-2-3 M	250 mg BID 500 mg BID		
Quadruple Therapy			
PPI *bismuth subsalicylate* *metronidazole* *tetracycline*	BID 2 tabs QID 250 mg QID 500 mg QID	7 days	$$$

a. Cost per treatment period; includes drug cost only.

b. Dose may be increased to 500 mg clarithromycin twice daily.[15]

Dosage adjustment may be required in renal impairment; see Appendices: Dosage Adjustment in Renal Impairment.

Abbreviations: PPI=proton pump inhibitor

Legend: $ <$15 $$ $15–30 $$$ $30–45

Prevention of Peptic Ulcer Disease in ASA/NSAID Users

- Any **PPI** dosed once daily or **misoprostol** *200 µg QID* are effective options for patients at high risk of NSAID-induced gastrointestinal complications (>65 years of age, use of more than one NSAID, higher doses of NSAIDs, use of concomitant corticosteroids or anticoagulants/ASA, history of ulcer disease and coexisting ischemic heart disease). Misoprostol, however, is associated with relatively poor tolerability due to GI adverse effects.[20]
- *Standard dose* PPIs are more efficacious than standard dose **H_2RAs** or misoprostol *400 µg daily* (but not 800 µg misoprostol) for the prevention of NSAID-associated gastric and duodenal ulcers.[20] , [21]
- Due to an additive effect between *H. pylori* infection and use of NSAIDs on the development of peptic ulcers, screen persons beginning long-term NSAIDs for *H. pylori* and treat if found positive.[16] , [22]
- In *H. pylori*-negative patients who have a history of ulcer bleeding on low-dose ASA alone, the combination of low-dose ASA and a PPI is associated with a lower risk of recurrence of ulcer complications at 1 year compared to clopidogrel alone.[23]
- There is no difference in ulcer recurrence and bleeding rates between COX-2 selective NSAIDs and the combination of PPI and conventional NSAIDs in patients with previous NSAID-associated upper GI bleeding.[24]
- Compared to regular NSAIDs, COX-2 inhibitors may reduce the risk of complicated peptic ulcer bleeding by 50–70%.[24] , [25] , [26] However, reports of cardiovascular complications with the use of COX-2 inhibitors have limited their use and challenged their safety.

Treatment of Peptic Ulcer Disease in ASA/NSAID Users

- Treat PUD in ASA/NSAID users with *standard dose* **PPI** therapy for 4–8 weeks. Stop the NSAID whenever possible.
- **H_2RAs** or **misoprostol** are less effective alternatives.
- Unlike *H. pylori*-associated ulcers, GU or DU caused by ASA or NSAIDs are more likely to be painless, and patients with such ulcers often present for the first time with a complication such as bleeding or perforation.[27] , [28]

Choices during Pregnancy and Breastfeeding

Dyspepsia may appear for the first time during pregnancy but usually resolves afterwards. Some patients with dyspepsia, including women of reproductive potential, may try to manage their symptoms with nonprescription **antacids**, **barrier agents** (e.g., alginates), **H_2 receptor antagonists** and **proton pump inhibitors**. These medications are considered to be generally safe to use during pregnancy and breastfeeding,[29] , [30] with the caveat that the symptoms are from a condition in the upper gastrointestinal tract and not from other pregnancy-associated conditions (e.g., constipation, cholelithiasis, urinary tract infection or hypertension).

Treat a pregnant woman with uninvestigated dyspepsia as outlined in the section "Uninvestigated Dyspepsia" above. If a diagnostic test for *H. pylori* (serology, endoscopy, urea breath test with the ^{13}C isotope) was done during pregnancy or breastfeeding, postpone treatment for the *H. pylori* infection until after pregnancy and breastfeeding. There is no need to test the infant for *H. pylori* if the mother is infected. It has been proposed that the ^{14}C (radioactive) and the ^{13}C (non-radioactive) urea breath tests are acceptable to use during pregnancy, since the radioactivity delivered to the fetus from the ^{14}C is very low and is estimated to be less than the total amount of natural radioactivity the fetus is exposed to in 1 day.[31]

The synthetic prostaglandin E_1 analogue, **misoprostol**, must not be used during pregnancy. If ASA/NSAID/COX-2 inhibitors are absolutely indicated during pregnancy, the guidance given in "Uninvestigated Dyspepsia" may be followed.

A discussion of general principles on the use of medications in these special populations can be found in Drug Use During Pregnancy and Drug Use During Breastfeeding. Other specialized reference sources are also provided in these appendices.

Figure 1 - Classification of Dyspepsia and its Causes

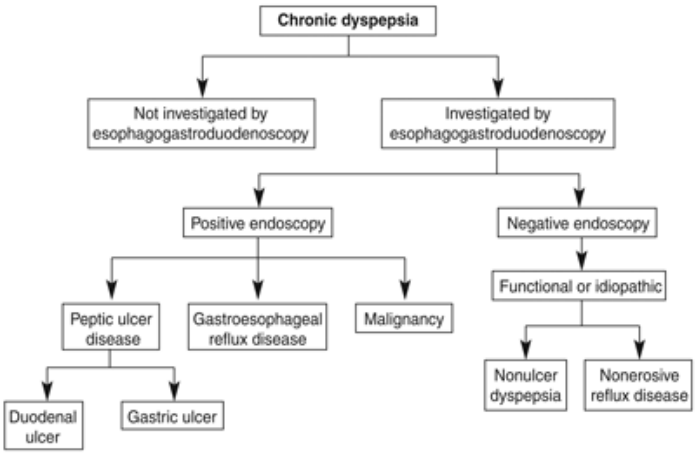
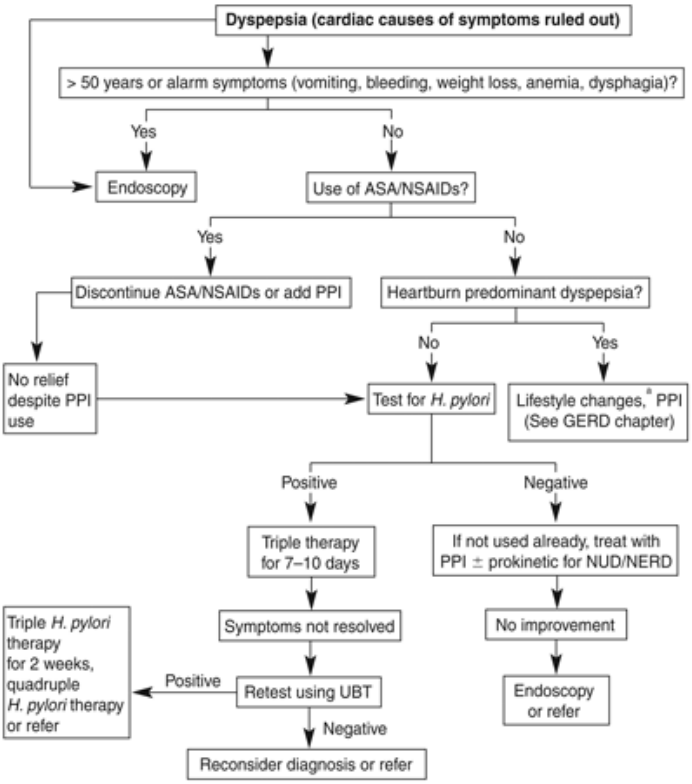


Figure 2 - Management of Dyspepsia and *H. pylori* Infections[2]



[a] Treat symptoms; lifestyle changes, diet, short courses (no more than 4 weeks) of nonprescription antacids/H_2-receptor antagonists (H_2RA) and therapeutic doses of H_2RA or preferentially a proton pump inhibitor.

Abbreviations: GERD=gastroesophageal reflux disease; NERD=nonerosive reflux disease; NSAIDs=nonsteroidal anti-inflammatory drugs; NUD=nonulcer dyspepsia; PPI=proton pump inhibitor; UBT=urea breath test

Adapted with permission from Thomson AB. A suggested approach to patients with dyspepsia. *Can J Gastroenterol* 1997;11(2):135-40.

Table 2: Drugs Used for Dyspepsia and Peptic Ulcer Disease

Class	Drug	Dose	Adverse Effects	Drug Interactions	Cost[a]
H_2-receptor antagonists	*cimetidine*, generics	Treatment: 300 mg BID po[b] Maintenance:	Diarrhea, constipation, headache, fatigue, confusion (most likely in elderly or in	Cimetidine ↓ cytochrome P450 metabolism of other drugs (e.g., phenytoin, theophylline, warfarin). Other H_2RAs (ranitidine or famotidine) have minimal effects.	$

		400 mg QPM po	poor renal function), cardiac effects, rash, gynecomastia, impotence (rare).		
H_2-receptor antagonists	*famotidine* Pepcid, generics	Treatment: 20 mg BID po[b] Maintenance: 20 mg QPM po	Diarrhea, constipation, headache, fatigue, confusion (most likely in elderly and those with poor renal function), cardiac effects, rash.		$
H_2-receptor antagonists	*nizatidine* Axid, generics	Treatment: 150 mg BID po[b] Maintenance: 150 mg QPM po	Diarrhea, constipation, headache, fatigue, confusion (most likely in elderly and those with poor renal function), cardiac effects, rash.		$
H_2-receptor antagonists	*ranitidine* Zantac, generics	Treatment: 150 mg BID po[b] Maintenance: 150 mg QPM po	Diarrhea, constipation, headache, fatigue, confusion (most likely in elderly and those with poor renal function), cardiac effects, rash.		$
Mucosal Protective Agents	*misoprostol* generics	Treatment: 200 µg QID po	Diarrhea (dose-related), abdominal cramps, flatulence. **Contraindicated in pregnancy** (abortifacient).		$$$$
Proton Pump Inhibitors	*esomeprazole* Nexium, generics	20 mg daily AC breakfast po[b] 20 mg BID po if part of *H. pylori* eradication regimen	Diarrhea, flatulence, abdominal pain.	Monitor for ↓ efficacy of drugs requiring an acidic medium for dissolution or absorption (e.g., itraconazole). Esomeprazole may interfere with cytochrome P450-metabolism of other drugs (e.g., diazepam, phenytoin, warfarin). Adjust dosages as needed when esomeprazole is added or discontinued.	$$$$
Proton Pump Inhibitors	*lansoprazole* Prevacid, generics	Treatment: 15–30 mg daily AC breakfast po[b] Maintenance: 15 mg daily AC breakfast po 30 mg BID po if part of *H. pylori* eradication regimen	Diarrhea, flatulence, abdominal pain.	Monitor for ↓ efficacy of drugs requiring an acidic medium for dissolution or absorption (e.g., itraconazole).	$
Proton Pump Inhibitors	*omeprazole* Losec Capsules, Losec Tablets, generics	20–40 mg daily AC breakfast po[b] 20 mg BID po if part of *H. pylori* eradication regimen	Diarrhea, flatulence, abdominal pain.	Monitor for ↓ efficacy of drugs requiring an acidic medium for dissolution or absorption (e.g., itraconazole). Esomeprazole may interfere with cytochrome P450-metabolism of other drugs (e.g., diazepam, phenytoin, warfarin). Adjust dosages as needed when esomeprazole is added or discontinued.	$$
Proton Pump Inhibitors	*pantoprazole magnesium* Tecta	40 mg daily AC breakfast po[b] 40 mg BID po if part of *H. pylori* eradication regimen	Diarrhea, flatulence, abdominal pain.	Monitor for ↓ efficacy of drugs requiring an acidic medium for dissolution or absorption (e.g., itraconazole).	$$
Proton Pump Inhibitors	*pantoprazole sodium* Pantoloc,	40 mg daily AC breakfast po[b] 40 mg BID po if	Diarrhea, flatulence, abdominal pain.	Monitor for ↓ efficacy of drugs requiring an acidic medium for dissolution or absorption (e.g., itraconazole).	$

	Pantoloc, generics	40 mg BID po if part of *H. pylori* eradication regimen			
Proton Pump Inhibitors	*rabeprazole* Pariet, generics	20 mg daily AC breakfast pob 20 mg BID po if part of *H. pylori* eradication regimen	Diarrhea, flatulence, abdominal pain.	Monitor for ↓ efficacy of drugs requiring an acidic medium for dissolution or absorption (e.g., itraconazole).	$

a. Cost of 30-day (treatment dosages) supply; includes drug cost only.

b. Duration of treatment for duodenal ulcer is 4–8 wk. Duration of treatment for gastric ulcer is 8–12 wk.

Dosage adjustment may be required in renal impairment; see Appendices: Dosage Adjustment in Renal Impairment.

Abbreviations: H2RA=histamine type–2 receptor antagonist

Legend: $ <$15 $$ $15–30 $$$ $30–45 $$$$ $45–60

Suggested Readings

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