Pharmacotherapy 2

Peptic Ulcer Disease (PUD)

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Topic Outline

- General Principles
- Diagnosis
- Treatment
- Complications
- Monitoring/Follow-Up

Peptic Ulcer Disease (PUD)

General Principles

- ✓ PUD consists of mucosal breaks in the stomach and duodenum when corrosive effects of acid and pepsin overwhelm mucosal defense mechanisms.
- ✓ Helicobacter pylori is responsible for at least half of all PUD & the majority of ulcers that are not due to NSAIDs.
- ✓ PUD can develop in 15-25% of chronic NSAID & aspirin users.
- ✓ A gastrin-secreting tumor accounts for < 1% of all PUs.
- ✓ When none of these etiologies are evident, PUD is designated idiopathic.

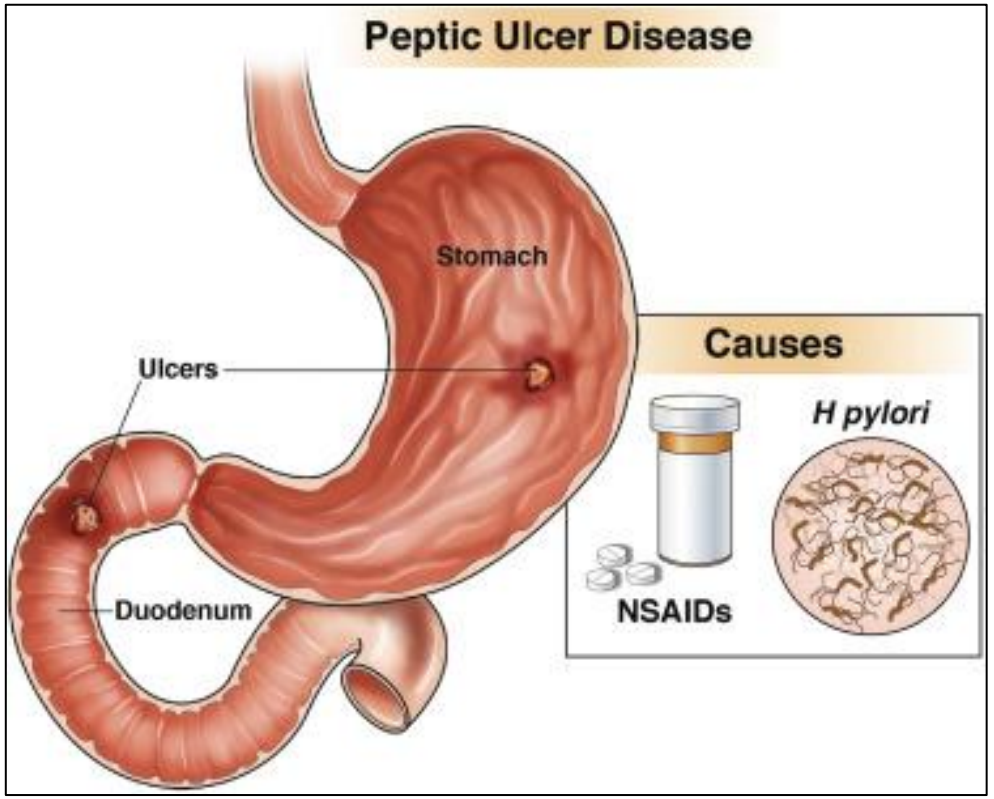


TABLE 50-1 Comparison of Common Forms of Peptic Ulcer

Characteristic	*H. pylori*–Induced	NSAID-Induced	SRMD
Condition	Chronic	Chronic	Acute
Site of damage	Duodenum > stomach	Stomach > duodenum	Stomach > duodenum
Intragastric pH	More dependent	Less dependent	Less dependent
Symptoms	Usually epigastric pain	Often asymptomatic	Asymptomatic
Ulcer depth	Superficial	Deep	Most superficial
GI bleeding	Less severe, single vessel	More severe, single vessel	More severe, superficial mucosal capillaries

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; SRMD, stress-related mucosal damage.

TABLE 50-2 Potential Causes of Peptic Ulcer

Common causes

Helicobacter pylori infection
NSAIDs
Critical illness (stress-related mucosal damage)

Uncommon causes of chronic peptic ulcer

Idiopathic (non–*H. pylori*, non-NSAID peptic ulcer)
Hypersecretion of gastric acid (eg, Zollinger-Ellison syndrome)
Viral infections (eg, cytomegalovirus)
Vascular insufficiency (eg, crack cocaine associated)
Radiation therapy
Chemotherapy (eg, hepatic artery infusions)
Infiltrating disease (eg, Crohn's disease), Roux-en-Y gastric bypass surgery

Diseases and medical conditions associated with chronic peptic ulcer

Cirrhosis
Chronic renal failure
Chronic obstructive pulmonary disease
Cardiovascular disease
Organ transplantation

NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 50-4 Risk Factors Associated with NSAID-Induced Ulcers and Upper GI Complications[a]

Age >65
Previous peptic ulcer
Previous ulcer-related upper GI complication
High-dose NSAIDs
Multiple NSAID use
Selection of NSAID (eg, COX-1 vs COX-2 inhibition)
NSAID-related dyspepsia
Aspirin (including cardioprotective dosages)
Concomitant use of
NSAID plus low-dose aspirin
Oral bisphosphonates (eg, alendronate)
Corticosteroids (Systemic)
Anticoagulant or coagulopathy
Antiplatelet drugs (eg, clopidogrel)
Selective serotonin reuptake inhibitor
Chronic debilitating disorders (eg, cardiovascular disease, rheumatoid arthritis)
Helicobacter pylori infection
Cigarette smoking
Alcohol consumption

[a]Combinations of risk factors are additive.

Diagnosis

✓ Clinical Presentation:

- Epigastric pain or dyspepsia may be presenting symptoms; however, symptoms are not always predictive of the presence of ulcers.

- In the presence of alarm symptoms (weight loss, early satiety, bleeding, anemia, persistent vomiting, epigastric mass, and lack of response to PPI), EGD should be performed to assess for complications or alternate diagnoses.

Clinical Presentation of PUD

General

- Mild epigastric pain or acute life-threatening upper GI complications

Symptoms

- Abdominal pain that is often epigastric and described as burning but may present as vague discomfort, abdominal fullness, or cramping
- A typical nocturnal pain that awakens the patient from sleep (especially between 12 and 3 AM)
- The severity of ulcer pain varies between patients and may be seasonal, occurring more frequently in the spring or fall; episodes of discomfort usually occur in clusters, lasting up to a few weeks and followed by a pain-free period or remission lasting from weeks to years
- Changes in the character of the pain may suggest the presence of complications
- Heartburn, belching, and bloating often accompany the pain
- Nausea, vomiting, and anorexia are more common for patients with gastric ulcer than with duodenal ulcer but may also be signs of an ulcer-related complication

Signs

- Weight loss associated with nausea, vomiting, and anorexia
- Complications including ulcer bleeding, perforation, penetration, or obstruction

Laboratory tests

- Gastric acid secretory studies
- The hematocrit and hemoglobin are low with bleeding, and stool hemoccult tests are positive
- Tests for *Helicobacter pylori* (see Table 51-6)

Diagnostic tests

- Fiber-optic upper endoscopy (esophagogastroduodenoscopy) detects more than 90% of peptic ulcers and permits direct inspection, biopsy, visualization of superficial erosions, and sites of active bleeding
- Upper GI radiography with barium has been replaced with upper endoscopy as the diagnostic procedure of choice for suspected peptic ulcer

GI, gastrointestinal; PUD, peptic ulcer disease.

✓ Diagnostic Testing:

- Endoscopy is the gold standard for diagnosis of peptic ulcers; tissue sampling for H. pylori or cancer can also be performed.

- Carbon-labeled urea breath testing is the most accurate noninvasive test for diagnosis, with sensitivity and specificity of 95%; it is often used to document successful eradication after therapy of H. pylori infection.

Treatment/ Desired Outcome

- ✓The goal for patients with PUD (regardless of the cause), is to relieve ulcer symptoms, heal the ulcer, and prevent recurrence.

- ✓In patients with NSAID- induced ulcer, withdrawal of the offending agent and careful consideration of the need for continued NSAID therapy can reduce the risk of ulcer recurrence.

- ✓In H. pylori–positive patients with an active ulcer, a previously documented ulcer, or a history of an ulcer-related complication, the goal is to eradicate H. pylori, heal the ulcer, and cure the disease.

- ✓Successful eradication heals ulcers and reduces the risk of recurrence for most patients.

✓ Medications

- Regardless of etiology, acid suppression forms the mainstay of therapy of PUD.
- Eradication of H. pylori is recommended in all patients who test positive, esp. in patients with an active ulcer, a documented history of a prior ulcer, or a history of ulcer-related complications.
- Two antibiotics and a PPI (triple therapy) was the mainstay of treatment for H. pylori eradication but strategy has shifted toward two antibiotics, PPI, and bismuth quadruple therapy because of rising incidence of clarithromycin resistance.
- A 10-day course of quadruple therapy was shown to be more effective than 14-day triple therapy.
- Another recommended first line therapy is concomitant therapy (PPI, clarithromycin, with amoxicillin or metronidazole) for 10 to 14 days.

- Levofloxacin-based sequential or triple therapy may be superior to standard triple therapy (clarithromycin, amoxicillin, PPI).

- Other regimens may include LOAD (levofloxacin, omeprazole, nitazoxanide, and doxycycline) for 7– 10 days; ofloxacin, azithromycin, omeprazole, and bismuth for 14 days; and PPI, bismuth, tetracycline, and levofloxacin for 10 days.

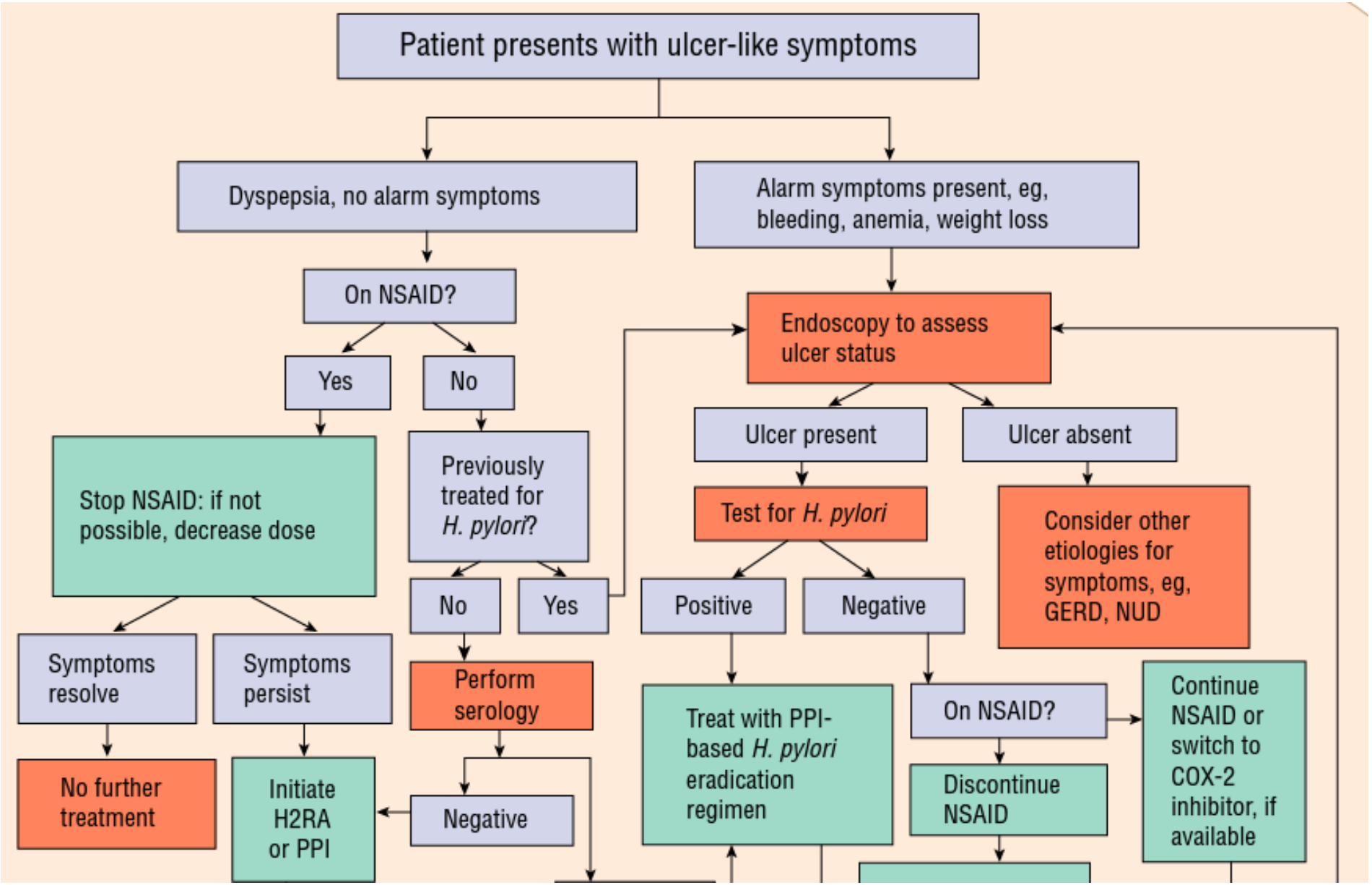
- Patients previously exposed to a macrolide antibiotic should be treated with a regimen that does not include clarithromycin.

- When using salvage regimens after initial treatment failure, choose drugs that have not been used before.

- NSAIDs and aspirin should be avoided when possible; if continued, maintenance PPI therapy is recommended.

- Antacids can be useful as supplemental therapy for pain relief in PUD.

- Nonpharmacologic measures:
  - Cessation of cigarette smoking should be encouraged.
  - Alcohol in high concentrations can damage the gastric mucosal barrier, but no evidence exists to link alcohol with ulcer recurrence.



Algorithm: Guidelines for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms.

NUD, nonulcer dyspepsia

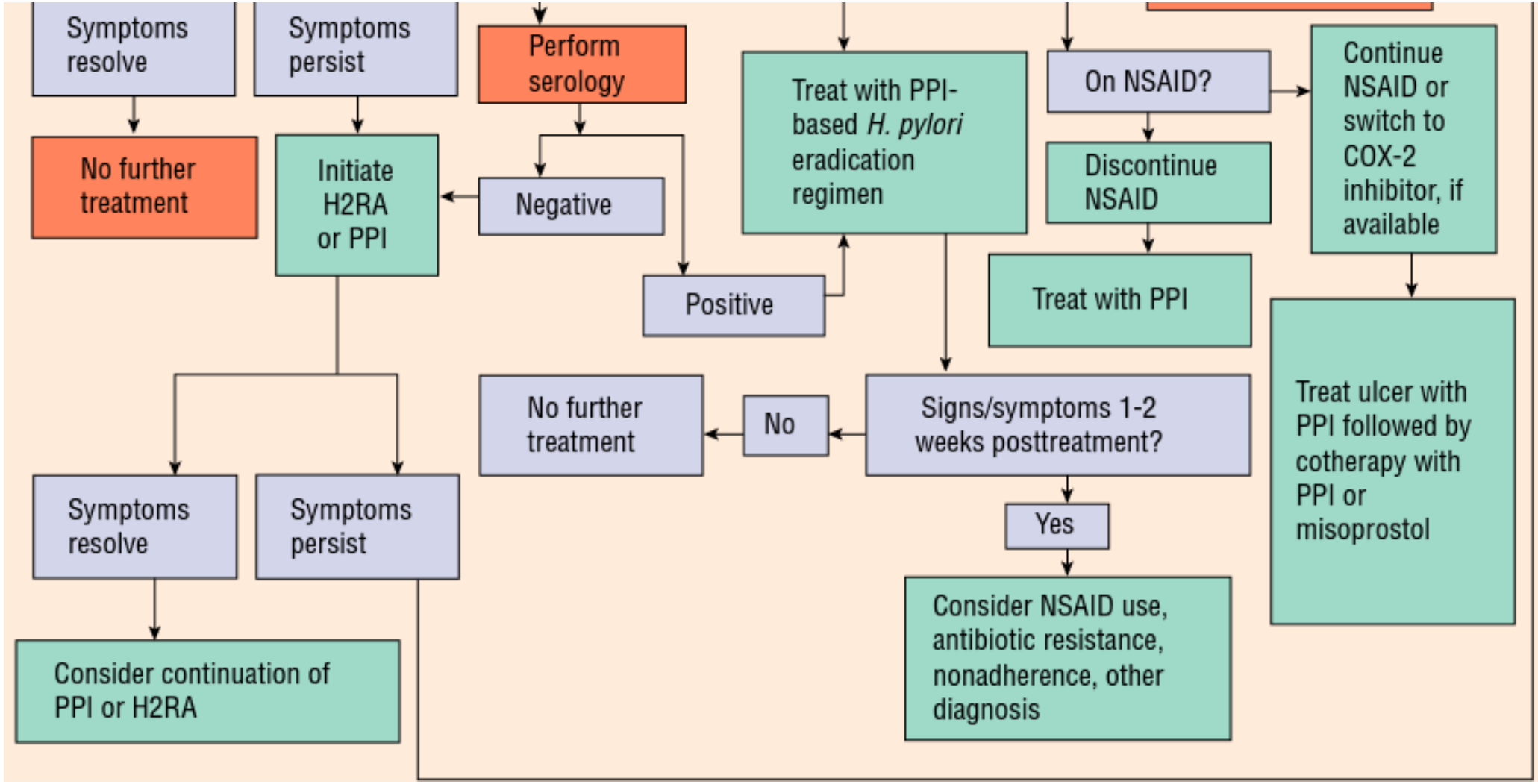

Symptoms resolve
Symptoms persist
Perform serology
Treat with PPI-based *H. pylori* eradication regimen
On NSAID?
Continue NSAID or switch to COX-2 inhibitor, if available
No further treatment
Initiate H2RA or PPI
Negative
Discontinue NSAID
Positive
Treat with PPI
Treat ulcer with PPI followed by cotherapy with PPI or misoprostol
No further treatment
No
Signs/symptoms 1-2 weeks posttreatment?
Symptoms resolve
Symptoms persist
Yes
Consider continuation of PPI or H2RA
Consider NSAID use, antibiotic resistance, nonadherence, other diagnosis

TABLE 50-7 Guidelines for the Eradication of *Helicobacter pylori* Infection

Indications for treatment of *H. pylori* infection

- Established indications for the treatment of *H. pylori* include active PUD, past history of PUD (unless eradication previously documented), MALT lymphoma, or after endoscopic resection of gastric cancer
- Controversial indications for the treatment of *H. pylori* infection include individuals with nonulcer dyspepsia*, gastroesophageal reflux disease, unexplained iron deficiency anemia, or idiopathic thrombocytopenic purpura; individuals taking long-term low-dose aspirin or initiating chronic treatment with NSAIDs; and individuals at high risk for gastric cancer

Initial treatment of *H. pylori* infection

- Bismuth quadruple therapy and concomitant (non-bismuth quadruple therapy), both administered for 10-14 days, are recommended first-line treatments.
- In penicillin-allergic patients, bismuth quadruple therapy is the preferred initial treatment. Consider referral for allergy testing in patients who fail initial therapy, since many patients who report penicillin allergy are not truly allergic.
- Alternate initial therapies (conditionally recommended) include: Sequential, hybrid, levofloxacin-triple, levofloxacin sequential, and LOAD therapies (see Table 50-8 for a full description).

* Nonulcer dyspepsia (older term) is the same as functional dyspepsia (newer & preferred term).

Eradication of *H. pylori* after initial treatment failure

- Bismuth quadruple therapy or levofloxacin regimens are preferred if the patient received initial treatment with clarithromycin.
- Clarithromycin- or levofloxacin-containing regimens are preferred if patients received initial treatment with bismuth quadruple therapy.
- Selection of the optimal salvage regimen should be based on local antibiotic resistance profile, if available, and the patient's prior antibiotic history.

TABLE 50-8 Drug Regimens Used to Eradicate *Helicobacter pylori*

Regimen	Duration	Drug #1	Drug #2	Drug #3	Drug #4
Proton Pump Inhibitor–Based Triple Therapy[a]	14 days	PPI once or twice daily[b]	Clarithromycin 500 mg twice daily	Amoxicillin 1 g twice daily *or* metronidazole 500 mg twice daily	
Bismuth Quadruple Therapy[a]	10-14 days	PPI or H2RA once or twice daily[b,c]	Bismuth subsalicylate[d] 525 mg four times daily	Metronidazole 250-500 mg four times daily	Tetracycline 500 mg four times daily
Non-Bismuth Quadruple or "Concomitant" Therapy[e]	10-14 days	PPI once or twice daily on days 1-10[b]	Clarithromycin 250–500 mg twice daily on days 1-10	Amoxicillin 1 g twice daily on days 1-10	Metronidazole 250-500 mg twice daily on days 1-10
Sequential Therapy[e]	10 days	PPI once or twice daily on days 1-10[b]	Amoxicillin 1 g twice daily on days 1-5	Metronidazole 250–500 mg twice daily on days 6-10	Clarithromycin 250-500 mg twice daily on days 6-10
Hybrid Therapy[e]	14 days	PPI once or twice daily on days 1-14[b]	Amoxicillin 1 g twice daily on days 1-14	Metronidazole 250–500 mg twice daily on days 7-14	Clarithromycin 250-500 mg twice daily on days 7-14
Levofloxacin triple	10-14 days	PPI twice daily	Levofloxacin 500 mg daily	Amoxacillin 1 g twice daily	
Levofloxacin Sequential	10 days	PPI twice daily on days 1-10	Amoxicillin 1 g twice daily on days 1-~~10~~ 5	Levofloxacin 500 mg once daily on days 6-10	Metronidazole 500 mg twice daily on days 6-10
LOAD	7-10 days	Levofloxacin 250 mg once daily	Omeprazole (or other PPI) at high dose once daily	Nitazoxanide (Alinia) 500 mg twice daily	Doxycycline 100 mg once daily
Rifabutin-based triple therapy	14 days	Omeprazole 40 mg every 8 hours	Amoxicillin 1 g every 8 hours	Ribabutin 50 mg every 8 hours	

a Although treatment is minimally effective if used for 7 days, 10-14 days is recommended. The antisecretory drug may be continued beyond antimicrobial treatment for patients with a history of a complicated ulcer, for example, bleeding, or in heavy smokers.

b Standard PPI peptic ulcer healing dosages given once or twice daily.

c Standard H2RA peptic ulcer healing dosages may be used in place of a PPI.

d Bismuth subcitrate potassium (biskalcitrate) 140 mg, as the bismuth salt, is contained in a prepackaged capsule (Pylera), along with metronidazole 125 mg and tetracycline 125 mg; three capsules are taken with each meal and at bedtime; a standard PPI dosage is added to the regimen and taken twice daily. All medications are taken for 10 days.

e Requires validation as first-line therapy in the United States.

TABLE 50-9 Drug Dosing Table

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Proton Pump Inhibitors					
Omeprazole, sodium bicarbonate	Prilosec, Zegerid	40 mg daily	20-40 mg/day	Consider adjustment for hepatic disease	Pregnancy Category C
Lansoprazole	Prevacid, various	30 mg daily	15-30 mg/day	Consider adjustment for hepatic disease	Pregnancy Category B
Rabeprazole	Aciphex	20 mg daily	20-40 mg/day	Use with caution in severe hepatic disease	Pregnancy Category B
Pantoprazole	Pantoprazole, various	40 mg daily	40-80 mg/day	Consider adjustment for severe hepatic disease	Pregnancy Category B
Esomeprazole	Nexium	40 mg daily	20-40 mg/day	Limit dose to 20 mg/day in severe hepatic disease	Pregnancy Category B
Dexlansoprazole	Dexilant	30-60 mg daily	30-60 mg/day	Consider dose limit of 30 mg/day in moderate hepatic impairment, dose not established in severe hepatic disease	Pregnancy Category B
H2-Receptor Antagonists					
Cimetidine	Tagamet, various	300 mg four times daily, 400 mg twice daily, or 800 mg at bedtime	800-1,600 mg/day in divided doses	Adjust dose for renal and severe hepatic impairment	Pregnancy Category B
Famotidine	Pepcid, various	20 mg twice daily, or 40 mg at bedtime	20-40 mg/day	Adjust dose for renal impairment	Pregnancy Category B
Nizatidine	Axid, various	150 mg twice daily, or 300 mg at bedtime	150-300 mg/day	Adjust dose for renal impairment	Pregnancy Category B

Table 50-9 Continued: Drug Dosing Table

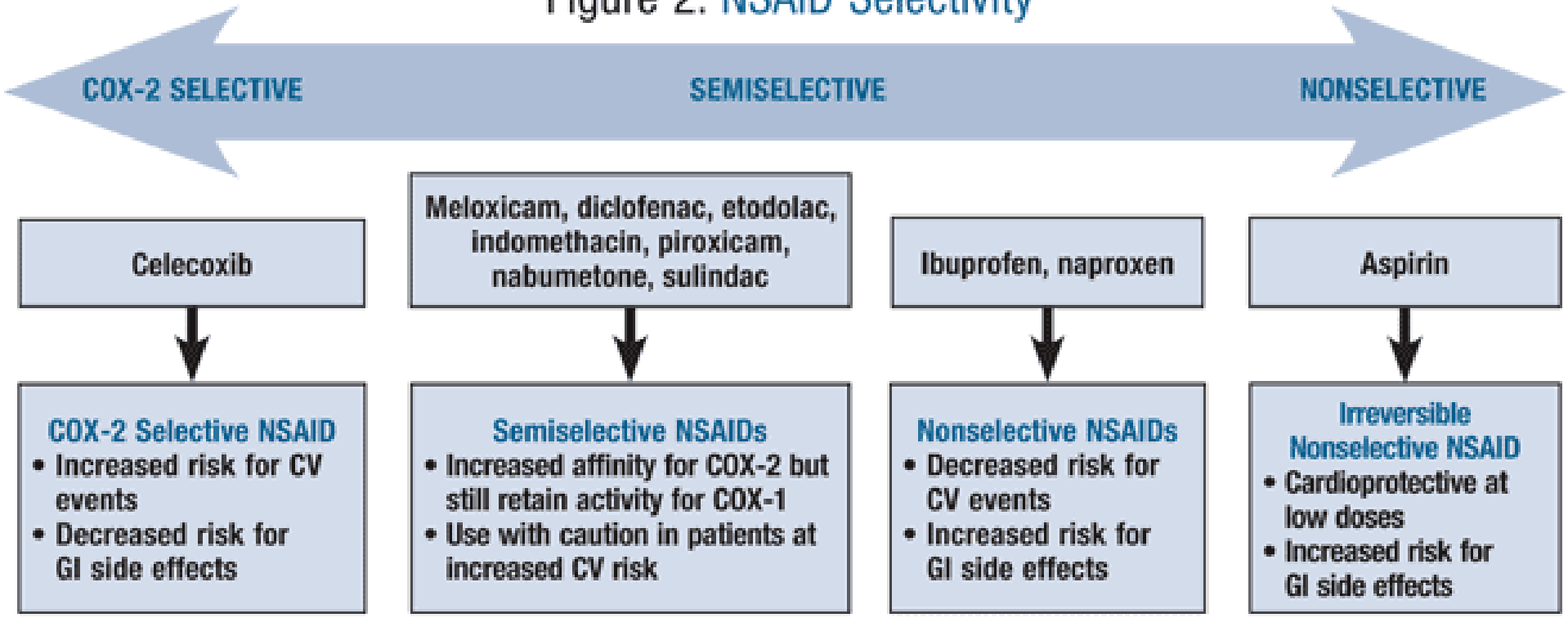
Ranitidine	Zantac, various	150 mg twice daily, or 300 mg at bedtime	150-300 mg/day	Adjust dose for renal impairment	Pregnancy Category B
Mucosal Protectants					
Sucralfate	Carafate, various	1 g four times daily, or 2 g twice daily	2-4 g/day		Aluminum may accumulate in renal failure, Pregnancy Category B
Misoprostol	Cytotec	100-200 mcg four times daily	400-800 mcg/day		Pregnancy Category X

TABLE 50-11 Prevention of Peptic Ulcer Disease in Patients Receiving Chronic NSAID Therapy

	Low Gastrointestinal Risk[a]	High Gastrointestinal Risk[b,c]
Low Cardiovascular Risk	Nonselective NSAIDs	Nonselective NSAIDs plus PPI; celecoxib plus PPI[d]
High Cardiovascular Risk[e]	Naproxen; add PPI if patient is taking aspirin	No NSAIDs; naproxen plus PPI; low-dose celecoxib plus aspirin plus PPI may be an alternative option[f]

a No risk factor
b Presence of risk factors (patients 60 years or older, history of peptic ulcers, receiving concomitant antiplatelet agents, anticoagulants, corticosteroids, or selective serotonin reuptake inhibitors).
c In patients with prior history of ulcers, adopt test-and-treat strategy to exclude H. pylori infection.
d Consider when patients have complicated ulcer history or presence of multiple risk factors.
e Use risk calculator (eg, Framingham or ASCVD risk calculators) to estimate cardiovascular risk on the basis of several variables. Patients with a history of cardiovascular events or diabetes are considered high cardiovascular risk.
f NSAIDs with increasing selectivity for COX-2 (ie, celecoxib) have been associated with increased cardiovascular risk, and this risk appears to be increased in patients with established cardiovascular disease. Patients with cardiovascular disease or risk factors, recommendations for pain management (in the order listed) include: acetaminophen, aspirin, tramadol, opioids (short-term), nonacetylated salicylates (eg, diflunisal), NSAIDs with low COX-2 selectivity (eg, naproxen), NSAIDs with some COX-2 selectivity (eg, nabumetone), and COX-2 selective agents (ie, celecoxib).

Figure 2. NSAID Selectivity



COX: cyclooxygenase; CV: cardiovascular; GI: gastrointestinal; NSAID: nonsteroidal anti-inflammatory drug. Source: References 3, 17.

US Pharm. 2014;39(3):35-38. https://www.uspharmacist.com/article/cardiovascular-risk-associated-with-nsaids-and-cox2-inhibitors

✓ Surgical Management

- Surgery is still occasionally required for intractable symptoms, GI bleeding, Zollinger– Ellison syndrome, and complicated PUD.

- Surgical options vary depending on the location of the ulcer and the presence of complications.

Complications

✓ GI bleeding

✓ Gastric outlet obstruction can occur with ulcers close to the pyloric channel and can manifest as nausea and vomiting, sometimes several hours after meals.

✓ Perforation occurs infrequently and usually necessitates emergent surgery.

✓ Pancreatitis can result from penetration into the pancreas from ulcers in the posterior wall of the stomach or duodenal bulb.

Monitoring/ Follow-Up

- ✓ Ulcer pain typically resolves in a few days when NSAIDs are discontinued and within 7 days upon initiation of antiulcer therapy.
- ✓ Patients with uncomplicated PUD are usually symptom free after treatment with any of the recommended antiulcer regimens. Persistent or recurrent symptoms within 14 days following treatment completion suggests failure of ulcer healing or H. pylori eradication or presence of an alternate diagnosis such as GERD.
- ✓ Eradication should be confirmed after treatment in all patients. Repeat EGD should be performed 8– 12 weeks after initial diagnosis of all gastric ulcers to document healing.
- ✓ Repeat endoscopic biopsy should be considered for nonhealing ulcers to exclude the possibility of a malignant ulcer.
- ✓ Duodenal ulcers are almost never malignant; therefore, documentation of healing is unnecessary in the absence of symptoms.

- ✓ The UBT and fecal antigen are the preferred methods to confirm H. pylori eradication when endoscopy is not indicated. Medication adherence should be assessed for patients who fail therapy.

Evaluation of therapeutic outcomes (1/2)

TABLE 51-13

Recommendations for Treating and Monitoring Patients with *Helicobacter Pylori*–Associated and NSAID-Induced Ulcers

***H. pylori*–associated ulcer**

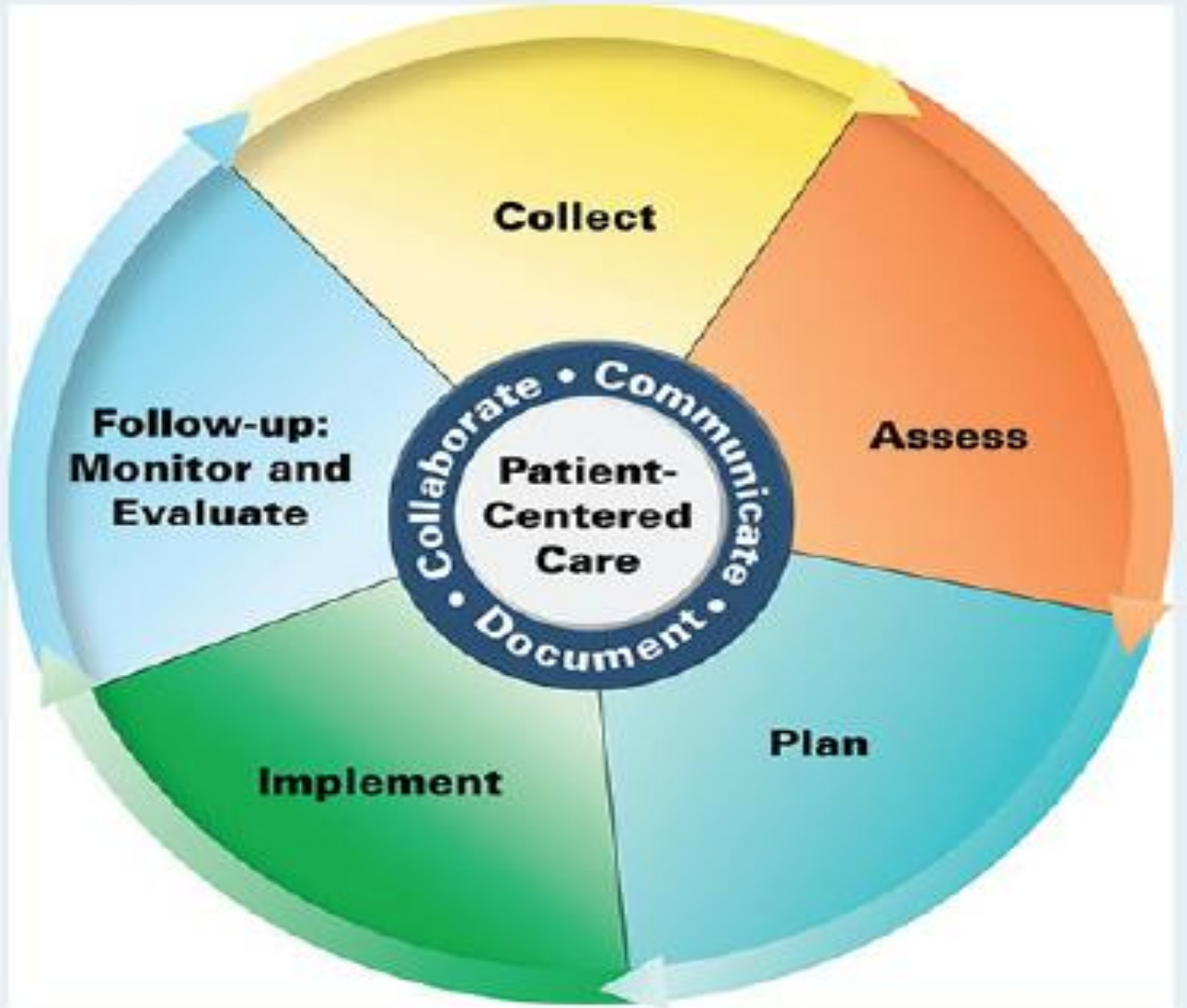
1. Recommend drug treatment as presented in the chapter text. See Tables 50–7 and 50–8
2. Assess patient allergies to determine if allergic to penicillin (or other antibiotics) so that drug regimens that contain penicillin (or other antibiotics) can be avoided. Avoid regimens that contain tetracycline in children
3. Assess patient use of alcohol or alcohol-containing products with metronidazole and oral birth control medications with antibiotics and counsel appropriately
4. Assess likelihood of nonadherence to the drug regimen as a cause of treatment failure
5. Recommend a different antibiotic combination if *H. pylori* eradication fails and a second treatment is planned
6. Inform the patient of change in stool color when bismuth salicylate is included in an *H. pylori* eradication regimen
7. Assess and monitor patients for potential adverse effects, especially those associated with metronidazole, clarithromycin, and amoxicillin
8. Assess and monitor patients for potential drug interactions, especially those receiving metronidazole, clarithromycin, or cimetidine
9. Monitor patients for salicylate toxicity, especially patients receiving co-therapy with other salicylates and anticoagulants and patients with renal insufficiency
10. Monitor patients for persistent or recurrent symptoms within 14 days after completion of a course of *H. pylori* eradication therapy
11. Provide education to patients who are receiving *H. pylori* eradication therapy and include why antibiotic and antiulcer combinations are used; when and how to take medications; adverse effects; alarm symptoms; the importance of adherence to the entire course of drug treatment; and contact their healthcare provider if alarm symptoms develop (eg, blood in the stools, black tarry stools, vomiting, severe abdominal pain), or if symptoms persist or return after *H. pylori* eradication

Evaluation of therapeutic outcomes (2/2)

NSAID-induced ulcer

1. Recommend drug treatment as presented in the chapter text
2. Assess risk factors for NSAID-induced ulcers and ulcer-related complications and recommend appropriate strategies for reducing ulcer risk (see Table 51-14)
3. Weigh patient risk factors for NSAID-related GI bleeding and cardiovascular events when selecting a strategy to reduce ulcer risk
4. Recommend eradication treatment for *H. pylori*–positive patients taking NSAIDs
5. Monitor patients for signs and symptoms of NSAID-related upper GI complications
6. Assess and monitor patients for potential drug interactions and adverse effects (especially misoprostol)
7. Provide patient education to patients who are at risk of NSAID-induced ulcers or GI-related complications and include why co-therapy is used with nonselective NSAIDs, when and how to take medications, adverse effects, alarm symptoms, when to contact their healthcare provider, and the importance of adherence to drug treatment

Patient Care Process for Peptic Ulcer Disease (PUD)



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family) especially prior history of *H. pylori* infection, previous peptic ulcers, or previous upper GI disorders (see Table 51-4)
- Social history (eg, tobacco and ethanol use) as well as recent medical procedures and stress levels (see Table 51-2)
- Current medications, especially NSAIDS (nonprescription and prescription) use of nonprescription proton pump inhibitors (PPIs), other acid reflux treatments, anticoagulants, and antiplatelet medications. If prior NSAID use, note medication, dosage, and duration of use
- Pain: presence or absence, rating (1-10), quality, and location (see Table 51-5)
- Objective Data
    - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
    - Labs including hemoglobin (Hgb), hematocrit, assessment of kidney and liver function, gastric acid secretory studies, and stool hemoccult
    - Urea breath test (UBT) for detection of *H. pylori*. Follow-up culture with endoscopy recommended (see Table 51-6)

- Imaging studies: Upper endoscopy

Assess

- Hemodynamic stability (eg, systolic BP >90 mm Hg, Hr >110 bpm, O_2 sat <90% [0.90])
- Presence of active gastric bleeding based on imaging studies
- Presence of GI-bleed provoking factors (low platelets, anticoagulant/antiplatelet use, NSAID use, age >65, recent surgery, severe co-morbidities, eg, cardiovascular disease) (see Table 51-4)
- Presence/absence of *H. pylori*
- Emotional status (eg, anxiety, depression, stress levels)
- Ability/willingness to pay for ulcer treatment options
- Ability/willingness to discontinue NSAIDS and switch to another pain reliever, if applicable
- Ability/willingness to obtain laboratory monitoring tests (eg, *H. pylori* status to confirm eradication) (see Table 51-7)
- Ability/willingness to follow a multiple drug regimen for 10 to 14 days, with some doses to be taken at specific times

Plan

- Drug therapy regimen based on ulcer classification and patient's antibiotic tolerance (eg, penicillin allergy) (see)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information, medication administration)
- Self-monitoring for resolution of symptoms such as epigastric pain, dyspepsia, when to seek emergency medical attention

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (endoscopic *H. pylori* culture, lab tests: CBC, serum electrolytes, renal/liver function; see Table 51-12)

Follow-Up: Monitor and Evaluate

- Resolution of PUD symptoms such as epigastric pain and dyspepsia
- Presence of adverse effects (eg, N/V/D [PPIs, H2RAs, metronidazole, other antibiotics]), headaches (PPIs and H2RAs)
- Patient adherence to treatment plan using multiple sources of information
- Monitor patient for symptoms of PUD recurrence, especially if their risk factors change

**Collaborate with patient, caregivers, and other healthcare professionals.*