Peptic Ulcer Disease (PUD)

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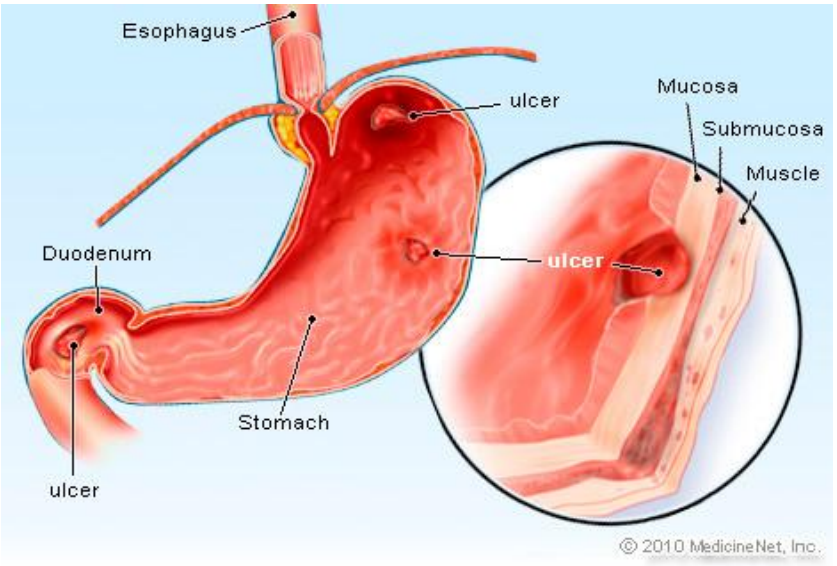
Board Specified Clinical pharmacy

What's the problem?

- PUD is one of the most common gastroenterologic diseases affecting the upper GI tract.
- A peptic ulcer is a defect in the gastric or duodenal mucosa that extends through the muscularis mucosa into the deeper layers of the wall.



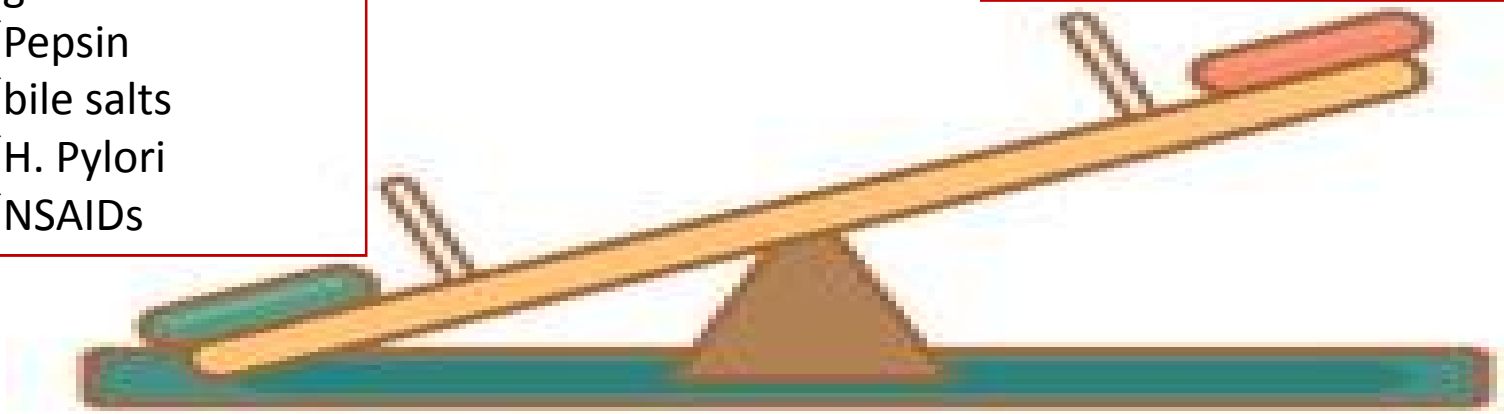
Phatophysiology

Mucosal defensive mechanisms

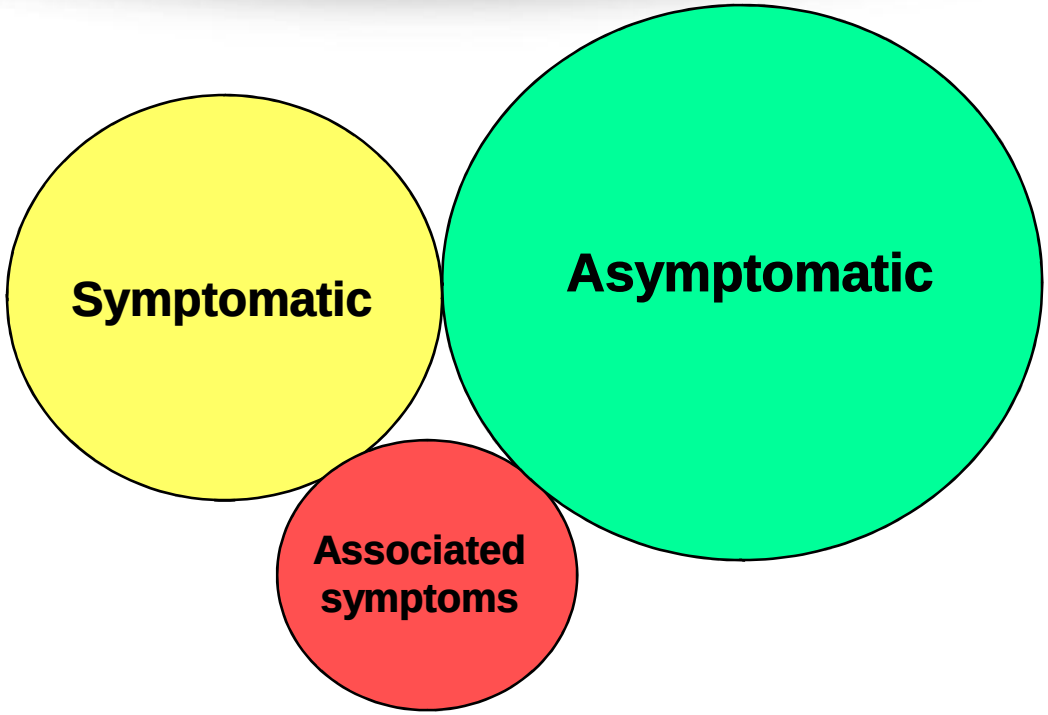
- ✓mucosal blood flow
- ✓Mucus
- ✓mucosal bicarbonate secretion
- ✓mucosal cell restitution
- ✓epithelial cell renewal

Aggressive factors:

- ✓gastric acid
- ✓Pepsin
- ✓bile salts
- ✓H. Pylori
- ✓NSAIDs



Clinical manifestation



Asymptomatic

- Approximately 70 percent of peptic ulcers are asymptomatic.
- Patients with silent peptic ulcers may later present with ulcer-related complications such as hemorrhage or perforation.
- Between 43 and 87 percent of patients with bleeding peptic ulcers present without antecedent dyspepsia or other heralding gastrointestinal symptom

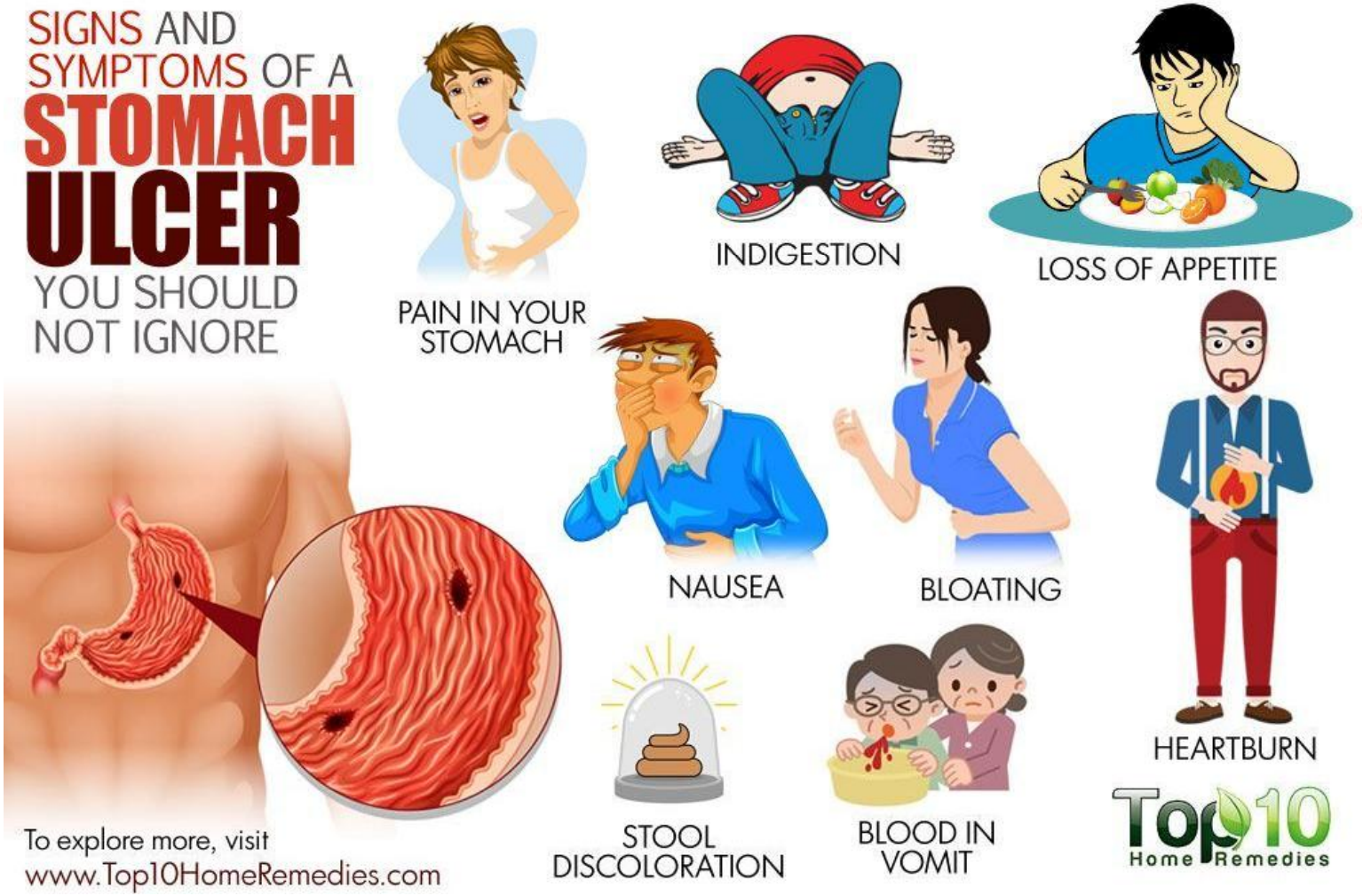
Symptomatic

Upper abdominal pain or discomfort is the most prominent symptom in patients with peptic ulcers.

Occasionally the discomfort localizes to the right or left upper quadrants of the hypochondrium

- ✓ **duodenal ulcers:** The "classic" pain of duodenal ulcers occurs 2-5 hours after a meal when acid is secreted in the absence of a food buffer, and at night (between about 11 PM and 2 AM) when the circadian pattern of acid secretion is maximal.
- ✓ **peptic ulcers:** particularly pyloric channel ulcers, may have food-provoked symptoms due to visceral sensitization and gastroduodenal dysmotility These symptoms include epigastric pain that worsens with eating, postprandial belching and epigastric fullness, early satiety, fatty food intolerance, nausea, and occasional vomiting.

Associated symptoms



Ulcer complications

Complications may be heralded by new ulcer symptoms or a change in symptoms or may occur in the absence of typical symptoms:

- ✓ **Bleeding**
- ✓ **Gastric outlet obstruction**
- ✓ **Penetration and fistulization**
- ✓ **Perforation**

complication

- The **bleeding** may be occult (hidden), present as melena (black-colored stools), or hematemesis (vomiting of blood).
- The pain associated with **perforation** is typically sudden, sharp, and severe, beginning in the epigastric area but quickly spreading throughout the upper abdominal area.
- Gastric outlet **obstruction**, the least frequent complication, is caused by previous ulcer healing and scarring or edema of the pylorus or duodenal bulb and can lead to symptoms of gastric retention, including early satiety, bloating, anorexia, nausea, vomiting, and weight loss.

Diagnosis

- **Laboratory findings**

✓ Most patients with uncomplicated peptic ulcers have a normal CBC.

✓ Patients may have iron deficiency anemia due to recurrent GI blood loss.

✓ Patients with acute gastrointestinal perforation may have leukocytosis.

✓ Fasting serum gastrin concentrations are only recommended for patients who are unresponsive to therapy.

- **Imaging findings**

✓ focal discontinuity of the mucosal hyperenhancement.

✓ Luminal outpouching

✓ gastric wall thickening

✓ perigastric or periduodenal inflammationand

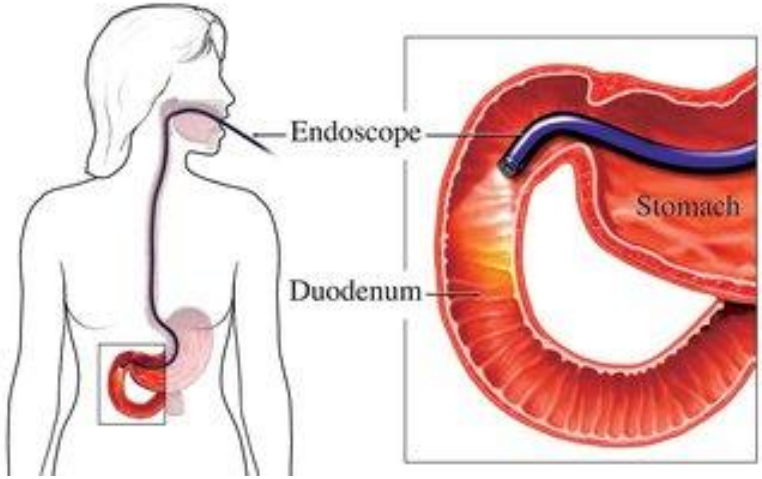
Abdominal CT is not sensitive for uncomplicated peptic ulcer disease and superficial ulcers may be missed

Endoscopy

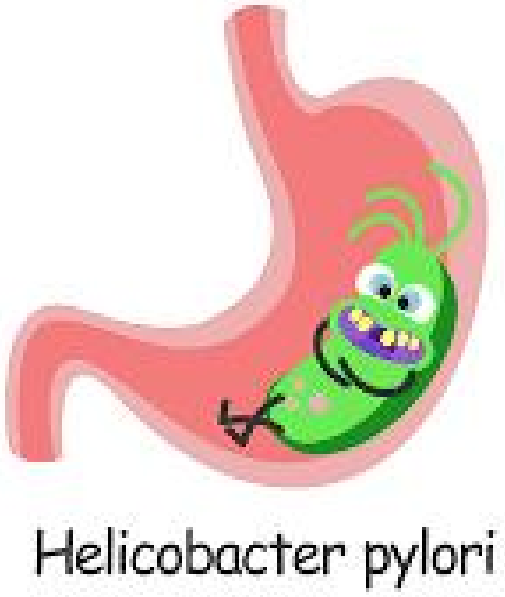
Endoscopy is the most accurate diagnostic test for PUD

- The sensitivity of upper endoscopy in the detection of gastroduodenal lesions is approximately 90 percent but varies based on the location of the ulcer and the experience of the endoscopis.
- **Biopsy:**

✓ Malignant appearing ulcers
✓ Selected benign appearing ulcers
✓ Specific etiology suspected
✓ Biopsy for H. pylori

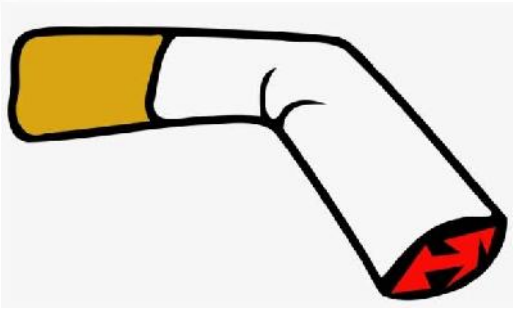


Etiology



There is no one sign or symptom that differentiates an H. pylori–related ulcer from an NSAID-induced ulcer

smoking



- **Mechanisms including:**

✓ delayed gastric emptying

✓ inhibition of pancreatic bicarbonate secretion

✓ promotion of duodenogastric reflux

✓ reduction in mucosal prostaglandin production

✓ increased gastric acid secretion

- Although cigarette smoking exacerbates PUD, there is insufficient evidence to conclude that it causes a peptic ulcer
- it is hypothesized that smoking or nicotine might provide an environment for H. pylori infection.

Etiologies and disease associations for peptic ulcer

Ulcers due to defined mechanisms
Infection
Helicobacter pylori
HSV
CMV
Helicobacter heilmannii
Other rare infections: TB, syphilis, mucormycosis, etc
Drug exposure (all probably worse when combined with NSAIDs or in high risk subjects)
NSAIDs and aspirin including low dose aspirin
Bisphosphonates (probably when combined with NSAIDs)
Clopidogrel (when combined with NSAIDs or in high risk subjects)
Corticosteroids (when combined with NSAIDs)
Sirolimus
Spironolactone (probable, no data with NSAID cotherapy)
Mycophenolate mofetil
Potassium chloride
Chemotherapy (eg, hepatic infusion with 5-fluorouracil)
Hormonal or mediator-induced, including acid hypersecretory states
Gastrinoma (Zollinger-Ellison syndrome)

H.Pylori

- H. pylori is a gram-negative, spiral-shaped bacillus that thrives in a micro aerophilic environment.
- The bacterium resides between the mucus layer and surface epithelial cells in the stomach or any location where gastric-type epithelium is found.
- exact method by which H. pylori induces hypochlorhydria is uncertain.
- it is hypothesized that its urease-producing ability hydrolyzes urea in the gastric juice and converts it to ammonia and carbon dioxide, which creates a neutral microenvironment that surrounds the bacterium.

Helicobacter pylori

H.Pylori

- The lifetime risk of exhibiting an endoscopic ulcer in H. pylori-positive individuals is **10% to 20%.**
- the risk for developing gastric cancer is **1% to 2%**
- H. pylori infection is causally linked to:

✓ chronic gastritis
✓ PUD
✓ mucosa-associated lymphoid tissue (MALT) lymphoma
✓ gastric cancer

Helicobacter pylori

Prevalence

- The prevalence of H. pylori varies by:

✓ geographic location

✓ socioeconomic status

✓ Ethnicity

✓ age

✓ more common in developing countries than in industrialized nations

- The overall prevalence in the United States is estimated to be **30% to 40%** but is higher in older individuals (50%–60%) than in children (10%–15%)

Helicobacter pylori

Transmition

- Usually during childhood from the infected person.
- by either the **gastro-oral** (vomitus) or **fecal–oral** (diarrhea) route or from fecal-contaminated water or food .
- H. pylori can also be transmitted through the use of inadequately sterilized endoscopes.

Helicobacter pylori

Diagnosis

- The selection of a specific method is influenced by the clinical circumstance and the availability and cost of the individual test.

- At least three biopsies are taken from different areas of the stomach because patchy distribution of H. pylori can result in false-negative results.

- antibiotics and bismuth salts should be withheld for 4 weeks, and H2RAs and PPIs for 1 to 2 weeks before endoscopic testing.

Helicobacter pylori

Diagnostic Tests for Helicobacter pylori Infection

Tests Using Gastric Mucosal Biopsy in Patients Undergoing Endoscopy
Rapid Urease Test
■ Tests for active H. pylori infection; >90% sensitivity and specificity. ■ In the presence of H. pylori urease, urea is metabolized to ammonia and bicarbonate resulting in an increase in pH, which changes the color of a pH-sensitive indicator. ■ Results are rapid (within 24 hours), and test is less expensive than histology or culture. ■ Withhold H_2RAs and PPIs 1–2 weeks before testing and antibiotics and bismuth salts 4 weeks before testing to reduce the risk of false negatives.
Histology
■ "Gold standard" for detection of active H. pylori infection; >95% sensitive and specific. ■ Permits further histologic analysis and evaluation of infected tissue (e.g., gastritis, ulceration, adenocarcinoma); tests for active H. pylori infection. ■ Results are not immediate; not recommended for initial diagnosis; more expensive than rapid urease test.
Culture
■ Permits sensitivity testing to determine antibiotic choice or resistance; 100% specific; tests for active H. pylori infection. ■ Use usually limited to patients who fail initial course of eradication therapy.
Polymerase Chain Reaction
■ Detects H. pylori DNA in gastric tissue; highly specific and sensitive. ■ High rate of false positives and false negatives; positive DNA does not correlate directly with presence of the organism; used primarily for research.

Nonendoscopic Tests That Do Not Use Gastric Mucosal Biopsy

Urea Breath Test

- Tests for active H. pylori infection; >95% sensitive and specific.
- Radiolabeled urea with either C^{13} or C^{14} is given orally; urease secreted by H. pylori in the stomach (if present) hydrolyzes radiolabeled urea to produce radiolabeled CO_2, which is exhaled and then quantified from the expired breath; radiation exposure is minimal.
- Withhold H_2RAs and PPIs 1–2 weeks before testing and antibiotics and bismuth salts 4 weeks before testing to reduce the risk of false negatives.
- Used to detect H. pylori before treatment and to document posttreatment eradication.
- Results usually take about 2 days; less expensive than tests that utilize gastric mucosal biopsy but more expensive than serologic tests; availability and reimbursement is inconsistent.

Antibody Detection (In-Office or Near Patient)

- Qualitative test; detects IgG antibodies to H. pylori in whole blood or fingerstick.
- Effective for primary diagnosis, but not of benefit in confirming eradication because antibodies to H. pylori remain positive for years after successful eradication of the infection.
- Results obtained quickly (usually within 15 minutes) but reduced sensitivity and specificity compared with laboratory-based tests; widely available and inexpensive.
- Results not affected by H_2RAs, PPIs, or bismuth; antibiotics given for other indications may result in a positive antibody test.

Antibody Detection (Laboratory)

- Quantitative test; detects IgG antibodies to H. pylori in serum using laboratory-based ELISA tests and latex agglutination techniques.
- More accurate than in-office tests; similar sensitivity and specificity to rapid urease biopsy and urea breath tests.
- Unable to determine if antibody is related to active or cured infection; antibody titers vary between individuals and take up to 6 months to 1 year to return to the uninfected state.
- Results not affected by H_2RAs, PPIs, or bismuth; antibiotics given for other indications may result in a positive antibody test.

Fecal Antigen Test

- An enzymatic immunoassay test that identifies H. pylori antigen in stool; sensitivity and specificity comparable to the UBT for initial diagnosis.
- H_2RAs, PPIs, antibiotics, and bismuth may cause false-negative results but to a lesser extent than the UBT.
- Considered an alternative to detecting H. pylori before treatment and documenting posttreatment eradication; patients may have a reluctance to obtain stool samples.

NSAIDs

- Endoscopically confirmed gastric and duodenal ulcers develop in **15% to 30%** of chronic NSAID users.
- **2% to 4%** experience ulcer-related bleeding or perforation.
- Gastric ulcer is most common and develops primarily in the antrum.
- NSAIDs may also cause ulcers in the esophagus and the colon, but these ulcers occur less frequently and differ in their underlying pathogenesis

Table 23-3

Risk Factors for Nonsteroidal Anti-Inflammatory Drug–Induced Ulcer and Ulcer-Related Upper Gastrointestinal Complications

Established
■ Confirmed prior ulcer or ulcer-related complication
■ Age >65 years
■ Multiple or high-dose NSAID use
■ Concomitant use of aspirin (including low cardioprotective dosages, e.g., 81 mg)
■ Concomitant use of an anticoagulant, corticosteroid, bisphosphonate, clopidogrel, or SSRI
■ Selection of NSAID (selectivity of COX-1 vs. COX-2)
Controversial
■ H. pylori
■ Alcohol consumption
■ Cigarette smoking

COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-infla
selective serotonin reuptake inhibitor.

Mechanism

- **systemically inhibiting protective prostaglandins** in the gastric mucosa. NSAIDs inhibit cyclooxygenase-1 (COX-1) The inhibition of COX-1 is associated with upper GI bleeding.
- diversion of arachidonate through the lipoxygenase pathway enhances **leukotriene synthesis** and results in vasoconstriction and release of oxygen free radicals, which may also contribute to impairment of mucosal defense.
- Aspirin and non-aspirin NSAIDs also have a **topical (direct) irritating effect** on the gastric mucosa, but the resulting inflammation and erosions usually heal within a few days.

COX1 OR 2?

- Two large randomized, placebo-controlled, multicenter, clinical trials compared the GI safety in patients taking COX-2 inhibitors with those taking nonselective and partially selective NSAIDs and reported a reduction of 50% to 60% in upper GI events with the COX-2 inhibitors.

- A 6-month trial (CLASS) of celecoxib in patients who were not taking low-dose aspirin revealed a statistically lower rate of ulcer complications when compared with that of ibuprofen or diclofenac but evaluation at 1 year found no GI safety advantage among those taking celecoxib.

Table 23-4

Selected Nonsteroidal Anti-Inflammatory Drugs

Salicylates
Acetylated: aspirin Nonacetylated: trisalicylate, salsalate
Nonsalicylates[a]
Nonselective (traditional) NSAIDs: ibuprofen, naproxen, tolmetin, fenoprofen, sulindac, indomethacin, ketoprofen, ketorolac, flurbiprofen, piroxicam Partially selective NSAIDs: etodolac, diclofenac, meloxicam, nabumetone
Selective COX-2 inhibitors: celecoxib[b], rofecoxib[c], valdecoxib[c]

[a]Based on COX-1/COX-2 selectivity ratio in vitro.
[b]Initially marketed as a COX-2 inhibitor, but current FDA labeling is consistent with nonselective and partially

✓The risk for upper GI events occur at any dosage even low doses of OTC NSAIDs

✓can occur at any time during treatment.

Prophylaxis

- co-therapy with a **PPI** or **misoprostol**
- the use of a **COX-2 inhibitor**
- various combinations of a **PPI, misoprostol, and a COX-2 inhibitor**
- Standard H2RA dosages should not be recommended as prophylactic co-therapy to reduce the risk of NSAID ulcers because they are not effective in reducing the risk of gastric ulcer
- Higher H2RA dosages (e.g., famotidine/ibuprofen 26.6/800 mg 3 times a day [DUEXIS]) reduce the risk of gastric and duodenal ulcer but are less effective than a PPI.
- H2RAs may be used when necessary to relieve NSAID-related dyspepsia

Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials

Benjamin Scally, Jonathan R Emberson*, Enti Spata, Christina Reith, Kelly Davies, Heather Halls, Lisa Holland, Kate Wilson, Neeraj Bhala, Christopher Hawkey, Marc Hochberg, Richard Hunt, Loren Laine, Angel Lanas, Carlo Patrono, Colin Baigent*

Findings We identified comparisons of gastroprotectant versus control in 849 trials (142 485 participants): 580 prevention trials (110 626 participants), 233 healing trials (24 033 participants), and 36 trials for the treatment of acute upper gastrointestinal bleeding (7826 participants). Comparisons of one gastroprotectant drug versus another were available in 345 trials (64 905 participants), comprising 160 prevention trials (32 959 participants), 167 healing trials (28 306 participants), and 18 trials for treatment of acute upper gastrointestinal bleeding (3640 participants). The median number of patients in each trial was 78 (IQR 44·0–210·5) and the median duration was 1·4 months (0·9–2·8). In prevention trials, gastroprotectant drugs reduced development of endoscopic ulcers (odds ratio [OR] 0·27, 95% CI 0·25–0·29; p<0·0001), symptomatic ulcers (0·25, 0·22–0·29; p<0·0001), and upper gastrointestinal bleeding (0·40, 0·32–0·50; p<0·0001), but did not significantly reduce mortality (0·85, 0·69–1·04; p=0·11). Larger proportional reductions in upper gastrointestinal bleeding were observed for PPIs than for other gastroprotectant drugs (PPIs 0·21, 99% CI 0·12–0·36; prostaglandin analogues 0·63, 0·35–1·12; H2RAs 0·49, 0·30–0·80; p_{het}=0·0005). Gastroprotectant drugs were effective in preventing bleeding irrespective of the use of non-steroidal anti-inflammatory drugs (p_{het}=0·56). In healing trials, gastroprotectants increased endoscopic ulcer healing (3·49, 95% CI 3·28–3·72; p<0·0001), with PPIs more effective (5·22, 99% CI 4·00–6·80) than prostaglandin analogues (2·27, 1·91–2·70) and H2RAs (3·80, 3·44–4·20; p_{het}<0·0001). In trials among patients with acute bleeding, gastroprotectants reduced further bleeding (OR 0·68, 95% CI 0·60–0·78; p<0·0001), blood transfusion (0·75, 0·65–0·88; p=0·0003), further endoscopic intervention (0·56, 0·45–0·70; p<0·0001), and surgery (0·72, 0·61–0·84; p<0·0001), but did not significantly reduce mortality (OR 0·90, 0·72–1·11; p=0·31). PPIs had larger

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BRIEF ARTICLE

Comparative study of therapeutic effects of PPI and H2RA on ulcers during continuous aspirin therapy

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infection, prevalence of ulcers before treatment, and lesion site between the two groups. The therapeutic effects were endoscopically evaluated as healed in 23 patients (88.5%) and not healed in 3 patients in the PPI group and as healed in 22 patients (84.6%) and not healed in 4 patients in the H2RA group. Abdominal symptoms before treatment were uncommon in both groups; the GSRS scores were not significantly reduced after treatment as compared with before treatment.

CONCLUSION: The healing rate of gastroduodenal ulcers during continuous use of low-dose aspirin was greater than 80% in both the PPI group and the H2RA group, with no significant difference between the two groups.

PPIs

Drug	Dose (adult)
Dexlansoprazole	30 to 60 mg
Esomeprazole	20 to 40 mg
Lansoprazole	30 mg
Omeprazole	20 to 40 mg
Pantoprazole	40 mg
Rabeprazole	20 mg
All administered by mouth daily before breakfast	

misoprostol

- Misoprostol reduces the risk of NSAID-induced gastric and duodenal ulcers as well as the risk of upper GI complications in high-risk patients.
- Initially, the recommended dosage was 200 mcg 4 times a day, but **diarrhea and abdominal cramping** limited its use. A lower daily dosage of **600 mcg/day** should be used because it reduces GI side effects and is comparable in efficacy.
- Dosage reductions to 400 mcg/day or less minimize GI side effects but compromise gastroprotective effects.
- containing misoprostol 200 mcg and diclofenac (50 mg or 75 mg) is available, but flexibility to individualize dosage is lost.

Table 23-3

Risk Factors for Nonsteroidal Anti-Inflammatory Drug–Induced Ulcer and Ulcer-Related Upper Gastrointestinal Complications

Established
■ Confirmed prior ulcer or ulcer-related complication
■ Age >65 years
■ Multiple or high-dose NSAID use
■ Concomitant use of aspirin (including low cardioprotective dosages, e.g., 81 mg)
■ Concomitant use of an anticoagulant, corticosteroid, bisphosphonate, clopidogrel, or SSRI
■ Selection of NSAID (selectivity of COX-1 vs. COX-2)
Controversial
■ H. pylori
■ Alcohol consumption
■ Cigarette smoking

COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-infla
selective serotonin reuptake inhibitor.

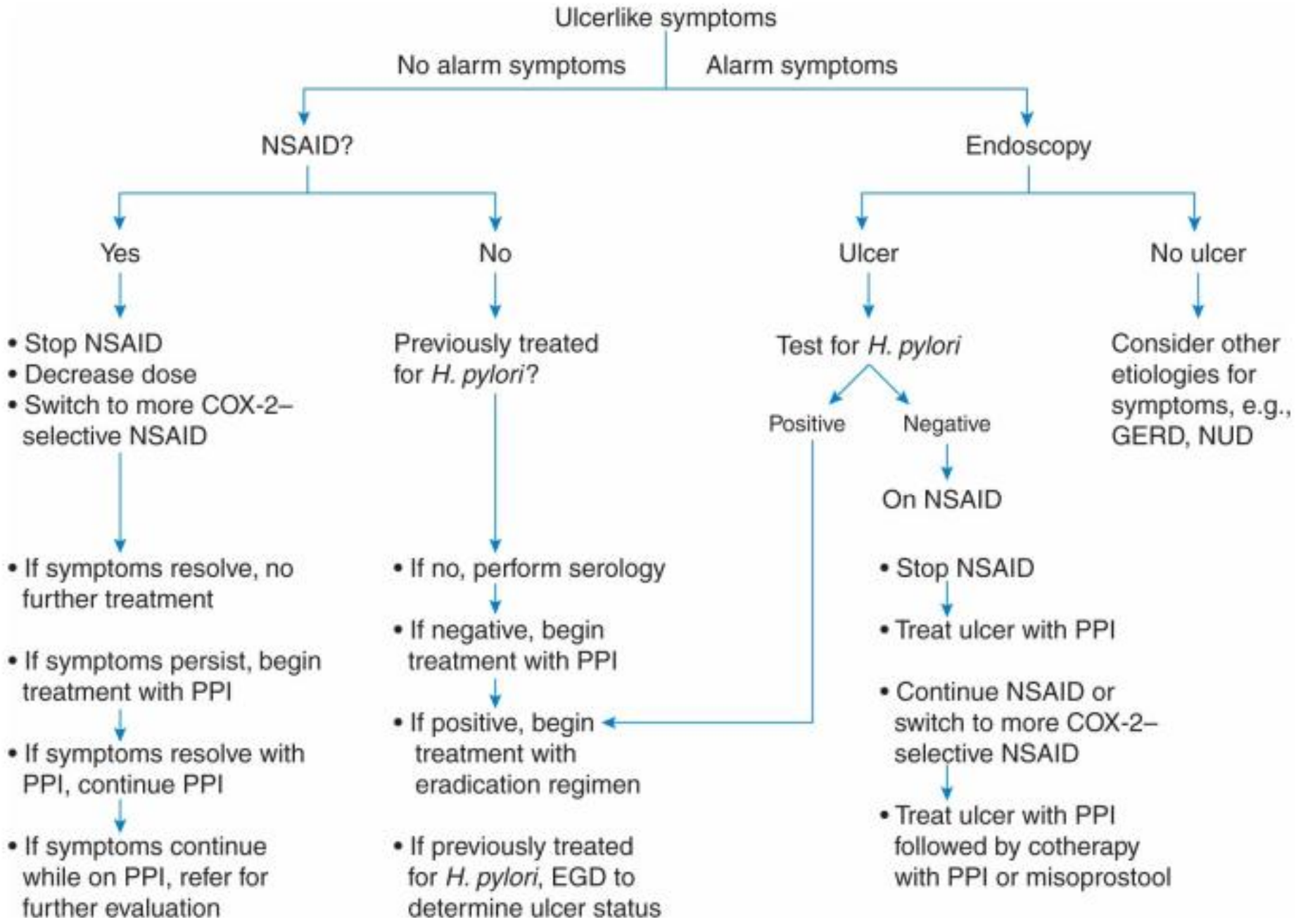
Treatment goal

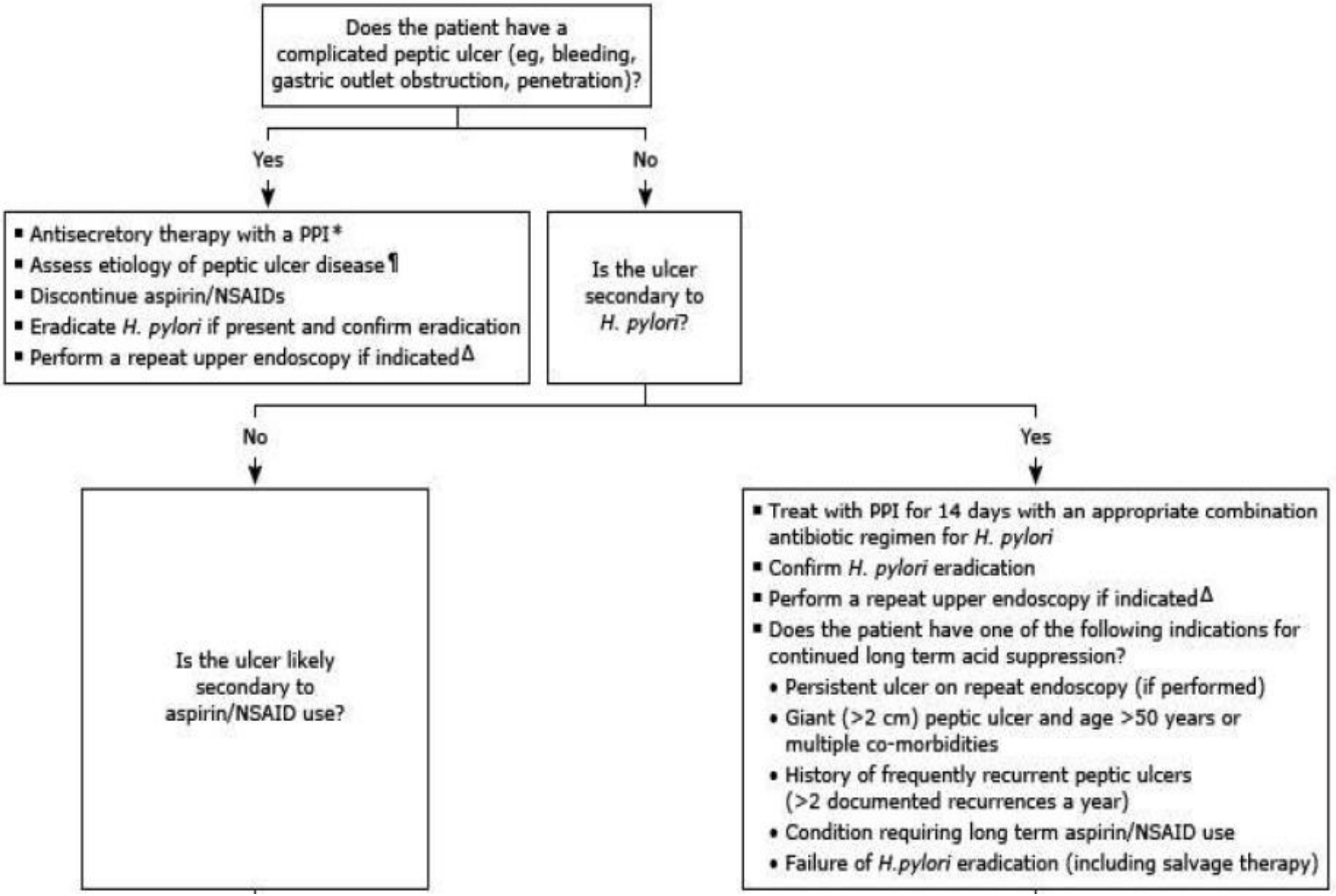
Treatment is aimed at:

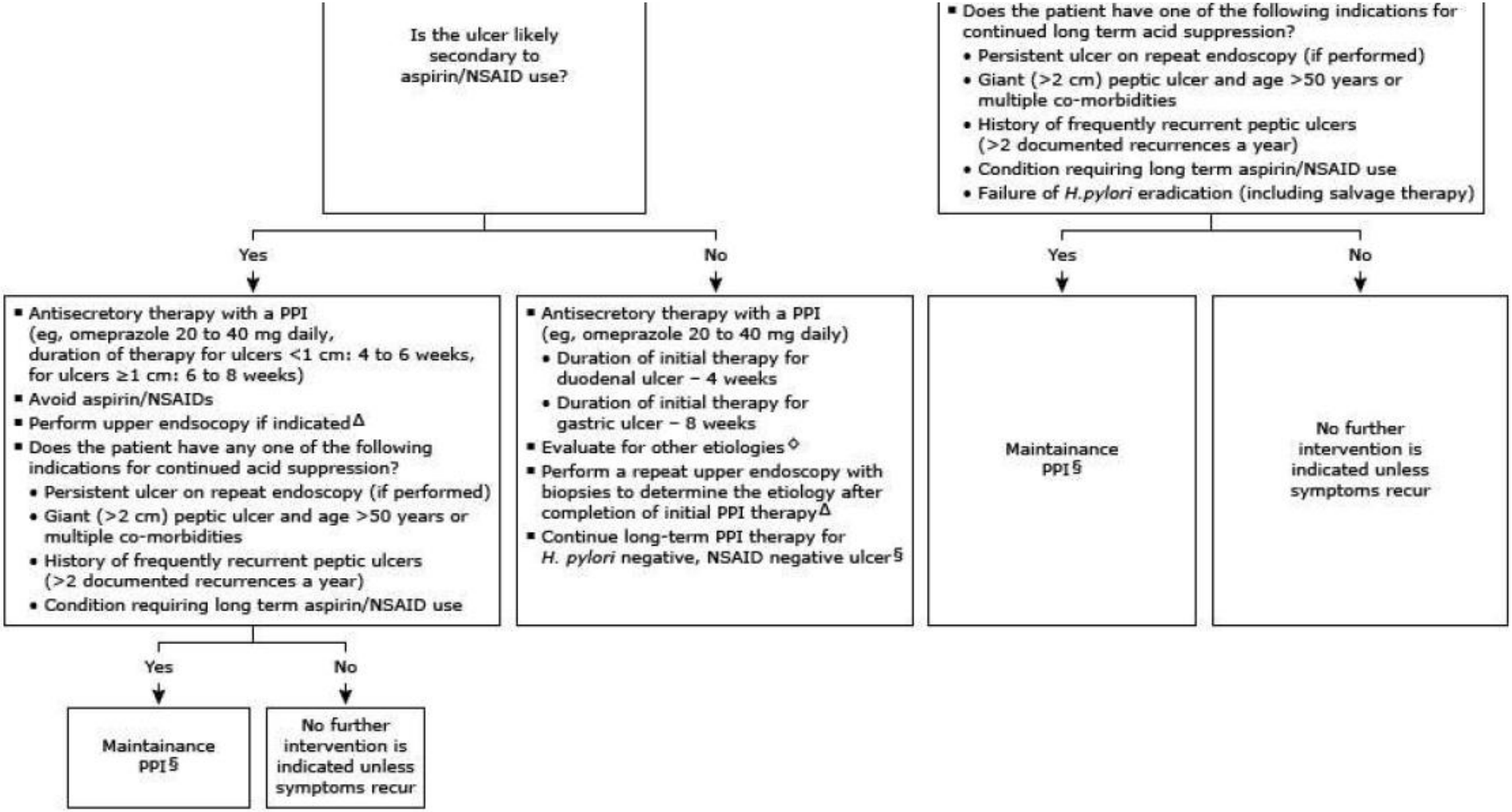
- ✓ relieving ulcer symptoms
- ✓ healing the ulcer
- ✓ preventing ulcer recurrence
- ✓ reducing ulcer-related complications

nonpharmacologic

- Patients with PUD should **discontinue NSAIDs** (including aspirin) if possible.
- Patients unable to tolerate certain foods and beverages (e.g., spicy foods, caffeine, and alcohol) may benefit from **dietary modifications**.
- **lifestyle modifications** like stress reduction.
- **Decreasing or stopping tobacco use**.
- **Probiotics**, especially strains of lactic acid–producing bacteria, such as Lactobacillus and Bifidobacterium; lactoferrin; and certain foods (e.g., cranberry juice, ginger, chili, oregano, some milk proteins) have been used to supplement H. pylori eradication


Ulcerlike symptoms
No alarm symptoms
Alarm symptoms
NSAID?
Endoscopy
Yes
No
Ulcer
No ulcer
• Stop NSAID
• Decrease dose
• Switch to more COX-2–selective NSAID
Previously treated for H. pylori?
Test for H. pylori
Positive
Negative
Consider other etiologies for symptoms, e.g., GERD, NUD
On NSAID
• If symptoms resolve, no further treatment
• If symptoms persist, begin treatment with PPI
• If symptoms resolve with PPI, continue PPI
• If symptoms continue while on PPI, refer for further evaluation
• If no, perform serology
• If negative, begin treatment with PPI
• If positive, begin treatment with eradication regimen
• If previously treated for H. pylori, EGD to determine ulcer status
• Stop NSAID
• Treat ulcer with PPI
• Continue NSAID or switch to more COX-2–selective NSAID
• Treat ulcer with PPI followed by cotherapy with PPI or misoprostool


Does the patient have a complicated peptic ulcer (eg, bleeding, gastric outlet obstruction, penetration)?
Yes
No
▪ Antisecretory therapy with a PPI*
▪ Assess etiology of peptic ulcer disease¶
▪ Discontinue aspirin/NSAIDs
▪ Eradicate H. pylori if present and confirm eradication
▪ Perform a repeat upper endoscopy if indicatedΔ
Is the ulcer secondary to H. pylori?
No
Yes
Is the ulcer likely secondary to aspirin/NSAID use?
▪ Treat with PPI for 14 days with an appropriate combination antibiotic regimen for H. pylori
▪ Confirm H. pylori eradication
▪ Perform a repeat upper endoscopy if indicatedΔ
▪ Does the patient have one of the following indications for continued long term acid suppression?
• Persistent ulcer on repeat endoscopy (if performed)
• Giant (>2 cm) peptic ulcer and age >50 years or multiple co-morbidities
• History of frequently recurrent peptic ulcers (>2 documented recurrences a year)
• Condition requiring long term aspirin/NSAID use
• Failure of H.pylori eradication (including salvage therapy)


Is the ulcer likely secondary to aspirin/NSAID use?
Yes
No
Antisecretory therapy with a PPI (eg, omeprazole 20 to 40 mg daily, duration of therapy for ulcers <1 cm: 4 to 6 weeks, for ulcers ≥1 cm: 6 to 8 weeks)
Avoid aspirin/NSAIDs
Perform upper endsocopy if indicated Δ
Does the patient have any one of the following indications for continued acid suppression?
Persistent ulcer on repeat endoscopy (if performed)
Giant (>2 cm) peptic ulcer and age >50 years or multiple co-morbidities
History of frequently recurrent peptic ulcers (>2 documented recurrences a year)
Condition requiring long term aspirin/NSAID use
Yes
No
Maintainance PPI §
No further intervention is indicated unless symptoms recur
Antisecretory therapy with a PPI (eg, omeprazole 20 to 40 mg daily)
Duration of initial therapy for duodenal ulcer – 4 weeks
Duration of initial therapy for gastric ulcer – 8 weeks
Evaluate for other etiologies ◇
Perform a repeat upper endoscopy with biopsies to determine the etiology after completion of initial PPI therapy Δ
Continue long-term PPI therapy for H. pylori negative, NSAID negative ulcer §
Does the patient have one of the following indications for continued long term acid suppression?
Persistent ulcer on repeat endoscopy (if performed)
Giant (>2 cm) peptic ulcer and age >50 years or multiple co-morbidities
History of frequently recurrent peptic ulcers (>2 documented recurrences a year)
Condition requiring long term aspirin/NSAID use
Failure of H.pylori eradication (including salvage therapy)
Yes
No
Maintainance PPI §
No further intervention is indicated unless symptoms recur

Choice of therapy

- All patients with peptic ulcers should receive antisecretory therapy with a proton pump inhibitor.
- PPI use results in faster control of peptic ulcer disease symptoms and **higher ulcer healing rates** as compared with H2RA as a consequence of stronger acid suppression. PPIs also heal NSAID-related ulcers **more effectively** as compared with H2RAs
- Although **antacids and sucralfate** can heal duodenal ulcers, they are not routinely recommended to treat peptic ulcers.
- combining PPIs and H2RAs adds to cost without enhancing healing.

h. pylori

- patients with uncomplicated ulcers, PPI given for **14 days**, along with the antibiotic regimen to treat H. pylori, is usually adequate to induce healing.
- Additional antisecretory therapy is not needed in the absence of persistent or recurrent symptoms.
- Maintenance PPI if:

✓ Persistent ulcer in repeated endoscopy

✓ Giant (>2 cm) peptic ulcer and age >50 years or multiple co-morbidities

✓ Failure to eradicate *H. pylori* (including salvage therapy)

✓ Frequently recurrent peptic ulcers (>2 documented recurrences a year)

✓ Continued NSAID use

Oral Drug Regimens Used to Eradicate Helicobacter pylori Infection

Drug Regimen	Dose	Frequency	Duration
Proton-Pump Inhibitor–Based Three-Drug Regimens			
PPI	Standard dose[a]	BID[a]	14 days[b]
Clarithromycin	500 mg	BID	14 days[b]
Amoxicillin[c]	1 g	BID	14 days[b]
Or			
PPI	Standard dose[a]	BID[a]	14 days[b]
Clarithromycin	500 mg	BID	14 days[b]
Metronidazole[c]	500 mg	BID	14 days[b]
Bismuth-Based Four-Drug Regimens			
Bismuth subsalicylate[d]	525 mg	QID	10–14 days
Metronidazole	250–500 mg	QID	10–14 days
Tetracycline plus	500 mg	QID	10–14 days
PPI	Standard dose[a]	Daily or BID[a]	10–14 days
Or			
H_2RA[e]	Standard dose[e]	BID[e]	4–6 weeks

Sequential Therapy[f]			
PPI	Standard dose[a]	BID[a]	Days 1–10
Amoxicillin	1 g	BID	Days 1–5
Clarithromycin	250–500 mg	BID	Days 6–10
Metronidazole	250–500 mg	BID	Days 6–10
Secondary or Rescue Therapy			
Bismuth subsalicylate[d]	525 mg	QID	10–14 days
Metronidazole	500 mg	QID	10–14 days
Tetracycline	500 mg	QID	10–14 days
PPI	Standard dose[a]	Daily or BID[a]	10–14 days
Or			
PPI	Standard dose[a]	BID[a]	10–14 days
Amoxicillin	1 g	BID	10–14 days
Levofloxacin	500 mg	Daily	10–14 days

[a]Omeprazole 20 mg BID, lansoprazole 30 mg BID, pantoprazole 40 mg BID, rabeprazole 20 mg daily or BID, esomeprazole 20 mg BID or 40 mg daily.

[b]Although 7 to 10 day regimens may provide acceptable eradication rates, the preferred treatment duration in the United States is 14 days.

[c]Use amoxicillin in non–penicillin-allergic individuals; substitute metronidazole for amoxicillin in penicillin-allergic patients.

First-line therapies for *H. pylori* infection

Regimen	Drugs (doses)	Dosing frequency	Duration (days)	FDA approval
Bismuth quadruple	PPI (standard dose ¶)	Twice daily	10 to 14 ◊	No §
	Bismuth subcitrate (120 to 300 mg [not available in US] or 420 mg [available in North America and elsewhere as part of Pylera combination pill])[1] **or** Bismuth subsalicylate (300 or 524 mg)[1]	Four times daily		
	Tetracycline (500 mg)	Four times daily		
	Metronidazole (250 to 500 mg)	Four times daily (250 mg)		
		Three to four times daily (500 mg)		
Clarithromycin triple*	PPI (standard ¶ or double the standard dose)	Twice daily	14	Yes Δ
	Clarithromycin (500 mg)	Twice daily		
	Amoxicillin (1 gram) **or** Metronidazole (500 mg)	Twice daily (amoxicillin) Three times daily (metronidazole)		

Clarithromycin-based concomitant*	PPI (standard dose ¶)	Twice daily	10 to 14	No
	Clarithromycin (500 mg)	Twice daily		
	Amoxicillin (1 gram)	Twice daily		
	Metronidazole or tinidazole (500 mg)	Twice daily		
Clarithromycin-based sequential ¥*	PPI (standard dose ¶) plus amoxicillin (1 gram) for 5 days followed by:	Twice daily	10 (total)	No
	PPI, clarithromycin (500 mg) plus either metronidazole or tinidazole (500 mg) for an additional 5 days	Twice daily		
Clarithromycin-based hybrid‡*	PPI (standard dose ¶) plus amoxicillin (1 gram) for 7 days followed by:	Twice daily	14 (total)	No
	PPI, amoxicillin, clarithromycin (500 mg), plus either metronidazole or tinidazole (500 mg) for an additional 7 days	Twice daily		

ACG guideline

What are evidence-based first-line treatment strategies for providers in North America?
Patients should be asked about any previous antibiotic exposure(s) and this information should be taken into consideration when choosing an *H. pylori* treatment regimen (conditional recommendation; moderate quality of evidence).
Clarithromycin triple therapy consisting of a PPI, clarithromycin, and amoxicillin or metronidazole for 14 days remains a recommended treatment in regions where *H. pylori* clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason (Conditional recommendation; low quality of evidence (for duration: moderate quality of evidence)).
Bismuth quadruple therapy consisting of a PPI, bismuth, tetracycline, and a nitroimidazole for 10–14 days is a recommended first-line treatment option. Bismuth quadruple therapy is particularly attractive in patients with any previous macrolide exposure or who are allergic to penicillin (strong recommendation; low quality of evidence).
Concomitant therapy consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole for 10–14 days is a recommended first-line treatment option (strong recommendation; low quality of evidence (for duration: very low quality of evidence)).
Sequential therapy consisting of a PPI and amoxicillin for 5–7 days followed by a PPI, clarithromycin, and a nitroimidazole for 5–7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (for duration: very low quality of evidence)).
Hybrid therapy consisting of a PPI and amoxicillin for 7 days followed by a PPI, amoxicillin, clarithromycin and a nitroimidazole for 7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (For duration: very low quality of evidence)).
Levofloxacin triple therapy consisting of a PPI, levofloxacin, and amoxicillin for 10–14 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (For duration: very low quality of evidence)).
Fluoroquinolone sequential therapy consisting of a PPI and amoxicillin for 5–7 days followed by a PPI, fluoroquinolone, and nitroimidazole for 5–7 days is a suggested first-line treatment option (conditional recommendation; low quality of evidence (for duration: very low quality of evidence)).

Furazolidone

- Furazolidone is most effective when administered as **100 mg three times daily**
- as part of a bismuth-tetracycline or bismuth-amoxicillin quadruple therapy.
- Resistance is rare.

Not to do?!

- A treatment duration of **less than 7 days** is not recommended and is associated with unacceptable eradication rates.
- Increasing the antibiotic **daily dose** or extending treatment **beyond 14 days** usually does not improve eradication rates.
- The PPI may be extended to 28 days if needed for ulcer healing.
- Twice-daily dosing of the PPI appears to be more effective than a single daily dose.
- **Pretreatment with a PPI** before initiating H. pylori eradication does not decrease the rate of eradication

Confirmation of eradication

- H. pylori infection is identified and treated testing to prove eradication should be performed using a urea breath test, fecal antigen test or biopsy based.

- testing at least 4 weeks after the completion of antibiotic therapy and after PPI therapy has been withheld for 1–2 weeks.

NSAID-induced ulcer

- Patients with NSAID-associated ulcers should be treated with a PPI for four to eight to weeks.

- In patients with peptic ulcers who need to remain on NSAIDs or ASA, maintenance antisecretory therapy with a PPI can reduce the risk of ulcer complications or recurrence.

Non-H. pylori, non-NSAID ulcer

- In patients with H. pylori-negative ulcers that are not associated with NSAID use, we suggest initial PPI therapy for four weeks for uncomplicated duodenal ulcers, and eight weeks for a gastric ulcer before repeat endoscopic evaluation to assess for ulcer healing.
- review the patient's history for the adequacy of *H. pylori* testing and for a history of NSAID use.
- they may be **more difficult to heal** and have a **higher rate of recurrence.**
- In the absence of *H. pylori* and NSAID use, we continue **long-term acid inhibitory therapy with PPIs**

Repeating endoscopy

- **Duodenal ulcers:** Given the low risk of malignancy in patients with duodenal ulcers, a repeat upper endoscopy is not routinely recommended.

- **Gastric ulcers:** after 8 to 12 weeks in patients with one of the following:

✓ Symptoms persist despite medical therapy.
✓ Unclear etiology.
✓ Giant ulcer (>2 cm).
✓ Biopsies not performed or inadequate sampling
✓ Ulcer appears suspicious for malignancy
✓ bleeding ulcers at initial presentation who show signs of continued bleeding
✓ Risks factors for gastric cancer

Gastric cancer

Risks factors for gasteric cancer:

- ✓ age >50 years
- ✓ Helicobacter pylori
- ✓ immigrants from a region with high prevalence of gastric cancer
- ✓ family history of gastric cancer
- ✓ the presence of gastric atrophy
- ✓ Adenoma
- ✓ Dysplasia
- ✓ intestinal metaplasia

Refractory peptic ulcer

- is defined as an endoscopically proven ulcer greater than 5 mm in diameter that does not heal after 8 to 12 weeks of treatment with a proton pump inhibiton
- **5 to 10 percent** of ulcers are refractory to 12 weeks of antisecretory therapy with a proton pump inhibitor (PPI).
- Even with continued PPI use, approximately **5 to 30 percent** of peptic ulcers recur within the first year.

Management

- Re-evaluate risk factors
- ✓ Eradicate *Helicobacter pylori* (*H. pylori*)
- ✓ Avoid culprit medications and tobacco
- ✓ Treat the underlying cause

- Antisecretory therapy: **Twice-daily PPI** is usually effective in inducing healing in patients with ulcers that were refractory to once daily standard dose.
- Repeat upper endoscopy
- Surgery in selected patients

THANK YOU
for your
ATTENTION!