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Gastrointestinal ulcers, role of aspirin, and clinical outcomes: pathobiology, diagnosis, and treatment

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Abstract: Peptic ulcer disease is a major cause of morbidity and mortality in the US with more than six million diagnoses annually. Ulcers are reported as the most common cause of hospitalization for upper gastrointestinal (GI) bleeding and are often a clinical concern due to the widespread use of aspirin and nonsteroidal anti-inflammatory drugs, both of which have been shown to induce ulcer formation. The finding that *Helicobacter pylori* infection (independent of aspirin use) is associated with the development of ulcers led to a more thorough understanding of the causes and pathogenesis of ulcers and an improvement in therapeutic options. However, many patients infected with *H. pylori* are asymptomatic and remain undiagnosed. Complicating matters is a current lack of understanding of the association between aspirin use and asymptomatic ulcer formation. Low-dose aspirin prescriptions have increased, particularly for cardioprotection. Unfortunately, the GI side effects associated with aspirin therapy continue to be a major complication in both symptomatic and asymptomatic patients. These safety concerns should be important considerations in the decision to use aspirin and warrant further education. The medical community needs to continue to improve awareness of aspirin-induced GI bleeding to better equip physicians and improve care for patients requiring aspirin therapy.

Keywords: low-dose aspirin, cardioprotection, ulcers, *Helicobacter pylori*, gastrointestinal bleeding, cardiovascular disease

Introduction

Peptic ulcer disease (PUD) has evolved as a major cause of morbidity and mortality throughout the 20th and 21st centuries,¹ with more than six million people affected each year in the US alone.² Ulcers are reported as the most common cause of hospitalization for upper gastrointestinal (GI) bleeding³ and remain an important clinical problem due to the increasingly widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, which are known to induce ulcers.¹ The most common ulcers associated with PUD arise in the stomach, duodenum, and jejunum, with gastric ulcers presenting most frequently (Figure 1).² Although ulcers are widely diagnosed and recognized, asymptomatic ulcers remain a pressing problem and may lead to long-term damage to the GI tract. While the risk of symptomatic ulcers with aspirin is well defined, the association between aspirin and asymptomatic ulcer formation remains less clear.

The general understanding of ulcer formation greatly changed with the discovery of *Helicobacter pylori* in 1982. Since the discovery of *H. pylori*, the causes and pathogenesis of ulcers are better understood and the treatment protocols have evolved. The belief that ulcers develop due to an acid-driven mechanism was transformed to an understanding that *H. pylori* and aspirin are both important contributors

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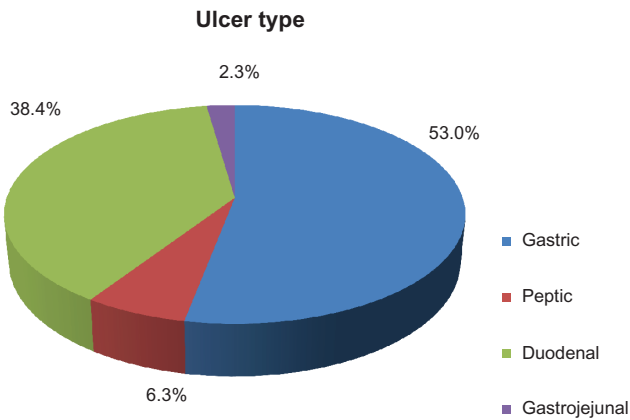


Figure 1 Hospitalizations based on ulcer type from 1998–2005.
Note: Data from Feinstein et al.²

to ulcer development. Now ulcer treatment efforts should focus on *H. pylori* eradication by antibiotics¹ and reduction of aspirin's contribution to ulcer pathogenesis. Strikingly, more than 50% of the population worldwide has chronic *H. pylori* infection, and an estimated 5%–10% of these persons will develop symptomatic ulcers.¹ Although infection with *H. pylori* is commonly associated with PUD, many of those infected are asymptomatic and, therefore, remain undiagnosed.⁴ Undiagnosed peptic ulcer perforation is recognized as a cause of severe complications, such as perforations, and can result in death.^{5,6} Although symptomatic ulcers may be masked or delayed in some high-risk patients by using appropriate GI protection therapy, any delay in making the correct diagnosis may result in increased risk of complications and mortality. Among patients with symptomatic ulcers, nearly 30% of associated upper GI events result in hospitalization or death,^{7–9} and the total direct and indirect costs for PUD have been reported to be approximately \$3.4 billion.¹⁰ Thus, evaluation of patients with ulcers for *H. pylori* infection is an important step in reducing the progression of uncomplicated ulcers to ulcers with complications.

H. pylori infection and NSAID (including aspirin) use are independently associated with adverse GI effects ranging from mild dyspepsia to serious GI bleeding, and may additively increase the risk of PUD.¹¹ Other causes of PUD exist, but are much less common (Table 1).¹² Aspirin is a common cause of ulcers, even in patients not infected with *H. pylori*.¹³ With administration of daily low-dose aspirin (LDA), GI mucosal damage^{14–16} occurs in approximately 40%–50% of patients; increased risk of GI bleeding¹⁷ is also observed. These risks typically peak closer to the beginning of therapy and increase with patient age.^{17,18} History of GI bleeding is important to consider, as 15% of patients who have bleeding from ulcers report recurrent bleeding within

Table 1 General classifications of peptic ulcers

Aspirin use	<i>H. pylori</i> infection	
	Yes	No
Yes	<i>H. pylori</i> and aspirin-positive	Aspirin-induced
No	<i>H. pylori</i> -positive	Other rare causes <ul style="list-style-type: none">– Acid hyper-secretion (eg, Zollinger-Ellison syndrome)– Tumors– Crohn's disease– Viral infections– Idiopathic ulcers

Abbreviation: *H. pylori*, *Helicobacter pylori*.

1 year.¹⁹ As such, physicians should be cognizant of the potential for their patients to develop asymptomatic ulcers throughout the course of aspirin administration during cardiovascular disease therapy. In rare cases, patients who are negative for *H. pylori* and who have no history of aspirin use can develop ulcers.¹ Due to the additive nature of these factors, all patients presenting with an ulcer, regardless of whether they are taking aspirin, should be tested for *H. pylori* infection to determine the best treatment plan.¹¹

For some patients, the clinical consequences beyond GI bleeding may be severe. Patients who continue to exhibit persistent symptoms of PUD should be referred for upper endoscopy. While GI bleeding is a common indication for surgery, the development of complications from PUD, unresponsiveness to therapy or a need for multiple rounds of medical therapy for ulcers, and high-risk factors (eg, history of PUD, dependence upon steroid or NSAID therapy) may increase the need for surgery. Surgical options for these patients include gastroduodenotomy and oversewing of the blood vessel, and excision of the ulcer with vagotomy and drainage/partial gastrectomy in bleeding gastric ulcers.²⁰ If endoscopy is unsuccessful (ie, bleeding continues) or patients are not candidates for surgical intervention, angiography is an option.²¹

Aspirin-induced ulcers

Aspirin is among the most widely used medications in the US²² and is administered for an extensive variety of indications. Further, it is readily available over the counter.²³ Aspirin originated as a medication to treat pain and inflammation, but due to its antiplatelet properties, it has evolved into a drug commonly used to prevent cardiovascular disease. Standard doses of aspirin ranging from 500 to 1,000 mg daily are mostly prescribed for inflammatory conditions and pain relief, whereas doses between 75 and 325 mg daily are

usually prescribed as antiplatelet therapy for primary and secondary prevention of cardiovascular and cerebrovascular events.^{24,25} While the LDA for cardiovascular disease refers to doses <300 mg or <162 mg, it will be categorized as ≤ 325 mg for the purpose of this review.

All antithrombotic agents increase bleeding; aspirin, in particular, significantly increases the risk of major bleeding by about 60%.²⁶ LDA is associated with intracranial or major extracranial events²⁷ as well as prolonged bleeding;²⁴ however, some of the most common side effects from aspirin are related to the upper GI tract. These range from mild conditions, such as dyspepsia, to more severe side effects, such as PUD and severe GI bleeding.²⁴ Chronic aspirin consumption is associated with lower GI bleeding in more than 50% of aspirin users, indicating that GI injury is not only limited to the upper GI tract.²⁸ Overall, aspirin has emerged as one of the most prominent causes of peptic ulcer bleeding in developed countries over the last 2 decades,²⁹ and is associated with a 2- to 4-fold increased risk of upper GI bleeding and ulcers.³⁰

Aspirin and *H. pylori* induce ulcers by different mechanisms, and the combination of the two can greatly increase the risk of ulceration (Figure 2).³¹ Theoretically, aspirin and *H. pylori* may interact in many ways to influence ulcer formation, yet *H. pylori* infection is not required for aspirin-associated ulcers to develop.¹² Specifically, GI damage attributable to aspirin use is typically caused by a combination of

epithelial and microvascular effects with little or no inflammation, while *H. pylori* ulcers are usually associated with diffuse inflammatory cell infiltration.¹² LDA causes GI mucosal and systemic effects from prostaglandin depletion via inhibition of cyclooxygenase-1,^{30,32,33} but the relative contributions of local versus systemic effects of aspirin-related GI injury remain to be fully elucidated.³⁴ Prostaglandins play a pivotal role in protecting gastric mucosal integrity via increasing local blood flow and promoting synthesis and secretion of mucus and bicarbonate. In the absence of normal prostaglandin synthesis, the gastric environment becomes more vulnerable to exogenous (eg, smoking) or endogenous factors (*H. pylori*, acid, pepsin, bile salts) and, consequently, more prone to develop peptic ulcer and bleeding complications.³⁵ The acidic environment causes aspirin to remain nonionized, forcing it to accumulate in gastric mucosal cells, which alters the permeability of the cell and causes ulceration.³⁰ Within only minutes of aspirin administration, topical gastric mucosa effects can be visualized by endoscopy.³⁶ Additionally, LDA promotes GI bleeding via its antiplatelet effect.³⁰

Major risk factors for upper GI events associated with aspirin use include a history of peptic ulcer or bleeding ulcer,^{37–42} concomitant use of other NSAIDs or antithrombotics,^{38,40,43–46} and *H. pylori* infection (Table 2).^{39,47–49} Other factors that may increase the risk of peptic ulcers are smoking, excessive alcohol consumption, drug use, and emotional stress. These factors are considered to be environmental, as they

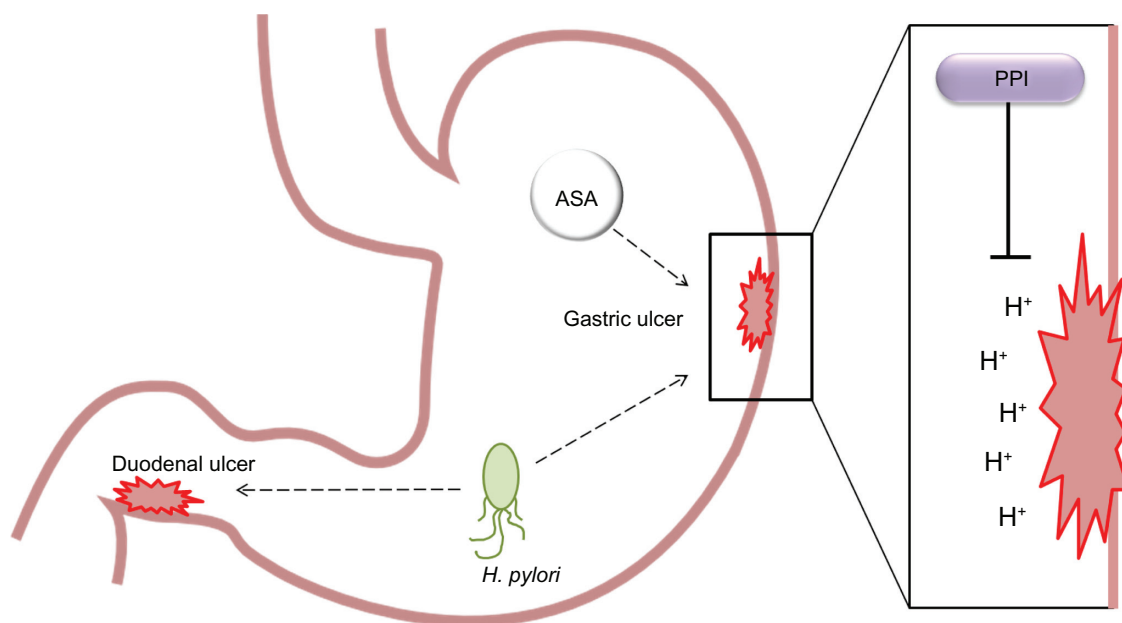


Figure 2 Model of peptic ulcer formation. In the stomach, both *Helicobacter pylori* and aspirin are able to induce gastric ulcer formation. Proton pump inhibitors act to reduce gastric acid production, thereby reducing ulceration in the stomach lining.

Abbreviations: ASA, aspirin; H⁺, hydrogen; PPI, proton pump inhibitor; *H. pylori*, *Helicobacter pylori*.

Table 2 Risk factors for aspirin-induced ulcers**Aspirin-related^a**

- High aspirin dose
- Concomitant use with
 - Other NSAIDs
 - Corticosteroids
 - Anticoagulants
 - Ticagrelor
 - Prasugrel
 - Clopidogrel
- Triple antithrombotic therapy (aspirin, clopidogrel, and warfarin)

Patient-related

- Helicobacter pylori* infection
- History of peptic ulcer disease or GI bleeding
- Older age
- Presence of severe comorbidities

Notes: ^aIt is important for physicians to be aware of the potential drug-drug interactions and subsequent adverse events (eg, gastric ulcers) in patients prescribed aspirin therapies for cardiovascular disease. Data from Valkhoff et al²⁴, Lanza et al⁹⁰, Quinlan et al⁹¹.

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal.

contribute to ulcer formation by increasing gastric acid secretion, ultimately resulting in a weakened mucosal barrier.¹ Among the risk factors for LDA-associated ulcer bleeding, *H. pylori* infection is one of the few that are treatable and curable.²⁹ Combination therapy of aspirin with other antiplatelet or anticoagulant therapy is increasingly common and includes dual antiplatelet therapy in patients treated with coronary stents or after acute coronary syndrome,^{50,51} in patients with cardiovascular disease who are on anticoagulant therapy for atrial fibrillation,⁵² or other indications. Dual antiplatelet therapy has clearly been shown to increase bleeding risk.⁵³ Meta-analyses and randomized clinical trials have demonstrated that, while effective in management of cardiovascular disease,⁵⁴ dual therapy can increase the risk of major bleeding events.^{55–58}

Patients who require triple therapy (dual antiplatelet therapy and anticoagulant therapy) face unique clinical challenges and an increased risk of bleeding.⁵⁹ Many studies have demonstrated a higher risk for bleeding,^{60–64} with the number of minor and major bleeds reported to be as high as 27.5%.^{63–66} As a result of these findings, the most critical element when determining the duration of triple therapy appears to be the risk of bleeding.⁶⁷ US Food and Drug Administration approval of several new oral anticoagulants (dabigatran, apixaban, and rivaroxaban), as well as the ease of use of these agents, may eventually increase the use of anticoagulant therapy compared with current practice patterns with warfarin. It is clear that intracranial hemorrhage is reduced significantly with these agents compared with warfarin. GI side effects and bleeding events may be increased compared with warfarin.^{68,69} Further work is

needed to better understand these observations and strategies to minimize patient risk.

Ulcer diagnosis

Several symptoms are associated with the diagnosis of ulcers, including epigastric pain, fullness, bloating, premature satiety, weight loss, and nausea.¹ In some cases, these symptoms are associated with other illnesses, such as gastroesophageal reflux disease, general dyspepsia, or gastritis, which makes evaluation more challenging. Asymptomatic ulcers may go undetected until clinical presentation of a GI bleed.¹ Physicians, including cardiologists, may be unaware of the occurrence of asymptomatic ulcers in patients taking LDA for cardioprotection, as these patients do not present with clinical signs or concerns after beginning the aspirin regimen. Awareness of PUD risk factors may help clinicians to identify patients at risk for ulcer formation and initiate appropriate gastric protection therapy.

All patients with an ulcer, regardless of whether they are taking aspirin, should be tested for *H. pylori* infection to determine the best treatment.¹¹ Surprisingly, up to 35% of patients at high-risk for GI bleeding are neither tested for *H. pylori* infection nor given proton pump inhibitor (PPI) gastroprotection during the course of their NSAID therapy.⁴⁹ Several invasive (eg, histology, rapid urease testing) and noninvasive (eg, antibody detection, nonendoscopic urease testing, fecal antigen testing) methods are used to diagnose ulcers and detect *H. pylori* infection.¹¹ Once a clinician has decided to test a patient for infection, the next step is to determine if endoscopy is necessary for the procedure, based on the patient's clinical presentation of symptoms.

Treatment, management, and prevention of ulcers

Upon diagnosis of an ulcer, patients' need for aspirin therapy should be reviewed on a case-by-case basis to evaluate their risk-to-benefit ratio. Patients using LDA for primary prevention have a lower benefit of cardiovascular risk reduction than those using it for secondary prophylaxis. In cases of secondary prevention, failure to resume LDA after ulcer bleeding is associated with an increased mortality rate.^{70,71} Alternative methods of antiplatelet therapy may be considered in patients with a high risk of GI bleeding who are using aspirin for primary prevention. Previously, clopidogrel was a substitute therapy for LDA in patients with major upper GI intolerance. In 2008, however, guidelines were revised by the American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association to state that

the use of clopidogrel is inferior to the combination of LDA and PPI for gastroprotection and is not recommended.²⁵

Aspirin modifications have been made in attempts to make aspirin more tolerable in the GI tract. For example, enteric-coated aspirin with cellulose or silicon resists disintegration in the stomach, allowing aspirin to dissolve specifically in the duodenum where the pH is more alkaline.⁷² In other cases, buffering agents, such as calcium carbonate, magnesium oxide, or magnesium carbonate, are used to lower the hydrogen ion concentration in the GI tract, resulting in an increased solubility of aspirin in the stomach, which increases the rate of absorption and reduces the contact time aspirin has with the gastric mucosa, thereby reducing GI irritation.⁷³ Although these modifications may reduce stomach upset in some people, they may not reduce the risk of GI bleeding.^{19,72} Enteric-coated aspirin has even been found to induce significant injury to the lower gut.²⁸

Many different types of drugs have been used over the years to treat ulcers; those aimed at inhibiting gastric acid secretion have been the most successful (Table 3). Originally, H₂-receptor antagonists were used to treat ulcers and were often used in maintenance therapy. Over time, they were gradually replaced with PPIs, which offer more potent acid inhibition and more rapid ulcer healing.¹ Although other classes of drugs can be used, including misoprostol (a prostaglandin analog) and bismuth salts, PPIs have become the hallmark in ulcer therapy. Fixed-dose combination medica-

tion consisting of aspirin plus a PPI offers an alternative to prescribing patients two separate medications and provides more convenient dosing. Several studies have shown that fixed-dose combination therapy with aspirin and the PPI esomeprazole reduced the incidence of peptic ulcers and dyspeptic symptoms when compared with aspirin with placebo.^{74–76} Although PPIs are known to reduce gastric symptoms, patient adherence to an aspirin and PPI cotherapy regimen for gastroprotection is poor.³⁴ A fixed-dose combination regimen, therefore, would likely increase patient adherence to an LDA treatment schedule. An additional class of drugs designed to treat ulcers is a noncovalent complex of aspirin and phosphatidylcholine.³⁴ This approach, currently in clinical development, is targeted at reducing aspirin-induced GI toxicity in patients with *H. pylori*-negative ulcers and may have potential as an alternative to PPIs in certain patient populations.

For the treatment and long-term prevention of recurrent bleeding ulcers, recommendations differ based on the nature of the ulcer. Patients with *H. pylori*-associated ulcers should receive therapy specific to *H. pylori* eradication, whereas patients taking aspirin are recommended to take gastroprotective measures, such as a daily PPI or fixed-dose combination therapy (Figure 3).³ If untreated, long-term infection with *H. pylori* could potentially lead to asymptomatic chronic gastritis, chronic dyspepsia, duodenal ulcer disease, gastric ulcer disease, or gastric malignancy.⁷⁷ The gold standard in

Table 3 Classification of treatments for peptic ulcers

Ulcer treatment	Typical use	Rating	<i>H. pylori</i> status
PPI	Standard treatment of <i>H. pylori</i> -positive and -negative ulcers; prevention of NSAID/aspirin-induced ulcers; intravenous administration for bleeding ulcers	Most potent acid inhibition	+ or –
– Omeprazole			
– Pantoprazole			
– Lansoprazole			
– Rabeprazole			
– Esomeprazole			
<i>H. pylori</i> eradication + PPI	Standard for <i>H. pylori</i> -positive ulcers	Most potent acid inhibition + cure for infection	+
H₂ receptor antagonists	<i>H. pylori</i> -negative ulcers	Acid inhibition	–
– Cimetidine			
– Ranitidine			
– Famotidine			
– Nizatidine			
– Roxatidine			
Prostaglandin analogs	<i>H. pylori</i> -negative ulcers; prevention of NSAID/aspirin-induced ulcers	Weak acid inhibition	–
– Misoprostol			
Bismuth salts	Quadruple therapy for <i>H. pylori</i> eradication	Weak antibacterial effect	+
– Subcitrate			
– Subsalicylate			
Phosphatidylcholine-aspirin	<i>H. pylori</i> -negative ulcers; prevention of aspirin-induced ulcers	Acid inhibition	–
– PL2200			

Abbreviations: *H. pylori*, *Helicobacter pylori*; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug.

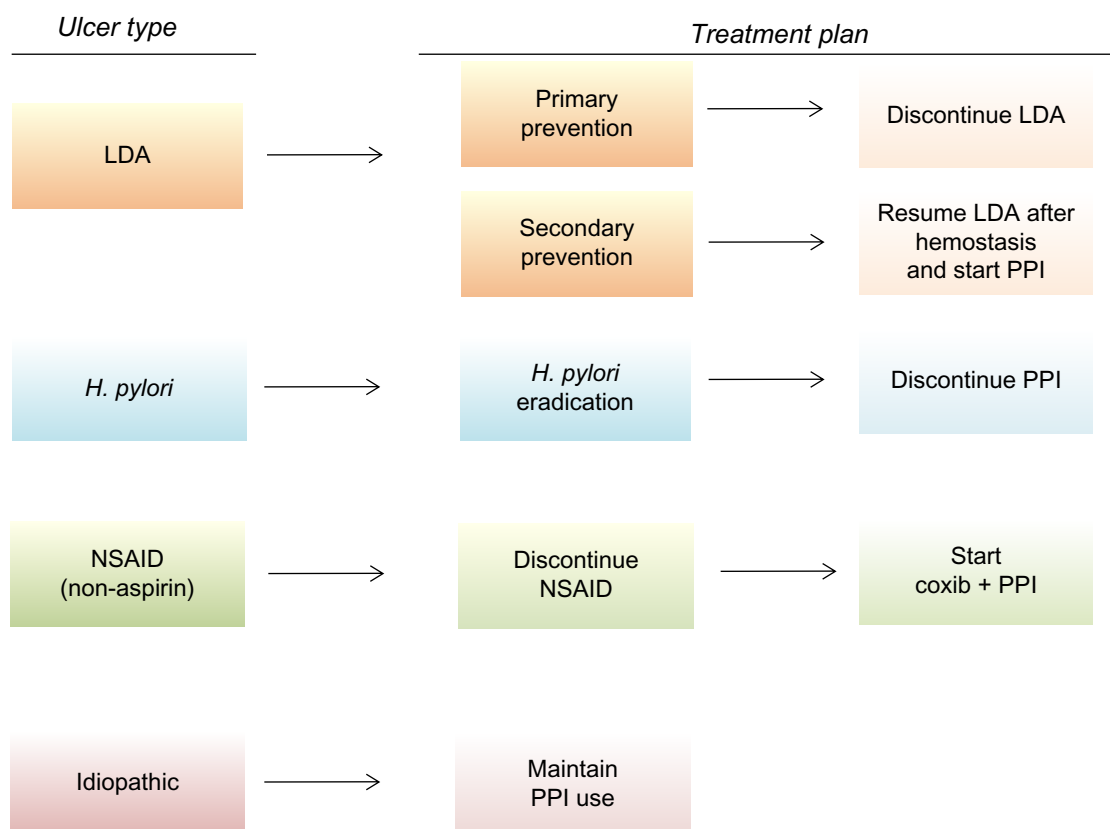


Figure 3 Flow chart of recommended management to prevent recurrent ulcer bleeding based on type. Reprinted by permission from Macmillan Publishers Ltd: American Journal of Gastroenterology. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol*. 2012;107(3):345–360. Copyright 2012.³

Abbreviations: LDA, low-dose aspirin; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; coxib, cyclooxygenase-2 inhibitor; *H. pylori*, *Helicobacter pylori*.

the eradication of *H. pylori* is a 1-week regimen of triple therapy, consisting of PPI treatment with two antibiotics.⁷⁸ In general, *H. pylori*-positive LDA users with bleeding ulcers showed a reduction in the rate of recurrent bleeding when *H. pylori* was eradicated or when a PPI was administered in conjunction with LDA.^{79,80} Another study found that eradicating *H. pylori* alone in patients undergoing LDA therapy, with a history of ulcer bleeding, was sufficient to reduce the long-term risk of recurrent bleeding.⁸¹ These data suggest a possible risk-reduction strategy by employing a test-and-treat tactic for the eradication of *H. pylori*; however, whether this method of reducing ulcer bleeding is cost-effective remains to be evaluated.

Raising awareness of possible asymptomatic ulcers

From 2007 to 2008, physicians prescribed aspirin and other antiplatelet medications in 46.9% of patient visits for patients with ischemic vascular disease.⁸² These data also showed that cardiologists prescribed antiplatelet drugs more frequently than primary care physicians (68% versus 35%, respectively),⁸² for unclear reasons.

Awareness of the GI adverse events related to aspirin use should rise in tandem with aspirin prescriptions. In fact, the American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association Task Force recommends that aspirin doses >81 mg should not be routinely prescribed, since the risk of GI adverse events increases with dose escalation.²⁵ Because the use of enteric-coated or buffered formulations of aspirin for cardioprotection is not sufficient to reduce the risk of GI bleeding, patients at risk of GI adverse events should be prescribed gastroprotection at the initiation of LDA therapy.

Proper review of patient history and follow-up are essential in the cardiology setting to appropriately risk stratify, manage, and educate patients about GI adverse events. One suggested strategy is to administer a patient history questionnaire with a special focus on the risk factors for GI bleeds at the time of prescription. Cardiologists will become aware of the patient's need for gastroprotection or *H. pylori* screening if the patient has a previous history of infection. This approach may help prevent future complications and ulcers. Overall, for patients with an increased ulcer risk, *H. pylori* screening is

recommended to avoid the additive effect of aspirin use with *H. pylori* infection. A dialogue about the symptoms of peptic ulcers may help both the patient and physician to recognize a potential peptic ulcer before it worsens, and potentially avoid any other serious complications.

Proper patient evaluation and physician awareness provide more than the obvious health benefits. Preventive and follow-up screening have the potential to both decrease adverse events and generate cost-savings to patients who fall within the high-risk population for GI bleeds and are prescribed an antibiotic eradication regimen.¹² Economic analysis has demonstrated the benefit of initial noninvasive *H. pylori* testing for patients with suspected PUD.⁸³ Cost-effectiveness data suggest that *H. pylori* testing and treatment are appropriate for all patients with suspected PUD, even if the majority of patients will not benefit.⁸³ Although clinicians are faced with several alternatives to eradicate *H. pylori*, few regimens are able to meet the criteria of being simple, inexpensive, and effective.⁸⁴ Moreover, even though the early detection of asymptomatic *H. pylori* infection may help to reduce the risk of ulcer formation, it is more difficult to diagnose an *H. pylori*-negative asymptomatic ulcer due to aspirin use alone. Endoscopic methods are available and sensitive to this detection; however, endoscopy is not always accessible or covered by health insurance for asymptomatic patients. Although early detection is not always possible, it can prevent serious complications and provide a cost benefit to patients.

Conclusion and future directions

Cardiovascular disease is well recognized as the leading cause of death in the US, as well as in many developing countries around the world.⁸⁵ Although the benefits of LDA use for cardioprotection are clear, GI side effects result in substantial morbidity for both symptomatic and asymptomatic patients. Gastroduodenal ulcers and erosions are observed in approximately one third of asymptomatic patients taking LDA and gastroprotective agents,³⁰ leading guidelines to recommend aspirin use only in patients with a risk of cardiovascular disease over a particular threshold.^{26,34,86–89} However, results from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey demonstrate that aspirin is prescribed in <50% of patients deemed appropriate for LDA therapy.⁸²

Although the GI effects of aspirin may result in substantial morbidity and mortality, a continued downward trend is observed for the rate of hospitalizations due to PUD over the past decade. The decline in PUD hospitalization rates is

attributed in part to a decline in *H. pylori* infections due to awareness, improvements in antibiotic treatment regimens, and possibly trends in safer use of NSAIDs and gastroprotective agents.² Data such as these suggest an optimistic future where physician and patient awareness may reduce aspirin-induced GI bleeding.

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