

The Differences between ulcers caused by *Helicobacter Pylori* and those caused by anti-inflammatory drugs (A Narrative Review)

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ABSTRACT

Peptic ulcers are a severe gastrointestinal disorder that is primarily caused by the use of non-steroidal anti-inflammatory medicines (NSAIDs) or a *Helicobacter pylori* (*H. pylori*) infection. This review compares the etiology, clinical presentation, pathophysiology, treatment, and recurrence risk of NSAID-induced and *H. pylori*-associated peptic ulcers. NSAID-induced ulcers result from inhibition of prostaglandin synthesis and direct mucosal damage, while *H. pylori*-associated ulcers are associated with chronic *H. pylori* infection, which stimulates infiltration of inflammatory cells into the gastric mucosa and induces acid secretion. Clinically, NSAID-related ulcers can be asymptomatic and go undetected until complications occur, while *H. pylori* ulcers are often symptomatic. Diagnosis is based on patient history, endoscopy, and laboratory tests. NSAID-induced ulcers are treated by withdrawing the offending agent and acid suppression, while *H. pylori* ulcers require eradication therapy. Distinguishing between *Helicobacter pylori*-related ulcers and NSAID-induced ulcers is important because it helps with early diagnoses, prevents ulcer complications, and provides necessary treatments.

Key words: *H. pylori*, NSAIDs, peptic ulcer disease, duodenal Ulcer, prostaglandin synthesis.

INTRODUCTION

Peptic ulcer disease (PUD) is a clinical condition defined by physiologic disruption of the gastric and/or duodenal mucosa, penetrating to the muscularis mucosa, resulting from excessive secretion of gastric acid. Peptic ulcers, commonly referred to as stomach ulcers, are due to an erosion in the lining of the stomach, the first part of the small intestine, and possibly the lower esophagus [1]. While the majority of patients remain asymptomatic, dyspepsia is the most common symptom and also often a defining feature of PUD [2]. *Helicobacter pylori* infection (present in 42% of patients) and nonsteroidal anti-inflammatory drug (NSAID) use (an etiologic factor in 36% of individuals) account for the majority of peptic ulcer disease. Other factors include critical illness (related to stress) or idiopathic conditions [2-5]. Additionally, peptic ulcers can result from an imbalance between defense (mucosa, blood flow, prostaglandin, and antioxidants) and offense (excessive gastric acid secretion, *H. pylori* infection, bile fluid reflux, and increased free radical formation) mechanisms to maintain mucosal integrity [6, 7].

Infections with *H. pylori* are found in more than 50% of people worldwide, and it is not only the major cause of chronic gastritis, but also peptic ulcers and stomach cancer. Its incidence differs substantially between countries. Earlier Indian studies show the prevalence of *H. pylori* may be as high as 80%. The existence of bacteria in the human stomach has been known for over 100 years [8,9]. But instead of living colonists in the stomach, they were thought to be contaminants from the digested food. The isolation and growth of a spiral-shaped bacterium was first reported approximately two decades ago by Barry Marshall and Robin Warren [10]; identification would subsequently prove this organism to be *Helicobacter pylori*.

The infection of *H. pylori*, if untreated, is associated with a very wide range of gastrointestinal diseases, including: gastritis, non-ulcer dyspepsia, peptic ulcer disease, antral polyps, gastric adenocarcinoma, MALT lymphoma, follicular esophagitis, gastroesophageal reflux disease, esophageal adenocarcinoma, diffuse duodenal nodular lymphoid hyperplasia, immunoproliferative small intestinal disease, and inflammatory bowel disease [11]. *H. pylori* infection is also attributed to several extraintestinal conditions, including hepatobiliary and pancreatic disorders, cardiovascular diseases, endocrine and metabolic abnormalities, dermatological conditions, hematological and neurological disorders, and ophthalmic diseases

[12]. 70% of patients with gastric ulcers and 95% of patients with duodenal ulcers tested positive for *H. pylori*. It is generally transmitted in early childhood through the fecal-oral route and may persist for decades if untreated [13]. The variability of infection depends on various factors, which include the bacterial virulence, genetic susceptibility of the host, and environmental contributors, such as smoking [13]. Meanwhile, commonly used pharmaceuticals for analgesia, antipyresis, or anti-inflammation are non-steroidal anti-inflammatory drugs (NSAIDs), which are also used in post-operative care [14]. Traditionally, NSAIDs were classified according to their chemical properties, with the majority of common NSAIDs being significant derivatives of salicylic acid, acetic acid, enolic acid, anthranilic acid, or propionic acid. However, as knowledge in science has advanced, the classification has altered to reflect their selectivity for inhibiting cyclooxygenase/prostaglandin-endoperoxide synthase (PGHS) enzymes, which are the primary targets of these medications [15]. However, long-term, uncontrolled use of these medications is linked to toxicity and disorders of the gastrointestinal, renal, and cardiovascular systems on the gastrointestinal, renal, and cardiovascular systems. Hepatotoxicity, increased blood pressure, peptic ulcers, and gastrointestinal (GIT) bleeding are the most prominent of these side effects and are caused by suppression of prostaglandins, a GIT mucosal protective factor [16,17]. Current evidence regarding NSAID adverse effects has several limitations, including variability in methodology, underrepresentation of high-risk populations, and lack of evidence on long-term effects. The future studies need to be based on long-term research, genetic risk differentiation, and other methods of pain management without losing the therapeutic effect. The multi-disciplinary approach that involves the use of pharmacologic and non-pharmacologic interventions is critical in enhancing the outcome of patients and reducing gastric ulcers caused by NSAIDs [18,19]. Epidemiologically, peptic ulcers occur more often in males than in females [20]. The ulcers caused by *H. pylori* are more prevalent in younger and middle-aged people. Whereas, the ulcers due to NSAIDs are more common among older adults due to greater exposure to these drugs [21]. NSAID-associated stomach ulcers commonly arise in the antrum and corpus, with bleeding. While ulcers induced by *H. pylori* typically affect the duodenum (duodenal ulcers), as well as the stomach [22]. Whether the association between *H. pylori* infection and non-steroidal anti-inflammatory drug (NSAID) use is valid or not is debatable. Yusuf et al. (2026) [23] found that there may be an interaction between the two risk factors on

peptic ulcer disease due to the use of anti-inflammatory drugs (NSAIDs) by most patients with *H. pylori* infection. His research found that 47.4% out of the patients with peptic ulcer and *H. pylori* infection had always taken non-steroidal anti-inflammatory drugs, 30.3% had occasionally taken non-steroidal anti-inflammatory drugs, and 22.4 % of the respondents had not taken non-steroidal anti-inflammatory drugs.

Pathophysiology of Peptic Ulcer Diseases

***H. pylori*–Induced Ulcers**

Helicobacter pylori is a microaerophilic, gram-negative spiral-shaped bacterium that does not form spores. Peptic ulcer disease is caused by *H. pylori* via several pathogenic mechanisms. It is the only type of bacteria present in the human stomach because it can produce the urease enzyme. This enzyme allows it to withstand the pH of the stomach and induces an ulcer [24,25]. Theories of the epidemic may include mutations in the chromosomes of the organism, environmental factors, or other factors affecting the human host. Although genetic modifications resulted in the creation of virulence factors, it is believed that they were created thousands of years ago, and little impact on gastritis is expected because they simultaneously suppress stomach immunity. On the other hand, the development of duodenum ulceration is best characterized by the change of the gastritis structure, where inflammation is present in the antrum, but relatively spared in the stomach body. The increased serum gastrin (particularly G17) caused by antral gastritis had a nutritive effect on the stomach parietal cells, leading to an increase in the size of the parietal cells and the production of gastric acid. Acid hypersecretion is considered the most significant risk factor in duodenal ulceration [26]. Additionally, *H. pylori* elicits chronic inflammation through host immune system activation and the production of pro-inflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). This continuous inflammatory process violates the mucous lining and causes damage to the epithelial cells. The presence of virulence factor-producing strains such as vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA), which interfere with immunomodulatory cellular signaling pathways, alter epithelial cell functions, including proliferation, apoptosis, inflammatory signaling, migration, and bias the mucosal injury response process towards a more destructive component; they are predictors for bacterial pathogenicity.

When taken simultaneously, these mechanisms lead to damage of the stomach mucosal barrier and ultimately, ulcer formation [27].

The epidermal growth factor receptor (EGFR) and mesenchymal epithelial transition factor (c-MET) signaling pathways are also activated by *H. pylori*, which promotes cell survival and inflammatory responses, exacerbating the effects of high gastrin levels in the stomach lining [27]. During the early stages of infection, the motility of bacteria and urease synthesis are critical for colonizing. Urease helps the organism thrive in the highly acidic stomach environment by converting urea into carbon dioxide and ammonia. In addition, the pH-regulated urea channel (Urel) regulates this procedure by opening under acidic conditions to allow urea entry and closing at neutral pH to prevent urea transport[9]. As shown in Figure 1.

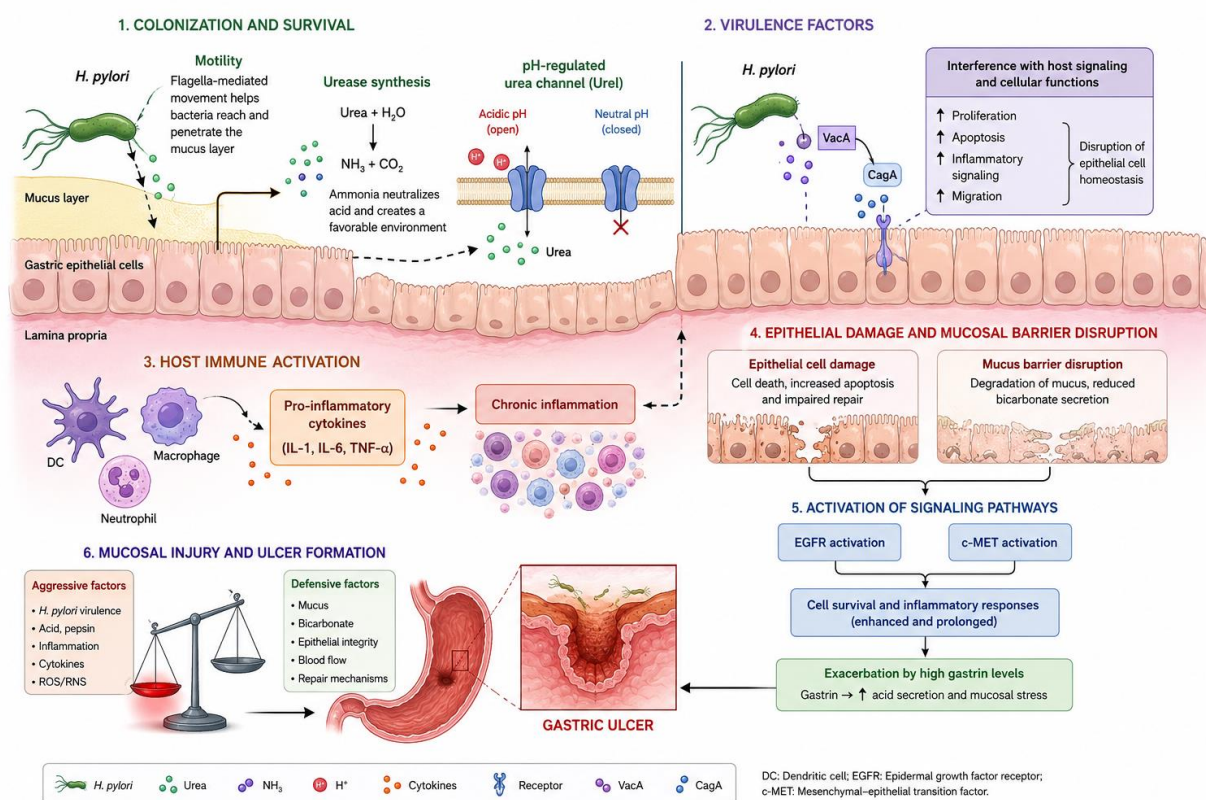


Figure 1. The mechanisms of *H. pylori*-Induced Ulcers.

NSAID-Induced Ulcers

Although NSAIDs are widely used in a variety of settings to assist in diminishing inflammation and pain, numerous patients experience gastrointestinal (GI) adverse reactions leading to foregut

discomfort, small intestinal edema, and/or peptic ulcer disease. The damage caused at the time of surgery is called iatrogenic, and this can be compounded by GI bleeds and perforations. NSAIDs affect the mucosa of the stomach and duodenum in multiple important ways [28, 29]. These mechanisms include inhibition of cyclooxygenase (COX), which decreases the synthesis of prostaglandin (PG) and depletes gastrointestinal defense systems. The decrease in intracellular levels of prostaglandin by this cyclooxygenase-inhibiting enzyme is a specific and necessary effect. Consequently, this impairment affects mucosal blood flow, the mucus-bicarbonate barrier, and epithelial repair capacity [14]. Intramucosal vasodilators stimulate local production of mucus and HCO_3^- while stimulating cell turnover and epithelialization [14], making them essential for salvaging the function of the gastroduodenal mucosa. More than 1:4 ratios of NSAID consumers pay attention to having PUD and its problems, along with bleeding and perforation [29]. One or more of several risk factors are statistically significant for potential ulcer formation and associated complications: advanced age, history of ulceration, concurrent use of anticoagulants or corticosteroids [12]. In addition, NSAIDs cause direct local damage to the stomach mucosa. Because of their acidic nature, NSAIDs readily diffuse into gastric epithelial cells in their non-ionized form and become trapped intracellularly following ionization. This process induces mitochondrial dysfunction, oxidative stress, and disruption of epithelial barrier integrity, thereby increasing mucosal permeability to hydrogen ions and promoting inflammation, erosion, and ulcer formation [30].

Clinical Features and Complications

The clinical presentation of PUD is primarily dependent on the underlying etiology, which in most cases can be either *H. pylori* infection or non-steroidal anti-inflammatory medicines (NSAIDs). *H. pylori* infection is associated with these ulcers, which frequently present as chronic epigastric pain often described by patients as burning or gnawing in quality. This pain can temporally follow meals, and frequently resolves with food intake (particularly in the setting of duodenal ulceration). On the other hand, NSAIDs-induced ulcers are mostly asymptomatic and are associated with major complications with clinical manifestations, such as gastrointestinal bleeding or perforation [31].

Infection with *H. pylori* may present clinically depending on the type of gastritis. Antral-dominant gastritis is characterized by increased secretion of stomach acid and is associated with a lower likelihood than the body-dominant variety to cause duodenal ulcers. In contrast, type 1 or pangastritis is associated with relatively lower secretion of acid and is more closely linked to gastric ulcers and increased distal gastric cancer risk. [32]. In contrast, NSAIDs induce mucosal damage, causing a form of chemical gastritis characterized by swollen and edematous mucosa with no inflammatory cell infiltration and mucosal thickening. This injury primarily results from inhibition of cyclooxygenase, leading to reduced prostaglandin production, which poorly protects the mucosa [32]. Both ulcers caused by *H. pylori*-related and ulcers caused by NSAID-induced may cause serious complications. The upper gastrointestinal bleeding, perforation, and gastric outlet obstruction are the most important complications. Bleeding occurs in up to 73% of affected individuals, whereas perforation and pyloric obstruction occur in around 9% and 3% of cases, respectively [3]. The lifetime risk of perforation in patients with PUD is estimated to be around 5%. The ulcers caused by NSAIDs are especially linked with acute upper gastrointestinal bleeding, and they are usually not preceded by any symptoms [32]. In particular, chronic *H. pylori* infection poses a further long-term oncological risk in the form of gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma [33]. Notably, the concomitant presence of *H. pylori* infection and NSAIDs is associated with a significantly higher risk of serious clinical outcomes in patients taking these drugs [5], reflecting an additive effect on mucosal injury. Recent clinical data emphasize the magnitude of NSAID-associated adverse events. For example, almost all (26.6%) patients presenting with bleeding ulcers give a history of NSAIDs, including low-dose aspirin, as an important risk for ulcer bleed [34]. Upper gastrointestinal bleeding (UGIB) is a substantial and common clinical condition in the pediatric population, constituting 6–20% of intensive care unit admissions. Although the prevalence of *H. pylori* infection is stable, use of NSAIDs has increased significantly (especially during COVID-19), causing a higher ratio of UGIB [35]. NSAIDs have long been recognized as a cause of upper gastrointestinal injury. Still, it is more recently that they have been increasingly implicated in small intestinal injury occurring distal to the stomach and duodenum. With the advent of newer diagnostic modalities like capsule endoscopy, up to 50% of chronic users of NSAIDs have been

found to have mucosal breaks in the small intestine. While many patients remain asymptomatic, some progress to clinically important enteropathy with ulceration and bleeding [36].

Diagnosis

Peptic ulcer disease (PUD) is most frequently diagnosed in patients with low risk for stomach cancer due to age less than 55, and the absence of alarm symptoms. A test-and-treat strategy is recommended for *H. pylori* detection. An upper endoscopy should be performed in most patients to exclude cancer and other serious causes of dyspepsia. The urea breath, stool antigen tests, and blood antibody tests, with endoscopic biopsy, are the most accurate methods for determining whether *H. pylori* is present or if eradication has occurred, but serologic assays also perform reasonably well as an inexpensive option that cannot confirm recovery [37]. NSAID-induced ulcers are diagnosed based on clinical history and endoscopy findings, with the exclusion of *H. pylori* infection [2].

Treatment and Management

Treatment of peptic ulcer disease (PUD) is predominantly aimed at facilitating mucosal healing and preventing recurrence. The mainstay of therapy is proton pump inhibitors (PPIs) because of their potent, long-lasting inhibition of gastric acid secretion. These agents heal approximately 80-100% of patients within four weeks, although treatment for up to eight weeks may be necessary in large gastric ulcers [3]. PPIs not only promote ulcer healing but are also an integral component of both primary and secondary prevention, especially in high-risk patients. Eradication therapy is most important for ulcers associated with *H. pylori*. Standard treatment consists of triple or quadruple regimens containing a PPI plus 2 antibiotics, such as clarithromycin and amoxicillin or metronidazole (with or without bismuth compounds [38,39]. Eradication of *H. pylori* is a critical antimicrobial treatment that can significantly reduce recurrence rates from 50–60% down to less than 2%, emphasizing the importance of precise targeting [3]. In clinical practice, a “test-and-treat” approach is typically recommended for younger patients with uncomplicated dyspepsia to diagnose *H. pylori* infection early and manage it appropriately [39]. The recent guidelines of the Maastricht VI/Florence Consensus highlight that the treatment of *Helicobacter pylori* infection has significantly changed due to rising antibiotic resistance, especially to clarithromycin. In areas where clarithromycin resistance is

greater than 15% or where local resistance statistics are not available, the empirical use of clarithromycin-based triple therapy (proton pump inhibitor [PPI], clarithromycin, and amoxicillin) should be discontinued. In contrast, the recommended first-line treatment in regions with strong or unknown clarithromycin resistance is bismuth-containing quadruple therapy (BQT) for 14 days. Non-bismuth concurrent quadruple therapy (PPI, amoxicillin, clarithromycin, and metronidazole) may be taken into consideration when BQT is not available [40].

On the contrary, the approach focuses on reducing NSAID exposure to treat ulceration. The best treatment is removal of NSAIDs, if possible, with success rates greater than 95%. For those patients who are continued on NSAIDs, elective methods of gastroprotection become paramount. These included the co-prescription of PPIs and therapy with selective cyclooxygenase-2 (COX-2) inhibitors, which carry a lower risk for gastrointestinal injury [41]. COX-2 inhibitors have to be selected with care, considering cardiovascular risk, but their use can increase the incidence of adverse cardiovascular events in susceptible population groups [42]. The relevance of the synergistic effect between *H. pylori* infection and NSAID consumption is an important clinical issue, as it significantly increases ulceration risk and outcomes. Therefore, *H. pylori* evaluation and eradication are recommended in patients who need long-term NSAID use, especially high-risk patients with gastrointestinal complications [43]. Other pharmacological options include histamine-2 receptor antagonists (H2RAs), prostaglandin analogues such as misoprostol, and mucosal protective agents. H2RAs are less effective than PPIs, although they can still suppress acid secretion. Although misoprostol is effective in the prevention of NSAID-induced mucosal injury, its gastrointestinal side effects often limit clinical usefulness [44]. Potassium-competitive acid blockers (P-CABs) are new pharmacologic agents that offer rapid and sustained acidity inhibition in the absence of proton pump activity. These drugs may represent alternative doses of typical PPIs for treatment and prevention, particularly in patients who are poor responders to conventional therapy. PPIs have limits, as expected considering their utility. However, long-term use has been associated with a range of adverse effects, potential pharmacological interactions, and issues relating to overuse. This necessitates careful prescribing and regular review, with consideration of prescribing if there is no valid clinical indication for ongoing treatment. PPIs decreased ulcer rate and adverse effects, but in some conditions are not clearly stronger than other treatment modalities such as misoprostol or H2RAs, indicating an urgent need for more

high-quality studies [45]. Future research interests are engaging in *H. pylori* vaccines and novel therapeutic methods to inhibit inflammatory and innate immunological pathways, particularly in NSAID-induced enteropathy, where drug therapies are inadequate. Accordingly, preventive interventions remain pivotal, including judicious use of NSAIDs, appropriate gastroprotection, and early identification and treatment of *H. pylori* infection [2]. The differences between these two types of ulcers are shown in Table 1.

Table 1. The differences between Ulcers caused by *H. pylori* and those caused by anti-inflammatory drugs

Aspect	Ulcers caused by <i>Helicobacter pylori</i>	Ulcers caused by NSAIDs (anti-inflammatory drugs)
Main cause	Infection with <i>Helicobacter pylori</i> , a gram-negative bacterium	Long-term usage of NSAIDs
Mechanism	Bacterial colonization → urease production → chronic inflammation → increased gastric acid secretion and mucosal damage	Inhibition of cyclooxygenase (COX) → ↓ prostaglandins → reduced mucus, bicarbonate, and blood flow + direct mucosal injury
Common location	Mainly the duodenum (duodenal ulcers), and also the stomach	Mainly stomach (gastric ulcers), especially the antrum and corpus
Pain pattern	Burning/gnawing epigastric pain; often relieved by food (especially duodenal ulcers)	Often asymptomatic; if present, pain is less predictable and not clearly related to meals
Associated symptoms	Dyspepsia, bloating, nausea; may have chronic symptoms	Frequently silent; may present suddenly with complications (bleeding, perforation)
Diagnosis	Urea breath test, stool antigen test, serology, or endoscopic biopsy	Clinical history of NSAID use + endoscopy; exclusion of <i>H. pylori</i> infection
Treatment	Eradication therapy: Proton pump inhibitor (PPI) + antibiotics (triple/quadruple therapy)	Discontinue NSAIDs (if possible) + PPI therapy; consider COX-2 inhibitors or gastroprotection

CONCLUSION

Peptic ulcers are characterized by multi-factorial gastrointestinal disease, usually associated with *H. pylori* infection and the use of NSAIDs. Although these etiologies can

produce the same signs and symptoms, such as epigastric pain, abdominal distention, and vomiting, their underlying pathophysiological mechanisms are quite different. In the case of *H. pylori*, ulcers arise after bacterial colonization that disturbs mucosal defenses, causes inflammation, and alters gastric acid secretion. On the other hand, NSAID-induced ulcers are due to the inhibition of cyclooxygenase enzymes that cause decreased synthesis of prostaglandins and the mechanism of mucosal defenses. Ulcers also differ in where they are located. In *H. pylori*, it occurs as a rupture of duodenal ulcers, and also the stomach, and in NSAID-induced ulcers are often in the stomach. Risk factors continue to distinguish these diseases. In endemic and epidemic situations, *H. pylori* infection is facilitated by poor hygiene, such as drinking contaminated water and direct transmission through person-to-person contact, while NSAID-related ulcers are associated with long-term treatment of the drug, especially in elderly patients and people who have comorbidities or receive concomitant drugs that ulcerate the gastric mucosa, like corticosteroid medications or anticoagulants. Management of PUD needs an individualized focus on root cause resolution, mucosal healing, and reduction in recurrences. Better nomination, in conjunction with preventive tactics and ongoing studies into fashionable treatments, to enhance medical outcomes. However, long-term therapy with no side effects and complications is an important issue in the management of peptic ulcer disease.

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