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Gastric Ulcer: An Overview of Pathophysiology, Diagnosis, and Management

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Abstract

Gastric ulcer (GU) remains a significant global health problem, affecting millions of individuals and contributing to considerable morbidity and economic burden. Despite major advances in understanding its pathophysiology and treatment, GU continues to present clinical challenges due to its multifactorial etiology and potential complications. The development of GU is primarily linked to an imbalance between aggressive factors, such as *Helicobacter pylori* (*H. pylori*) infection, nonsteroidal anti-inflammatory drug (NSAID) use, gastric acid hypersecretion, oxidative stress, and protective mechanisms including mucus-bicarbonate barrier, prostaglandins, and mucosal blood flow. Lifestyle factors, smoking, alcohol intake, and comorbidities further exacerbate disease progression. Advances in diagnostic tools, ranging from endoscopy to molecular biomarkers, have improved detection and risk stratification. Current therapeutic strategies include proton pump inhibitors, H2 receptor antagonists, eradication regimens for *H. pylori*, and mucosal protective agents, with emerging interest in antioxidants, immunomodulators, and phytochemicals as adjunctive therapies. However, rising antibiotic resistance, adverse drug effects, and ulcer recurrence underscore the need for novel pharmacological targets and alternative therapies. This review provides a comprehensive overview of GU, covering its epidemiology, risk factors, pathophysiological mechanisms, diagnostic approaches, current treatment options, and future perspectives, with emphasis on integrating clinical, pharmacological, and experimental evidence to guide effective management and identify research gaps.

Keywords: Gastric ulcer; NSAID; *H. pylori*; oxidative stress; Therapeutic strategies.

1. Introduction

Gastric ulcer (GU) is a chronic and recurrent lesion of the stomach characterized by a localized breach in the gastric mucosa that extends through the muscularis mucosa into the submucosa or deeper layers. It remains one of the most common gastrointestinal disorders worldwide, contributing substantially to morbidity, impaired quality of life, and healthcare costs. Despite significant progress in understanding its pathogenesis and in developing potent pharmacological agents, GU continues to

pose a clinical challenge due to its multifactorial etiology, complications, and recurrence **(Khan et al., 2023)**.

The pathophysiology of GU is traditionally viewed as an imbalance between aggressive factors, such as *Helicobacter pylori* (*H. pylori*) infection, gastric acid secretion, pepsin activity, nonsteroidal anti-inflammatory drugs (NSAIDs), oxidative stress, and impaired mucosal defense mechanisms including mucus-bicarbonate secretion, prostaglandin synthesis, and mucosal blood flow. In addition, host-related factors, lifestyle behaviors (such as smoking and alcohol consumption), and comorbid illnesses contribute to disease onset and progression **(Joshi et al., 2024)**.

Globally, GU represents a significant burden. Although the prevalence has declined in some regions due to improved hygiene, widespread use of eradication therapy for *H. pylori*, and better accessibility to proton pump inhibitors (PPIs), the condition remains prevalent, particularly in developing countries where *H. pylori* infection and inappropriate NSAID use are common. Complications such as bleeding, perforation, and gastric outlet obstruction still account for notable morbidity and mortality, especially in elderly patients or those with comorbidities **(Xie et al., 2022)**.

Recent years have witnessed advances in diagnostic modalities, including high-definition endoscopy and non-invasive *H. pylori* detection methods, which have improved accuracy in detection and follow-up **(Ren et al., 2022)**. Therapeutically, PPIs, H2 receptor antagonists, and eradication regimens remain the mainstay of treatment; however, antibiotic resistance, adverse effects, and ulcer recurrence continue to limit their effectiveness. This has prompted the exploration of novel pharmacological targets, antioxidants, phytochemicals, immunomodulatory agents, and probiotics as adjunctive or alternative therapies **(Zhang et al., 2023)**.

This review aims to provide a comprehensive and updated overview of GU, encompassing its epidemiology, risk factors, pathophysiological mechanisms, clinical presentation, diagnostic approaches, and management strategies. Furthermore, emerging therapies and future perspectives will be highlighted to address current limitations and identify potential research directions for improved patient outcomes.

2. Epidemiology

2.1. Global Prevalence and Incidence

Gastric ulcer (GU) is a major component of peptic ulcer disease (PUD), which includes both gastric and duodenal ulcers. Globally, the prevalence of PUD has declined over the past decades due to improved sanitation, reduced *H. pylori* infection rates, and widespread use of proton pump inhibitors (PPIs). Nevertheless, GU remains a considerable health burden, particularly in developing countries. Current estimates suggest that the global prevalence of PUD ranges from 5–10%, with GU accounting for a substantial proportion of cases. The incidence of GU varies geographically, with higher rates in regions where *H. pylori* infection is endemic and the use of NSAIDs is widespread **(Salari et al., 2022)**.

2.2. Demographic Distribution (Age, Sex, Geography)

Gastric ulcer is most frequently diagnosed in adults, with peak incidence occurring between the ages of 50 and 70 years. Unlike duodenal ulcers, which are more common in younger individuals, gastric ulcers tend to affect older populations, reflecting the cumulative impact of risk factors such as NSAID use, comorbid illnesses, and impaired mucosal defence mechanisms **(Zhuo et al., 2025)**.

- **Sex distribution:** Historically, GU showed a male predominance; however, this gap has narrowed, particularly in elderly populations, largely due to increased NSAID consumption among women **(Zhuo et al., 2025)**.

- **Geographic variation:** In high-income countries, improved hygiene and declining *H. pylori* infection have reduced GU incidence. Conversely, in low- and middle-income regions, GU remains prevalent, largely attributed to high *H. pylori* carriage, limited healthcare access, and unregulated use of gastrotoxic medications **(Li et al., 2023b; Zhuo et al., 2025)**.

2.3. Trends Over the Past Decades

Over recent decades, the epidemiology of GU has shifted. The overall prevalence has decreased, but the etiological contribution of NSAIDs and low-

dose aspirin has increased, particularly in aging populations. While *H. pylori* remains a major global risk factor, its role is diminishing in developed countries due to effective eradication programs. Meanwhile, in regions where eradication therapy is less accessible, *H. pylori* continues to dominate as the primary cause. Importantly, GU-related complications such as bleeding and perforation have shown a relative increase in older patients, reflecting polypharmacy, comorbid conditions, and chronic use of anticoagulants or antiplatelet agents **(Yuan et al., 2022)**.

2.4. Socioeconomic and Healthcare Impact

The burden of GU extends beyond clinical outcomes, exerting a significant socioeconomic toll. Patients often experience recurrent symptoms, diminished quality of life, work absenteeism, and healthcare dependency **(Ashinze et al., 2025)**. Direct costs include diagnostic procedures, hospitalization, and long-term pharmacotherapy, while indirect costs stem from productivity loss and complications requiring surgical or endoscopic intervention. In resource-limited settings, the impact is more pronounced due to delayed diagnosis, poor access to healthcare facilities, and lack of standardized treatment protocols. Collectively, GU represents not only a medical but also a socioeconomic challenge, particularly in populations with limited healthcare infrastructure **(Zhang et al., 2023)**.

3. Etiology and Risk Factors **(Fig.1)**

3.1. *Helicobacter pylori* Infection

H. pylori infection remains one of the most important biological risk factors for GU **(Elbehiry et al., 2023)**. This Gram-negative, microaerophilic bacterium colonizes the gastric mucosa of nearly half of the world's population, although prevalence varies widely across regions. Chronic colonization induces persistent gastritis, disruption of the mucosal barrier, and alterations in gastric acid secretion, all of which predispose to ulcer formation **(Elbehiry et al., 2023; Ali and AlHussaini, 2024)**.

The pathogenicity of *H. pylori* is largely attributed to its virulence factors, including **(Xu et al., 2022; Reyes, 2023)**:

a) **Cytotoxin-associated gene A (CagA):** A major determinant of severe inflammation and ulcer risk. CagA-positive strains are associated with more aggressive mucosal injury.

b) **Vacuolating cytotoxin A (VacA):** Promotes epithelial cell damage, apoptosis, and impairment of host immunity.

c) **Urease enzyme:** Neutralizes gastric acid to facilitate bacterial survival but also causes mucosal irritation.

d) **Adhesins (e.g., BabA, SabA):** Enhance bacterial attachment to gastric epithelial cells.

The outcome of infection depends on a complex interplay between bacterial virulence, host immune response, and environmental factors. Although many infected individuals remain asymptomatic, approximately 10–20% develop peptic ulcer disease, and a smaller proportion may progress to gastric cancer. Importantly, eradication of *H. pylori* markedly reduces ulcer recurrence and complications, highlighting its central etiological role **(Xu et al., 2022)**.

3.2. Genetic Predisposition

Host genetic factors also play a pivotal role in determining susceptibility to GU. Several genetic polymorphisms have been implicated in influencing the severity of mucosal injury and the risk of ulceration, often by modulating the host inflammatory response **(Miftahussurur and Yamaoka, 2015)**:

a) **Cytokine gene polymorphisms:** Variants in interleukin-1β (IL-1β), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α) genes affect the magnitude of gastric inflammation and acid secretion. For example, IL-1β polymorphisms are linked to hypochlorhydria and increased mucosal damage (**Rad et al., 2004)**.

b) **Prostaglandin pathway genes:** Genetic variations in cyclooxygenase-2 (COX-2) and prostaglandin synthase enzymes may influence mucosal protection and ulcer healing capacity **(Takeuchi and Amagase, 2018)**.

c) **Genes regulating oxidative stress:** Polymorphisms in antioxidant defense genes, such as superoxide dismutase (SOD) and

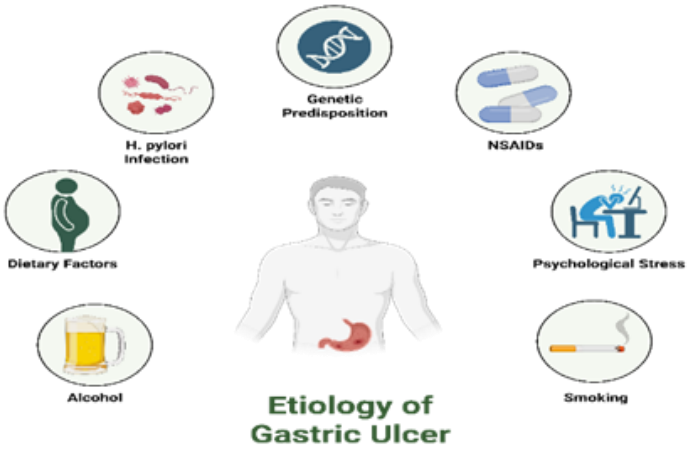

Fig. 1. Etiology of gastric ulcer

glutathione peroxidase (GPx), can predispose to greater oxidative injury **(Gusti et al., 2021)**.

d) **Blood group and mucosal receptors:** Individuals with blood group O have historically been reported to carry a higher risk of PUD, possibly due to differences in mucosal glycoprotein expression and bacterial adherence **(Teshome et al., 2019)**.

Collectively, genetic predisposition does not act in isolation but rather interacts with *H. pylori* infection and environmental exposures. For instance, individuals carrying pro-inflammatory genetic variants who are infected with virulent *H. pylori* strains face a significantly higher risk of developing GU compared to those without these risk factors.

3.3. Drug-Related Factors

Pharmacological agents are among the most significant contributors to GU, particularly in older populations with multiple comorbidities.

3.3.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are the leading cause of non–*H. pylori* ulcers. Their ulcerogenic potential arises from inhibition of cyclooxygenase (COX)-1 and COX-2 enzymes, resulting in reduced prostaglandin synthesis. Prostaglandins normally maintain mucosal defense by enhancing mucus and bicarbonate secretion, regulating mucosal blood flow, and promoting epithelial repair. Additionally, NSAIDs exert direct topical irritant effects on the gastric epithelium. The risk of ulceration increases with higher doses, prolonged duration, and concomitant use of multiple NSAIDs or aspirin **(Ruiz-Hurtado et al., 2021)**.

3.3.2. Corticosteroids

Corticosteroids alone are weak ulcerogenic agents, but when used in combination with NSAIDs, they synergistically increase the risk of ulcer formation and complications such as bleeding and perforation. Their effects are mediated through impaired mucosal healing, inhibition of prostaglandin synthesis, and suppression of protective immune responses **(Yaghoobi and Armstrong, 2022)**.

3.3.3. Anticoagulants and Antiplatelet Agents

Drugs such as warfarin, direct oral anticoagulants (DOACs), and antiplatelet agents (e.g., aspirin, clopidogrel) do not directly cause mucosal injury but potentiate bleeding from pre-existing ulcers. The widespread use of low-dose aspirin for cardiovascular prevention has significantly contributed to GU-related bleeding in elderly patients **(Batool and Bui, 2021)**.

3.4. Lifestyle Factors

3.4.1. Smoking

Smoking is a well-established risk factor for GU. Nicotine reduces gastric mucosal blood flow, impairs prostaglandin synthesis, and increases gastric acid secretion. It also interferes with ulcer healing and increases recurrence rates, particularly in patients infected with *H. pylori* **(Bushra et al., 2024)**.

3.4.2. Alcohol

Chronic alcohol intake directly damages the gastric mucosa by disrupting the lipid membrane, increasing oxidative stress, and impairing mucosal repair mechanisms. While moderate alcohol consumption may not independently cause GU, heavy or chronic intake significantly increases susceptibility, especially when combined with NSAID use or *H. pylori* infection **(Caputo et al., 2024)**.

3.4.3. Dietary Factors

The role of diet in GU is complex. Spicy foods, caffeine, and high-salt diets can exacerbate gastric irritation and impair mucosal defense. Conversely, diets rich in fruits, vegetables, and antioxidants may offer protective effects through their anti-inflammatory and cytoprotective properties **(Khesbak, 2023)**.

3.4.4. Psychological Stress

While once considered a primary cause of ulcers, stress is now recognized as a modulating factor. Severe physiological stress (e.g., critical illness, major surgery, trauma, or burns) can precipitate "stress-related mucosal disease." Chronic psychological stress may exacerbate ulcer risk indirectly by promoting smoking, alcohol use, and dysregulation of neuroendocrine pathways **(Yim et al., 2021)**.

3.5. Comorbid Conditions

3.5.1. Chronic Liver Disease

Patients with cirrhosis have an increased risk of GU due to portal hypertension, impaired mucosal blood flow, and coagulopathy, which also increases the risk of ulcer-related bleeding **(Wehmeyer et al., 2022)**.

3.5.2. Chronic Kidney Disease (CKD)

Uremia alters mucosal defense mechanisms and impairs healing. Moreover, CKD patients are often exposed to NSAIDs, antiplatelet agents, and anticoagulants, further amplifying their risk **(Al-Taee et al., 2021)**.

3.5.3. Metabolic Disorders

Diabetes mellitus is associated with delayed gastric emptying, impaired microvascular circulation, and reduced mucosal healing capacity. Insulin resistance and chronic low-grade inflammation may further contribute to ulcer susceptibility **(Jalleh et al., 2022)**.

3.6. Interaction of Multiple Risk Factors

The etiology of GU is rarely attributable to a single factor. Instead, interactions between risk factors amplify the likelihood of disease development and complications **(Yang et al., 2021b)**. For example: An elderly patient with *H. pylori* infection who regularly uses NSAIDs is at markedly increased risk of GU compared with either risk factor alone. Smoking and alcohol use compound the ulcerogenic effects of NSAIDs and impair healing after *H. pylori* eradication **(Joshi et al., 2024)**. Patients with comorbidities such as diabetes or cirrhosis, when combined with drug exposure or infection, are at a particularly high risk of recurrent and complicated ulcers **(Jalleh et al., 2022)**.

4. Pathophysiology

The development of GU is the result of a dynamic imbalance between aggressive factors that damage the gastric mucosa and defensive mechanisms that maintain mucosal integrity. Under normal physiological conditions, the stomach is equipped with robust protective barriers that resist constant exposure to acid, pepsin, and ingested irritants. However, disruption of these defenses, combined with enhanced mucosal injury, leads to ulcer formation **(Qiao et al., 2024)**.

4.1. Aggressive Factors

4.1.1. Gastric Acid and Pepsin

Excess gastric acid secretion alone is not sufficient to cause GU, but in the presence of compromised mucosal defenses, it significantly contributes to epithelial injury. Acid and pepsin synergistically digest exposed mucosal surfaces, deepening ulcer craters **(Yaghoobi and Armstrong, 2022)**.

4.1.2. *Helicobacter pylori* Infection

H. pylori induces chronic gastritis by secreting virulence factors (CagA, VacA, urease) that damage epithelial cells, stimulate inflammatory mediators, and alter gastric acid secretion patterns. Infection can lead to either hyperchlorhydria (more

common in duodenal ulcers) or hypochlorhydria, depending on the pattern of gastritis. The net effect is impaired mucosal protection and increased susceptibility to ulceration **(Wei et al., 2021)**.

4.1.3. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs contribute through both systemic and local mechanisms. Systemically, they inhibit COX enzymes, reducing prostaglandin synthesis that normally stimulates mucus, bicarbonate secretion, and mucosal blood flow. Locally, they cause topical injury by uncoupling oxidative phosphorylation in epithelial cells and increasing mucosal permeability **(Sohail et al., 2023)**.

4.1.4. Reactive Oxygen Species (ROS) and Oxidative Stress

Excessive generation of ROS, from *H. pylori* infection, alcohol intake, or inflammation, damages cellular lipids, proteins, and DNA. This oxidative burden overwhelms antioxidant defences (e.g., superoxide dismutase, glutathione peroxidase), resulting in apoptosis and impaired mucosal healing **(Sah et al., 2023)**.

4.1.5. Inflammatory Mediators

Inflammation plays a central role in the initiation, progression, and impaired healing of gastric ulcers. The gastric mucosa responds to injurious stimuli such as *H. pylori* infection, nonsteroidal anti-inflammatory drugs (NSAIDs), ethanol, and oxidative stress by releasing a wide array of pro-inflammatory cytokines, chemokines, and enzymes. These mediators orchestrate immune cell infiltration, disrupt mucosal integrity, and perpetuate tissue injury **(Fornai et al., 2011)**.

Pro-inflammatory mediators play a pivotal role in the initiation and progression of gastric ulceration, orchestrating the inflammatory cascade that disrupts mucosal homeostasis. Among these, cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) are particularly important **(Ansari et al., 2023)**. TNF-α, produced mainly by activated macrophages and infiltrating neutrophils, increases mucosal vascular permeability, enhances leukocyte adhesion, and stimulates the generation of reactive oxygen species (ROS) and matrix metalloproteinases (MMPs), all of which exacerbate epithelial injury. Similarly, IL-1β promotes neutrophil recruitment, amplifies ROS production, and induces the release of nitric oxide, leading to further impairment of epithelial barrier integrity and delayed healing **(Kumar et al., 2025)**.

Interleukin-6 (IL-6) acts as both a pro-inflammatory and pro-healing cytokine; however, in the acute phase of gastric mucosal damage, its overproduction contributes to leukocyte infiltration and sustains the inflammatory environment. Elevated serum and mucosal levels of IL-6 have been consistently reported in patients with peptic ulcer disease, reflecting its contribution to disease activity **(Shen et al., 2025)**.

Beyond cytokines, chemokines such as interleukin-8 (IL-8, CXCL8) are key drivers of neutrophil chemotaxis and activation. IL-8, secreted by gastric epithelial cells upon stimulation with *H. pylori* or NSAIDs, recruits neutrophils to the gastric mucosa, where they release proteolytic enzymes and ROS, intensifying mucosal damage. The strong correlation between IL-8 expression and *H. pylori* colonization underlines its central role in inflammation-driven ulcerogenesis **(Russo et al., 2014)**.

Additionally, eicosanoids derived from arachidonic acid metabolism significantly influence the inflammatory balance. While prostaglandins (particularly PGE_2) are cytoprotective by enhancing mucus and bicarbonate secretion and improving mucosal blood flow, their synthesis is markedly reduced by cyclooxygenase (COX) inhibition during NSAID therapy, predisposing to mucosal injury. Conversely, increased leukotriene production, especially leukotriene B_4 (LTB_4), promotes neutrophil chemotaxis and vascular leakage, thereby aggravating ulcer severity. This imbalance between protective prostaglandins and injurious leukotrienes is a hallmark of NSAID-induced ulcers **(Shen et al., 2025)**.

While pro-inflammatory mediators drive the initiation and progression of gastric ulceration, the resolution of mucosal injury and restoration of homeostasis rely heavily on anti-inflammatory pathways. Among the most studied mediators, interleukin-10 (IL-10) plays a central role (Steen et al., 2020). Produced by regulatory T cells, macrophages, and gastric epithelial cells, IL-10 suppresses the synthesis of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, while simultaneously downregulating antigen presentation and inhibiting nuclear factor-kappa B (NF-κB) activation. Through these mechanisms,

IL-10 dampens excessive leukocyte infiltration and oxidative damage, thereby limiting mucosal destruction and favoring tissue repair. Clinical observations show reduced IL-10 levels in *H. pylori*–infected patients with active ulcers, highlighting its protective role in gastric mucosal defence **(Wei et al., 2020)**.

Another important mediator is transforming growth factor-beta (TGF-β), which exerts dual anti-inflammatory and pro-repair effects. TGF-β inhibits neutrophil and macrophage activation, suppresses the release of ROS and proteolytic enzymes, and promotes extracellular matrix deposition essential for mucosal regeneration. Furthermore, TGF-β stimulates angiogenesis and epithelial cell proliferation, processes fundamental to ulcer healing. Its upregulation during the healing phase of gastric ulcers underscores its role as a critical driver of resolution and tissue remodeling **(Sadeghi et al., 2025)**.

The prostaglandins (PGs), particularly prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2), are also indispensable anti-inflammatory and cytoprotective agents within the gastric mucosa. Synthesized via cyclooxygenase (COX) enzymes, these lipid mediators enhance mucus and bicarbonate secretion, improve mucosal blood flow, and maintain epithelial barrier function. Beyond cytoprotection, prostaglandins attenuate leukocyte adhesion and infiltration, while suppressing pro-inflammatory cytokine production. Their depletion, as seen with NSAID therapy, shifts the mucosal environment toward inflammation and injury, underscoring the balance between prostaglandins and other arachidonic acid metabolites in ulcer pathophysiology **(Takeuchi and Amagase, 2018)**.

In addition, lipoxins, derived from arachidonic acid through lipoxygenase (LOX) pathways, serve as endogenous "stop signals" for inflammation. Lipoxin A_4 (LXA_4), in particular, promotes resolution by inhibiting neutrophil recruitment, enhancing macrophage-mediated clearance of apoptotic cells, and stimulating epithelial restitution. Although less extensively studied in gastric ulcers than prostaglandins, lipoxins are increasingly recognized as potent modulators of mucosal healing **(Kantarci and Van Dyke, 2003)**.

4.2. Defensive Mechanisms

4.2.1. Mucus-Bicarbonate Barrier

The gastric epithelium is shielded by a continuous mucus layer, rich in bicarbonate, that maintains near-neutral pH at the mucosal surface. Disruption of this layer by NSAIDs, alcohol, or *H. pylori* weakens the primary defense **(Kvietys et al., 2014)**.

4.2.2. Prostaglandins (especially PGE_2)

Prostaglandins enhance mucus and bicarbonate secretion, regulate mucosal blood flow, and promote epithelial regeneration. NSAID-induced prostaglandin depletion is a cornerstone of drug-related ulcerogenesis **(Fornai et al., 2011)**.

4.2.3. Mucosal Blood Flow

Adequate perfusion supplies oxygen and nutrients, removes toxins, and maintains tissue viability. Hypoperfusion due to smoking, stress, or systemic illness compromises defense and delays healing **(Munteanu et al., 2023)**.

4.2.4. Cellular Restitution and Repair

The gastric epithelium has an inherent ability to rapidly reseal superficial injuries through epithelial cell migration and growth factor-mediated regeneration. Factors that impair restitution (e.g., corticosteroids, diabetes) predispose persistent ulcers **(Predescu et al., 2013)**.

4.2.5. Antioxidant Defenses

Endogenous antioxidants (e.g., glutathione, catalase, superoxide dismutase) counterbalance ROS. A decline in these defenses promotes oxidative damage and chronic inflammation **(Sharifi-Rad et al., 2020)**.

4.3. Molecular and Genetic Mechanisms

Recent studies highlight that GU pathogenesis extends beyond simple acid-peptic damage.

- **NF-κB and MAPK pathways:** Activated by *H. pylori* and cytokines, leading to upregulation of pro-inflammatory genes **(Maeda et al., 2000)**.
- **Apoptosis and autophagy:** Dysregulated in GU, contributing to epithelial loss and impaired mucosal healing **(Lu et al., 2021)**.

- **Genetic polymorphisms:** Variations in cytokine genes (IL-1β and TNF-α) and antioxidant enzymes influence ulcer susceptibility and severity **(Sugimoto et al., 2007)**.

- **Angiogenesis impairment:** Downregulation of vascular endothelial growth factor (VEGF) and endothelial dysfunction delay repair of the ulcer bed **(Tarnawski et al., 2014)**.

4.4. Integrated Pathophysiological Model

Gastric ulcer formation is therefore a consequence of cumulative insults **(Yang et al., 2021a)**:

a) *H. pylori* infection initiates chronic gastritis and mucosal vulnerability.

b) NSAIDs/aspirin diminish prostaglandin-mediated protection.

c) Acid and pepsin amplify mucosal injury.

d) Lifestyle factors (smoking, alcohol) and comorbidities (liver disease, renal failure, diabetes) reduce repair capacity.

e) Molecular pathways (oxidative stress, cytokine cascades, impaired angiogenesis) sustain chronic inflammation and hinder healing.

5. Clinical Presentation and Complications of Gastric Ulcer

Gastric ulcers present with a wide spectrum of symptoms, often making their diagnosis challenging without endoscopic confirmation. The most characteristic feature is epigastric pain, typically described as a gnawing or burning sensation localized to the upper abdomen. Unlike duodenal ulcers, where pain is often relieved by meals, gastric ulcer pain is usually exacerbated shortly after food intake, often within thirty minutes to two hours, which may lead patients to alter their eating habits or avoid food altogether **(Choung and Talley, 2008)**. Associated symptoms such as nausea, bloating, early satiety, and dyspepsia are frequently reported, while nocturnal pain, though possible, is less common than in duodenal ulcer disease. In elderly individuals or those with comorbidities, ulcers may remain clinically silent until complications develop, which highlights the importance of vigilance in high-risk groups. Alarm features such as unexplained weight loss, persistent vomiting, hematemesis, melena, or anemia-related fatigue warrant urgent evaluation, since these may signal severe complications or underlying malignancy. Because gastric ulcers can mimic or coexist with carcinoma, endoscopic biopsy is essential for establishing a definitive diagnosis **(Lohsiriwat et al., 2009)**.

If untreated or inadequately controlled, gastric ulcers may progress to serious complications that account for considerable morbidity and mortality. Hemorrhage is the most frequent and potentially life-threatening outcome, resulting from erosion into gastric vessels and manifesting as hematemesis, melena, or, in severe cases, hematochezia; slower occult bleeding may present with iron-deficiency anemia, fatigue, and pallor. Another major complication is perforation, which occurs when the ulcer penetrates the full thickness of the gastric wall, spilling gastric contents into the peritoneal cavity **(Milosavljevic et al., 2011)**. This presents dramatically with sudden, severe epigastric pain, abdominal rigidity, and signs of peritonitis, with radiographs often revealing free air beneath the diaphragm. In contrast, penetration involves extension of the ulcer into adjacent organs such as the pancreas or liver without free perforation, producing persistent and sometimes radiating abdominal pain. Chronic ulcers, especially those near the pylorus, can also lead to gastric outlet obstruction as a result of inflammation, edema, or fibrotic scarring. Patients typically develop recurrent postprandial vomiting, early satiety, and abdominal distension, with prolonged obstruction predisposing to electrolyte disturbances like hypokalemic metabolic alkalosis. Finally, although most gastric ulcers are benign, a subset may undergo malignant transformation, particularly in the setting of chronic *H. pylori* infection or atrophic gastritis, making repeated biopsies from the ulcer base and margins an indispensable diagnostic step **(Proctor and Deans, 2014)**.

Taken together, gastric ulcers may initially manifest as nonspecific upper gastrointestinal complaints but have the potential to progress into life-threatening complications. Timely recognition of warning signs, thorough endoscopic evaluation, and appropriate intervention are therefore crucial not only to alleviate symptoms but also to prevent severe outcomes and detect early malignant change **(Sugimoto et al., 2007)**.

6. Diagnosis of Gastric Ulcer

6.1. Endoscopy

Upper gastrointestinal endoscopy remains the gold standard for diagnosing gastric ulcer. It allows direct visualization of the lesion, determination of its size, depth, and exact anatomical location, and assessment of mucosal changes surrounding the ulcer. Critically, endoscopy enables tissue biopsy from the ulcer base and margins, which is essential to differentiate benign gastric ulcers from malignant lesions, as carcinoma may mimic or coexist with ulcers. Endoscopic evaluation also permits therapeutic interventions in cases of active bleeding, including injection therapy, thermal coagulation, or hemostatic clipping **(Teh et al., 2020)**.

6.2. Laboratory Tests

Although laboratory studies cannot establish the diagnosis of gastric ulcer, they provide valuable information regarding complications and underlying causes. A complete blood count is useful for detecting anemia resulting from chronic blood loss, while iron studies help confirm iron-deficiency anemia. Serum electrolytes and renal function tests may be indicated in patients presenting with persistent vomiting or suspected gastric outlet obstruction, since metabolic alkalosis and electrolyte imbalances can occur. In addition, assessment for *H. pylori* infection is a crucial component of the diagnostic workup. Endoscopic biopsy specimens can be subjected to rapid urease testing, histological examination, or culture. Noninvasive methods such as the urea breath test, stool antigen testing, or serology are also widely used, particularly in follow-up or in patients not undergoing endoscopy **(Gisbert and Abraira, 2006)**.

6.3. Testing for *Helicobacter pylori* Infection

Detection of *H. pylori* is a cornerstone in the diagnostic evaluation of patients with gastric ulcer, as eradication of the bacterium is strongly associated with ulcer healing, reduction of recurrence, and prevention of complications such as gastric carcinoma. Diagnostic methods are broadly categorized into invasive tests, requiring endoscopy, and non-invasive tests, which are widely used in clinical practice depending on patient presentation and available resources **(Gisbert and Abraira, 2006)**.

6.4. Invasive Tests (Endoscopy-Based)

6.4.1. Rapid Urease Test (RUT)

Utilizes the organism's ability to produce urease, which hydrolyzes urea into ammonia, increasing the local pH and causing a color change in the test medium. The advantages of RUT are Rapid, cost-effective, and extremely specialized, although with some drawbacks as False negatives may be due to low bacterial load, recent use of proton pump inhibitors (PPIs) or antibiotics, or the presence of gastrointestinal hemorrhage **(Uotani and Graham, 2015)**.

6.4.2. Histology (Aziz et al., 2020)

Gastric biopsy specimens, typically from the antrum and corpus, are stained (e.g., hematoxylin and eosin, Giemsa, or immunohistochemistry) to visualize the bacteria.

Advantages: Allows assessment of gastritis, atrophy, intestinal metaplasia, and dysplasia.

Limitations: Requires expertise, more costly, and results are not immediate.

6.4.3. Culture (Reyes, 2023)

Enables bacterial growth from biopsy specimens under microaerophilic conditions.

Advantages: 100% specificity and permits antimicrobial susceptibility testing, which is increasingly important in the context of rising antibiotic resistance.

Limitations: Technically demanding, limited availability, and lower sensitivity compared to other methods.

6.4.4. Stool Antigen Test (SAT) (Shimoyama, 2013)

Detects *H. pylori* antigens in stool using enzyme immunoassay or immunochromatography.

Advantages: High sensitivity and specificity, widely available, inexpensive, and effective for both diagnosis and confirmation of eradication.

Limitations: Reduced sensitivity after recent PPI

or antibiotic therapy; proper stool handling required.

6.4.5. Serology

Measures circulating IgG antibodies against *H. pylori*. The Benefits Despite being economical, widely available, and uncomplicated, there are limitations. Its failure to differentiate between ongoing and old infections restricts its effectiveness in post-treatment monitoring **(Molina et al., 2008)**.

6.4.6. Imaging

Radiological imaging is not routinely necessary for uncomplicated gastric ulcers but becomes essential in the evaluation of complications. Upright abdominal radiography may reveal free intraperitoneal air in cases of perforation, while computed tomography (CT) scans are more sensitive for detecting small amounts of free air, extraluminal collections, or adjacent organ involvement. Ultrasonography may have a supportive role in identifying complications or excluding alternative abdominal pathologies. For gastric outlet obstruction, imaging can demonstrate gastric dilatation and help distinguish peptic ulcer disease from malignant obstruction **(Tonolini et al., 2017)**.

6.4.7. Differential Diagnosis

Because the symptoms of gastric ulcers are often nonspecific and overlap with other upper gastrointestinal disorders, establishing a differential diagnosis is imperative. Conditions such as gastritis, functional dyspepsia, gastroesophageal reflux disease, and pancreatobiliary disease can mimic ulcer symptoms. Importantly, gastric carcinoma must always be considered in patients with gastric ulcers, especially in older individuals or those with alarm features such as weight loss, persistent vomiting, or gastrointestinal bleeding. Biopsy during endoscopy remains the definitive step in excluding malignancy **(Talley et al., 1987)**.

7. Management

Upon confirmation of diagnosis and exclusion of cancer, the therapeutic objective is to eliminate the underlying reasons of ulcer development, eradicate *H. pylori*, and diminish acid secretion. Patients should be interrogated about the utilization of ulcerogenic medicines, namely non-steroidal anti-inflammatory drugs or steroids, which should be terminated or reduced to the greatest extent feasible **(Vakil, 2024)**.

Without therapy, spontaneous cure of *H. pylori* infected ulcers occurs in fewer than 1% of cases. The most prevalent therapy regimens consist of an antisecretory agent, either the H2 receptor antagonist ranitidine or the proton pump inhibitor omeprazole, in conjunction with two antibiotics, clarithromycin and either amoxicillin or metronidazole. Numerous studies indicate that triple combination antibiotic therapy is more efficacious than monotherapy, with a treatment duration of 7–14 days leading to ulcer healing in over 90% of patients after 8 weeks, as confirmed by repeat endoscopy **(Lee and Simeone, 2009)**.

Individuals with stomach ulcers not associated with *H. pylori* infection should discontinue the causative agent and initiate antisecretory medication. In individuals necessitating prolonged NSAID or steroid therapy, elective surgery may be contemplated for the management of their ulcer condition. All patients with a confirmed stomach ulcer must have repeat endoscopy 8–12 weeks post-therapy to evaluate healing **(Peterson, 1997)**.

If an ulcer has not fully healed after 12 weeks of continuous medical treatment or if the patient experiences many recurrences, the patient is said to have intractable illness. The differential diagnosis for a non-healing ulcer encompasses chronic *H. pylori* infection, Zollinger-Ellison syndrome, NSAID abuse, mesenteric ischemia, and microscopic cancer. In cases of a non-healing gastric ulcer, it is advisable to have a repeat endoscopy with several biopsies to reassess the gastric mucosa for ongoing *H. pylori* infection or concealed malignancy **(Lee and Simeone, 2009)**.

Zollinger-Ellison syndrome should be ruled out by assessing the patient's basal serum gastrin levels or performing a secretion stimulation test. After excluding hidden, curable reasons of intractability, elective surgery may be scheduled **(Berna et al., 2006)**.

7.1. Surgical therapy: Elective

Surgical intervention for ulcer disease is designated for patients who have not responded to or are unable to adhere to medical treatment, or for those who exhibit complications. Ulcers that have not responded to optimal medical treatment for 12 weeks or when an undetected cancer cannot be

Table 1: Pharmacological Agents in the Management of Peptic Ulcer

Drug Class	Examples	Mechanism of Action	Clinical Use	Key Notes / Adverse Effects
Proton Pump Inhibitors (PPIs) (Shanika et al., 2023)	Omeprazole, Esomeprazole, Pantoprazole, Lansoprazole	Irreversibly inhibit H^+/K^+-ATPase in gastric parietal cells → profound acid suppression	First-line therapy for peptic ulcers, GERD, stress ulcers, *H. pylori* eradication regimens	Highly effective; risk of long-term use: hypomagnesemia, vitamin B12 deficiency, osteoporosis, rebound acid hypersecretion
H2 Receptor Antagonists (Meng et al., 2023)	Ranitidine*, Famotidine, Nizatidine	Block H2 receptors on parietal cells → reduce acid secretion (especially nocturnal)	Alternative to PPIs, mild to moderate ulcers	*Ranitidine withdrawn in many countries due to NDMA contamination; less potent than PPIs (**Gold and Margulis, 2023**)
Prostaglandin Analogs (Ahmed, 2024)	Misoprostol	PGE1 analog → ↑ mucosal protection, ↑ bicarbonate & mucus, ↓ acid secretion	Prevention of NSAID-induced ulcers	GI cramps, diarrhea, contraindicated in pregnancy (uterotonic effect)
Antacids (Vakil, 2024)	Aluminum hydroxide, Magnesium hydroxide, Calcium carbonate	Neutralize gastric acid → rapid but short-lived relief	Symptomatic relief of dyspepsia, adjunct therapy	Mg salts → diarrhea, Al salts → constipation; not suitable for long-term management
Mucosal Protective Agents (Včev et al., 2025)	Sucralfate, Bismuth subsalicylate	Sucralfate: forms protective barrier on ulcer base. Bismuth: coats mucosa, antimicrobial effect vs. *H. pylori*	Sucralfate: stress ulcers, adjunct therapy. Bismuth: part of *H. pylori* eradication (quadruple therapy)	Sucralfate requires acidic environment; Bismuth → black stools, constipation
Antibiotics (for *H. pylori*) (Tshibangu-Kabamba and Yamaoka, 2021)	Clarithromycin, Amoxicillin, Metronidazole, Tetracycline, Levofloxacin	Eradicate *H. pylori* infection (combination therapy with PPI + bismuth or other antibiotics)	First-line and salvage eradication regimens	Resistance is a growing challenge; therapy guided by local resistance rates
Cytoprotective / Novel Agents (Scarpignato and Hunt, 2021)	Rebamipide, Ecabet, Vonoprazan (potassium-competitive acid blocker, P-CAB)	Rebamipide & Ecabet: enhance mucosal defense & healing. Vonoprazan: blocks K^+ binding in proton pump → stronger, longer acid suppression than PPIs	Emerging therapies, effective in *H. pylori* eradication and refractory ulcers	Limited availability; vonoprazan widely used in Japan.

excluded are indications for elective surgical surgery **(Gurusamy and Pallari, 2016)**.

For *Type I* gastric ulcers, a distal gastrectomy with Billroth I or II **(Fig. 2)**. Reconstruction is advised for the majority of patients, as this method eliminates both the ulcer and the harmed antrum. The excision of the affected portion enables a more comprehensive assessment of a possible underlying cancer. Antrectomy and rebuilding diminish acid secretory potential and expedite gastric drainage **(Marsh and Lopez, 2024)**.

Recurrence rates are typically low (0–5%), accompanied by significant symptomatic improvement. Operative mortality has been documented to vary from 0% to 6%. Due to the infrequent association of *Type I* gastric ulcers with acid hypersecretion, the incorporation of a vagotomy is seen superfluous **(Seeras et al., 2022)**.

Type II and *III* ulcers, linked to excessive acid secretion, necessitate an operational therapy that involves ulcer removal and vagotomy. *Type II* gastric ulcers manifest concurrently with scarring or ulceration in the duodenum or pyloric channel. They are often extensive, profound ulcers with indistinct borders. A truncal vagotomy and antrectomy with Billroth I reconstruction is the optimal surgical approach, achieving both ulcer excision and reduction of acid secretion **(Seeras et al., 2022)**.

Recurrence rates are below 5%, while the operative mortality rate is approximately 1%. *Type III* ulcers, located in the prepyloric region, may be treated through antrectomy and vagotomy followed by Billroth I reconstruction. A Billroth II reconstruction involving the creation of a gastrojejunostomy is applicable for *Type II* or *Type III* ulcers when a more physiologic Billroth I reconstruction is technically difficult, particularly in instances of significant scarring or inflammation of the duodenum. Highly selective vagotomy is an option; however, it has been linked to suboptimal outcomes for both *Type II* and *Type III* ulcers, with ulcer recurrence rates reported between 16% and 44% across various studies **(Lipof et al., 2006)**.

Type IV gastric ulcers are rare and may present technical challenges due to their anatomical positioning near the gastroesophageal junction along the lesser curvature. The size of the ulcer, its closeness to the gastroesophageal junction, and the presence of surrounding inflammation are critical factors influencing the technical approach. *Type IV* ulcers, similar to *Type I* ulcers, are not linked to acid hypersecretion, and a vagotomy is therefore unnecessary. Ulcers located 2–5 cm from the cardia may be treated with a distal gastrectomy, which extends along the lesser curvature to encompass the ulcer (the Pauchet procedure) and includes a Billroth I reconstruction. In cases of ulcers located near the gastroesophageal junction, a subtotal gastrectomy accompanied by Roux-en-Y jejunal reconstruction, known as Csendes' procedure, may be necessary **(Kamarajah and Markar 2024) (Fig. 3)**.

7.2. Surgical therapy: Emergent

Bleeding, perforation, and obstruction represent the primary complications associated with gastric ulcer disease. Patients with complications from gastric ulcers are often elderly and have comorbidities, leading to a high overall mortality rate associated with emergency operations, which ranges from 10% to 40%. In patients with bleeding gastric ulcers, indications for urgent surgical intervention include **(Tarasconi et al., 2020)**:

1. hemodynamic instability despite vigorous resuscitation (>3-unit transfusion),

2. failure of endoscopic techniques to arrest hemorrhage, and

3. recurrent hemorrhage after initial stabilization with up to two attempts at obtaining endoscopic hemostasis.

Additional relative indications for surgery encompass rare blood types or challenging crossmatches, refusal of transfusion, presentation in shock, and chronic gastric ulcer bleeding. In hemodynamically unstable patients, vessel ligation with oversewing or excision of the ulcer should be performed promptly. The status of *H. pylori* can be assessed through mucosal biopsy and rapid urease testing if it is not already known. Excision alone is associated with rebleeding in up to 20% of patients **(Alimam et al., 2018)**.

In hemodynamically stable patients, a definitive approach involves distal gastrectomy with Billroth I or II reconstruction. Bilateral truncal vagotomy is conducted to mitigate acid hypersecretion in individuals with *Type II* and *III* ulcers. Patients undergoing truncal or parietal cell vagotomy exhibit elevated rates of ulcer recurrence

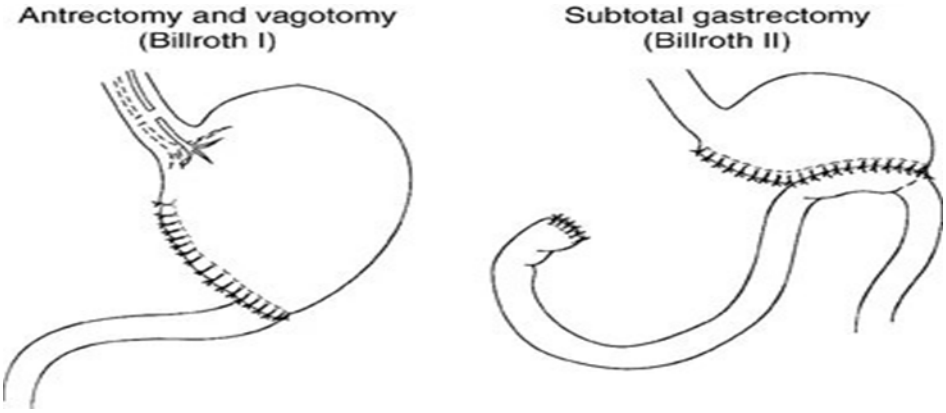

Fig. 2. Billroth I and Billroth II reconstruction **(Lee and Simeone, 2009)**

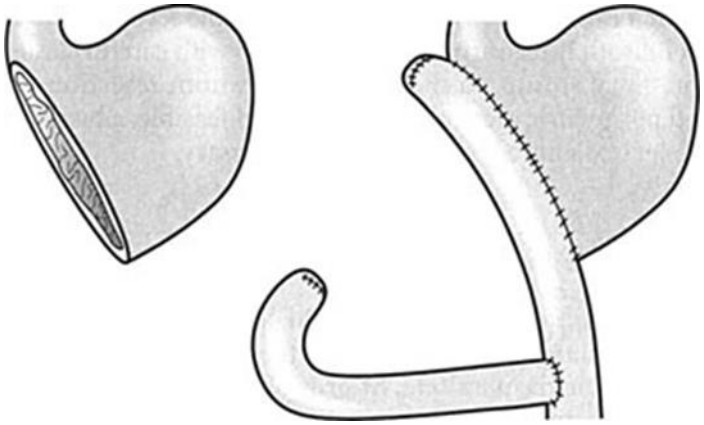

Fig. 3. Csendes' procedure, used to treat gastric ulcers close to the gastroesophageal junction **(Lee and Simeone, 2009)**

postoperatively, and their application in urgent or emergent situations is not advised. An antrectomy that extends to encompass the ulcer is preferred for managing bleeding *Type IV* ulcers. If this approach proves technically challenging, an alternative is to identify and ligate the left gastric artery, followed by biopsy and oversewing of the ulcer via a high anterior gastrotomy **(Becker and Caspary 2012)**.

In patients with a perforated gastric ulcer, hemodynamic stability and medical comorbidities are critical considerations in surgical decision-making. The optimal management for a patient with a perforated ulcer involves a definitive antrectomy that includes the ulcer, along with a vagotomy if deemed necessary. In cases where the patient presents an unacceptably high risk due to advanced age, comorbid conditions, intraoperative instability, or significant peritoneal contamination, omental plication of the perforation accompanied by biopsy may be indicated **(Tarasconi et al., 2020)**.

In specific patients exhibiting a sealed perforation, the implementation of nasogastric suction, broad-spectrum antibiotics, and supportive therapy may be warranted. In patients with perforation as the initial manifestation of gastric ulcer disease due to untreated *H. pylori* infection, non-resectional surgical therapy is a viable option, accompanied by postoperative medical treatment for *H. pylori*. Effective treatment of *H. pylori* in these specific patients results in reduced rates of ulcer recurrence. In this patient cohort, repeat endoscopy should be conducted approximately 6 weeks postoperatively to assess ulcer healing adequacy. Patients with a long-standing history of ulcers who are stable should receive definitive ulcer surgery, including antrectomy and Billroth I or II reconstruction, in the event of a perforation. In patients with medication-induced gastric ulcers presenting with perforation, where the medications are essential, definitive anti-ulcer surgery should be considered **(Stern et al., 2023)**.

Gastric outlet obstruction commonly arises as a complication of *Type II* and *III* ulcers. The

underlying cause is typically chronic scarring of the duodenum or acute inflammation accompanied by subsequent edema. Following the correction of fluid and electrolyte imbalances, surgical intervention is typically warranted if obstruction does not resolve within 72 hours despite antisecretory treatment and nasogastric tube decompression. Endoscopic dilatation has been successfully performed in certain instances; however, the long-term patency rates are inferior to those achieved through surgical treatment of gastric outlet obstruction **(Latchu and Lokesh, 2015)**.

In patients requiring surgical intervention, antrectomy with Billroth I or II reconstruction is the preferred procedure. The surgical placement of a feeding jejunostomy tube is typically advised to enhance the patient's nutritional status, as chronic gastric outlet obstruction can lead to delayed postoperative gastric emptying **(Sigmon and Lopez, 2020)**.

7.3. Laparoscopic surgery

In recent years, laparoscopic surgical approaches have gained popularity for the management of peptic ulcer disease. Several series in the literature demonstrate that a laparoscopic approach is a viable option for perforated peptic ulcer, with outcomes comparable to open surgery **(Pansa et al., 2020)**.

Evidence from these series indicates that laparoscopy results in decreased postoperative pain, fewer pulmonary complications, a shorter hospital stay, and a quicker return to normal daily activities compared to conventional open repair. The majority of these studies have concentrated on the omental repair of perforated duodenal or juxtapyloric ulcers, with limited evidence available concerning the repair of other types of perforated gastric ulcers. The laparoscopic method for managing refractory gastric ulcers, as well as those complicated by bleeding and gastric outlet obstruction, is viable; however, it has not been extensively researched **(Pansa et al., 2020)**.

7.4. Postoperative management and potential complications

During the postoperative period, low continuous nasogastric suction is maintained until the patient demonstrates signs of resolving ileus. The patient receives intravenous fluids or parenteral nutrition, as necessary, until they can sustain oral intake.

Patients experiencing prolonged gastric ileus may necessitate enteral nutrition via a feeding tube. A naso-enteric feeding access or feeding jejunostomy may be established during the operation if prolonged ileus is expected. Antibiotic administration should be restricted to the perioperative period, except in cases of peritonitis and contamination due to a perforated ulcer, where postoperative antibiotic therapy should persist until the resolution of fever and leukocytosis is achieved **(Vather and Bissett, 2013)**.

Early complications following gastric ulcer surgery include superficial and deep infections, bleeding, delayed gastric emptying, and anastomotic leaks. Patients undergoing emergent surgical intervention may experience postoperative complications associated with preexisting comorbidities, including cardiac and respiratory diseases. The late sequelae of gastrectomy are primarily attributed to complications arising from vagotomy rather than the gastric resection itself; however, these effects are collectively referred to as post-gastrectomy syndromes **(Nevmerzhytskyi, 2021)**.

A majority of patients report alterations in their digestive habits following surgery, with approximately 20% experiencing significant effects. Approximately 95% of patients adapt over time, while 5% experience lifelong symptoms, and 1% are severely debilitated by these symptoms. Late complications following gastric ulcer surgery encompass delayed gastric emptying, dumping syndrome, post-vagotomy diarrhea, chronic gastroparesis, alkaline reflux gastritis, and afferent or efferent loop syndrome **(Mogoanta et al., 2021)**.

Post-vagotomy diarrhea occurs in roughly 30% of patients after truncal vagotomy. The condition may be associated with the swift transit of unconjugated bile salts from the denervated biliary tree into the colon, where they induce secretion. In most instances, it is self-limiting. Cholestyramine administration has demonstrated benefits in persistent cases **(Li et al., 2023a)**.

Dumping syndrome affects approximately 20% of patients following gastrectomy or vagotomy with drainage procedures. Patients report postprandial gastrointestinal discomfort, which may manifest as nausea, vomiting, diarrhea, and cramps, accompanied by vasomotor symptoms including diaphoresis, palpitations, and flushing. The pathogenesis remains partially elucidated; however, the syndrome is often linked to the rapid delivery

of hyperosmolar food, especially carbohydrates, into the small intestine. Rapid intraluminal fluid shifts occur due to the osmotic gradient and may be influenced by the release of vasoactive hormones, including serotonin and vasoactive intestinal polypeptide **(Davis and Ripley, 2017)**.

Patients may report a similar set of symptoms occurring hours postprandially, referred to as late dumping. This condition arises from hypoglycemia due to a postprandial insulin peak and can be addressed through carbohydrate intake. Patients experiencing early dumping syndrome can often be managed conservatively through dietary modifications, specifically by adopting frequent small meals that are rich in protein and fat while minimizing carbohydrate intake. The administration of octreotide has demonstrated efficacy in certain cases. Patients exhibiting intractable symptoms may be candidates for surgical intervention aimed at delaying gastric emptying. This objective is optimally achieved by converting an antrectomy and Billroth reconstruction to a Roux-en-Y reconstruction **(Anandavadivelan et al., 2021) (Fig. 4)**.

Bile reflux into the stomach frequently occurs following surgeries that remove the pyloric sphincter; however, only approximately 2% of patients who undergo gastric ulcer surgery will develop alkaline reflux gastritis. Alkaline reflux gastritis generally manifests as postprandial burning epigastric pain. Despite the availability of various medical treatments, none have demonstrated significant efficacy in addressing this issue. Surgical revision of a Roux-En Y reconstruction may be required to adequately address this issue, particularly in severe cases **(Zobolas et al., 2006)**.

Afferent and efferent loop syndromes can occur following Billroth II reconstruction or gastroenterostomy. Patients may report postprandial epigastric pain and vomiting in both scenarios; however, bilious vomiting is exclusively associated with efferent loop syndrome. Both pertain to mechanical obstruction of the limbs caused by kinking, anastomotic narrowing, or adhesions. The identification of a distended afferent loop on CT is diagnostic for afferent loop syndrome. In this context, surgical intervention utilizing a Roux-En Y reconstruction is indicated **(Kim et al., 2016)**.

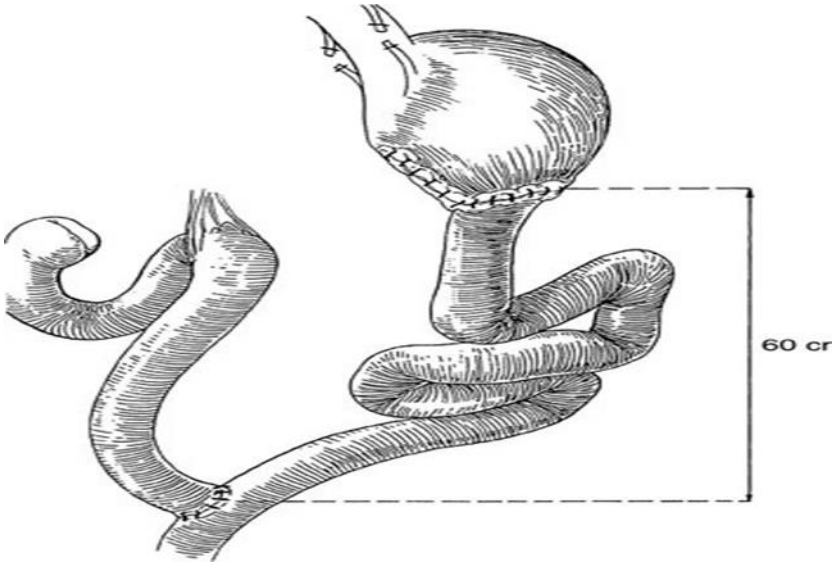

Fig. 4. Conversion of an antrectomy with Billroth X reconstruction to a Roux-en-Y reconstruction **(Lee and Simeone 2009)**.

7.5. Drug Repurposing in Gastric Ulcer

Drug repurposing has emerged as an innovative approach in gastric ulcer management, aiming to identify new therapeutic utilities for established agents with known safety profiles. Several drugs primarily indicated for cardiovascular, metabolic, or neurological disorders have demonstrated gastroprotective properties through mechanisms such as modulation of oxidative stress, attenuation of inflammation, or enhancement of mucosal defence **(Khan et al., 2025)**.

1. **Statins**, widely prescribed for hyperlipidemia and cardiovascular prevention, have shown promising anti-inflammatory and antioxidant effects in gastric ulcer models. Beyond their lipid-lowering properties, statins reduce proinflammatory cytokines such as TNF-α and IL-6, enhance nitric oxide bioavailability, and improve endothelial function, thereby contributing to mucosal protection and improved healing. Preclinical and limited clinical evidence suggests that statins may decrease ulcer recurrence rates and enhance the efficacy of standard anti-ulcer therapies **(Singh and Singh, 2013)**.

2. **Metformin**, the cornerstone of type 2 diabetes mellitus management, also exhibits beneficial effects on gastric ulcer healing. Its mechanism is attributed to activation of AMP-activated protein kinase (AMPK), leading to reduced oxidative stress, suppression of proinflammatory signaling pathways, and enhancement of angiogenesis within the ulcer bed. Studies in diabetic and non-diabetic ulcer models have demonstrated accelerated healing with metformin, suggesting a therapeutic potential independent of glycemic control **(AbdelAziz et al., 2021)**.

3. **Pentoxifylline**, a methylxanthine derivative primarily used in peripheral vascular disease, exerts anti-inflammatory and rheological effects by inhibiting TNF-α production and improving microcirculatory blood flow. In gastric ulcer research, pentoxifylline has been shown to attenuate oxidative damage, reduce neutrophil infiltration, and enhance mucosal repair. Its ability to modulate both inflammatory mediators and vascular dynamics positions it as a promising adjunct in ulcer therapy, particularly in ischemia-related lesions **(Paredes et al., 2024)**.

4. **N-acetylcysteine (NAC)**, a well-known mucolytic and antioxidant agent, has attracted attention for its gastroprotective properties. Acting as a precursor of glutathione, NAC replenishes cellular antioxidant defenses and neutralizes reactive oxygen species (ROS), thereby reducing mucosal injury. Furthermore, NAC promotes angiogenesis and enhances the bioavailability of nitric oxide, supporting mucosal defense and repair. Its dual antioxidant and cytoprotective actions make it an attractive candidate for repurposing in gastric ulcer prevention and healing **(Soliman et al., 2017)**.

5. **Selective serotonin reuptake inhibitors (SSRIs)**, commonly prescribed antidepressants, have demonstrated conflicting roles in gastric mucosal injury and healing. While some studies suggest that SSRIs increase the risk of gastrointestinal bleeding by impairing platelet aggregation, others indicate potential protective roles in ulcer healing due to their modulatory effects on inflammatory mediators and neurogenic pathways. The therapeutic potential of SSRIs in gastric ulcer therefore remains controversial and warrants further investigation before clinical application **(Dall et al., 2010)**.

6. **Sodium-glucose cotransporter-2 (SGLT2) inhibitors**, another class of antidiabetic agents, have also been explored for their impact on gastric mucosal injury. Preclinical studies reveal that these agents may attenuate oxidative stress, suppress inflammatory signaling, and improve tissue repair processes. Their pleiotropic effects beyond glycemic control highlight a novel avenue for gastric ulcer therapy, although clinical validation is still lacking **(Chou et al., 2024)**.

7. **Curcumin** has attracted sustained interest for gastroprotection owing to its multimodal actions on oxidative stress and inflammation. By inhibiting NF-κB signaling and upregulating cytoprotective pathways (including Nrf2/HO-1) **(Fig. 5)**, curcumin reduces lipid peroxidation, limits neutrophil infiltration, and promotes epithelial restitution. Formulation matters: conventional curcumin has low bioavailability, whereas phytosomal, nanoparticle, or piperine-enhanced preparations achieve higher systemic exposure and more consistent mucosal effects. It is generally well tolerated; mild gastrointestinal upset is the most common complaint, and it should be used cautiously with anticoagulants due to theoretical antiplatelet effects **(Kwiecien et al., 2019)**.

8. **Melatonin**—endogenously produced in both the pineal gland and gastrointestinal tract—exerts potent antioxidant and pro-healing effects in the stomach. It enhances mucosal blood flow, limits leukocyte adhesion, and triggers Nrf2/HO-1 induction while tempering pro-inflammatory cytokines. In preclinical ulcer models, melatonin accelerates re-

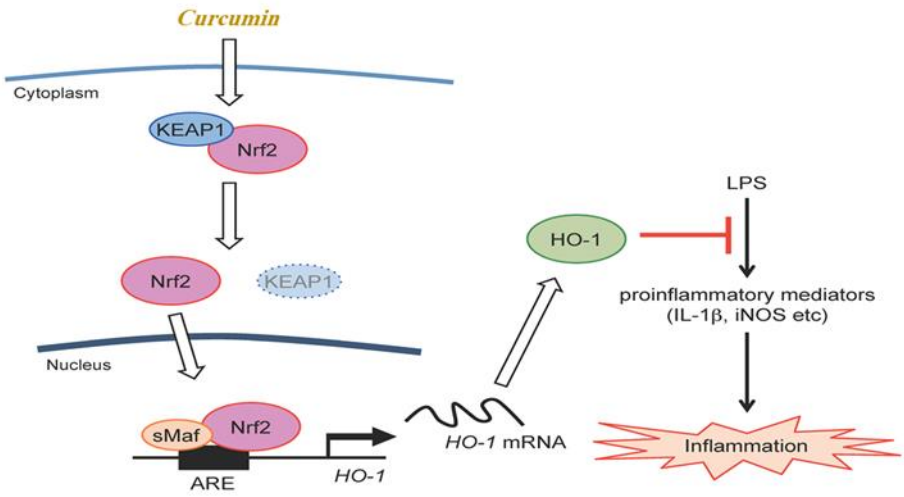

Fig. 5. Induction of HO-1 via the KEAP1/Nrf2 Pathway

epithelialization and angiogenesis and reduces ulcer indices; small clinical experiences suggest symptom relief and faster healing when added to acid suppression. Sedation is the main adverse effect; interactions are few but additive drowsiness with CNS depressants is possible **(Bandyopadhyay and Chattopadhyay 2006)**.

9. **Resveratrol** offers complementary antioxidative and anti-inflammatory actions through SIRT1 activation, down-modulation of NF-κB, and improvement of microvascular function. It has shown reductions in ulcer area and oxidative biomarkers in animal models of NSAID- and ethanol-induced injury, alongside improved mucus quality. Bioavailability is modest due to rapid metabolism; micronized or liposomal forms may improve exposure. It is typically well tolerated, but high doses can cause GI upset and may theoretically potentiate antiplatelet drugs **(Guha et al., 2010)**.

10. **Quercetin**, a dietary flavonol, demonstrates membrane-stabilizing, radical-scavenging, and COX/LOX-modulating properties that can rebalance the prostaglandin–leukotriene axis unfavorable in NSAID ulcers. Experimental data show smaller lesions, less edema, and improved antioxidant enzyme activity (SOD, catalase) with quercetin administration. It is generally safe at nutritional doses; occasional headache or dyspepsia can occur, and it may interact with some drug-metabolizing enzymes at high supplemental levels **(Abdel-Tawab et al., 2020)**.

11. **Berberine** combines antimicrobial, anti-inflammatory, and barrier-enhancing effects that are relevant to *H. pylori*–associated disease. It can reduce bacterial adhesion, attenuate IL-8–driven neutrophil chemotaxis and strengthen tight junction integrity. In models of ulceration, berberine decreases mucosal oxidative damage and improves histologic healing. GI cramping or constipation are the most frequent side effects; it may interact with cytochrome P450 and P-glycoprotein substrates **(Guo et al., 2024)**.

12. **Lactoferrin**, a natural iron-binding glycoprotein, shows promise as a biologic adjunct by inhibiting *H. pylori* growth and biofilm formation while modulating mucosal immunity toward an anti-inflammatory phenotype. As part of eradication regimens, lactoferrin has been explored to enhance bacterial clearance and reduce antibiotic-related dysbiosis; it may also limit iron-driven Fenton chemistry in the ulcer microenvironment. It is typically well tolerated; hypersensitivity is rare **(Imoto et al., 2023)**.

13. **Probiotics** (e.g., *Lactobacillus*, *Bifidobacterium*, *Saccharomyces boulardii*) can lower *H. pylori* load, improve eradication tolerability, and reduce diarrhea, nausea, and dyspepsia during antibiotic therapy. Mechanistically, they compete with *H. pylori* for adhesion sites, produce bacteriocins and short-chain fatty acids, reinforce tight junctions, and downregulate pro-inflammatory signaling. Effects are **strain-specific** and adjunctive; they are not stand-alone treatments for active ulcers. Immunocompromised patients should use them cautiously due to rare

cases of translocation **(McFarland et al., 2015)**.

14. **Omega-3 polyunsaturated fatty acids** provide anti-inflammatory lipid mediators (resolvins, protectins) that help terminate neutrophil-driven injury and support mucosal restitution. Supplementation in preclinical ulcer models reduces leukotriene-biased signaling, improves microcirculation, and enhances epithelial healing. Fishy aftertaste and mild GI upset are common; high doses can modestly prolong bleeding time and should be coordinated with antithrombotic therapy **(Motawee et al., 2022)**.

15. **Vitamin D**—through VDR-mediated immunomodulation—can temper excessive Th1/Th17 responses, promote antimicrobial peptides, and support epithelial integrity. Observational data link deficiency with dyspepsia and poorer *H. pylori* eradication, while supplementation may improve immune balance and barrier function. Over-supplementation risks hypercalcemia; dosing should be guided by baseline levels **(Rateb et al., 2021)**.

16. **Honey and propolis** represent traditional products with modern mechanistic support: they exhibit antioxidant capacity, broad-spectrum antimicrobial activity (including anti–*H. pylori* effects in vitro), and stimulation of tissue granulation and angiogenesis. Standardization and dosing vary widely among preparations; they may soothe symptoms and aid healing as adjuncts but should not replace evidence-based therapy. Allergy to bee products is the principal contraindication **(Ruiz-Hurtado et al. 2021)**.

8. Future Perspectives and Research Gaps

Despite significant progress in the understanding and management of gastric ulcers (GU), several challenges remain unresolved, necessitating further research and innovation.

8.1. Antibiotic Resistance and Alternative Eradication Strategies

The increasing prevalence of antibiotic resistance, particularly against clarithromycin and metronidazole, has reduced the efficacy of conventional *H. pylori* eradication regimens. This trend highlights the urgent need to develop alternative strategies such as the use of novel antimicrobials, antimicrobial peptides, bacteriophage therapy, and probiotics as adjuncts. Additionally, tailored therapies guided by molecular diagnostic tools to detect resistance mutations may improve eradication success rates **(Cardos et al., 2021)**.

8.2. Antibiotic Resistance and Alternative Eradication Strategies

Current therapeutic approaches often follow a "one-size-fits-all" model, which overlooks patient-specific variations in genetic background, drug metabolism, and ulcer risk profiles. Advances in pharmacogenomics and precision medicine hold promise for optimizing drug selection and dosing based on individual genetic polymorphisms (e.g., CYP2C19 affecting PPI metabolism). Personalized medicine may also integrate biomarker-driven risk stratification to predict recurrence, guide preventive strategies, and reduce adverse drug effects **(Wong and Yau 2012; Marques et al., 2024)**.

8.3. Role of Gut Microbiome in Ulcer Pathogenesis and Healing

Emerging evidence suggests that the gut microbiome plays a crucial role in modulating mucosal immunity, inflammation, and healing responses. Dysbiosis may contribute to ulcer persistence or recurrence, even after *H. pylori* eradication. Future research should focus on characterizing specific microbial signatures associated with GU and exploring microbiota-targeted interventions such as probiotics, prebiotics, and fecal microbiota transplantation (FMT) as therapeutic options **(Alam and Neish 2018; Sahle et al., 2024)**.

8.4. Preventive Approaches in High-Risk Populations

Patients with chronic NSAID use, anticoagulant therapy, or comorbid conditions such as cirrhosis and chronic kidney disease remain at elevated risk for GU and its complications. Preventive strategies—including prophylactic use of PPIs, safer anti-inflammatory agents, and screening protocols for *H. pylori*—require further validation. Moreover, public health measures aimed at lifestyle modifications (smoking cessation, reduced alcohol

intake, and healthy diet) are essential to reduce the global burden of GU **(Roderick et al., 2003)**.

8.5. Integrating Traditional and Modern Therapies

Natural products and phytochemicals have shown promising gastroprotective, antioxidant, and anti-inflammatory properties in preclinical studies. However, their clinical translation remains limited due to variability in formulations, lack of standardized dosing, and insufficient clinical trials. Integrating evidence-based traditional medicine with modern pharmacology could provide novel adjunctive therapies, provided rigorous safety and efficacy evaluations are conducted **(Chiu et al., 2021; Nisar et al., 2023)**.

9. Conclusion

Gastric ulcer remains a significant global health challenge, arising from a complex interplay of *H. pylori* infection, NSAID use, oxidative stress, inflammation, and host susceptibility. Despite major advances in diagnostic techniques and the availability of effective therapies such as proton pump inhibitors and *H. pylori* eradication regimens, the persistence of complications, recurrent disease, and rising antibiotic resistance continue to limit optimal outcomes.

Recent insights into the molecular pathways of gastric mucosal injury—particularly the roles of oxidative stress, inflammatory mediators, and the gut microbiome—have broadened the understanding of disease mechanisms and opened avenues for novel interventions. Emerging therapies, including antioxidants, immunomodulators, phytochemicals, probiotics, and innovative drug delivery systems, show promise in enhancing ulcer healing and preventing recurrence. However, translation into clinical practice requires robust evidence from large-scale trials.

Future management of gastric ulcer will likely rely on an integrated, personalized approach that combines conventional pharmacological strategies with targeted molecular therapies, microbiome modulation, and evidence-based traditional remedies. In addition, preventive measures in high-risk populations and innovative solutions to combat antibiotic resistance remain pressing priorities.

In summary, while considerable progress has been made, gastric ulcer research and treatment are still evolving. Bridging the current knowledge gaps through translational research, precision medicine, and integrative therapeutic strategies holds the key to reducing the burden of gastric ulcer and improving patient outcomes worldwide.

10. Recommendations

10.1. Clinical and Practical Recommendations

From a clinical standpoint, prevention and early detection should remain at the forefront of gastric ulcer management. Routine screening for *H. pylori* in high-risk populations and judicious use of non-steroidal anti-inflammatory drugs (NSAIDs) are critical to minimizing disease burden. When NSAID therapy is unavoidable, the co-prescription of gastroprotective agents such as proton pump inhibitors should be strongly encouraged. Lifestyle modification also plays a pivotal role, with smoking cessation, moderation of alcohol consumption, adoption of a diet rich in natural antioxidants, and effective stress management representing essential preventive measures. In terms of pharmacological therapy, rational prescribing of proton pump inhibitors and H2 receptor antagonists is necessary to avoid the risks associated with long-term overuse. Eradication therapy for *H. pylori* should be guided by local antibiotic resistance profiles, ensuring optimal treatment efficacy. Clinicians should also prioritize patient follow-up, particularly through repeat endoscopy in cases of refractory, complicated, or high-risk ulcers, while non-invasive diagnostic tools may serve as valuable adjuncts for monitoring therapeutic response. Collectively, these measures can improve patient outcomes, reduce complications, and lower recurrence rates.

10.2. Research Oriented Recommendations

From a research perspective, future efforts should focus on addressing the challenges of rising antibiotic resistance in *H. pylori* eradication, with emphasis on developing alternative treatment strategies and resistance-guided therapies. There is a pressing need for well-designed clinical trials evaluating emerging therapeutic approaches, including antioxidants, probiotics, and phytochemicals, which have shown promise in

experimental models but require validation in human populations. The gut microbiome represents another important frontier, as its complex interaction with mucosal integrity, inflammation, and healing could provide novel therapeutic targets. Molecular pathways such as Nrf2/HO-1 signaling and inflammatory cytokine regulation also warrant deeper exploration, both to understand ulcer pathogenesis and to identify potential druggable targets. Personalized medicine should be integrated into gastric ulcer management, tailoring therapy based on individual genetic, microbial, and clinical profiles. Finally, rigorous scientific evaluation of traditional and complementary therapies will be essential to determine their safety, efficacy, and potential role in combination with modern pharmacological regimens.

Conflict of interests

Nothing to declare.

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