Available online on 15.11.2026 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

From Cause to Cure: A Comprehensive Review on Epidemiology, Pathophysiology, and Management of Peptic Ulcer Disease

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Article Info:

Article History:

Received 23 Aug 2026
Reviewed 28 Sep 2026
Accepted 23 Oct 2026
Published 15 Nov 2026

Cite this article as:

Gaur S, Negi H, Gupta D, Ali Z, Yadav N, Mittal S, From Cause to Cure: A Comprehensive Review on Epidemiology, Pathophysiology, and Management of Peptic Ulcer Disease, Journal of Drug Delivery and Therapeutics. 2026; 16(11):134-142 *DOI:* https://doi.org/10.22270/jddt.v16i11.8060

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Abstract

A common gastrointestinal condition known as peptic ulcer disease (PUD) is marked by ulceration of the stomach and duodenal mucosa due to an imbalance between mucosal defensive and aggressive stimuli. PUD continues to be a major global health burden despite advancements in diagnosis as well as treatment, which results in major complications like perforation, gastrointestinal bleeding, and obstruction. Helicobacter pylori *(H. pylori)*infection and Non-steroidal anti-inflammatory drug (NSAID) use remain the main underlying causes, but genetics, lifestyle, physiological factors, and environmental factors may also play a role. Dysfunction of mucosal defence, increased acid and pepsin activity, decreased bicarbonate and mucus secretion, inflammation, oxidative stress and alteration in stomach mucosal blood flow are all aspects of the pathogenesis of PUD. With a focus on the basic pathophysiological mechanism behind PUD, this review provides a summary of the disease's epidemiology and major risk factors. Mucosal protective medicines, proton pump inhibitors, and histamine H2-receptor antagonists. *H.pylori* eradication regimens and the management of NSAID-associated ulcers are some of the current diagnostic and therapeutic methods that are covered. Additionally, emphasized are emerging therapy approaches and preventive strategies are emphasized. Improved clinical outcomes, early diagnosis, and the prevention of coexisting conditions can all be made possible by a greater awareness of the intricate processes underlying PUD.

Keywords: Duodenal ulcer; Gastric ulcer; *Helicobacter pylori*; NSAIDs; Proton pump inhibitor; Peptic ulcer disease

Introduction

A Peptic ulcer is severe destruction of the lining of the stomach and/or duodenum that extends beyond the muscularis mucosa, particularly into the muscularis layer, due to increased gastric acid. The two main widespread causes that trigger peptic ulcers are Helicobacter pylori and NSAIDs[1]. Gastrinoma is a Zollinger-Ellison syndrome, a neuroendocrine tumor that is found near the head of the pancreas and in the wall of the duodenum; it secretes gastrin and is very active[2,3]. Spiral-shaped, gram-negative *H. Pylori* bacteria colonize the human stomach mucosa can cause infection. Some upper gastrointestinal disorders such as gastric mucosa, chronic gastritis, gastric cancer, gastric mucosal associated lymphoid tissue lymphoma, and gastric peptic ulcer disease are caused by *H. pylori*[4]. The imbalance between the natural defensive components of the mucosa of the stomach (secretion of mucus, bicarbonate, proper blood flow, nitric oxide, and prostaglandin PGE) and some aggressive components such as pepsin secretion as well as acid secretionleads to a peptic ulcer[5]. Thus,the mucosal layer possesses a special capacity to withstand the damage brought by increasing peptic acid concentration and bile inflow, as well as pepsin[6]. The mucosal surface epithelium, which is hydrophobic, is also one of the protective factors that can repel water-soluble substances and acids. Aggressors that compromise the integrity of the mucosal layer, including *H. pylori* and NSAIDs, are the second-most causative agents[7].

Types of Peptic Ulcers

Peptic ulcers are of different types:

1) Gastric/stomach ulcer: Ulcers that occur on the lining of the wall of the stomach are known as gastric ulcers, and they are correlated with drugs such as NSAIDs as well as *H. pylori* infection, whereas stomach ulcers represent 20% of peptic ulcers[8].

2) Duodenal ulcer: Peptic ulcers that arise in the duodenum, which is the first lining of the small intestine, are known as duodenal ulcers. They are more widespread than stomach ulcers and also occur with NSAID use and *H. pylori* infection; duodenal ulcers represent 80% of peptic ulcers[9].

3) Stress ulcer: It is also called "acute stress ulcers. It

appears in response to extreme physical stressors, including major surgery, trauma, burns, or life-threatening sickness[10]. Fig. 1 represents the diagram of different types of peptic ulcers.

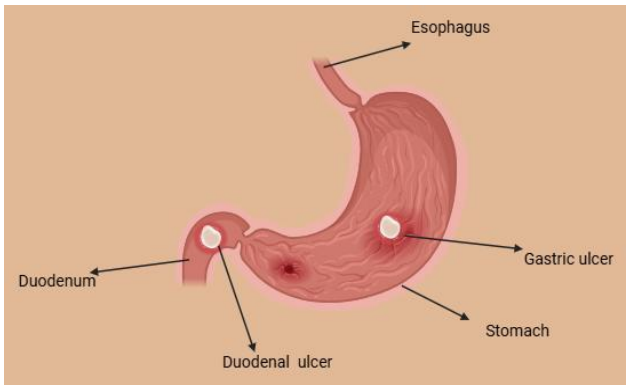


FIG. 1: Diagrammatic representation of the stomach peptic ulcer and the duodenum peptic ulcer

Causes of peptic ulcer

Peptic ulcers have both common and infrequent causes. Table 1 represents the common and infrequent causes of peptic ulcers, whereas Fig. 2 illustrates additional factors such as smoking, alcohol consumption, *H. pylori*, and NSAIDs[11].

Table 1: Lists the common and infrequent causes of peptic ulcers.

Common causes	Infrequent causes
H. Pylori infection	Hyperplasia
ASA and NSAIDs treatment	Gastronome
Stress ulcers	Systemic mastocytosis
	Viral infection
	Chron's disease
	Type II amyloidosis
	Neuhauser syndrome

Symptoms

Symptoms of a peptic ulcer include anorexia, nausea, abnormal weight loss, stool containing blood, and abdominal pain. Epigastric pain occurs at nighttime as well as before breakfast if the patient is suffering from a duodenal ulcer. Some patients may suffer from heartburn in the absence of esophagitis[12,13]. The abdominal discomfort occurs several days a week; generally, it occurs just after a meal or in the middle of the nighton an empty stomach. Many other symptoms include blood loss, which further results in anemia, poor appetite, bloating, and burping. Some emergency symptoms include sudden, sharp, persistent pain in the stomach, bloody or black stools, and blood in vomit[14]. Fig. 2 represents the symptoms of peptic ulcer.

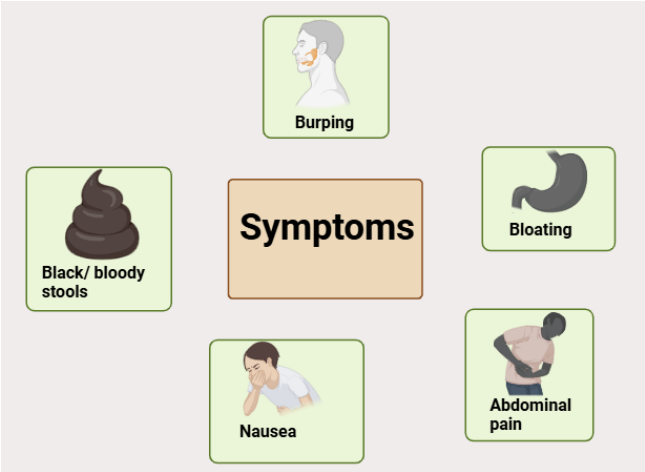


FIG. 2: Symptoms of a peptic ulcer

Complications

Peptic ulcers have serious complications, and 30% of people suffer from them, including hemorrhage, perforation, or obstruction in the gastric outlet. These types of complications are more common in older patients or patients who are taking NSAIDS.

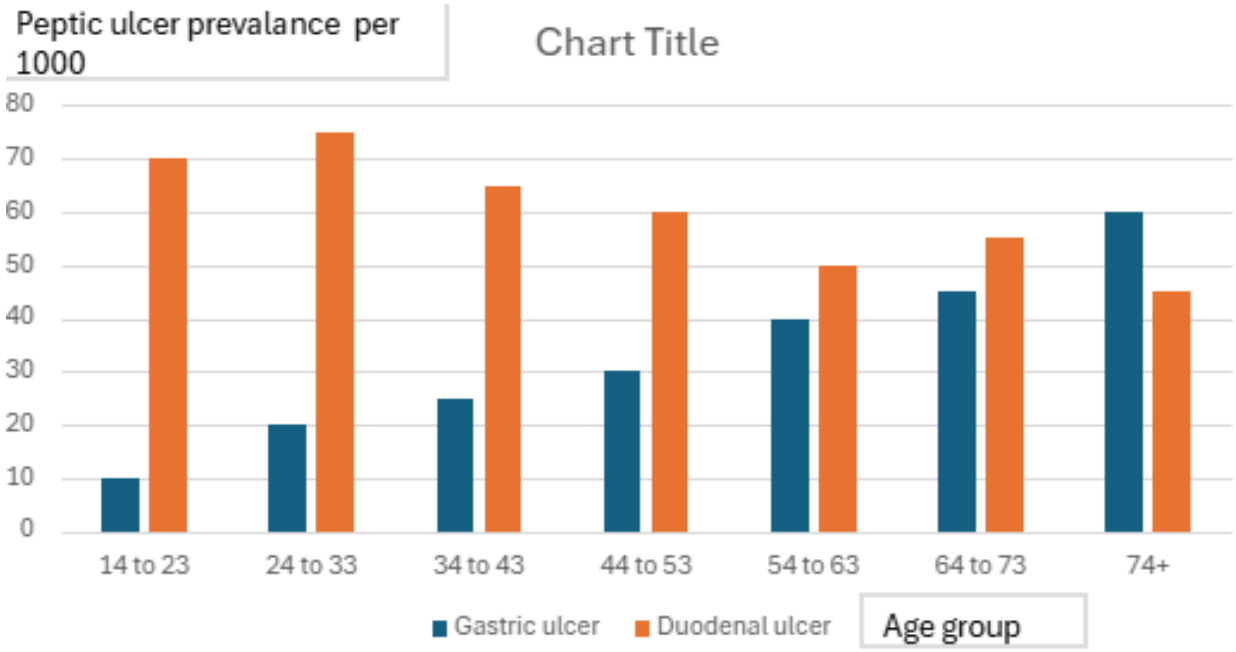
A. Perforation- It occurs in 5% of patients, whereas it results in 67% of ulcer death[15]

B. Bleeding- It is a more common complication that occurs in 15-20% of patients, whereas it results in 25% of ulcer deaths[16].

C. Obstruction from edema- It occurs in 2% of patients, due to a pyloric channel ulcer, which causes cramps as well as abdominal pain[17].

Epidemiology

Prevalence and incidence- According to 21 studies with a total sample size of 788525, ranging in age from 17 to 82, the prevalence of peptic ulcers worldwide was found to be 8.4% (95% CI 5–13.7).According to WHO in India, the prevalence of peptic ulcer was found to be 4.72%, whereas the lifetime incidence was 11.22%[18]. Graph 1 represents the peptic ulcer prevalence per 1000, in which the peak represents gastric ulcer in blue and duodenal ulcer in orange, according to age group.



Graph 1. Prevalence of peptic ulcer according to age group

Pathophysiology

Under normal conditions, the mucus bicarbonate barrier, neutral pH, and constant epithelial cell renewal keep the duodenal and stomach mucosa intact. A distinguishing factor in stomach homeostasis is improper blood flow[19]. NO and PGs are good for the maintenance of proper perfusion to the stomach mucosa, ensuring that O2 and nutrients are delivered, as well as the harmful metabolites are eliminated to prevent tissue damage[20,21].

H. pylori infection

H. pylori causes an inflammatory reaction in the mucosal layer, resulting in epithelial cell loss and damage[8]. When *H. pylori* colonizes the stomach mucosa, it can cause inflammation to damage the mucosal barrier and reduces its ability to protect the stomach. The factor of the bacteria, such as vacuolating cytotoxin A (Vac A) and cytotoxin-associated gene A (Cyt A) causes inflammation and damage to epithelial cells, which cause mucosal injury[22].

Non-steroidal anti- inflammatory drugs (NSAIDs) induced damage

Many people experience gastrointestinal adverse effects from using NSAIDs, which are used to relieve pain and inflammation in a range of illnesses. NSAIDs give rise to 90% of ulcers, in which 25% of NSAID- related ulcers develop peptic ulcer disease[23]. NSAIDs block the cyclooxygenase enzyme, which produces prostaglandins synthesis, and prostaglandin are essential for maintaining the integrity of the mucosa by encouraging mucus and bicarbonate, improving and promoting mucosal blood flow, and promoting the multiplication of epithelial cells. On the other hand, NSAIDs cause COX inhibition, which diminishes these safeguarding processes, making the mucosa prone to harm from stomach acid and pepsin[24]. By inhibiting the synthesis of prostaglandin, the NSAIDs interfere with mucosal defense as described in the following points:

1. Secretion of mucin and surface-active phospholipid by mucous cells. Mucin is a polysaccharide substance that the stomach secretes in response to both PGE and PGF. It serves as a barrier for the protection of the stomach against ulcers caused by pepsin and HCl; this advice that NSAIDs prevent the formation of stomach ulcers by the cytoprotective substance secretion[25].

2. Secretion of basal bicarbonate from gastric mucosa.

3. Ulcer healing: mucosal proliferation is necessary.

4. Feedback inhibition by physiological regulation of gastric acid secretion[22].

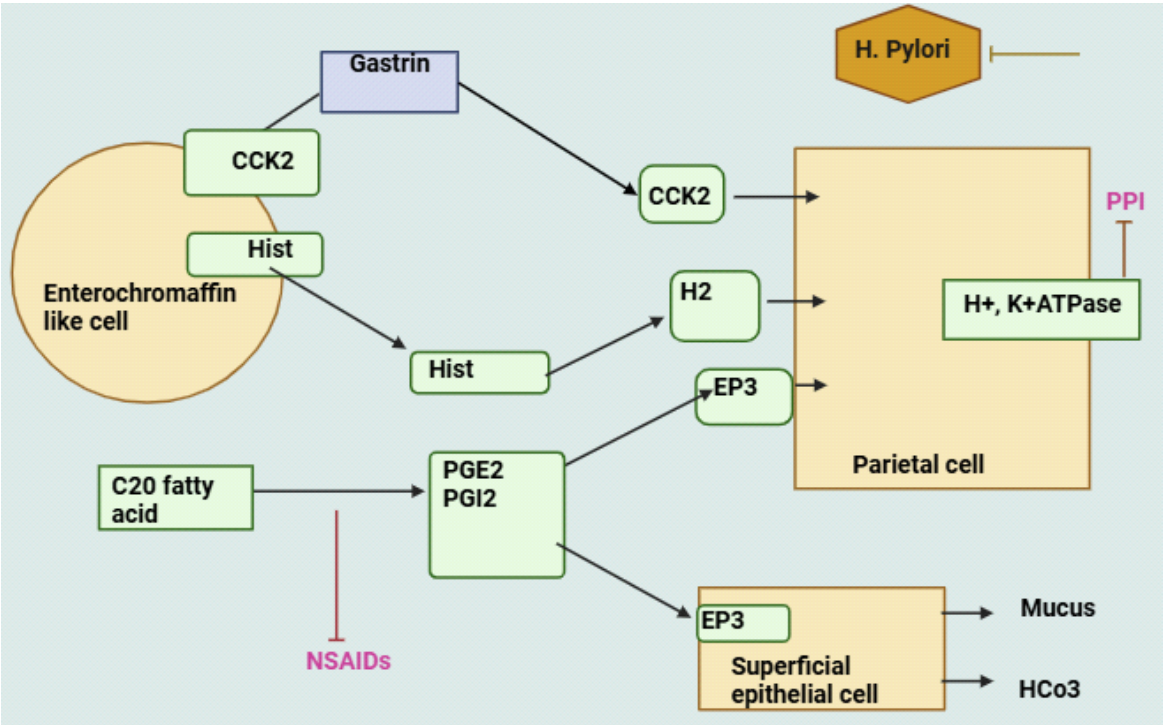


FIG. 3: Diagrammatic representation of the primary pathophysiological pathways behind the development of peptic ulcers,and various pharmacological options for the treatment of peptic ulcers.

Management of peptic ulcer disease

The purpose of management is to lower ulcer discomfort by treating the ulcer, preventing the ulcer from returning, as well as lessening related problems and removing *H. pylori* from people whose result is test positive.

Synthetic drugs for treating peptic ulcer disease

Removal of *H. pylori* on its own can heal the peptic ulcer, but it is difficult because *H. pylori* is becoming resistant to antibiotics, whereas peptic ulcer disease is caused by an imbalance between defensive and aggressive factors[26]. Further, Table 2 summarizes the synthetic drugs used in the treatment of PUD.

Table 2: Synthetic drugs with anti-ulcer activity

Drug class	Mechanism of action	Examples	Limitations
Antacid[27]	Reduction of diarrhea, prevent erosion by gastric acid, acid neutralizing effect, increase gastric pH	Magnesium Hydroxide, Aluminum Hydroxide	Causes hyperacidity by dose dependence, milk-alkali syndrome
Mucosal increasing resistance agents[28]	Protects the stomach's mucus lining from acid by protecting it from acid damage	Misoprostol, Sucralfate, Chelated bismuthate	It has propensity of causing emesis
Gastric muscle stimulants[29]	Accelerates gastric emptying	Domperidone, Metoclopramide	Headache, nausea, vomiting, constipation
Antisecretory medications (Anticholinergic and H2 antagonist)[30]	Reduces gastric acidity, output and volume, reduce gastric acid secretion, Histamine H2 receptor antagonist act as competitor antagonist with gastrin by inhibiting it and binding of histamine and reducing gastric acid release	Methantheline, Propantheline, Atropine	Photophobia, dry mouth, hallucination, disorientation
Proton pump inhibitors[31]	Inhibits H+/K+ ATPase in parietal cell or block of gastric acid secretion in parietal cell	Pantoprazole, Esomeprazole, Rabeprazole, Omeprazole etc.	Rebound acid deficiency, vitamin deficiency, hypomagnesemia

Natural agents with anti-ulcer properties

In nature, plant extracts are commonly used to treat a wide range of illnesses, including diabetes, cancer, and gastric ulcers. Different plants contain different phytochemical constituents, which are used to treat peptic ulcer disease. Further, Table 3 summarizes the natural drugs usedto treat peptic ulcer disease, along with their ulcer model, doses, duration, route, as well as their parameters.

Table 3: Natural extracts that possess anti-ulcer activity

Scientific name	Family	Part used	Solvent used	Ulcer model	Doses, Route, Duration	Parameters
Apodytes dimidiata[32]	Icacinaceae	Leaves	Chloroform, methanol, chloroform, acetone	Gastric ulcer in rats induced by ethanol	Dose-100 and 250 mg/kg Route-orally Duration-4 hours	96.7% 100% MDA Activity ↓ SOD Activity ↑ GSH Level ↑ GPx Activity ↑ CAT Activity ↑
Mucuna prureins[33]	Leguminosae	Leaves	Ethanol 95%	Gastric mucosal injury in rats induced by ethanol	Dose-62.5, 125, 250, 500 mg/kg Route-orally Duration-5 days	59% 79% 87% 89% Gastric wall mucus ↑ CAT ↑ NO ↑ SOD ↑ GSH ↑ PGE2 ↑ MDA↑ Bax protein expression ↓
Foeniculum vulgare[34]	Apiaceae	Leaves	Distilled water	Gastric mucosal injury in rats induced by ethanol	Dose-75, 150 and 300 mg/kg Route-orally Duration-6 weeks	37.8% 27.9% 68.2% MDA Level ↓ GSH ↑ Nitrite level ↑ Nitrate Level ↑

Brassica oleracea var. Acephala DC[35]	Brasicaceae	-	Aqueous ethanol mixture 50% (v/v)	Nonsteroidal anti-inflammatory drugs induce ulcer in mice by the induction of ethanol/HCl	Dose-25,50,100 mg/kg Route-orally Duration-7 days	Ethanolic gastric ulcer15.7% 58.8% 86.2% NSAIDs gastric ulcer14.5% 68.3% 66.4% pH ↑ Mucosa volume ↑ Gastric juice ↓
Curcuma Xanthorrhiza[36,37]	Zingeberaceae	-	Ethanol 95%	Ethanol induce gastric mucosal lesions in rat	Dose-250 and 500 mg/kg Route-orally Duration-6 days	100% Mucus weight ↑ SOD ↑ PGE2↑ MDA↓

New chemical agents with anti-ulcer properties

Numerous investigations regarding the anti-ulcer properties of several chemical compounds have been carried out in recent decades. Further, Table 4 summarizes the new synthetic compounds used in the treatment of PUD, their mechanisms of gastroprotection, and their doses in the ulcer model.

Table 4: New synthetic compounds with anti-ulcer activity

Synthetic compounds	Ulcer model	Doses	Parameters
Topiramate[38]	Gastric ulcer induced in rat's by ethanol	Dose- 50,100,200 mg/kg	Gastric secretion ↓ Gastric acidity ↓ Expression of p53↓ MPO activity ↓
Sildenafil[39]	Gastric ulcer induced in rats by indomethacin	Dose-10 mg/kg	MDA ↓ TNF α ↓ No ↑ Gastric pH ↑
Mesalazine[40]	Gastric ulcer induced in rats by ethanol	Dose- 50,100 mg/kg	pH ↑ GSH Level↑ CAT Level ↑ PCO Level ↑ Gastric juice ↓ ROS Level ↓

Cilostrazol[41]	Gastric lesions and pylorus ligation induced in rats by ethanol	Dose- 5,10 mg/kg	GSH Level ↑ NO Level ↑ PGE2↑ TNF α ↓ Bax expression ↓
N-acetylcysteine[42]	Gastric injury in rats induced by indomethacin	Dose- 500 mg/kg	NO Level ↑ PGE2 Level ↑ SOD Level ↑ MDA Level ↓ MPA Level ↓ TNF α ↓

Novel compounds with anti-Ulcer properties

In recent decades, numerous studies have been conducted to examine the ulcer-preventiveproperties of various pharmacological agents. The forms and procedures of these compounds are capable of preventing as well as treating ulcers. Table 5 summarizes the new compounds used in the treatment of PUD.

Table 5: Novel compounds with anti-ulcer activity

Clinical trial number	Compound name	Study type	Clinical trial phase	Outcomes measures	Sponsor
NCT06439563	JP-1366	Interventional	Phase 3	Evaluation of cumulative proportion of subjects who develop peptic ulcer as well as gastric, duodenal endo scoping bleeding	Ongoing Therapeutics Inc.
NCT06526455	Esomeprazole	Interventional	Phase 4	Evaluation of size if ulcer, rate of ulcer healing, rate of bumpy, post-operative symptom relief rate	Shicai Ye
NCT05656092	HIP0612	Interventional	Phase 3	Evaluated the proportion of subjects who newly develop peptic ulcer until week 14 as well as heart burn until 2 weeks	Hanmi Pharmaceutical Company Limited
NCT05010954	LXI-15028	Interventional	Phase 3	Evaluated the endoscopy healing rate at week 4	Shandong Luoxin Pharmaceutical Group Stock Co.Limited
NCT04784910	DWP14012	Interventional	Phase 3	Evaluated the percentage of heartburn for 4 weeks and mucosal healing in 8 weeks	Daewoong Pharmaceutical Co. Limited
NCT06284876	Ilaprazole	Interventional	Phase 3	Evaluated the proportion of subjects who newly develop peptic ulcer until week 12 after the IP treatment	Il-Yang Pharm, co. Ltd.

Conclusion

The study revealed that NSAID consumption and Helicobacter pylori are the primary causes of peptic ulcer (PUD), which remains a major gastrointestinal disorder worldwide. A complex imbalance between mucosal defenses, such as bicarbonate secretion, prostaglandins, epithelial integrity, and adequate mucosal blood flow, as well as *H. pylori*, NSAIDs, stomach acid, and pepsin, contributes to the development of PUD. Although clinical outcomes have improved due to improvements in medical diagnosis and pharmaceutical therapies, complications such as perforation and gastrointestinal bleeding contribute to substantial mortality and morbidity.

Acid suppression, particularly with the inhibition of proton pump inhibitors (PPIs), *H. pylori* eradication, and discontinuing or altering NSAID therapy, are primarily involved in the current management. The elimination of *H. pylori* is becoming more challenging because of increasing antimicrobial resistance, which emphasizes the importance of choosing treatment strategies based on previous antibiotic exposures or individual resistance occurrences. Further investigations into the molecular mechanisms underlying antimicrobial resistance, mucosal injury and repair, and individual-specific responses could facilitate the development of more effective and preventive strategies for management of PUD.

Author's Contributions: All authors have made substantial contributions to the work reported in the manuscript.

Conflicts of Interest: All the authors hereby declare that there are no conflicts of interest.

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