EuropeanJournalofClinicalPharmacy
PrintISSN:2385-409X**OnlineISSN**:3105-0409
Website: https://farmclin.com/

Original Research Article

A Comprehensive Analysis of Peptic Ulcer Disease: Etiopathogenesis, Clinical Characteristics, and Therapeutic Approaches

Article History:

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Received: 05-11-2025
Revised: 19-11-2025
Accepted: 05-12-2025
Published: 20-12-2025

Abstract: Peptic ulcer is a persistent condition that impacts around 10% of the global population. Peptic ulcer arises from an inequity in the protective factors of the mucosal lining, including mucus secretion, bicarbonate release, endogenous antioxidants, cell regeneration, and the ongoing production and release of prostaglandin E2, nitric oxide, and sulfhydryl compounds. Conversely, it is exacerbated by harmful agents such as smoking, alcohol consumption, dietary factors, stress, prolonged and excessive use of nonsteroidal anti-inflammatory drugs, and infection with Helicobacter pylori, among other factors. The disorder is often linked to severe complications, such as excessive bleeding, perforation, gastrointestinal blockage, and cancer. Several therapies are offered, including as proton pump inhibitors, H2 receptor antagonists, antacids, antibiotics, and mucosal protective agents.The secretion of gastric acid, which is the primary cause of irritation, can be stopped or partially neutralized by antacids. H2 receptor antagonists inhibit the binding of histamine to H2 receptors on parietal cells, which stops the activation of adenylate cyclase. This prevents the increase in cAMP levels and the activation of protein kinase and H+/K+ATPase. Prostaglandins primarily hinder the release of acid by reducing the increase of cAMP generated by histamine. Proton pump inhibitors attach to the H+/K+ATPase enzyme. Antimuscarinics hinder the functioning of acetylcholine receptors on the parietal cell, therefore preventing the entry of Ca2+ and the subsequent activation of protein kinase and the proton pump. The primary objective of this review article is to provide a concise overview of the epidemiology, pathophysiology, diagnosis, clinical presentation, and therapy of peptic ulcer.

Keywords: Peptic ulcer, anti-inflammatory, NSAIDs, GI bleeding, Cyclooxygenase

INTRODUCTION

Peptic ulcers are "acid-induced lesions of the digestive tract characterized by denuded mucosa with the defect extending into the submucosa or muscularis propria," and they "usually occur in the stomach or proximal duodenum." [1]. It is estimated that 5-10% of the population suffers from peptic ulcer disease [2]. Epidemiological studies [3, 4] conducted recently, however, have shown that peptic ulcer incidence, hospitalization rates, and death are on the

decrease. Helicobacter pylori (H. pylori) infections have declined.

Hypersecretory acidic environment plus dietary variables or stress have long been regarded to be the root cause of mucosal disruption in persons with acid peptic disease. Peptic ulcer risk factors include but are not limited to H. pylori infection, heavy alcohol and cigarette use, NSAID use, and Zollinger-Ellison syndrome [5]. Risk factors for both stomach and duodenal ulcers include H. pylori infection and the use of nonsteroidal anti-inflammatory drugs [6]. Individual vulnerability is crucial within the initiation of mucosal damage, since only a small percentage of persons with H. pylori or who take NSAIDs develop peptic ulcers. Disorder. Peptic ulcers have been linked to functional polymorphisms in a number of different cytokine genes. In the case of H. pylori-related gastroduodenal disorders, polymorphisms of interleukin 1 beta (IL 1B) affect mucosal interleukin 1 beta production [7].However, "the risk of complications from stomach ulcers was two- to four-fold higher in aspirin and NSAID users."[8]. When used with anticoagulants, corticosteroids, or selective serotonin reuptake inhibitors, NSAIDs and aspirin increase the risk of upper gastrointestinal bleeding. [9].

Although H. pylori infections are widespread in people who use NSAIDs or aspirin, the exact function these drugs play in the onset of gastric ulcer disease is controversial. Multiple observational studies have shown that the usage of increases the incidence of stomach ulcer illness. Aspirin and nonsteroidal anti-inflammatory drug (NSAID) resistance are risk factors for idiopathic stomach ulcer diseasedetected in around 15% of all instances" According to "The pathogenic process underlying the development ofthe exact origin of idiopathic stomach ulcer is unclear,[11], although it is related to a disruption in the equilibrium of factors that maintain mucosal integrity and protect against aggressive stroke. [5]. Danish research confirmed that emotional distress might raise the risk of developing stomach ulcers. [12]. Ischemia is only one of many potential reasons; additional factors include medication (steroids, chemotherapeutic drugs), radiation treatment, infections, histamine, eosinophil infiltration, gastric bypass surgery, and metabolic issues. [13].

2. TYPES OF ULCERS:

2.1 Peptic Ulcer: Gastric ulcers are chronic, usually isolated lesions that may form anywhere in the digestive system that is subjected to the forceful action of acid-peptic fluids. Approximately four times as many duodenal ulcers as stomach ulcers occur in this initial region [14]. Peptic ulcers are caused by a number of factors, including infection with the microorganism H. pylori and acid pepsin secretion, as well as NSAIDs, shock, severe trauma, septicaemia, intracranial lesions, nearly any irritant, such as alcohol, smoking, and spices in food. [15]. Peptic ulcers are characterized by the following symptoms: nausea, vomiting, stomach pain, weight loss, lack of appetite, bloating, and sometimes blood in the stool or vomit. [16].

Gastric ulcers and duodenal ulcers are two types of gastrointestinal ulcers that differ based on their locations in the digestive tract. It may also be broken down into acute and chronic forms, depending on how severe they are. Single or numerous lesions involving submucosal tissue everywhere in the stomach and at depths up to the first centimetre of the duodenum are characteristic of acute gastric ulcers. Chronic gastric ulcers arise independently in the pyloric antrum of the stomach and duodenum and may spread to the neighbouring pancreas or liver by penetrating the epithelial and muscular layers of the aforementioned digestive organs [17]. Obstruction, haemorrhage, perforation, and malignant transformation are only some of the problems that might arise [15].

2.2 Oesophageal Ulcer: Erosions that form in the oesophagus (the food pipe) are referred to as oesophageal ulcers. These form most often along the oesophageal edge and may produce discomfort just below the sternum, where heartburn sensation is also experienced. Gastroesophageal reflux disease (GERD), nonsteroidal anti-inflammatory medications (NSAIDs), and smoking are all linked to oesophageal ulcers [18].

2.3 Aphthous Ulcer: Aphthous ulcers are chronic, recurring sores or ulcers that form within the mouth on regions where the skin is not adhered to the underlying tissue. Bone that is just under the skin, as in the case of the tongue base or the inside of the lips and cheeks. These ulcers or sores are characterized by a yellowish-grey pseudo-membrane, elevated edges, and an erythematous central cavity. Aphthous stomatitis, canker sores, and mouth ulcers are all names for the same condition [19,20]. Anaemia, ulcers, viral infections, oral candidiasis, chronic infections, laryngeal cancer, mouth cancer, and vitamin B deficiency are all common causes of mouth ulcers, and up to 40% of cases are inherited.
The prevalence of mouth ulcers is estimated to be between 50 and 66 percent in North America and 15 to 20 percent worldwide [16]. Large ulcers (above 10 mm in size, more than 2 weeks in length), moderate ulcers (size 510 mm, duration 10-14 days, prevalence 75-80%), and herpetiform ulcers (less than 5 mm in size, 10-14 percent duration, and 5-10 percent prevalence) are all described. [20].

3. PREVALENCE:"The early identification and treatment of H. pylori infections, together with the widespread use of proton pump inhibitors (PPIs),

have contributed to a decrease in the prevalence of peptic ulcer disease (PUD) in modern times. Gastric ulcers are caused when the gram-negative spiral bacillus H. pylori infects the stomach's epithelium. The majority of peptic ulcer disease (PUD) cases (95% of duodenal ulcers and 70% of stomach ulcers) are still attributable to infection with Helicobacter pylori [21]. PUD, which is responsible for most of the remaining 30% of stomach ulcer illness, has been shown to grow in prevalence along with the increased use of NSAIDs (21). In addition, using NSAIDs is associated with an increased risk of haemorrhagic PUD consequences [22,23]. "Gastric ulcer disease predisposition includes corticosteroid usage, physiological depression, anxiety, and the gastrointestinal disorders known as IBD and Zollinger-Ellison" [24]. On top of that,more severe PUD and slower recovery from treated illness occur in those who smoke and drink [25].

4. PATHOGENS: The formation of gastric ulcers is related to lesions, defences, and repairs of the gastric mucosa that are constantly exposed to the damaged environment [26]. Pepsin, acid, and H. pylori infection are all toxic, whereas Prostaglandins, mucins, nitrogen monoxide, bicarbonate, and growth factors are all helpful. This explains why. Stomach ulcer risk factors include chronic nonsteroidal anti-inflammatory drug (NSAID) usage, excessive drinking, poor nutrition, smoking, and emotional or physical stress [27]. Overuse of nonsteroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori are major contributors to peptic ulcer etiology (Fig. 1).

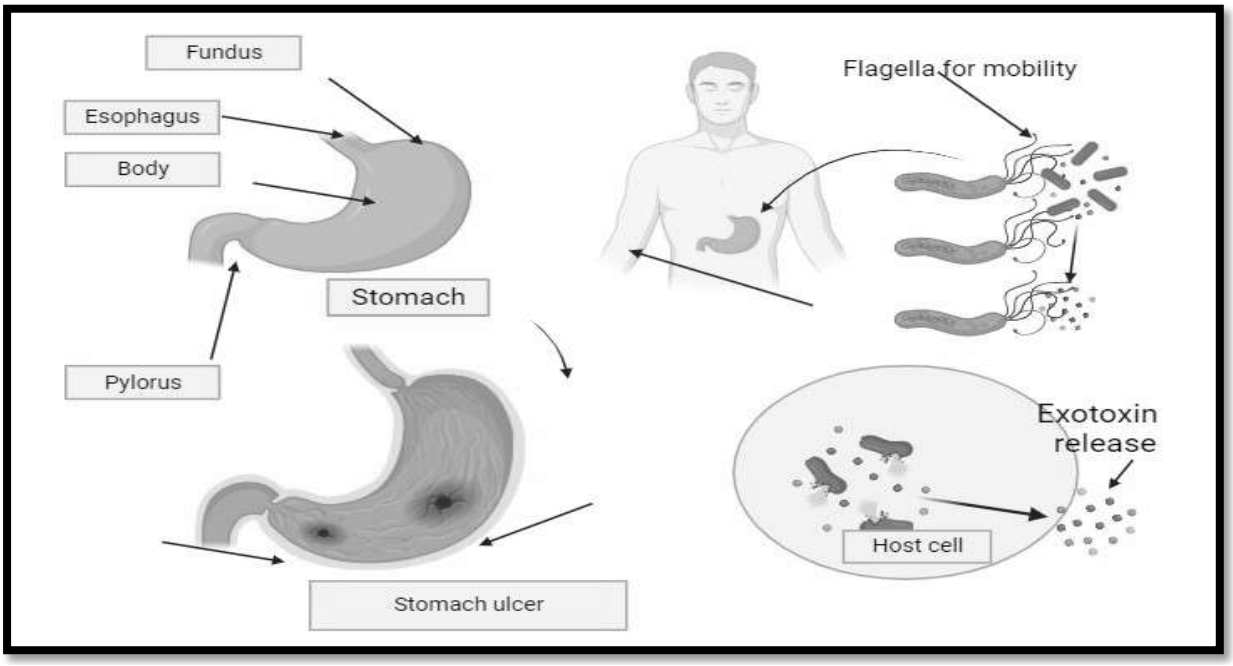

Figure:1
Pathogenesis of peptic ulcer disease. The secretion during the pathogenesis is shows. The normal stomach and the formation of peptic ulcer are also displayed.

4.1 Helicobacter Pylori and Its Role to Induce Ulcer: H. pylori has been shown to be the leading cause of both duodenal and gastric ulcers (Fig. 1). Human stomach antral mucosa is colonized mostly by H. pylori, a pathogen. Which also causes over 95% of gastric and 70% of duodenal ulcerations in humans, according to [28]. [29]. Damage to the epithelium results from a mucosal inflammatory response to the local irritation caused by H. pylori infection. While Helicobacter pylori has several virulence genes, vacuolating cytotoxin (VacA) and cytotoxin associated gene A (CagA) are the most dangerous because of their association with peptic ulcer disease. [30]. Translocation of a carcinogenic substance into the host gastric cells is mediated by the CagA gene. The cag pathogenicity island (cag-PAI) encodes the type IV secretion system (T4SS), which is responsible for the actual translocation. [31]. The pathogenicity island, a collection of 31 genes, has been found in a few different types of bacteria. [32]. T4ss [33], "which formed a syringe-like pilus structure that extended from the bacterial surface into host cells for the delivery of the virulence factors, primarily CagA," was found in some of the cag-PAI genes, as stated in previous papers. [34]. Tyrosine phosphorylation of CagA upon injection alters the intracellular signalling pathway, paving the way for infection. A high T4SS level is very indicative of an infected gastric ulcer.

Therefore, it is crucial to conduct cutting-edge studies to learn how T4SS contributes to the spread of CagA.important. Cagl is a T4SS component that can bind to integrin membrane 1, and it plays a role in CagA secretion as well. [26]. The pattern of gastric inflammatory development in duodenal or gastric ulcers is thought to be heavily influenced by the host's genetic composition. [32] Only through producing the urease enzyme, which breaks down urea into ammonia and carbon dioxide, can H. pylori assure its own existence.To protect themselves from the acidic gastric environment, bacteria create the urease enzyme, which in turn causes a buffering of stomach acid. [35] Alkalinity in the environment is known to inhibit the production of stimulating somatostatin from antral D cells. Less somatostatin stimulation reduces antral G cells' ability to regulate gastrin secretion.[36]. The unchecked generation of gastrin "results in hypergastrinemia, excessive gastric acid secretion, and parietal cell hyperplasia [37]." The neuronal circuits of the brain that control the secretion of stomach acid are disrupted by H. pylori infection, impeding the inhibitory response that normally reduces acid production. Inadequate signals from the brain's nerves may also cause the stomach to produce too much acid, which in turn lowers the duodenal pH. This may be found in the bulb of the duodenum. Ulceration is caused by H. pylori, and metaplasia is the ideal setting for H. pylori colonization.

4.2 Diagnosis of Peptic Ulcer: The most common approach of identifying ulcers is based on symptoms, which take into account the patient's age and the ulcer's location. A stomach ulcer is a painful ailment that often begins on an empty stomach, responds to antacids and food, and may be triggered by consuming alcohol or caffeine. However, weight loss and gastrointestinal bleeding are more often associated with stomach ulcer illness. Mornings are the worst for pain from duodenal ulcers, and eating and getting some sleep at night are the only ways to alleviate it. Diagnosing a duodenal ulcer requires the presence of symptoms such as bleeding, nausea, vomiting, or stomach discomfort. According to [38], "a definitive diagnosis of peptic ulcer may be detection of H. pylori using a variety of endoscopic and non-endoscopic assays, as well as direct imaging using endoscopy or radiography. Non-endoscopic tests include the detection of antibodies to H. pylori in serum, the Urea breathe test (H. pylori urease breaks down ingested labelled C urea, patient exhales labelled CO2), and the stool antigen test (the presence of antigen against H. pylori in stool changes the colour of the stool, which can be detected visually or by spectrophotometer). [39]

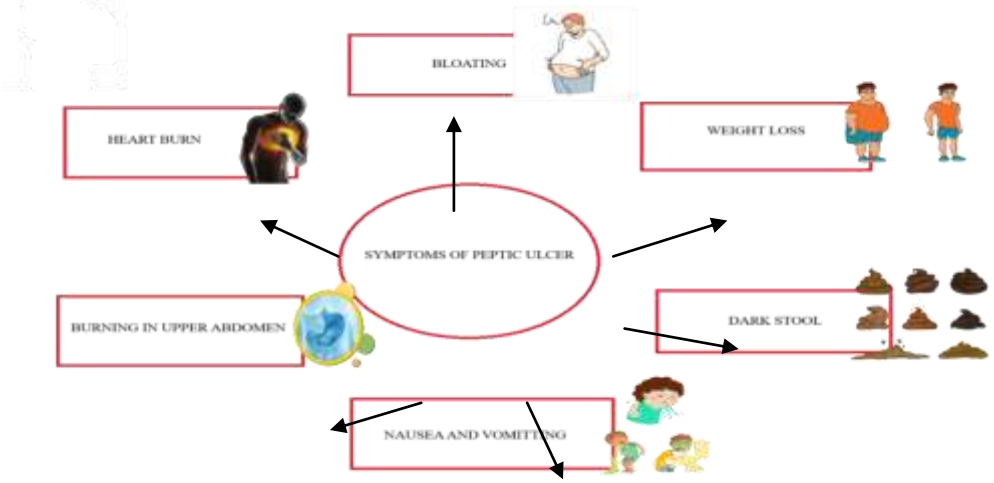

Figure: 2

4.3 Anatomy and Location of Peptic Ulcer Disease: Peptic ulcers are common in both the duodenum and the stomach. There are many distinct regions inside the stomach, including the cardia, fundus, body, antrum, and pylorus. Each gut wall is covered with visceral peritoneum. The stomach's body and antrum are separated by the incisura angularis, an acute angle indentation along the wall's minor curvature.[Fig. 1] Ulcers of the stomach most often develop in the minor curvature, near the gastric antrum. [40]. Peptic ulcers, especially along the stomach's greater arc, have been linked to nonsteroidal anti-inflammatory drug usage. [41].

The duodenum lacks a mesentery and is only partly covered by the peritoneum. [42]In the duodenum, you'll find four distinct divisions. The beginning of the duodenum is made up of the duodenal bulb, which emerges from the pylorus. The only part of the duodenum not covered by visceral peritoneum is the bulb. The remaining portions of the duodenum are located retroperitoneally. The second part of the duodenum runs downward, and it is here that the pancreatic duct and the common bile duct are found. The third (horizontal) segment crosses the retroperitoneal midline at the level of the second lumbar vertebral body. The fourth section of the duodenum extends from the aorta to the Treitz ligaments. [42]

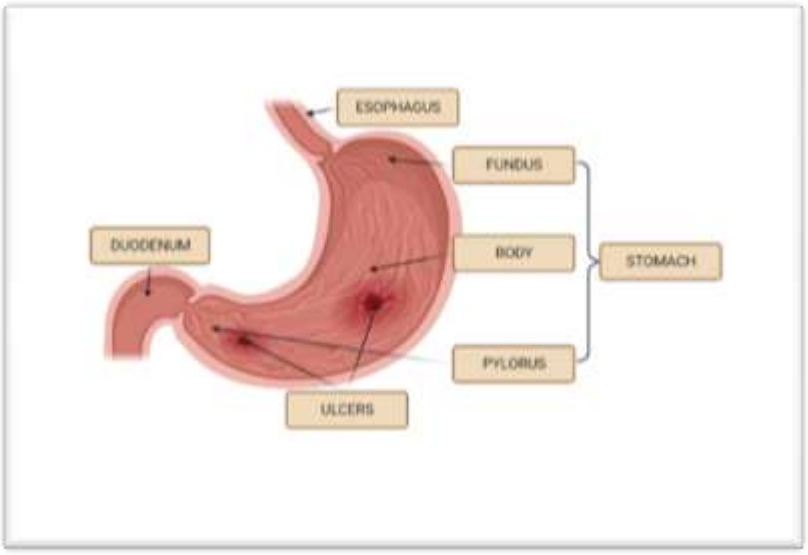

Figure:3

The duodenal bulb is the most common site (95% of all cases) for duodenal ulcers[40,43,44]. Post-bulbar ulcers, which develop beyond the duodenal bulb, are very rare, affecting around 3%-5% of affected people at most. If post-bulbar ulcers are seen, uncommon causes such Zollinger-Ellison Syndrome or Crohn's disease should be considered. [40,43,44]. Because to its proximity to the gastroduodenal artery [44], post-bulbar ulcers are thus more prone to bleed than bulbar ulcers.

Near the duodenum's ampulla, on its anterior wall, is where most posterior duodenal ulcers form. Duodenal ulcers may exhibit an inward bending of the opposite all due to oedema, reactive tissue, and spasm at the ulcer disease site, which might mask the out pouching typical of an ulcer crater. Ulcer craters, a distinguishing characteristic seen on fluoroscopic imaging, may be obscured by the inflammatory response, making diagnosis more challenging" [44].

4.4 Epidemiology and Etiologic Factors: Worldwide, gastric ulcers are a leading cause of death and disability. The outcomes might be anything from gastric outlet blockage or perforation to severe abdominal discomfort and gastrointestinal haemorrhage.

The prevalence of stomach ulcers in the United States is estimated at 8.4 percent [45]. Male gender, smoking, and chronic diseases have all been linked to an increased risk of developing stomach ulcer disease [45,46]. Gastric Ulcer Worldwide, gastric ulcers are a leading cause of death and disability. The end results include anything from bloating and cramping to gastrointestinal haemorrhage, blockage, and perforation. stomach opening.

The prevalence of stomach ulcers in the United States is estimated at 8.4 percent [45]. Male gender, smoking, and chronic diseases have all been linked to an increased risk of developing stomach ulcer disease [45,46]. Gastric Ulcer The development of stomach ulcer illness has also been linked to becoming older.[47] The prevalence of stomach ulcers and their accompanying consequences have decreased over time in the United States and abroad [48,49].

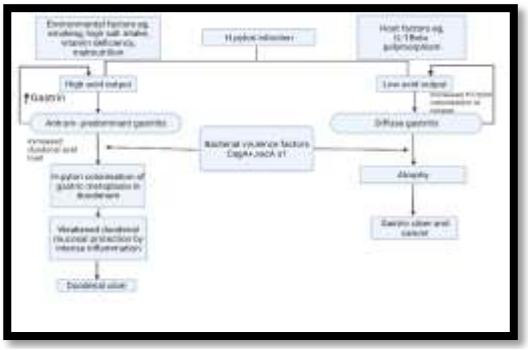

Figure:4

At present, pylori infection and/or the use of NSAIDs are thought to be the primary causes of peptic ulcer disease.[50] Helicobacter pylori is a gram-negative bacterium that may colonize the stomach lining and lead to symptoms including heartburn, ulcers, and even cancer.[51;52] Although H. pylori affects a sizable percentage of

the population, it only causes an increase in scientific illness in a tiny fraction of those infected.[52] Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used, leading to an increased risk of adverse gastrointestinal events such peptic ulcer disease. Non-aspirin NSAID users had a 4.0 times greater relative risk of developing a symptomatic ulcer than people using aspirin. [53]

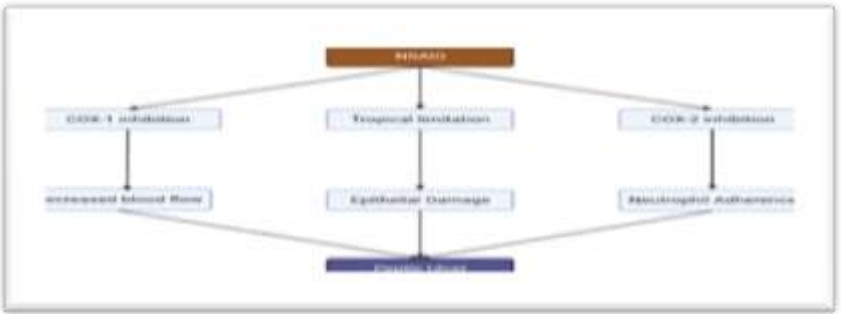

Figure :5Although Helicobacter pylori and nonsteroidal anti-inflammatory medications (NSAIDs) are the most prevalent causes of gastric ulcer illness, additional, less common causes have been found, as shown in Table 1 [54,55]. These include gastronomes (such as Zollinger-Ellison syndrome), other medicines, and other aetiology Fig. 5.

4.5 Treatment: Overview of conventional antiulcer treatment options is summarized in Table 1 and 2

SNo	Category	Name Of Drugs	Mode of action	Adverse/Side Effects	References
1.	**H2 Receptor Blockers**	Ranitidine Cimetidine Famotidine Nizatidine	Blocking the activity of histamine on parietal cells' histamine H2 receptors.	Headache, Dizziness, Depression, Anxiety, Cardiovascular, Events, Thrombocytopenia.	[56]
2.	**Proton pump inhibitors(PPIs)**	Esomeprazole Omeprazole Pantoprazole Lansoprazole Rabeprazole	Inhibition of the gastric H/K-ATPase (proton pump) enzyme system	Headache Abdominal pain Nausea Vomiting Constipation Vitamin B12 Deficiency Osteoporosis Flatulence	[57,58]
3.	**Antacids**	Aluminium Hydroxide Magnesium Hydroxide	Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin Causes osmotic retention of fluid	Frequency not defined: Nausea Vomiting Hypophosphatemia Chalky taste Constipation Abdominal Cramping Diarrhoea Electrolyte imbalance	[59]
4.	**Potassium-competitive acid blocker**	Vonoprazan	Inhibits H+, K+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway	Contusion Nasopharyngitis Fall Upper respiratory Tract inflammation Eczema Diarrhoea Constipation	[60,61,62,63,64]

Category	Duration of action	Efficacy	References
First line PPI+two antibiotics (clarithromycin + metronidazole or amoxicillin)	7-14 days	70-85%	[65]
Second line ***Bismuth-containing quadruple therapy:*** PPI + bismuth salt + tetracycline + metronidazole	14 days	77-93%	[66,67]
Non- bismuth based concomitant therapy: PPI + clarithromycin + amoxicillin + metronidazole	14 days	75-90%	
Levofloxacin triple therapy: PPI+ amoxicillin + levofloxacin	14 days	74-90%	
Salvage regimens ***Rifabutin- based triple therapy:*** PPI + rifabutin + amoxicillin	10 days	66-70%	[68]

5. COMPLICATION: The long-term effects of PUD (adenocarcinoma and MALT lymphoma) included persistent symptoms, bleeding, perforation, penetration, limitation of the stomach outlet, and malignancy. Bleeding is the most common adverse effect, occurring in 15% to 20% of patients. PUD is the leading cause of acute bleeding in the upper digestive tract (40-60%) [70]. The bleeding in the upper digestive tract is an emergency that needs immediate attention. Coordinating the management of critically sick patients is facilitated by early notification to a GI expert during examination of a bleeding patient. Risk stratification was performed using the Glasgow-Blatchford and Rockall ratings [71]. Haemoglobin levels over 7 should be maintained with appropriate intravenous fluid and blood product resuscitation [72].

All patients undergoing intravenous PPI medication should start with the top GI bladder on the presentation [73] to reduce the likelihood of IV PPI to detect High risk- Stigma during endoscopy and discard risk. They raise stomach pH, which aids in clot durability, and encourage platelet aggregation. Endoscopic visibility and diagnostic yield may also be increased by the presence of occupants like as erythromycin or metoclopramide, as this has been hypothesized before [74]. An early (ideally within 24 hours) endoscopy may have beneficial effects on both prognosis and treatment. If bleeding indicates a High-Risk Stigmata, a proton pump inhibitor (PPI) should be started or maintained following an endoscopy administered intravenously twice daily is equally effective as PPI administered constantly [75,76], but costs much less.Recurrent bleeding is associated with a high mortality rate and may need repeated endoscopy, angiographic embolization utilizing interventional radiology, or surgical intervention.Warfarin-induced coagulation difficulties need the use of antidotes such vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), or recombinant factor VIIa.However, these drugs should be taken with care due to the possibility of unfavourable outcomes. Large doses of vitamin K, for instance, increase the time it takes for warfarin to reach therapeutic levels, which might be problematic when the bleeding has stopped and therapeutic anticoagulant medication must be restarted (for example, while removing a prosthetic heart valve). It's quite probable. Recombinant factor VIIa raises the risk of thrombosis and is expensive, whereas fresh frozen plasma bears the danger of volume overload. More often used are new oral anticoagulants (ZOACs), which are irreversible when combined with vitamin K. When compared to warfarin, the NOACs rivaroxaban and dabigatran increase the risk of gastrointestinal bleeding, but apixaban does not seem to do so [77]. Activated charcoal may be used to treat a NOAC overdose if given within four hours. Haemodialysis in combination with idarucizumab may stop life-threatening bleeding caused by dabigatran [78]. Haemostasis must be confirmed before anticoagulants and antiplatelet drugs may be used again. When it comes to restoring anticoagulation, time is of the essence. Due to increased risk of acute thrombosis after implantation of a drug-eluting stent, patients on dual antiplatelet treatment should not abruptly discontinue either medication.

Patients who begin aspirin treatment shortly (within 1–3 or 7 days) after haemostasis has been achieved [74]. Because their warfarin levels are too low, patients with mechanical mitral valves or other thrombotic disorders should cross-link with low molecular weight heparin. The second most frequent consequence of PUD is perforation, which affects 2%-10% of patients. Gastrointestinal ulcers, which may cause acute stomach discomfort accompanied by a drop in blood pressure. A state of instability or shock [79]. Physical examination findings of hyperactive bowel movements may give way to those of a rigid, bouncing belly, which may be indicative of peritonitis. The presence of free air on the picture is consistent with this diagnosis, suggesting that

endoscopy should be avoided. Surgery is the gold standard treatment for perforated gastric ulcers [80]. Perforations that have been confined for more than 24 hours (as shown by trials using water-soluble contrast media) are amenable to medical therapy, which includes nasal gastric (NG) aspiration, infusion, antibiotics, and acid suppression in individuals who are not surgical candidates. You may choose to do this. Organs including the pancreas, liver, bile ducts, and colon may all be eroded by a penetrating ulcer.

Premature satiety, abdominal fullness, weight loss, dyspepsia, nausea, and vomiting may all be symptoms of gastric outlet obstruction (GOO), another possible result of a peptic ulcer disease. Squirting sounds may be audible during a physical examination if air and water have been trapped in the stomach. Pyloric or duodenal bulb ulcers are common locations for GOO ulcers. NG aspiration and antisecretory treatment are common components of drug therapy. Endoscopic balloon dilation or pylorus surgery are possibilities for treating persistent blockage [79].

6. PREVENTION OF PEPTIC ULCER DISEASE: Patients with a history of stomach ulcer should avoid NSAIDs since they increase the risk of rebleeding. The 2012 ACG Recommendations for the Care of Patients with haemorrhagic Ulcers In patients with a history of gastric ulcer disease, it is important to keep in mind the need of continued NSAID use and, if at all possible, the permanent discontinuation of NSAIDs.

A review of [81] is suggested. Combining PPIs with low-dose cyclooxygenase-2 (COX-2) selective NSAIDs is recommended. Re bleeding is less likely while using proton pump inhibitors along with COX2 selective NSAIDs. The reduced effect of COX1 on the GI mucosa is thought to be at fault for this [82,83]. Furthermore, while co-using NSAIDs and Infection, the risk of bleeding increases compared to those using NSAIDs alone [84].In those with H. pylori infection who are unable to discontinue use of NSAIDs, eradication reduces the risk of future bleeding. H. pylori infection with prolonged use of proton pump inhibitors. For those who have a 57H. H. pylori-only stomach ulcer. The H. pylori infection can be adequately cured; thus, these individuals do not need PPI medication on a long-term basis [81].

Gastric ulcers and bleeding are also strongly linked to aspirin use. One research found that compared to a placebo, low doses of aspirin increased the risk of bleeding by 1.80 (95% confidence range 1.59 to 2.03). Patients using aspirin for secondary prevention of cardiovascular and cerebrovascular disorders had a much-decreased death risk if they resume aspirin promptly upon discharge. One research found that patients with concomitant cardiovascular disease who stopped taking aspirin after admission because of gastric ulcer bleeding had a higher risk of dying and experiencing cardiovascular events during the first 6 months following discharge than those who started taking aspirin again. Three times as many people experienced bleeding as those who did not [86]. Continuous aspirin treatment was used to manage gastric ulcer bleeding in a 2011 randomized controlled trial with patients taking low doses of aspirin and undergoing endoscopic haemostatic therapy. We observed that although mortality may go down, the probability of recurrence goes up. Because of this, it may be suggested to patients in the ACG recommendations. Aspirin secondary prophylaxis will resume as soon as possible. Aspirin therapy should be restarted between 1 and 3 days, and no later than 7 days, in these patients [87,88]. In addition to aspirin treatment, PPI should be given. Each case must be considered separately, but in general aspirin should not be used for primary prophylaxis again until advised to do so [81].

Idiopathic ulcers (ulcers not attributable to H. pylori or NSAIDs) are more difficult to cure since less is known about their causes and mechanisms. H. pylori patients with idiopathic ulcers exhibited a higher relative risk of rebleeding and death compared to those with pylori-positive ulcers [89]. Despite a lack of evidence, the ACG Guideline suggests daily PPI medication for these individuals. [81]

6.1 Evaluation Techniques for Anti-ulcer Activity: Stomach ulcers in rats are often induced by physiological, pharmacological, or surgical procedures that are pathogenically related to the formation of stomach ulcers. The following are examples of experimental models used to assess the performance of anti-ulcer medications: [90,91].

• Subacute gastric ulcer in rats; Immobilization stress-induced stress ulcer;
• Alcohol-induced mucosal injury in rats (cytoprotective action);
• Rats with gastric ischemia-reperfusion damage
• Cold water constraint or water immersion stress
• Gastric ulcers caused by NSAIDs (indomethacin, aspirin, and ibuprofen)
• Acid reflux brought on by acetic acid
• Gastric ulcers caused by reserpine
• Gastric ulcers caused by histamine
• Gastric ulcers brought on by serotonin
• peptic ulcers brought on by a ligated pylorus
• Methylene blue-induced ulcers
• Diethyl-dithio-carbamate (DDC)-induced peptic ulcers
• Ischemia-reperfusion induced gastric ulcers
• Cysteamine induced duodenal ulcers
• Indomethacin-histamine-induced duodenal ulcers

• Acetic acid-H-pylori-induced ulcers
• Ferrous iron-ascorbic acid-induced gastric ulcers

CONCLUSION

Due to a drop in H. pylori infections, more accessibility to anti-secretory medications, and more cautious NSAID use, the clinical burden of PUD is reducing. However, early detection and treatment are crucial due to its high lifetime incidence and varied clinical presentation. For serious repercussions to be avoided or minimized, PUD treatment is crucial. The review could be useful in enhancing knowledge on recognizing symptoms, diagnosing them, treating them, figuring out how common they are, managing them, and treating ulcers with allopathic drugs. This article inspires researchers and aids in the diagnosis of ulcer disease.

REFERENCES

1. Narayanan M., Reddy K.M., Marsicano E. Peptic ulcer disease and Helicobacter pylori infection. Mo. Med. 2018;115:219–224. [PMC free article] [PubMed] [Google Scholar]
2. Lanas A., Chan F.K.L. Peptic ulcer disease. Lancet. 2017;390:613–624. doi: 10.1016/S0140-6736(16)32404-7. [PubMed] [CrossRef] [Google Scholar]
3. Lanas A., García-Rodríguez L.A., Polo-Tomás M., Ponce M., Quintero E., Perez-Aisa M.A., Gisbert J.P., Bujanda L., Castro M., Muñoz M., et al. The changing face of hospitalisation due to gastrointestinal bleeding and perforation. Aliment. Pharmacol. Ther. 2011;33:585–591. doi: 10.1111/j.1365-2036.2010.04563.x. [PubMed] [CrossRef] [Google Scholar]
4. Sonnenberg A. Review article: Historic changes of helicobacter pylori-associated diseases. Aliment. Pharmacol. Ther. 2013;38:329–342. doi: 10.1111/apt.12380. [PubMed] [CrossRef] [Google Scholar]
5. Søreide K., Thorsen K., Harrison E.M., Bingener J., Møller M.H., Ohene-Yeboah M., Søreide J.A. Perforated peptic ulcer. Lancet. 2015;386:1288–1298. doi: 10.1016/S0140-6736(15)00276-7. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
6. Zhang B.B., Li Y., Liu X.Q., Wang P.J., Yang B., Bian D.L. Association between vacA genotypes and the risk of duodenal ulcer: A meta-analysis. Mol. Biol. Rep. 2014;41:7241–7254. doi: 10.1007/s11033-014-3610-y. [PubMed] [CrossRef] [Google Scholar]
7. Datta De D., Roychoudhury S. To be or not to be: The host genetic factor and beyond in Helicobacter pylori mediated gastro-duodenal diseases. World J. Gastroenterol. 2015;21:2883–2895. doi: 10.3748/wjg.v21.i10.2883. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
8. Lanas Á., Carrera-Lasfuentes P., Arguedas Y., García S., Bujanda L., Calvet X., Ponce J., Perez-Aísa Á., Castro M., Muñoz M., et al. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. Clin. Gastroenterol. Hepatol. 2015;13:906–912.e2. doi: 10.1016/j.cgh.2014.11.007. [PubMed] [CrossRef] [Google Scholar]
9. Masclee G.M., Valkhoff V.E., Coloma P.M., de Ridder M., Romio S., Schuemie M.J., Herings R., Gini R., Mazzaglia G., Picelli G., et al. Risk of upper gastrointestinal bleeding from different drug combinations. Gastroenterology. 2014;147:784–792. doi: 10.1053/j.gastro.2014.06.007. [PubMed] [CrossRef] [Google Scholar]
10. Huang J.Q., Sridhar S., Hunt R.H. Role of helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: A meta-analysis. Lancet. 2002;359:14–22. doi: 10.1016/S0140-6736(02)07273-2. [PubMed] [CrossRef] [Google Scholar]
11. Charpignon C., Lesgourgues B., Pariente A., Nahon S., Pelaquier A., Gatineau-Sailliant G., Roucayrol A.M., Courillon-Mallet A., Group de l'Observatoire National des Ulcères de l'AssociationNationale des HépatoGastroentérologues des HôpitauxGénéraux (ANGH) Peptic ulcer disease: One in five is related to neither Helicobacter pylori nor aspirin/NSAID intake. Aliment. Pharmacol. Ther. 2013;38:946–954. doi: 10.1111/apt.12465. [PubMed] [CrossRef] [Google Scholar]
12. Levenstein S., Rosenstock S., Jacobsen R.K., Jorgensen T. Psychological stress increases risk for peptic ulcer, regardless of Helicobacter pylori infection or use of nonsteroidal anti-inflammatory drugs. Clin. Gastroenterol. Hepatol. 2015;13:498–506.e1. doi: 10.1016/j.cgh.2014.07.052. [PubMed] [CrossRef] [Google Scholar]
13. McColl K.E. Helicobacter pylori-negative nonsteroidal anti-inflammatory drug-negative ulcer. Gastroenterol. Clin. N. Am. 2009;38:353–361. doi: 10.1016/j.gtc.2009.03.004. [PubMed] [CrossRef] [Google Scholar]
14. Vinay Kumar, Abbas AK, Nelson Fausto. Robbins and Cotran Pathologic basis of disease. 7th edition. New Delhi. Elsevier India Private Limited 2006.
15. Harsh Mohan. Text book of Pathology. 6th edition. New Delhi. Jaypee brother's medical publisher (P) Ltd 2013.
16. Kumar Amandeep, Singh Robin, Sharma Ramica, Kumar Sunil. Peptic ulcer: a review on etiology and pathogenesis. International Research Journal of Pharmacy 2012;3(6):34-38.

17. Rakesh Pahwa, Neeta, Vipin Kumar, Kanchan Kohli. Clinical manifestations, causes and management strategies of peptic ulcer disease. International Journal of Pharmaceutical Sciences and Drug Research 2010;2(2):99-106.
18. Mohammad A. Al-Mofarreh, Ibrahim A. Al-Mofleh. Esophageal ulceration complicating doxycycline therapy. Word J Gastroenterol 2003;9:609-611.
19. Subiksha PS. Various remedies for recurrent Aphthous ulcer: a review. Journal of Pharmaceutical Science and Research 2014;6(6):251-253.
20. Crispian Scully, Meir Gorsky, Francina Lozada-Nur. The Diagnosis and management of recurrent Aphthous Stomatitis. The Journal of the American Dental Association 2003;134(2):200-207.
21. Brant WE, Helms CA. Fundamentals of diagnostic radiology. 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2007. xix, 1559 p. p.
22. al-Assi MT, Genta RM, Karttunen TJ, Graham DY. Ulcer site and complications: relation to Helicobacter pylori infection and NSAID use. Endoscopy. 1996;28(2):229-33. doi: 10.1055/s2007-1005433. PubMed PMID: 87
23. Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer. Nonsteroidal antiinflammatory drugs, Helicobacter pylori, and smoking. J Clin Gastroenterol. 1997;24(1):2- 17. PubMed PMID: 9013343.
24. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. Lancet. 2009;374(9699):1449-61. doi: 10.1016/S0140-6736(09)60938-7. PubMed PMID: 19683340.
25. Soreide K, Thorsen K, Harrison EM, Bingener J, Moller MH, Ohene-Yeboah M, Soreide JA. Perforated peptic ulcer. Lancet. 2015;386(10000):1288-98. doi: 10.1016/S0140-6736(15)00276-7. PubMed PMID: 26460663; PMCID: PMC4618390.
26. S.-Y. Wang, H.-Y. Wang, T.-E. Wang, H.-H. Wang, W.-H. Chang, C.-H. Chu, S.-C. Lin, H.-I. Yeh, S.-C. Shih, Delayed healing of gastric ulcer is associated with downregulation of connexin 32 in the gastric mucosa, Adv. Dig. Med. 2 (2015) 67–73, https://doi.org/10.1016/J.AIDM.2015.01.004.
27. Q. Li, L. Yang, L. Fan, C. Liang, Q. Wang, H. Wen, J. Dai, X. Li, Y. Zhang, Activity of Bruceajavanica oil emulsion against gastric ulcers in rodents, Asian J. Pharm. Sci. 13 (2018) 279–288, https://doi.org/10.1016/J.AJPS.2017.12.005.
28. A.C. Wotherspoon, C. Ortiz-Hidalgo, M.R. Falzon, P.G. Isaacson, Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma, Lancet. 338 (1991) 1175–1176, https://doi.org/10.1016/0140-6736(91)92035-Z.
29. M.J. Proctor, C. Deans, Complications of peptic ulcers, Surg. 32 (2014) 599–607,https://doi.org/10.1016/J.MPSUR.2014.09.005.
30. D. Stewart, R. Ackroyd, Peptic ulcers and their complication, Surg. 29 (2011) 568–569.
31. C.-Y. Kao, B.-S. Sheu, J.-J. Wu, Helicobacter pylori infection: an overview of bacterial virulence factors and pathogenesis, Biomed. J. 39 (2016) 14–23, https://doi.org/10.1016/J.BJ.2015.06.002.
32. D. Majumdar, J. Atherton.Peptic ulcers and their complications, Surg. 24 (2006) 110–114, https://doi.org/10.1383/SURG.2006.24.3.110.
33. Q. Zhong, S. Shao, R. Mu, H. Wang, S. Huang, J. Han, H. Huang, S. Tian, Characterization of peptidoglycan hydrolase in Cag pathogenicity island of Helicobacter pylori, Mol. Biol. Rep. 38 (2011) 503–509, https://doi.org/10.1007/s11033-010-0134-y.
34. N. Tegtmeyer, S. Wessler, S. Backert, Role of the cag-pathogenicity island encoded type IV secretion system in Helicobacter pylori pathogenesis, FEBS J. 278 (2011) 1190–1202, https://doi.org/10.1111/j.1742-4658.2011.08035.x.
35. S. Fagoonee, R. Pellicano, Helicobacter pylori: molecular basis for colonization and survival in gastric environment and resistance to antibiotics, A short review, Infect. Dis. (Auckl). 4235 (2019), https://doi.org/10.1080/23744235.2019.1588472.
36. J.W. Love, Peptic ulceration may be a hormonal deficiency disease, Med. Hypotheses 70 (2008) 1103–1107, https://doi.org/10.1016/J.MEHY.2007.12.011.
37. A. Lanas, F.K.L. Chan, Peptic ulcer disease, Lancet. 390 (2017) 613–624, https://doi.org/10.1016/S0140-6736(16)32404-7.
38. Ilse Truter. Evidence-based pharmacy practice (EBPP): peptic ulcer disease. South African Pharmaceutical Journal 2009;76(1):10-20.
39. Yuvraj Gulia, Manjusha Choudhary. Peptic ulcer disease: a review. Pharmacologyonline 2011; 3:48-70.
40. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. Lancet. 2009;374(9699):1449-61. doi: 10.1016/S0140-6736(09)60938-7. PubMed PMID: 19683340.
41. al-Assi MT, Genta RM, Karttunen TJ, Graham DY. Ulcer site and complications: relation to Helicobacter pylori infection and NSAID use. Endoscopy. 1996;28(2):229-33. doi: 10.1055/s2007-1005433. PubMed PM
42. Jayaraman MV, Mayo-Smith WW, Movson JS, Dupuy DE, Wallach MT. CT of the duodenum: an overlooked segment gets its due. Radiographics. 2001;21 Spec No:S147-60. doi: 10.1148/radiographics.21.suppl_1.g01oc01s147. PubMed PMID: 11598254.

43. Roy PK, Venzon DJ, Shojamanesh H, Abou-Saif A, Peghini P, Doppman JL, Gibril F, Jensen RT. Zollinger-Ellison syndrome. Clinical presentation in 261 patients. Medicine (Baltimore). 2000;79(6):379-411. PubMed PMID: 11144036.
44. Carucci LR, Levine MS, Rubesin SE, Laufer I. Upper gastrointestinal tract barium examination of postbulbar duodenal ulcers. AJR Am J Roentgenol. 2004;182(4):927-30. doi: 10.2214/ajr.182.4.1820927. PubMed PMID: 15039165.
45. Garrow D, Delegge MH. Risk factors for gastrointestinal ulcer disease in the US population. Dig Dis Sci. 2010;55(1):66-72.
46. Lin KJ, Garcia Rodriguez LA, Hernandez-Diaz S. Systematic review of peptic ulcer disease incidence rates: do studies without validation provide reliable estimates? Pharmacoepidemiol Drug Saf. 2011;20(7):718-728.
47. Kang JY, Tinto A, Higham J, Majeed A. Peptic ulceration in general practice in England and Wales 1994-98: period prevalence and drug management. Aliment PharmacolTher. 2002;16(6):1067-1074.
48. Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment PharmacolTher. 2009;29(9):938-946.
49. Laine L, Yang H, Chang SC, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. Am J Gastroenterol. 2012;107(8):1190-1195; quiz 1196.
50. Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer. Nonsteroidal antiinflammatory drugs, Helicobacter pylori, and smoking. J Clin Gastroenterol. 1997;24(1):2-17.
51. Lochhead P, EI-Omar EM. Helicobacterpylori infection and gastric cancer. Best Pract Res Clin Gastroenterol.2007:21(2):281-297.
52. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. Clin microbiol Rev.2006;19(3):449-440.
53. Garcia Rodriguez LA, Hernandez-Diaz S. Risk of uncomplicated peptic ulcer among users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. Am J Epidemiol. 2004;159(1):23-31.
54. Tsamakidis K, Panotopoulou E, Dimitroulopoulos D, et al. Herpes simplex virus type 1 in peptic ulcer disease: an inverse association with Helicobacter pylori. World J Gastroenterol. 2005;11(42):6644-6649.
55. Orton DI, Orteu CH, Rustin MH. Cytomegalovirus-associated gastric ulcer in an immunosuppressed patient with pemphigus vulgaris. Clin Exp Dermatol. 2001;26(2):170-172.
56. Pension J., Wormsley K.G. Adverse reactions and interactions with H2-receptor antagonists. Med. Toxicol. 1986;1:192–216. doi: 10.1007/BF03259837. [PubMed] [CrossRef] [Google Scholar]
57. Mössner J. The indications, applications, and risks of proton pump inhibitors. Dtsch. Arztebl. Int. 2016;113:477–483. doi: 10.3238/arztebl.2016.0477. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
58. Maes M.L., Fixen D.R., Linnebur S.A. Adverse effects of proton-pump inhibitor use in older adults: A review of the evidence. Ther. Adv. Drug Saf. 2017;8:273–297. doi: 10.1177/2042098617715381. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
59. Maton P.N., Burton M.E. Antacids revisited: A review of their clinical pharmacology and recommended therapeutic use. Drugs. 1999;57:855–870. doi: 10.2165/00003495-199957060-00003. [PubMed] [CrossRef] [Google Scholar]
60. Mizokami Y., Oda K., Funao N., Nishimura A., Soen S., Kawai T., Ashida K., Sugano K. Vonoprazan prevents ulcer recurrence during long-term NSAID therapy: Randomised, lansoprazolecontrolled non-inferiority and single-blind extension study. Gut. 2018;67:1042–1051. doi: 10.1136/gutjnl-2017-314010. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
61. Yamasaki A., Yoshio T., Muramatsu Y., Horiuchi Y., Ishiyama A., Hirasawa T., Tsuchida T., Sasaki Y., Fujisaki J. Vonoprazan is superior to rabeprazole for healing endoscopic submucosal dissection: Induced ulcers. Digestion. 2018;97:170–176. doi: 10.1159/000485028. [PubMed] [CrossRef] [Google Scholar]
62. Kawai T., Oda K., Funao N., Nishimura A., Matsumoto Y., Mizokami Y., Ashida K., Sugano K. Vonoprazan prevents low-dose aspirin-associated ulcer recurrence: Randomised phase 3 study. Gut. 2018;67:1033–1041. doi: 10.1136/gutjnl-2017-314852. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
63. Kagawa T., Iwamuro M., Ishikawa S., Ishida M., Kuraoka S., Sasaki K., Sakakihara I., Izumikawa K., Yamamoto K., Takahashi S., et al. Vonoprazan prevents bleeding from endoscopic submucosal dissection-induced gastric ulcers. Aliment. Pharmacol. Ther. 2016;44:583–591. doi: 10.1111/apt.13747. [PubMed] [CrossRef] [Google Scholar]
64. Tsuchiya I., Kato Y., Tanida E., Masui Y., Kato S., Nakajima A., Izumi M. Effect of vonoprazan on the treatment of artificial gastric ulcers after endoscopic submucosal dissection: Prospective randomized controlled trial. Dig. Endosc.

2017;29:576–583. doi: 10.1111/den.12857. [PubMed] [CrossRef] [Google Scholar]
65. Malfertheiner P., Megraud F., O'Morain C.A., Gisbert J.P., Kuipers E.J., Axon A.T., Bazzoli F., Gasbarrini A., Atherton J., Graham D.Y., et al. Management of Helicobacter pylori infection-the maastricht V/Florence consensus report. Gut. 2017;66:6–30. doi: 10.1136/gutjnl-2016-312288. [PubMed] [CrossRef] [Google Scholar]
66. Chen P.Y., Wu M.S., Chen C.Y., Bair M.J., Chou C.K., Lin J.T., Liou J.M., Taiwan Gastrointestinal Disease and Helicobacter Consortium Systematic review with meta-analysis: The efficacy of levofloxacin triple therapy as the first- or second-line treatments of Helicobacter pylori infection. Aliment. Pharmacol. Ther. 2016;44:427–437. doi: 10.1111/apt.13712. [PubMed] [CrossRef] [Google Scholar]
67. Shiota, S., Reddy, R., Alsarraj, A., El-Serag, H. B., & Graham, D. Y. (2015). Antibiotic resistance of Helicobacter pylori among male United States veterans. Clinical Gastroenterology and Hepatology, 13(9), 1616-1624.
68. Graham D.Y., Lee Y.C., Wu M.S. Rational Helicobacter pylori therapy: Evidence-based medicine rather than medicine-based evidence. Clin. Gastroenterol. Hepatol. 2014;12:177–186. doi: 10.1016/j.cgh.2013.05.028. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
69. Lanas, A., García-Rodríguez, L. A., Polo-Tomás, M., Ponce, M., Quintero, E., Perez-Aisa, M. A., ... &Calvet, X. (2011). The changing face of hospitalisation due to gastrointestinal bleeding and perforation. Alimentary pharmacology & therapeutics, 33(5), 585-591.
70. Stanley AJ, Dalton HR, Blatchford O, Ashley D, Mowat C, Cahill A, et al. Multicentre comparison of the Glasgow Blatchford and Rockall Scores in the prediction of clinical end-points after upper gastrointestinal haemorrhage. Aliment PharmacolTher. 2011;34:470–475. [PubMed] [Google Scholar]
71. Villanueva, C., Colomo, A., Bosch, A., Concepción, M., Hernandez-Gea, V., Aracil, C., ... &Guarner, C. (2013). Transfusion strategies for acute upper gastrointestinal bleeding. New England Journal of Medicine, 368(1), 11-21.
72. Strand, D. S., Kim, D., & Peura, D. A. (2017). 25 years of proton pump inhibitors: a comprehensive review. Gut and liver, 11(1), 27.
73. Laine, L., & Jensen, D. M. (2012). Management of patients with ulcer bleeding. Official journal of the American College of Gastroenterology| ACG, 107(3), 345-360.
74. Sachar, H., Vaidya, K., & Laine, L. (2014). Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. JAMA internal medicine, 174(11), 1755-1762.
75. Wang, C. H., Ma, M. H. M., Chou, H. C., Yen, Z. S., Yang, C. W., Fang, C. C., & Chen, S. C. (2010). High-dose vs non–high-dose proton pump inhibitors after endoscopic treatment in patients with bleeding peptic ulcer: a systematic review and meta-analysis of randomized controlled trials. Archives of internal medicine, 170(9), 751-758.
76. Lanas-Gimeno, A., & Lanas, A. (2017). Risk of gastrointestinal bleeding during anticoagulant treatment. Expert opinion on drug safety, 16(6), 673-685.
77. Lanas, A., & Chan, F. K. (2017). Peptic ulcer disease. The Lancet, 390(10094), 613-624.
78. Behrman SW. Management of complicated peptic ulcer disease. Arch Surg. 2005;140:201–208. [PubMed] [Google Scholar]
79. Ramakrishnan, K., & Salinas, R. C. (2007). Peptic ulcer disease. American family physician, 76(7), 1005-1012.
80. Laine, L., & Jensen, D. M. (2012). Management of patients with ulcer bleeding. Official journal of the American College of Gastroenterology| ACG, 107(3), 345-360..
81. Chan, F. K. L., Wong, V. W. S., Suen, B. Y., Wu, J. C. Y., Ching, J. Y. L., Hung, L. C. T., ... & Sung, J. J. Y. (2007). Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. The Lancet, 369(9573), 1621-1626.
82. Laine, L., Takeuchi, K., & Tarnawski, A. (2008). Gastric mucosal defense and cytoprotection: bench to bedside. Gastroenterology, 135(1), 41-60.
83. Sostres, C., Carrera-Lasfuentes, P., Benito, R., Roncales, P., Arruebo, M., Arroyo, M. T., ... & Lanas, A. (2015). Peptic ulcer bleeding risk. The role of Helicobacter pylori infection in NSAID/low-dose aspirin users. Official journal of the American College of Gastroenterology| ACG, 110(5), 684-689..
84. García Rodríguez, L. A., Lin, K. J., Hernández-Díaz, S., & Johansson, S. (2011). Risk of upper gastrointestinal bleeding with low-dose acetylsalicylic acid alone and in combination with clopidogrel and other medications. Circulation, 123(10), 1108-1115.
85. Derogar, M., Sandblom, G., Lundell, L., Orsini, N., Bottai, M., Lu, Y., & Sadr–Azodi, O. (2013). Discontinuation of low-dose aspirin therapy after peptic ulcer bleeding increases risk of death and acute cardiovascular events. Clinical Gastroenterology and Hepatology, 11(1), 38-42..
86. Gralnek, I. M., Dumonceau, J. M., Kuipers, E. J., Lanas, A., Sanders, D. S., Kurien, M., ... & Hassan, C. (2015). Diagnosis and management

of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy, 47(10), a1-a46..
87. Laine, L. (2016). Upper gastrointestinal bleeding due to a peptic ulcer. New England Journal of Medicine, 374(24), 2367-2376.
88. Wong, G. L. H., Au, K. W. L., Lo, A. O. S., Tse, Y. K., Ching, J. Y. L., To, K. F., & Chan, F. K. L. (2012). Gastroprotective therapy does not improve outcomes of patients with Helicobacter pylori–negative idiopathic bleeding ulcers. Clinical Gastroenterology and Hepatology, 10(10), 1124-1129.
89. Adinortey, M. B., Ansah, C., Galyuon, I., & Nyarko, A. (2013). In vivo models used for evaluation of potential antigastroduodenal ulcer agents. Ulcers, 2013.
90. Vogel HG. Discovery and evaluation, Pharmacological assays. 2nd Edition. Berlin Springer publication 2002.
91. Kuna, L., Jakab, J., Smolic, R., Raguz-Lucic, N., Vcev, A., & Smolic, M. (2019). Peptic ulcer disease: a brief review of conventional therapy and herbal treatment options. Journal of clinical medicine, 8(2), 179.

