Chapter

Peptic Ulcer Disease

Monjur Ahmed

Abstract

Peptic ulcer disease (PUD) is one of the commonest diseases seen throughout the world. There are various risk factors for the development of peptic ulcer disease, but the most important ones are *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drugs (NSAIDs). Patients generally present with dyspepsia or peptic ulcer bleeding. Acid suppressant therapy, *H. pylori* eradication, and avoidance of nonsteroidal anti-inflammatory drugs are the cornerstones of treatment of peptic ulcer disease. Peptic ulcer bleeding could be life-threatening. It is managed by appropriate supportive care, intravenous proton pump inhibitor therapy, and endoscopic hemostasis. Transarterial embolization (TAE) and surgery are rarely required if endoscopic therapy fails.

Keywords: peptic ulcer disease, dyspepsia, *H. pylori* infection, peptic ulcer bleeding, endoscopic treatment of peptic ulcer bleeding

1. Introduction

Peptic ulcer disease (PUD) is defined as the mucosal break of the upper gastrointestinal tract due to acid peptic digestion resulting in ulcer formation which extends beyond the muscularis mucosae into the submucosa. Most commonly it occurs in the stomach and first part of the duodenum but can also occur in the distal esophagus, distal duodenum, and jejunum and in the Meckel's diverticulum with heterotrophic gastric mucosa [1]. The size of the ulcer varies from 5 mm to several centimeters. On the other hand, erosions are superficial, less than 5 mm in size, and limited to the mucosa. PUD is still one of the commonest disorders we encounter in our clinical practice. The term "peptic" comes from the hormone pepsin which plays an important role in causing mucosal break. Peptic ulcer (PU) bleeding is the most common cause of upper gastrointestinal bleeding in the western world [2] and results in significant morbidity, mortality, and healthcare costs [3]. PUD is a benign condition, is easily treatable by medical therapy, and rarely requires surgery.

2. Epidemiology

PUD affects about 4.5 million persons per year in the United States (US) and causes huge healthcare cost of about $3.3. billion/year [4]. The prevalence of PUD varies with the prevalence of *Helicobacter pylori* (*H. pylori*) infection. In the United States, the seroprevalence of *H. pylori* infection varies with age: 16.7% in young age (20–29 years) group and 56.9% in older age (>70 years) group. It is also different among different ethnicities: non-Hispanic whites 26.2%, non-Hispanic blacks 52.7%, and Mexican Americans 61.6% [5]. In developing countries, the prevalence

of infection can be as high as 90% [6]. Systematic review of the literature from developed countries estimated that the global incidence and prevalence of physician-diagnosed PUD were 0.10–0.19% and 0.12–1.50%, respectively. But the incidence and prevalence of PUD have decreased with the universal use of acid suppressant therapy and decrease in prevalence of *Helicobacter pylori* infection due to improved socioeconomic status and eradication of *H. pylori* infection after detection [7].

3. Etiopathogenesis

H. pylori infection and nonsteroidal anti-inflammatory drugs (NSAIDs) account for majority of the cases of PUD. More than 90% of duodenal ulcers and >70% of gastric ulcers are *H. pylori* positive [8]. A prospective study from Turkey found that *H. pylori* infection alone was responsible for PUD in 75% of cases, both *H. pylori* infection and NSAIDs in 50% of cases and NSAIDs alone in 10% of cases [9]. A Japanese study showed that the long-term use of low-dose aspirin could cause PUD in 6.2% of cases. The risk is increased in diabetic patients and in patients taking anticoagulants [9]. Both NSAIDs and aspirin inhibit the cyclooxygenase pathway and decrease the production of prostaglandin which is responsible for cytoprotection of gastric mucosa by stimulating mucus and bicarbonate secretion and increasing mucosal blood flow [10]. The chance of developing NSAID-induced PUD increases in the presence of certain risk factors which include age more than 65, heart disease, past history of PUD, and co-administration of corticosteroid, antiplatelets, and anticoagulants [11]. All NSAIDs can cause gastrointestinal injuries which include inflammation, erosions, ulcerations, and bleeding. The relative risk varies: the highest risk is associated with piroxicam and ketorolac; high risk with indomethacin and naproxen; intermediate risk with meloxicam, diclofenac, and ketoprofen; and low risk with ibuprofen and celecoxib [12]. About 11% of the US population take NSAIDs on a regular basis. 15–30% of them have PUD on endoscopy although clinical upper gastrointestinal events can occur in 1.5–4.5% of patients taking NSAIDs [13].

H. pylori virulence factors are important in the pathogenesis of PUD. Cytotoxin-associated gene A (Cag A), vacuolating cytotoxin A (Vac A), and induced by contact with epithelium antigen (ice A) are associated with PUD. After entering the stomach, *H. pylori* utilizes its urease enzyme to neutralize the gastric acidity. *H. pylori* then moves toward the gastric epithelium where it binds to the gastric epithelial cell receptors by its adhesion molecule [14]. Cag A is a strong immunogenic protein and measures the virulence of *H. pylori* infection. Cag A gene increases production of IL-8 and activates nuclear factor-kB [15], and ice A increases mucosal IL-8 expression. Gastric epithelial layer then activates its innate immunity and neutrophils leading to gastritis and peptic ulcer formation. Vac A toxin is a pore-forming toxin, and it not only stimulates vacuole formation in gastric epithelial cells, parietal cells, T cells, and other immune cells but also helps *H. pylori* in colonizing the stomach [16].

How H. pylori can cause duodenal ulcer while residing in the gastric mucus layer? In *H. pylori* gastritis, the cytokine tumor necrosis factor inhibits somatostatin cells (D cells) in the antral mucosa. As a result, gastrin secretion becomes uninhibited, leading to hypergastrinemia, hyperacidity, and duodenal ulcer formation [17]. Another study suggests that gastric metaplasia and *H. pylori* colonization in the duodenal bulb could play a critically important role in the pathogenesis of duodenal

ulcer [18]. The gastric metaplasia becomes inflamed by *H. pylori* infection which disrupts mucosal regeneration leading to duodenal ulcer formation [19].

There are certain *unusual causes of PUD* which we come across now and then in our clinical practice.

Gastrinoma or Zollinger-Ellison syndrome may present as multiple gastric and duodenal ulcers and accounts for 0.1% or more cases of PUD [20]. Other hormone (histamine)-mediated PUD include systemic mastocytosis, polycythemia vera, and basophilia in myeloproliferative diseases [21].

Besides NSAIDs and low-dose aspirin, few other medications can cause PUD. These include clopidogrel (in combination with NSAIDs), corticosteroids (in combination with NSAIDs), bisphosphonates, potassium chloride, spironolactone, sirolimus, mycophenolate mofetil, hepatic artery infusion of 5-fluorouracil, and selective serotonin reuptake inhibitors [22].

PUD can be due to another helicobacter infection called *Helicobacter heilmannii* [23]. Gastrointestinal ulcerations due to cytomegalovirus, herpes simplex virus, gastric and duodenal tuberculosis, and syphilis can mimic PUD.

Certain infiltrative diseases like Crohn's disease and sarcoidosis can present like PUD [24].

Family history is an independent risk factor for the development of PUD [25]. Blood group O individuals have higher susceptibility of getting *H. pylori* infection [26] and are 35–40% more prone to develop duodenal ulcer than people with other blood groups [27]. Salivary secretory status of A, B, and H antigens was also found to be significant. Nonsecretor phenotypes of ABH antigens are more susceptible to develop *H. pylori* infection and duodenal ulcer [28]. Genetic influence on the formation of PUD is modest, and it is independent of the genetic susceptibility of acquiring *H. pylori* infection [29]. Other risk factors for the development of PUD include smoking and psychological stress [30].

When we think about the pathogenesis of PUD, we must consider two factors:

1. Mucosal protective factors: gastric mucus layer, prostaglandin, bicarbonate, and mucosal blood flow.

2. Mucosal damaging factors: gastric acidity, pepsin, *H. pylori* infection, and NSAIDs.

PU occurs when there is an imbalance between these factors.

3.1 Clinical features

Patients with PUD may be symptomatic or asymptomatic. Symptomatic patients generally present with dyspepsia, i.e., upper abdominal pain or discomfort. Most of the time, the pain is felt in the epigastric region, but sometimes it can be in the right upper quadrant or left upper quadrant of the abdomen. The pain is burning, gnawing, or dull aching in nature and generally non-radiating but rarely can radiate to the back in the case of posterior penetrating ulcer. Patients with gastric ulcer may feel pain shortly after taking food, but in the case of duodenal ulcer, pain is generally felt 2–3 h after taking meal, or sometimes patients wake up at night with epigastric pain. Duodenal ulcer pain is generally relieved after taking antacids or food which has minimal effect on relieving gastric ulcer pain [31]. Sometimes patients may feel gas and bloating sensation in the abdomen and sometimes may

experience nausea and vomiting. About 30% of elderly patients with PUD may remain asymptomatic [32]. This is also common in patients taking NSAIDs. Silent PU generally presents with gastrointestinal bleeding [33].

Physical examination can be entirely normal except epigastric tenderness.

3.2 Diagnosis and evaluation

A thorough history and physical examination is necessary to evaluate the patient. In each case, we should look for alarm features which include [34]:

1. Evidence of overt or occult gastrointestinal bleeding: hematemesis, melena, anemia, heme-positive stool
2. Iron deficiency anemia
3. Dysphagia
4. Left supraclavicular lymphadenopathy (Virchow's nodes)
5. Palpable abdominal mass
6. Symptom of impending perforation: severe persistent epigastric pain
7. Symptom of obstruction: persistent vomiting
8. Malignancy: anorexia, unintended weight loss
9. Age: >55 years

Diagnostic tests should include complete blood count, esophagogastroduodenoscopy (EGD), or upper gastrointestinal (UGI) series and tests for detection *H. pylori* infection. EGD is preferred over UGI series as it has much higher diagnostic yield and mucosal biopsy can be taken. Endoscopic views of clean-based duodenal ulcer and gastric ulcer are shown in **Figures 1** and **2**. During endoscopy, the location, size, depth, and any sign or stigmata of bleeding can be evaluated, and gastric biopsy from antrum, body, and incisura can be taken to detect *H. pylori* infection [35]. Although endoscopic evaluation is the gold standard of diagnosis of PUD, it is not cost-effective to perform EGD in all suspected cases of PUD. The

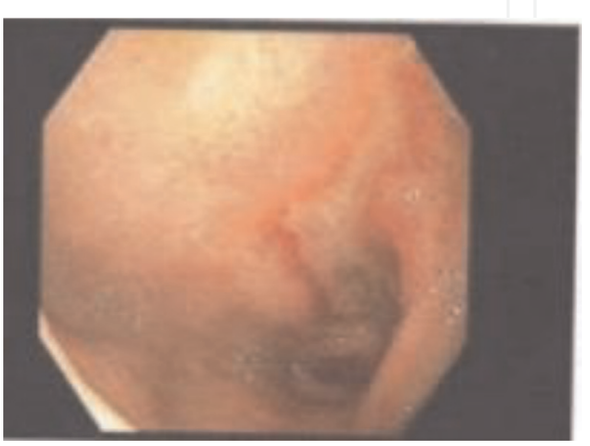

Figure 1.
Duodenal ulcer.

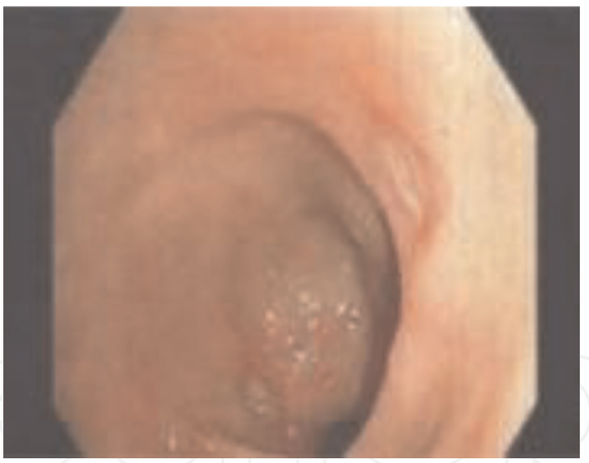

Figure 2.
Gastric ulcers.

alternative non-endoscopic strategies can be considered in the absence of alarm features:

1. *H. pylori* test and treat: In a population where the prevalence of *H. pylori* infection exceeds 20%, patients should get tested for *H. pylori* infection and, if positive, should be treated by anti-*H. pylori* therapy [36, 37]. If *H. pylori* test is negative or patients still remain symptomatic after anti-*H. pylori* therapy, they should be given a 4–6 week course of proton pump inhibitor (PPI) therapy. If PPI therapy fails, patients should be reassured, diagnosis should be reassessed, and EGD should be considered. If patients respond to anti-*H. pylori* treatment or PPI therapy, they can be managed without further investigation [38].

Stool for *H. pylori antigen* and urea breath tests are most accurate not only for identification of active *H. pylori* infection but also for confirmation of eradication of infection. Serology for *H. pylori* antibody is less reliable and cannot be used for confirmation of cure.

2. Empiric acid suppression therapy: In a population where the prevalence of *H. pylori* infection is 10% or less, empiric PPI therapy is most cost-effective. In case of PPI failure, test-and-treat strategy should be applied as mentioned above [39].

Physicians should make decision between test-and-treat strategy and empiric PPI therapy for 4–6 weeks in the absence of alarm features. EGD should be considered in the presence of alarm features. The American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology (CAG) suggest that patients ≥60 years of age presenting with dyspepsia should undergo upper endoscopy to exclude any organic cause [40].

4. Management

4.1 Uncomplicated PUD

Risk factors for the development of PUD should be evaluated. Patients should be advised to avoid NSAID intake, stop smoking, and limit drinking of alcohol. If the patient is *H. pylori* positive, it should be treated, and eradication of infection should be confirmed ≥4 weeks after completion of therapy [37]. There are different

Regimen	Drugs	Duration	Eradication rate (%)
PAC therapy	PPI standard dose BID plus amoxicillin 1 g BID plus clarithromycin 500 mg BID	14 days	70–85
PAM therapy	PPI standard dose BID plus amoxicillin 1 g BID plus metronidazole 500 mg TID	14 days	70–85
Bismuth quadruple therapy	PPI standard dose BID plus bismuth subcitrate (120–300 mg) or subsalicylate (300 mg) QID plus tetracycline 500 mg QID plus metronidazole 250 MG QID	10–14 days	75–90
Concomitant therapy	PPI standard dose BID plus amoxicillin 1 g BID plus clarithromycin 500 mg BID plus metronidazole or tinidazole 500 mg BID	10–14 days	94.4
Sequential therapy	PPI standard dose plus amoxicillin 1 g BID for 5 days followed by PPI plus clarithromycin 500 mg plus either metronidazole or tinidazole 500 mg BID for additional 5 days	Total 10 days	84.4
Hybrid therapy	PPI standard dose plus amoxicillin 1 g BID for 7 days followed by PPI standard dose plus amoxicillin 1 g plus clarithromycin 500 mg plus metronidazole 500 mg BID for additional 7 days	Total 14 days	93.4
Levofloxacin triple therapy	PPI standard dose and amoxicillin 1 g BID plus levofloxacin 500 mg QD	10–14 days	83.1
Levofloxacin sequential therapy	PPI standard dose plus amoxicillin 1 g BID for 5–7 days followed by PPI standard dose plus amoxicillin 1 g plus metronidazole 500 mg BID and levofloxacin 500 mg QD for additional 5–7 days	Total 10–14 days	92.2
LOAD therapy	PPI (double dose) plus levofloxacin 250 mg plus doxycycline 100 mg QD and nitazoxanide 500 mg BID	7–10 days	88.9
Novel concomitant therapy	PPI standard dose and amoxicillin 1 g TID (if allergic to penicillin, bismuth subcitrate 240 mg QID) plus rifabutin 150 mg and ciprofloxacin 500 mg BID	10 days	Regimen with amoxicillin 95.2 Regimen with bismuth subcitrate 94.2

BID, twice a day; QID, four times a day; QD, once a day.

Table 1.
Treatment of H. pylori infection.

regimens of anti-*H. pylori* therapy available. Patients' previous history of antibiotic exposure and prevalence of regional antibiotic resistance should be taken into consideration. Treatment of *H. pylori* infection is summarized in **Table 1** [41]. Antibiotics, histamine 2 receptor antagonists (H2RA), PPI, sucralfate, and bismuth-containing medications (Pepto-Bismol) can interfere with the results of urea breath test and stool for *H. pylori* antigen test and may give a false-negative result. Patients should stop taking these medications at least 2 weeks prior to these tests [42, 43]. But patients can continue taking antacids (except Maalox total relief) as they do not affect the accuracy of the tests.

Bismuth quadruple therapy or concomitant therapy can be considered as the first-line therapy against *H. pylori* infection. PAC therapy should be considered as

first-line treatment in patients without history of exposure to macrolide and living in an area where *H. pylori* clarithromycin resistance is low. If the first-line therapy fails, susceptibility testing should be done if available, and susceptibility-based therapy should be given. If susceptibility testing is not available, salvage therapy should not contain the antibiotics used before. For example, if bismuth quadruple therapy fails, clarithromycin- or levofloxacin-based therapy should be used as salvage therapy. If clarithromycin-based therapy fails, bismuth quadruple therapy or levofloxacin-based therapy should be used as salvage therapy. First-line therapy generally fails in 25% of cases as a result of non-compliance, antibiotic resistance, prior exposure to antibiotic, smoking, and younger age [44–46].

Acid suppressant therapy and mucosal cytoprotective agents are the main modes of therapy for the healing of PU. Acid suppressant therapy includes H2RAs and PPIs which are listed in **Tables 2** and **3**.

Duration of H2RA therapy: 90% of duodenal ulcers are healed by H2RA in 6–8 weeks, whereas 90% of gastric ulcers are healed by H2RA in 12 weeks [48].

Duration of PPI therapy: in the case of *H. pylori*-associated peptic ulcers, 90% of the ulcers are healed by a 2-week course of PPI plus antibiotics for eradication of *H. pylori* infection. This regimen followed by additional 2 weeks of PPI does not make much difference in healing of peptic ulcer. PPI therapy should be

H2RA	Dose	Side effects
Cimetidine	800 mg qhs × 4–8 weeks	Gynecomastia, impotence, polymyositis, interstitial nephritis, confusion, agitation, vitamin B12 deficiency
Ranitidine	150 mg BID × 4–8 weeks	Diarrhea, constipation, xerostomia, xeroderma Vitamin B12 deficiency
Famotidine	40 mg qhs × 4–8 weeks	Agranulocytosis, angioedema, anaphylaxis, seizure
Nizatidine	300 mg qhs × 4–8 weeks	Nausea, vomiting, dyspepsia, insomnia, somnolence, vitamin B12 deficiency

qhs, every night at bed time.

Table 2.
H2RA with dose and side effects.

PPI	Dose	Side effects
Omeprazole	20–40 mg qd × 4–8 weeks	Acute: headache, diarrhea
Esomeprazole	20–40 mg qd × 4–8 weeks	Chronic: hypocalcemia, hypomagnesemia, iron deficiency, vitamin B12 deficiency, *Clostridium difficile* infection, pneumonia, acute interstitial nephritis, risk of fracture, drug-induced lupus erythematosus [47]
Lansoprazole	15–30 mg qd × 4–8 weeks	
Dexlansoprazole	30–60 mg qd × 4–8 weeks	
Pantoprazole	20–40 mg qd × 4–8 weeks	
Rabeprazole	20 mg qd × 4–8 weeks	

qd, daily.

Table 3.
PPI with dose and side effects.

continued for 8 weeks in case of gastric ulcer and 4 weeks in case of duodenal ulcer [49].

In the case of NSAID-induced PUD, NSAIDs should be withdrawn if possible, but PPIs are the drugs of choice. PPIs should be continued for at least 8 weeks for the healing of PU. But maintenance dose of PPI should be continued to prevent ulcer complications if the patient needs to be on NSAID or aspirin for other medical conditions.

5. Mucosal cytoprotective agents

Misoprostol and sucralfate are mucosal cytoprotective agents.

Misoprostol is a synthetic analogue of prostaglandin E which is trophic to gastroduodenal mucosa, stimulates mucus and bicarbonate secretion from the gastroduodenal mucosa, and can form hydrophobic surfactant-like phospholipids in the gastric epithelial cells [50]. Misoprostol can also inhibit gastric acid secretion by suppressing histamine-stimulated cyclic AMP production but does not induce hypergastrinemia [51]. Misoprostol can heal both gastric and duodenal ulcers. Misoprostol 200 microgram four times a day should be given for 12 weeks. It can prevent mucosal damage and formation of ulcers from the deleterious effects of low-dose aspirin, NSAIDs, smoking, and alcohol [52]. Misoprostol is approved in the United States for the prevention of NSAID-induced PUD. As misoprostol can accelerate intestinal transit time and increase intestinal water and electrolyte secretion, abdominal cramps and mild to moderate diarrhea can happen in up to 30% of cases. Diarrhea can be reduced by taking food with misoprostol. Misoprostol can also cause nausea, vomiting, menstrual cramps, and vaginal bleeding (due to uterine contraction). Misoprostol is contraindicated in pregnant patients.

Sucralfate is the aluminum salt of sulfated sucrose. It coats the gastroduodenal mucosa (both ulcerated and non-ulcerated areas); binds acid and pepsin; stimulates the secretion of bicarbonate, prostaglandin, and epidermal growth factor; and thus helps in healing of PU. Sucralfate is as good as H2RA in healing PU (duodenal ulcer 60–90% at 4–6 weeks and gastric ulcer 90% at 12 weeks) and has a lower rate of recurrence of duodenal ulcer after healing as compared to H2RA [53, 54]. In the United States, sucralfate is approved for the treatment of active duodenal ulcer not related to NSAID. Side effects of sucralfate include nausea, vomiting, gastric upset, itching, and skin rash. Less than 5% of sucralfate is absorbed from the gastrointestinal tract into the systemic circulation and eliminated primarily in the urine. Sucralfate should be avoided in patients with chronic kidney disease as it contains aluminum.

6. Role of follow-up endoscopy

In the case of gastric ulcer, follow-up endoscopy is recommended 12 weeks after medical therapy to evaluate for underlying malignancy. Surveillance endoscopy should be individualized:

1. Surveillance endoscopy is necessary in patients with giant ulcer (>2 cm) and malignant-looking ulcer (thick mucosal folds, irregular ulcer edges, mass lesion) on index endoscopy; ulcer biopsy was not done on initial endoscopy; initial endoscopy was done for upper gastrointestinal bleeding and unknown etiology of the ulcer; patient remains symptomatic even after taking medical therapy; index endoscopy showed gastric atrophy, intestinal metaplasia,

dysplasia, or adenoma; and patient has risk factors for gastric cancer which include *H. pylori* positivity, age > 50 years, family history of gastric cancer, and coming from a high prevalent area of gastric cancer (South Korea, Mongolia, Japan, China, Bhutan, Kyrgyzstan, Chile, etc.). If the gastric ulcer seems to be active or healing on surveillance endoscopy, four-quadrant biopsies from the edges and base of the ulcer should be taken [55].

2. Surveillance endoscopy may not be necessary if the patient does not have any risk factor for malignancy and the gastric ulcer is small, benign appearing, and antral in location due to NSAID and the initial biopsy does not show any dysplasia or malignancy [56].

In case of duodenal ulcer, surveillance endoscopy is generally not required because of low risk of malignancy. But if the patient remains symptomatic or symptoms recur despite medical therapy, surveillance endoscopy should be considered to evaluate for refractory ulcer or non-peptic nature of the ulcer which includes Crohn's disease, lymphoma, or tuberculosis.

7. Refractory and recurrent ulcers

When the ulcer does not heal up after a 12-week course of PPI therapy, it is called refractory ulcer. 5–10% ulcers are refractory ulcers. When the ulcer recurs after complete healing of the ulcer, it is called recurrent ulcer. 5–30% ulcers are recurrent ulcers. The two most important causes of refractory and recurrent ulcers are continued NSAID use and persistent *H. pylori* infection [57]. Other important factors include cigarette smoking, smoking of crack cocaine, concurrent use of corticosteroid, cytotoxic drugs (sirolimus, mycophenolate mofetil), alendronate, methamphetamine, idiopathic hypersecretory duodenal ulcer, antral G-cell hyperplasia, gastrinoma, Crohn's disease, sarcoidosis, cancer, non-*H. pylori* infection (*Helicobacter heilmannii*), and infiltrative condition like gastrointestinal stromal tumor and Kaposi sarcoma.

Patients with refractory or recurrent ulcers should be thoroughly investigated to find out the causative factors which should be addressed. Twice daily PPI therapy should be given for another 12 weeks. Then upper endoscopy should be done to document complete healing of the ulcer. Patients with gastric ulcer should be referred for surgery if ulcer does not heal by 24 weeks.

8. Complications

Common complications of PUD include bleeding, perforation, penetration, and gastric outlet obstruction.

8.1 Bleeding

About 50% of all cases of upper gastrointestinal bleeding are caused by PUD [58]. Patients may present with hematemesis, melena, anemia, or heme-positive stool. At presentation, the patient's hemodynamic status (pulse, blood pressure) should be checked and resuscitative measures should be started. Patients should be given intravenous crystalloid fluid to maintain blood pressure, and parenteral PPI (esomeprazole or pantoprazole) should be started (continuous infusion or twice daily intravenously). PPI therapy increases intragastric pH with stabilization of

blood clot and reduces the risk of rebleeding and the need for surgery but does not decrease overall mortality [59]. Blood transfusion should be given to keep the hemoglobin ≥7 gm/dl, but in patients with hypovolemia or comorbidities like coronary artery disease, hemoglobin target should be higher. Risk assessment should be done to categorize high-risk or low-risk patients, level of care, need for blood transfusion, timing of endoscopy, and timing of discharge. The Glasgow-Blatchford bleeding score (GBS) is a useful screening tool (**Table 4**) to determine the need for intervention [60]. Patients with a score of 0 are considered as low risk with minimum risk of needing interventions like blood transfusion, endoscopy, and surgery, and they should be considered for early discharge from the hospital. But all other values (>0) fall into the category of high risk in terms of need for blood transfusion, endoscopy, and surgery. A score of 6 or more has >50% risk of needing intervention.

After resuscitation and stabilization, EGD should be done for diagnostic and therapeutic purposes. During endoscopy, Forrest classification should be used to assess the need for endoscopic intervention [61]. The different Forrest classes with their prevalence and risk of rebleeding are mentioned in **Table 5** [62]. Patients with Forrest classes Ia, Ib, IIa, and IIb are considered to be high-risk candidates, and endoscopic treatment should be provided to reduce the risk of rebleeding. Patients with Forrest classes IIc and III do not require any endoscopic intervention. In fact,

Admission risk marker	Score component value
Blood urea (mmol/L)	
6.5–8.0	2
8.0–10.0	3
10.0–25	4
>25	6
Hemoglobin (g/dL) for men	
12.0–12.9	1
10.0–11.9	3
<10.0	6
Hemoglobin (g/dL) for women	
10.0–11.9	1
<10.0	6
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
<90	3
Other markers	
Pulse ≥100 (per min)	1
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

Table 4.
GBS.

Forrest class	Endoscopic finding	Prevalence (%)	Risk of recurrent bleeding on medical management (%)
Ia	Spurting arterial bleed	10	90
Ib	Oozing of blood without visible vessel	10	10–20
IIa	Non-bleeding visible vessel	25	50
IIb	Adherent blood clot	10	25–30
IIc	Flat pigmented spot	10	7–10
III	Clean-based ulcer	35	3–5

Table 5.
Forrest classes with prevalence and risk of recurrent bleeding.

patients with Forrest class III can resume a regular diet and can be discharged home as long as they are hemodynamically stable, with stable hemoglobin and without other comorbidities, and they have somebody at home to watch them [63].

Endoscopic treatment options can categorized into three main types:

1. *Injection therapy*: it is the oldest endoscopic hemostatic method. Epinephrine (1:10,000 dilution) 0.2–2 ml aliquots are injected in four quadrants of the bleeding stigmata. Initial hemostasis is obtained by its tamponade effect as well as vasoconstrictive effect. But as it is less effective as a monotherapy, other modalities of endoscopic treatment are added for better hemostasis [64].

2. *Thermal therapy*: it includes contact methods by bipolar or monopolar cauterization and noncontact method by argon plasma coagulation (APC). Contact methods work by coaptive coagulation. Bipolar cauterization is most commonly used nowadays. A combination of epinephrine injection and bipolar cauterization is more effective than either modality alone in achieving hemostasis [65]. The APC machine has a high-frequency monopolar electrosurgical generator, argon gas chamber, gas flowmeter, grounding pad, flexible APC delivery catheter, and foot switch to activate gas and energy. Argon gas release with delivery of electric current is synchronized by the foot switch. The APC probe should be within 2–8 mm from the site of the targeted tissue to induce plasma coagulation. The depth of the burn can be preset between 0.5 and 3 mm. APC is an effective method of hemostasis in bleeding peptic ulcer [66]. But APC can cause superficial ulcerations which are generally healed up in 2–3 weeks.

3. *Mechanical therapy*: endoclips are widely used to stop bleeding from peptic ulcer. There are different clips available which include resolution clip, endoscopic hemoclip, Quick Clip2 (rotatable clip), Duraclip, and SureClip. All these clips can go through the standard 2.8 mm endoscope channel and can stop bleeding by grasping the bleeding vessel, reducing the chance of rebleeding and need for surgery. Endoclips have been found to be superior to injection therapy but comparable to thermocoagulation in bleeding PU [67]. They do not cause any tissue trauma, and as a result, ulcer healing is not impaired. They are also MRI compatible. Disadvantages of endoclipping include the following: (a) sometimes technical difficulty to clip the lesions in locations like the posterior duodenal bulb, posterior gastric body, and proximal lesser curve of the stomach, (b) limitation of use in large blood vessel (>2 mm

in diameter), (c) difficulty to grasp fibrotic tissue, and (d) requirement of multiple clips [68].

Another clip called Ovesco clip is an over-the-scope clip used to stop peptic ulcer bleeding. The bleeding area is suctioned into a cup attached to the scope, and then the clip is deployed like band ligation.

A combination of at least two modalities of endoscopic treatment (injection, thermal, or mechanical) is now the standard of care in the treatment of peptic ulcer bleeding.

9. Endoscopic Doppler ultrasound

An ultrasound probe is passed through the endoscope channel and placed directly onto the area of bleeding. An audible sound is heard if there is blood flow. Arterial or venous blood flow can be detected. It is useful after endoscopic treatment to evaluate the presence of any residual blood flow which can increase the potential for rebleeding. It is also useful in Forrest IIc and III ulcers to find out any vascular signal. Doppler ultrasound-guided endoscopic hemostasis reduces 30-day rebleeding rate significantly and is also cost-effective [69].

Hemospray or hemostatic nanopowder is an alternative approach to obtain hemostasis. The powder is delivered through a catheter which passes through the endoscope channel, and the powder is then sprayed over the bleeding site. The powder forms a stable mechanical barrier at the site of bleeding. Initial success rate in obtaining hemostasis is 75–100%, but rebleeding rate is 10–49% [70]. So hemospray should be used as a bridge therapy in massive peptic ulcer bleeding when standard endoscopic treatment fails.

Endoscopic therapy can control acute peptic ulcer bleeding with high success. Primary hemostasis can be obtained in more than 90% of cases, but rebleeding can occur in up to 15% of cases after therapeutic endoscopic procedure [71].

10. Role of second-look endoscopy

Second-look endoscopy is not routinely recommended after initial endoscopy for the management of PU bleeding unless the endoscopist is concerned that suboptimal treatment was given in the first endoscopy or there was poor visualization due to blood or food debris during the first endoscopy [72].

11. Complications of endoscopic treatment

Complications could be due to sedation, patients' comorbidities, and endoscopy itself. Sedation-related complications include hypoventilation, hypoxia, aspiration pneumonia, airway obstruction, arrhythmia, pulmonary embolism, myocardial infarction, phlebitis, and vasovagal attack [73]. The complications of endoscopic hemostasis include exacerbation of bleeding and perforation, but the overall incidence is $<0.5\%$. The rate of perforation after contact thermal therapy could be as high as 2%. Following thermal therapy, induction or exacerbation of bleeding can occur in up to 5% of cases [74].

12. Failure of endoscopic therapy

If the endoscopic therapy fails to achieve hemostasis, the next step will be angiography with transarterial embolization (TAE). Different agents are used for embolization, and these include Gelfoam, endocoils, cyanoacrylic glues, and polyvinyl alcohol. The success rate of TAE in obtaining hemostasis is 52–98%, but recurrent bleeding can occur in 10–20%, requiring repeat TAE [75].

13. Role of surgery

Surgery is indicated if TAE fails to stop PU bleeding. Emergency surgery involves plication or oversewing of the ulcer with ligation of the bleeding artery and truncal vagotomy and pyloroplasty. Wong et al. compared surgery vs. TAE in bleeding PU patients who had failed endoscopic therapy. Surgery was associated with less recurrent bleeding but more complications when compared with TAE. There was no significant difference in the mean length of hospital stay, need for blood transfusion, and 30-day mortality between the two groups [76]. In practice, the surgical intervention continues to diminish, but the radiological intervention continues to increase in acute PU bleeding patients who have unsuccessful endoscopic therapy. Surgery is also recommended for (a) patients with perforation, (b) shock due to recurrent bleeding, (c) patients with hemodynamic instability despite adequate resuscitative measures needing more than three units of blood transfusion, and (d) unavailability of interventional radiology.

14. Prognosis of bleeding peptic ulcer

The outcome depends on successful endoscopic hemostasis without recurrent bleeding. The risk factors for recurrent bleeding include patients with renal failure on dialysis; elderly patients on NSAID, antiplatelet agents, and anticoagulants; patients with ulcer located on the posterior duodenal wall and lesser curve of the stomach; and patients with active bleeding ulcer during endoscopy. Despite the tremendous advances in technology, the mortality of acute PU bleeding remains about 10% [77].

15. Perforation

In patients with PUD, the lifetime prevalence of perforation is 5%. Patients generally present with acute abdomen. The triad of sudden onset of abdominal pain, tachycardia, and abdominal rigidity is highly suggestive of PU perforation. Smoking, NSAIDs, corticosteroids, old age, *H. pylori* infection, stress, and previous history of PUD are risk factors for perforation [78]. Upright chest X-ray is generally diagnostic, but it can miss free air under the diaphragm in 15% of cases. CT (computerized tomography) is very sensitive in detecting the presence and site of perforation [79]. CT with oral contrast may also show leak. Exploratory laparotomy with omental patch is the treatment of choice. PU perforation carries increased risk of morbidity and mortality if not treated early.

16. Penetration

When the ulcer crater erodes through the gastric wall or intestinal wall into the surrounding structure but there is no free perforation or leakage of luminal contents into the peritoneal cavity, it is called penetration [80]. The pancreas is the commonest site of penetration. Other sites of penetration include the omentum, biliary tract, liver, colon, mesocolon, and blood vessels. Patients may notice change in pattern of abdominal pain, i.e., pain not being relieved by taking food or medication. Diagnosis is confirmed by CT with contrast which may show loss of fascial plane between the gastric wall or intestinal wall and the surrounding structure, band of soft tissue density between them, ulcer crater, sinus tract, and enlargement of head of the pancreas in case of penetration into the pancreas [81]. Treatment is surgical intervention.

17. Gastric outlet obstruction (GOO)

It occurs in less than 5% cases of PUD. Duodenal ulcer and pyloric channel ulcer are generally associated with GOO. Pathophysiologically, reversible causes like inflammation, edema, spasm, and pyloric dysmotility and irreversible cause like fibrosis may lead to GOO. Patients present with nausea, vomiting, early satiety, epigastric pain, and weight loss. Patients may develop severe dehydration, azotemia, hyponatremia, and hypochloremic and hypokalemic metabolic alkalosis with paradoxical aciduria due to prolonged vomiting. First, the fluid and electrolyte deficit should be corrected. Gastric contents should be removed by large-bore Ewald tube, and then intermittent nasogastric tube suction should be continued for a few days. Many cases of GOO due to PUD have reversible components which may respond to this conservative treatment. Patients not responding to the conservative treatment need endoscopic dilation or surgery [82, 83].

18. Conclusion

PUD is a common clinical problem. The two most important risk factors are *H. pylori* infection and NSAIDs. Patients may present with dyspepsia or may remain asymptomatic. Endoscopy is the gold standard for the diagnosis of PUD. But as it is not possible to endoscope so many dyspeptic patients, there are some non-endoscopic approaches depending on the prevalence of *H. pylori* infection in the population. But ACG and CAG recommend EGD to be done in patients ≥60 years of age presenting with dyspepsia irrespective of alarm features. Bismuth quadruple therapy or concomitant therapy should be considered as the first-line therapy against *H. pylori* infection. In patients with PUD, eradication of *H. pylori* infection (if positive) should be confirmed ≥4 weeks after completion of therapy. PPI, H2RA, misoprostol, and sucralfate are the main agents used for healing of PU. Surveillance endoscopy is recommended in certain gastric ulcers. PUD can be complicated by bleeding, perforation, penetration, and gastric outlet obstruction. Patients with bleeding peptic ulcer should be evaluated, resuscitated, and started on intravenous/infusion of PPI. Diagnostic and therapeutic endoscopy should be done to achieve endoscopic hemostasis. If endoscopic therapy fails, the next step will be TAE or surgery. The mortality for peptic ulcer bleeding still remains high.

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Author details

Monjur Ahmed
Jefferson University Hospital, Philadelphia, USA

*Address all correspondence to: monjur.ahmed@jefferson.edu

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