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Peptic ulcer disease

— the disease and non-drug treatment

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Peptic ulcer disease is a common condition that is now recognised as being caused by *Helicobacter pylori* infection in most cases.

This article, the first in a special feature on the condition, describes the clinical features and diagnosis of the disease



Helicobacter pylori bacteria are usually present in patients with peptic ulcers

Until the 1980s, peptic ulcer disease (PUD) was thought to be a chronic, incurable, relapsing disorder. This changed when *Helicobacter pylori* bacteria were identified as being responsible for the disease in most cases.

This article outlines the epidemiology, pathophysiology, clinical manifestations and diagnosis of PUD, and briefly describes endoscopic therapies. A second article (p245) describes the pharmacological treatment of the disease.

— Aetiology

An ulcer is defined as a breach in the continuity of the epithelial lining of more than 5mm in diameter, with associated inflammation. Ulcers develop when there is an imbalance between mechanisms that protect the epithelium and agents which attack it, such as gastric acid, pepsin, drugs and bacteria. Three main factors play a role in the epithelial defence system: a hydrophobic surface barrier created by the mucus layer, a pH gradient above the surface epithelium due to bicarbonate secretion, and the epithelial cell barrier itself. Prostaglandins also play a major role in epithelial protection. They are derived from arachidonic acid in the gastric mucosa, and regulate the secretion of mucosal bicarbonate and mucus, inhibit

parietal cell secretion and help maintain mucosal blood flow. Cyclo-oxygenase (COX)-1 isoform, a key enzyme in the synthesis of prostaglandins, is expressed in the gastric mucosa.

There are two types of glands in the stomach. Gastric glands are located in the oxyntic mucosa (gastric body) and contain acid-secreting parietal cells, and pyloric glands are located in the antrum and contain mucus cells and gastrin cells. The gastroduodenal mucosa is constantly exposed to both endogenous and exogenous substances which can breach the integrity of the epithelial lining. However, the mucosal defence system is normally effective in preventing ulceration.

Peptic ulcers occur mainly in the stomach and the proximal duodenum. However, they can also occur in the oesophagus, jejunum, gastric anastomotic site and, rarely, in the Meckel's diverticulum (a hollow pouch sometimes found attached to the small intestine, lined with cells similar to those which line the stomach).

Gastric ulcers can occur in any part of the stomach but are more common along the lesser curvature. Duodenal ulcers occur mainly in the first part of duodenum involving the gastric metaplasia and are commonly associated with *H pylori*-induced antral gastritis. Ulcers in the oesophagus are caused by gastroesophageal acid reflux, whereas post bulbular ulcers (ie, ulcers beyond the first part of duodenum) and jejunal ulcers are secondary to the true hyperacidity seen in patients with Zollinger-Ellison syndrome.

— Epidemiology

The lifetime prevalence of PUD in the UK population is around 10 per cent. Approximately 4,500 people in the UK and 15,000 in the US die from complications of PUD each year. A lifetime prevalence of 13 per cent in men and 11 per cent in women with an average annual incidence of 1.7 cases per 1,000 people has been recorded.¹

There is a relative increase in PUD prevalence in the elderly population, which is thought to be due to a high incidence of *H pylori* infection when this population was young. Peptic ulcer-related mortality also increases with age, mainly due to comorbid conditions. The overall incidence of PUD in the younger population is now decreasing in the developed world due to the decreasing prevalence of *H pylori* infection. Duodenal ulcers are four times more common than gastric ulcers and tend to occur in younger people.²

Peptic ulcers are more common in smokers than in non-smokers and there is a strong association with chronic disorders such as systemic mastocytosis (abnormally excessive infiltration of mast cells in various organs), chronic pulmonary disease, cirrhosis, and chronic renal failure. People with blood group O are also more likely to develop PUD since *H pylori* preferentially bind to the blood group O antigen. Regular use of aspirin and prolonged use of steroids in combination with non-steroidal anti-inflammatory drugs (NSAIDs) are also associated with the development of peptic ulcers.²

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Genetic factors play a role in both duodenal and gastric ulcers. First degree relatives of patients who have had a duodenal ulcer have a two- to three-fold increase in risk of developing a duodenal ulcer themselves, and a similar risk has been noted for gastric ulcer occurrence.²

Risk factors for developing PUD include *H pylori* infection, use of NSAIDs, smoking, alcohol, lower socio-economic status, family history of PUD, and hyperacidity (Zollinger-Ellison syndrome).

— *H pylori* infection

Helicobacter pylori are spiral, gram-negative, microaerophilic, rod-shaped bacteria with multiple flagella. They are highly motile and produce the enzyme urease to alter the surrounding pH to protect themselves from gastric acid. *H pylori* were cultured for the first time by pathologists Barry Marshall and Robin Warren, joint winners of the Nobel prize in 2005 for their discovery of the bacteria and its role in gastritis and PUD. They were able to isolate the bacteria in 58 out of 100 patients undergoing endoscopy, and found that the bacteria were present in almost all patients with active chronic gastritis, duodenal ulcer or gastric ulcer.³ Multiple strains of *H pylori* have subsequently been identified. The bacterium was known as *Campylobacter pylori* until the late 1980s when it was renamed following new microbiological data.

H pylori is present in the gastrointestinal systems of up to 80 per cent of the population in the developing world and around 30 to 50 per cent in western Europe. In developing nations, 60–70 per cent of children are infected with the bacteria by age 10, probably because of overcrowding and poor sanitation. In the US the rate of *H pylori* infection has fallen by over 50 per cent in the past 30 years.

In earlier studies, *H pylori* was found to be present in 65 per cent of patients with gas-

Panel 1: Complications of peptic ulcer disease (PUD)

- Bleeding (most common complication), seen in 10 per cent of PUD patients
- Perforation (second most common complication), seen in 7 per cent of PUD patients
- Pyloric obstruction (less common), seen in around 1 per cent of PUD patients
- Penetration (sealed perforation into the pancreas)
- Gastric adenocarcinoma and mucosal associated lymphoid tissue (MALT) lymphoma secondary to chronic *H pylori* infection

Panel 2: Differential diagnoses for patients with suspected ulcers

The following conditions should be considered in patients presenting with dyspeptic symptoms:

- **Biliary colic** — episodic, epigastric or right upper quadrant pain. May awake the patient from sleep.
- **Pancreatitis** — Epigastric pain worsens with food and can radiate to the back.
- **Non-ulcer dyspepsia** — Difficult to differentiate from PUD except by endoscopy. May respond to acid suppression.
- **Malignant lesions of the stomach and, rarely, the duodenum** — Malignant lesions cause ulceration and clinically present as peptic ulcer-type symptoms.
- **Crohn's disease** — Presence of granulomas on biopsy and small or large bowel symptoms should raise the suspicion of Crohn's disease.
- **Mesenteric ischaemia** — Postprandial pain, and weight loss in a patient with significant cardiovascular disease should point towards the diagnosis.
- **Abdominal migraine** — A variant of migraine that occurs mainly in children and is characterised by periodic abdominal pain lasting for a few hours.

tritis, 85 per cent of gastric ulcer patients and 100 per cent of duodenal ulcer patients not taking NSAIDs.⁴

— Pathophysiology

H pylori mainly infects the gastric antrum (this accounts for the majority of cases of PUD) and the proximal stomach but does not normally invade the epithelial cells — only a minority of people infected with the bacteria will develop PUD. The bacteria are found in the deeper layers of the mucus and produce adhesins to help them attach to cells. *H pylori* also produce urease, vacuolating cytotoxin (vac A), pic B and cag A in addition to several other proteins. These proteins play a role in bacterial protection and pathogenesis. Expression of cytotoxins may differ between various strains and may be responsible for different *H pylori*-associated infections.

Infection of the gastric antrum predisposes to duodenal ulceration, whereas that of proximal stomach predisposes to gastric ulceration. *H pylori* infection also plays a role in the development of gastric mucosal associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma.

The mechanism by which *H pylori* causes duodenal ulceration is unclear. It can infect the duodenal mucosa after the development of gastric metaplasia and can cause mucosal damage, mediated by various virulent factors. Antral infection with *H pylori* will result in increased gastrin levels and increased acid secretion, with resultant exposure of duodenal mucosa to high acid levels leading to ulceration.

Somatostatin is an acid regulatory hormone secreted by specialised endocrine cells (D cells) in response to hydrochloric acid. Somatostatin inhibits the acid secretion by a direct effect on parietal cells and also indirectly by decreasing gastrin release. *H pylori* infection of the antral mucosa may lead to

decreased number of D cells and thus somatostatin, causing increased acid secretion. The protective bicarbonate secretion of the duodenal mucosa is also reduced by *H pylori* infection. The bacteria also secrete proteases and phospholipases to disrupt the mucus layer defence. Chronic *H pylori* infection will lead to atrophic gastritis and intestinal metaplasia.

PUD not associated with *H pylori* infection and NSAID use is less common and it tends to be a chronic, relapsing disease. However these patients have similar acid secretory patterns to *H Pylori*-positive patients. Zollinger–Ellison syndrome is a rare cause of multiple and/or recurrent peptic ulcers secondary to hypergastrinaemia due to gastrinoma.

— NSAIDs and peptic ulcer

NSAIDs are the most commonly used medicines throughout the world. Nevertheless, peptic ulcers and complications occur in up to 25 per cent of patients taking these drugs.⁵ The gastrointestinal side effects of NSAIDs are dose-dependent, although no dose of NSAID can be considered to be completely free from gastric side effects. Of patients who present with complications of PUD, such as bleeding or perforation of the ulcer, 50 to 60 per cent will have no previous dyspeptic symptoms.⁵ This is partly due to the inhibition of prostaglandin synthesis and the local analgesic effect of NSAIDs. Inhibition of prostaglandin synthesis by NSAIDs will lead to the breakdown of the mucosal barrier in the GI tract by reduced mucus production, increased acid production and reduced bicarbonate production. Topical NSAIDs and enteric coated preparations can also cause ulceration.

H pylori infection and NSAID use are independent and synergistic risk factors for complicated and bleeding peptic ulcers. Uncomplicated peptic ulcers are more

common in *H pylori*-positive than *H pylori*-negative NSAID users. The risk of developing an ulcer is over 17.5 times higher in *H pylori*-positive NSAID users than *H pylori*-negative NSAID non-users. Patients with bleeding ulcers have also been found to be more frequent users of NSAIDs than those without bleeding ulcers.⁶

Peptic ulcer bleeding is strongly associated with the use of any type of non-aspirin NSAID, with an odds ratio of 4.5. One study found the odds ratios for peptic ulcer bleeding to be lowest for ibuprofen (2.0) and diclofenac (4.2), intermediate with naproxen (9.1), indometacin (11.3), and piroxicam (13.7), and highest with ketoprofen (23.7) and azapropazone (31.5).⁷ Increasing the NSAID dose was found to increase the risk of a bleeding ulcer for all drugs combined (odds ratio for low dose NSAID = 2.5, intermediate = 4.5 and high = 8.6).⁷

Similarly, no dose of aspirin between 75mg and 300mg daily is considered to be free from the risk of causing a peptic ulcer bleed. It has been estimated that there are about 10,000 episodes of ulcer bleeding in people aged 60 years and over each year in England and Wales. Among them, 3,500 will be taking NSAIDs and 900 will be taking prophylactic aspirin. Reducing the aspirin dose from 300mg to 75mg would reduce the risk of developing a bleeding ulcer by about 40 per cent, and reducing the dose from 150mg to 75 mg would reduce the risk by 30 per cent.⁸

Risk factors for NSAID-induced ulcers include advanced age, previous history of PUD, concomitant steroid therapy, high doses of NSAIDs, taking combinations of NSAIDs, systemic disease, *H pylori* infection, smoking and concomitant anticoagulant therapy.

Smoking has been shown to decrease the bicarbonate secretion from duodenal epithelial cells. This, in combination with increased acid secretion, can lead to PUD. Smoking is also associated with delayed healing of ulcers and increased frequency of complications. No specific personality type is associated with PUD, although stress is known to increase gastric acid secretion and may lead to PUD in the presence of other risk factors. Life difficulties and lower socio-economic status are associated with PUD.⁹

— Clinical features

Both gastric ulcers and duodenal ulcers may not cause symptoms for some time and may first present with complications like bleeding or perforation, although this is more common with gastric ulcers. Patients with gastric ulcers are less symptomatic than patients with duodenal ulcers and may present with complications.

Burning or gnawing epigastric discomfort can be the presenting symptom of both duodenal and gastric ulcers. Typical duodenal

Panel 3: Sensitivity of tests for *Helicobacter pylori*

Test	Sensitivity/specificity (per cent)
Invasive (needs endoscopy and biopsy)	
Rapid urease test	80–95 / 95–100
Histology	80–90 / >95
Culture	
Non-invasive	
Serology	>80/>90
Urea breath test	>90/>90
Stool antigen test	>90/> 90

ulcer pain is an epigastric, dull ache occurring on an empty stomach, that is relieved by food or antacids. Gastric ulcer pain, on the other hand, can be aggravated by food. Pain can radiate to the back in post bulbar ulcers and occurs at night in two thirds of patients. Peptic ulcer pain can be periodic and each episode may last for several weeks. NSAID-induced ulcers can be asymptomatic until the patient develops complications.

Abdominal pain has poor predictive value for PUD. On endoscopy, a peptic ulcer is found in less than 30 per cent of patients who present with dyspepsia.

Typically, patients with duodenal ulcers will gain weight while those with gastric ulcers can lose a significant amount of weight. Persistent vomiting (caused by gastric outlet obstruction), blood in the faeces or haematemesis (caused by a bleeding ulcer), or constant worsening pain (from perforation) are some of the complications of PUD (see Panel 1, p240).

Epigastric tenderness may be the only feature on examination in uncomplicated PUD. However, in complicated PUD general and systemic examination can uncover vital clues. Signs of bleeding, peritonitis and shock in acutely unwell patients should be recognised and prompt resuscitation with fluids and blood may be required. Complications are common in elderly patients who often have significant comorbid diseases.

There is poor correlation between ulcer healing and symptom remission.

— Diagnosis

Peptic ulcers can be diagnosed by direct visualisation using an endoscope or by using contrast radiography to view the ulcer crater.

If PUD is suspected in a young patient with no alarm symptoms, the primary aim should be confirmation of *H pylori* infection and subsequent eradication. In patients over 50 years of age, endoscopy is recommended to confirm the presence of an ulcer and exclude other causes such as cancer.

Differential diagnoses Gastric malignancy can present as an ulcer and should always be considered as a differential diagnosis, but malignant ulcers are extremely rare in the

duodenum. Panel 2 (p240) lists some other conditions with symptoms similar to those of PUD.

The presence of the following alarm symptoms raises the possibility of either a complicated ulcer or underlying malignancy.

- Anaemia
- Weight loss
- Haematemesis and melaena
- Recurrent vomiting

H pylori infection can be diagnosed using a number of techniques, including urease detection. Several different urease tests are commercially available, which use a pH indicator to detect ammonia generated by the urease produced by *H pylori*. These tests require endoscopic biopsy from the gastric antrum. However, patients who have recently been taking proton pump inhibitors (PPIs) may falsely test negative for urease because PPIs temporarily suppress *H pylori*.

The urease breath test (13C or 14C) is a simple test used commonly to diagnose *H pylori* infection and to confirm its eradication. Stool tests, which detect the specific *H pylori* antigen, are less expensive than invasive tests and easy to perform. Non-invasive tests such as these are useful in primary care settings as well as in hospital practice. The sensitivity of *H pylori* tests is shown in Panel 3.

Endoscopy Endoscopy is commonly used in clinical practice to diagnose peptic ulcers, and to exclude malignant ulcers and other conditions that could be causing the dyspepsia. Endoscopy also has a large role to play in the treatment of PUD complications such as bleeding ulcers and pyloric strictures, as described below.

Radiology A double contrast barium study is a radiological technique which can easily detect ulcers both in the stomach and duodenum, but it is only used where endoscopy is either technically difficult or where the patient prefers it to endoscopy. Endoscopy is preferred because it also allows for biopsies and *H pylori* testing. Endoscopy is also useful for confirmation of the source of bleeding and evaluation of small ulcers.

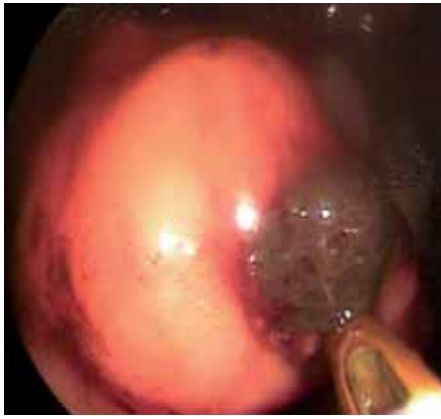


Figure 1. Thermal therapy with a heater probe

Blood tests Blood tests can be useful for diagnosing infection with *H pylori*, although serology may remain positive even after eradication because of the lasting presence of antibodies. Hence, blood tests are not useful for confirmation of eradication. However, serum gastrin measurement is useful in the case of suspected Zollinger-Ellison syndrome.

— Endoscopic therapy

Endoscopic therapy is superior to medical therapy in the treatment of bleeding peptic ulcers, to achieve haemostasis and reduce

rates of rebleeding. With the aid of endoscopy, adrenaline 1:10,000 mixed with saline is injected into the base of the ulcer where it causes vasoconstriction and mechanical plugging.

Thermal coagulation of the bleeding vessel by using either a heater probe (see Figure 1) or argon plasma gas is another technique carried out using endoscopy and is effective in high risk bleeders (ie, those with a spurting vessel or a visible vessel which indicates a recent bleed). Ligation with small metal pins known as endoclips (see Figure 2) is also effective in high risk bleeders, although this can be a technically difficult procedure. The combination of injection therapy with either endoclips or thermal coagulation achieves better results than one technique alone in controlling the bleeding and preventing rebleeding of an ulcer. Following endoscopic therapy, the re-bleeding risk in high risk bleeders is around 20 per cent in the first 48 to 72 hours.

Effective endoscopic therapy reduces the need for surgery in peptic ulcer bleeding. However, despite advances in this field endoscopic therapy has failed to alter the mortality rates related to upper gastrointestinal bleeding, which currently stand at 10–14 per cent. This is mainly due to the presence of significant comorbidity.



Figure 2. Endoclips on a duodenal ulcer

— Summary

The most common cause of PUD is *H pylori* infection. Eradication of these bacteria reduces the morbidity and mortality associated with the condition and the risk of gastric adenocarcinoma. Use of NSAIDs is associated with peptic ulceration, especially in the elderly. Bleeding and perforation are the two most common complications of PUD, and endoscopic therapy is useful in the management of bleeding ulcers. Uncontrolled bleeding and perforation of ulcers will require immediate surgical intervention.

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Suggestions for future special features

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