Helicobacter pylori infection and peptic ulcers

Debabrata Majumdar
James Bebb

Abstract

Nearly all peptic ulcers are caused by either *Helicobacter pylori* infection or the use of non-steroidal anti-inflammatory drugs (NSAIDs), which include aspirin. As *H. pylori* infection is becoming less prevalent in developed countries, NSAIDs are an increasingly important cause of ulceration, including ulcers complicated by gastrointestinal (GI) bleeding. Only about 15% of *H. pylori*-infected people develop an ulcer in their lifetime, with the risk determined by virulence of the *H. pylori* strain, host genetics and environment (particularly smoking). NSAID-induced ulcers are largely the result of suppression of gastroprotective cyclooxygenase (COX)-1. The presence and type of ulcers cannot be accurately predicted from symptoms, and the differential diagnosis is broad. Older dyspeptic patients and those with 'alarm' symptoms or signs require upper GI endoscopy to exclude upper GI cancer and make a diagnosis. Younger patients with simple dyspepsia are treated empirically with a course of proton pump inhibitors (PPIs) or an *H. pylori* 'test-and-treat' strategy. For *H. pylori*-associated ulcers, *H. pylori* eradication treatment induces healing and prevents relapse. NSAID ulcers are treated by NSAID withdrawal and a course of PPI; NSAID-naive users requiring continuing treatment who are positive for *H. pylori* need bacterial eradication, whereas others should be prescribed a concomitant PPI or selective COX-2 inhibitor. Treatment of functional dyspepsia is difficult and requires a multifactorial approach.

Keywords Duodenal ulcer; functional dyspepsia; gastric ulcer; gastritis; *Helicobacter pylori*; MRCP; non-ulcer dyspepsia; peptic ulcer

Key points

- In developed countries, *Helicobacter pylori* is becoming less common; instead non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are increasingly common causes of peptic ulceration
- Guidelines suggest that younger patients (in the UK, aged <55 years) with dyspepsia and no alarm signals should be managed either with a non-invasive *H. pylori* 'test-and-treat' approach to eradicate the infection if positive, or (particularly where the community prevalence of *H. pylori* is <10%) with an empirical course of proton pump inhibitor (PPI)
- Urea breath-testing is useful to diagnose infection and confirm eradication. The stool antigen test is an alternative to the urea breath test for non-invasive detection of active *H. pylori*; it is as accurate and more convenient
- In areas with low clarithromycin resistance (<20%), a clarithromycin-containing triple therapy regimen should be used
- PPIs should be co-prescribed in patients with NSAID-induced ulceration who need to continue these drugs, to reduce the risk of recurrent ulceration; in NSAID-naive patients, prior testing and eradication of *H. pylori* is useful in reducing the risk

Introduction

A peptic ulcer is a breach in the gastric or duodenal mucosa with penetration of the muscularis mucosa.[1] Small or shallow breaches of <5 mm in size are termed 'erosions';[1] although sometimes insignificant, these can precede frank ulceration. Worldwide, the two most common causes of peptic ulceration are *Helicobacter pylori* infection and use of non-steroidal anti-inflammatory drugs (NSAIDs), which includes aspirin. Other important causes of gastric ulceration are gastric adenocarcinoma and lymphoma, and these must be excluded by biopsy and follow-up (Table 1).

Gastritis is defined as inflammation of the gastric mucosa. It is diagnosed and classified histologically because endoscopic appearances such as erythema are frequently subjective and misleading; however, advanced high-definition magnification endoscopy can increase diagnostic accuracy even before histological confirmation. Gastritis is seldom, if ever, symptomatic but can have important clinical sequelae in a minority of patients. Sequelae vary depending on the type of gastritis but include duodenal and gastric ulceration, gastric adenocarcinoma and primary gastric lymphoma. The three most important causes of gastritis are *H. pylori* infection, NSAIDs/aspirin and autoimmunity (Table 2):

- ***Helicobacter pylori*** can cause either antral-predominant gastritis (associated with increased meal-stimulated acid production), which predisposes to duodenal ulceration, or corpus-predominant or pangastritis (associated with low gastric acid production), which predisposes to gastric ulceration and distal gastric adenocarcinoma. However, most people with *H. pylori*-induced gastritis develop none of these clinical problems and remain asymptomatic.
- **Aspirin/NSAIDs** cause a 'chemical gastritis', which is characterized by mucosal hyperplasia and oedema but minimal inflammatory cell infiltration.
- **Autoimmune gastritis** is virtually confined to the body of the stomach and is associated with antiparietal cell and

Debabrata Majumdar *MD FRCP is a Consultant Physician and Gastroenterologist and Hepatobiliary Lead at Ashford and St Peter's Hospital NHS Foundation Trust, Chertsey, UK. Competing interests: none declared.*

James Bebb *PhD FRCP is a Consultant Physician and Gastroenterologist at The Royal Cornwall Hospital, Cornwall, UK. Competing interests: none declared.*

Causes of non-*H. pylori*, non-NSAID peptic ulcers

- Gastric adenocarcinoma
- Gastric lymphoma
- Local drug irritation
- Irritation at the neck of a hiatus hernia (Cameron's ulcer)
- Idiopathic
- Anastomotic ulceration after previous gastric surgery
- After radiotherapy
- Zollinger–Ellison syndrome (gastrinoma) — particularly for duodenal ulcers
- Multiple endocrine neoplasia type I
- Hyperparathyroidism without multiple endocrine neoplasia type I
- Systemic mastocytosis
- Severe systemic illness stress ulcers (Cushing's ulcers)
- Idiopathic eosinophilic and lymphocytic gastritis
- Duodenal Crohn's disease
- Coeliac axis stenosis
- Hepatic artery chemotherapy
- Prescribed medicines including bisphosphonates, sirolimus, mycophenolate and corticosteroids (when combined with NSAIDs)
- Recreational drugs including crack cocaine

Table 1

often intrinsic factor antibodies. It can result in vitamin B_{12} deficiency and pernicious anaemia, and, like *H. pylori* infection but unlike aspirin and NSAIDs, is an independent risk factor for gastric adenocarcinoma.

Helicobacter pylori was first described by Barry Marshall and Robin Warren in 1983,[2] for which they were awarded the Nobel Prize in 2005. It is a Gram-negative, microaerophilic, non-invasive, spiral bacillus that has the ability to colonize the gastric mucosa. It has a powerful urease enzyme that catalyses hydrolysis of urea to ammonia, enabling the bacteria to survive in the acid milieu. Although it induces a strong host local and systemic immune response (which is important in pathogenesis), it has also developed mechanisms to evade host immunity. This means that, after initial infection, which usually occurs in childhood, it is able to persist life-long in the absence of effective treatment. This persistent infection and inflammation underlies disease, which usually occurs in adults. Worldwide, *H. pylori* colonizes >50% of the population[2] and is thus by far the most important cause of peptic ulcers and gastric adenocarcinoma. Its prevalence varies from >80% in developing countries to 6–25% in developed countries, where prevalence is steadily falling owing to improved hygiene and sanitation, and possibly also increased antibiotic use.

Classification of gastritis[1]

Type of gastritis	Aetiology
Infectious gastritis	*Helicobacter pylori*
Autoimmune	Autoimmunity
Other infections	Bacteria other than *H. pylori*: other gastric helicobacters (*H. heilmannii*), mycobacteria and secondary syphilis Viruses: Cytomegalovirus Fungi: *Candida* spp., *Histoplasma capsulatum*, *Mucoraceae*
Chemical	NSAIDs, bile (duodenal reflux), alcohol
Radiation	Radiation injury
Lymphocytic	Gluten (coeliac disease), *H. pylori*, idiopathic, drugs
Eosinophilic	Food sensitivity?, other allergies
Non-infectious granulomatous	Crohn's disease, sarcoidosis, Wegener's granulomatosis and other vasculitides, foreign substances, idiopathic
Others	Ménétrier's disease

Table 2

Epidemiology

Peptic ulcers were rare before the 20th century. Gastric ulcers and, later, duodenal ulcers were increasingly described in the late 19th century, the incidence of duodenal ulcers increasing progressively and reaching a peak in the 1950s. The cause of this is unclear, because *H. pylori* is thought to have been ubiquitous in the human population for thousands of years.

The prevalence of gastric and duodenal ulceration has decreased in Western Europe and the USA in recent decades, after a decrease in the prevalence of *H. pylori*. Hospitalization rates have also steadily declined, with mortality from peptic ulcers showing a significant reduction in the USA from 1993 to 2003.[3] *Helicobacter pylori* infection is present in about 25% of adults in most developed countries, and in a much smaller proportion in some. It is mostly acquired in childhood, up to the age of 12, and strongly associated with greater age, and with markers of overcrowding and poor hygiene in childhood. These associations arise because progressively fewer children became infected over the second half of the 20th century owing to improved social and living conditions. On the other hand, in some developing countries the prevalence of *H. pylori* infection is still much higher, and migrants from developing to developed countries exhibit a high prevalence. *Helicobacter pylori* is acquired by human contact, usually oro-oral rather than faecal-oral transmission. In developed countries, it is usually acquired by intrafamilial transmission; in developing countries, it is more often acquired from other children outside the family group.[1] There are no significant animal or environmental reservoirs.

Aspirin and other non-selective NSAIDs are independent causes of duodenal and gastric ulceration; they also have a synergistic influence on development of peptic ulcers and their complications. The epidemiology of NSAID-induced ulcers reflects patterns of use; for example, although the absolute risk from low-dose aspirin is low, increasing use of such treatment means that it is an increasingly important cause of peptic ulceration. In the UK, aspirin is now a more common cause of ulcer bleeding than other NSAIDs. Concomitant use of gastroprotective agents (mainly proton pump inhibitors (PPIs) and to some extent H_2-receptor antagonists) reduces the risk, although suboptimal adherence to such treatment is also associated with an increased risk of upper gastrointestinal (GI) events.

Concerns have been raised about the risks of long-term PPI (in those with previous *H. pylori* infection) use, particularly with an increased risk of gastric cancers as reported in a recent study from Hong Kong. The applicability of such findings in the Western population has been questioned, particularly because, compared with the Far East, gastric cancer is relatively rare (with a falling incidence), as is *H. pylori* incidence. A recent statement from the British Society of Gastroenterology has suggested that if acid suppression is required after *H. pylori* eradication, H_2-receptor antagonists should be used first. Patients should be counselled that there is a low but absolute risk of around 1 in 2000 per year.

Pathogenesis

Only about 15% of individuals infected with *H. pylori* ever develop a peptic ulcer: who develops disease depends on bacterial, host and environmental factors. The risk of ulceration is higher with more virulent strains. The best-described virulence determinants are the expression of active forms of a vacuolating cytotoxin (VacA) and the possession of a protein secretory apparatus called Cag (cytotoxin-associated gene products), which stimulates the host inflammatory response. Cag^+ strains interact more closely with epithelial cells and induce the release of proinflammatory cytokines, thereby increasing inflammation. However, it is unclear whether it is this or the direct translocation of a bacterial protein (CagA) into the gastric epithelial cells that is the primary cause of the inflammation and epithelial damage underlying disease, including gastric adenocarcinoma. Host genetic susceptibility and environmental factors also affect disease risk; for example, smoking is strongly associated with peptic ulceration in *H. pylori*-infected individuals.

Helicobacter pylori causes chronic active gastritis in almost all colonized individuals.[1] *Helicobacter pylori*-induced duodenal ulceration arises in people with non-atrophic, antral-predominant gastritis (Figure 1). Hypergastrinaemia, and a decreased somatostatin concentration in the antrum as a consequence of antral inflammation, leads to increased acid production from the uninflamed proximal acid-secreting areas of the stomach in response to food and other stimuli. The resulting increased acid load in the duodenum is one factor encouraging duodenal ulceration.

Gastric ulceration occurs on a background of atrophic pangastritis, often arising at the highly inflamed transitional zone between antrum and corpus, particularly on the lesser curve. Similar hormonal changes occur, but the inflamed corpus cannot produce more acid, and acid production is instead reduced or normal. This group of patients tend to develop proximal ulcers and are at increased risk of pre-cancerous lesions and cancers.[1]

Although aspirin and NSAIDs are independent risk factors for peptic ulcer disease, studies have shown that concomitant NSAID use increases the risk of peptic ulcers in *H. pylori*-infected individuals.[3] Aspirin and NSAIDs cause gastric and duodenal damage through inhibition of the enzyme cyclooxygenase (COX)-1, which is important for the formation of protective prostaglandins in the stomach. The anti-inflammatory effects of NSAIDs are mediated through another isoform of cyclooxygenase, COX-2. Selective COX-2-inhibiting NSAIDs are less gastrotoxic than non-selective NSAIDs (even when co-prescribed with PPIs); their adverse cardiovascular effects have limited their use, although these have now been shown be no worse than many non-selective NSAIDs. The effects of *H. pylori* in patients taking low-dose maintenance aspirin is less clear, although eradication of *H. pylori* has been noted to reduce risk of peptic ulcer bleeding.[3]

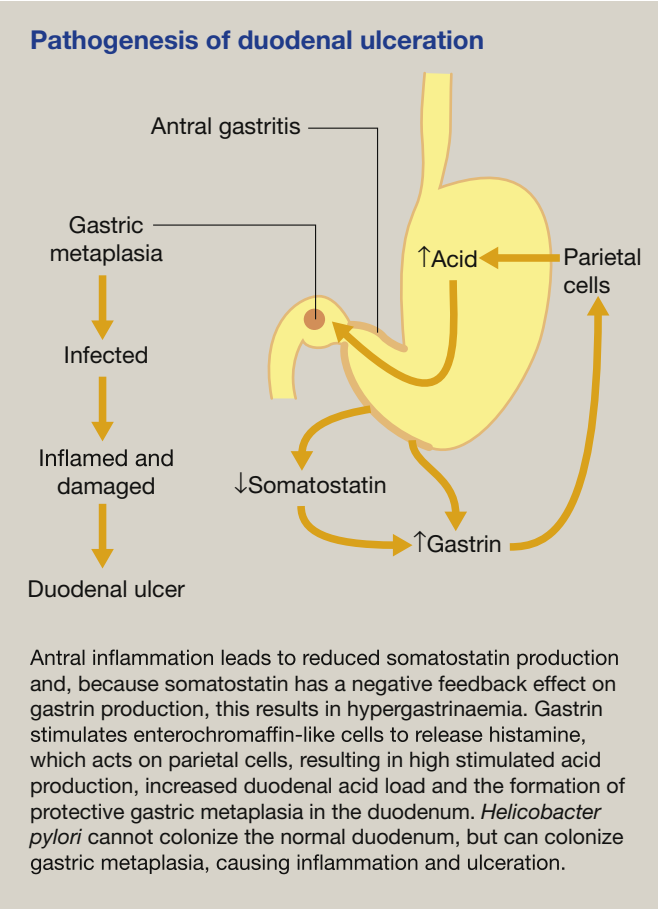

Figure 1

Clinical features

Chronic *H. pylori*-associated gastritis per se is often asymptomatic, but the initial acquisition of the infection causes acute gastritis with hypochlorhydria. This can cause abdominal pain, nausea and vomiting that resolve within a few days. Gastritis can result in dyspeptic symptoms; eradication of *H. pylori* usually results in relief of such symptoms, although this can take up to 6 months.[3] Uncomplicated peptic ulcers typically cause epigastric pain and, less commonly, nausea, vomiting and weight loss, whereas some ulcers (particularly NSAID-related ulcers) are asymptomatic. The classically described pain of a duodenal ulcer is felt as a gnawing or burning sensation. It is often related to meals, occurring 1–3 hours after meals and/or at night, and is relieved by food. Gastric ulcer pain is instead often precipitated by food. However, symptoms are very poorly discriminatory for site of ulceration and even for whether or not an ulcer is present. Examination usually reveals epigastric tenderness but can be normal.

The differential diagnosis of peptic ulcer disease includes:

- gastro-oesophageal reflux disease (GORD), which usually causes predominant heartburn but cannot reliably be discriminated from ulcer disease based on symptoms
- functional dyspepsia (non-ulcer dyspepsia (NUD)), which can also be indistinguishable from ulcers based on symptoms
- gallstone disease
- gastric cancer or lymphoma
- irritable bowel syndrome
- Crohn's disease
- pancreatitis
- pancreatic cancer.

Complications

H. pylori ulcers usually heal and relapse spontaneously, but ulcers of any cause, particularly NSAID-induced ulcers, can cause serious complications. Acutely bleeding ulcers cause haematemesis and/or melaena, and chronic bleeding can cause anaemia. Perforation results in peritonism, and gastric outlet obstruction causes persistent vomiting (physical examination can reveal a succussion splash).

Management

The discovery of *H. pylori* has revolutionized the management of peptic ulcers — its eradication heals *H. pylori*-induced ulcers and prevents their relapse.

Dyspepsia in the community[4]

In young patients with uninvestigated dyspepsia, a 'test-and-treat' approach is cost-effective and is advocated over more invasive investigations, such as upper GI endoscopy. Patients should be non-invasively tested for *H. pylori* (breath test or stool antigen) and given treatment to eradicate *H. pylori* if the results are positive. In populations with a lower prevalence of *H. pylori* (<10%), screening for *H. pylori* can be less effective because of the likelihood of false-positive results, leading to unnecessary treatment; a more cost-effective approach is a trial of PPI.[1,3] In either case, if the first approach fails, the other can be tried.

Older patients presenting for the first time with recent-onset, unexplained and persistent dyspepsia (over 4–6 weeks), and those with 'alarm' symptoms or signs (e.g. weight loss, dysphagia, persistent vomiting, GI bleeding, unexplained anaemia, epigastric mass, previous gastric ulcer or gastric surgery) should be referred for upper GI endoscopy and/or other investigations, both to exclude malignancy and to make a positive diagnosis. The advised 'cut-off' age varies by country and region, but in the UK an age of 55 years has been advocated in the most recent guidelines from the National Institute for Health and Care Excellence (NICE).[3,4]

Upper gastrointestinal endoscopy

Upper GI endoscopy is the investigation of choice in older patients with dyspepsia and those with 'alarm' symptoms because it enables diagnosis of ulceration and other macroscopic abnormalities such as malignancy and oesophagitis. Histological examination of gastric mucosal biopsy specimens is useful in confirming the nature of any abnormalities seen, identifying whether gastritis is present and suggesting its cause. However, it is seldom necessary if macroscopic appearances are normal.

Treatment with acid-suppressing drugs before endoscopy can heal ulcers, rendering endoscopic findings misleading. Similarly, PPIs, bismuth compounds and antibiotics can cause false-negative *H. pylori* tests. If possible, acid-suppressing agents should be avoided for at least 2 weeks and preferably 4, and bismuth compounds and antibiotics avoided for at least 4 weeks, before endoscopy.

Patients with persistent, non-responsive gastro-oesophageal symptoms, those considering surgery for GORD and those with *H. pylori* colonization not responding to second-line eradication therapy should probably be referred to specialist services for consideration of upper GI endoscopy.

Tests for *Helicobacter pylori* not requiring endoscopy

Serology: serological tests involve detection of immunoglobulin G antibodies against *H. pylori*, and the best are very accurate. However, accuracy depends critically on the precise serological test used. The main use of serology is for testing dyspeptic patients and patients with known ulceration in whom the diagnostic sensitivity of non-serological tests is likely to be low. This includes situations where the *H. pylori* load in the stomach is low, for example active GI bleeding, atrophic gastritis, mucosa-associated lymphoid tissue (MALT) lymphoma and gastric carcinoma. Serology can remain positive for years after successful eradication of *H. pylori* and is therefore not useful for assessing effectiveness of eradication treatment.[3]

A panel of serological tests has been proposed in dyspeptic patients for identifying atrophic gastritis because this group of patients are at an increased risk of gastric cancers. Tests include pepsinogen I and II anti *H. pylori* antibody assays. These tests are not, however, easily available.[3]

Urea breath test (UBT): the UBT (Figure 2) is a simple, non-invasive test based on *H. pylori* urease. It is particularly useful for checking the success of treatment. It is also more accurate than serology so is often used as a first-line diagnostic test. It must be performed at least 4–8 weeks after eradication treatment and 2 weeks after PPIs have been stopped; if not, false-negative results are common. It is inexpensive and readily available in most countries.[3]

Stool antigen test: this is a more recently developed alternative to UBTs. Like UBTs, it assesses active infection so can be used for assessing treatment success, although with the same caveats relating to its use.[3] It is usually less expensive than UBTs and is in many ways more convenient, but in some countries there are problems with the social acceptability of stool tests. As for UBTs, PPIs should be discontinued for 2 weeks before the test, and it should not be done until 4 weeks after antibiotic and bismuth use.

Tests for *Heliobacter pylori* requiring endoscopy

Biopsy urease test: this is the most widely used endoscopic gastric biopsy-based test. The biopsy is placed in a urea solution or gel with a pH indicator; when *H. pylori* is present, the urea is hydrolysed by its urease, resulting in a colour change. Some positive results can be available within minutes, although in

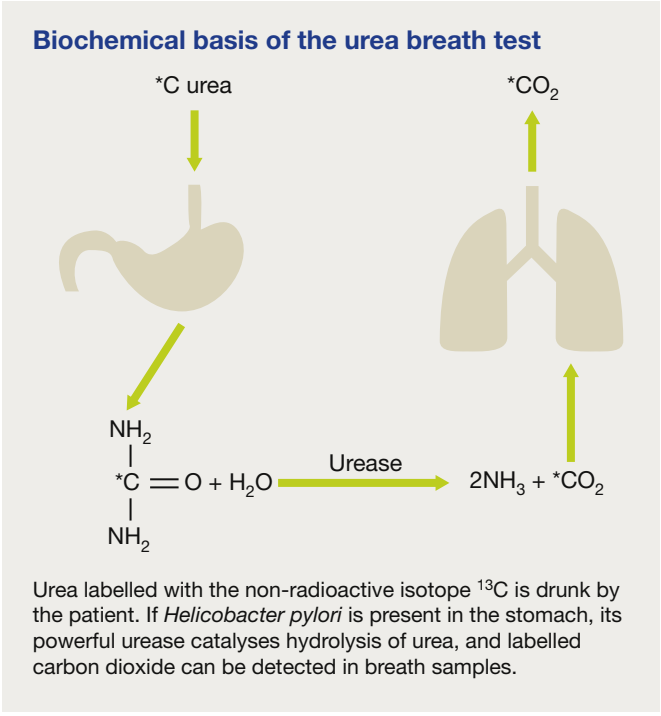

Figure 2

most commercially available forms of the test, initially negative tests must be kept for 24 hours to avoid occasional false-negative results. Blood in the upper GI tract and excessive gastric atrophy with intestinal metaplasia sometimes result in false-negative results.[3] The same restrictions on timing with respect to PPI and antibiotic use apply as for UBTs, and this is common to all gastric biopsy-based tests. The biopsy urease test is cheap and widely available; tests from most manufacturers are accurate.

Histology: *H. pylori* infection can be diagnosed accurately by histology if special stains are used. The distribution of gastritis can give information on disease risk if biopsies are taken from antrum and corpus. Histology can also give further information, for example on whether gastric atrophy or intestinal metaplasia — markers of increased risk of gastric adenocarcinoma — is present. Histology is relatively expensive, particularly if special stains are used.

Culture: endoscopic mucosal biopsy specimens can be cultured for *H. pylori*. This is not useful as a purely diagnostic test as *H. pylori* is not straightforward to grow, and culture is often falsely negative. However, success rates are high in specialist laboratories, and culture has the advantage of allowing antibiotic sensitivity testing. This is very useful in selected patients for guiding treatment in specific situations, such as previous multiple treatment failure. In our opinion, it is greatly underused.

Treatment of peptic ulcers and non-ulcer dyspepsia

The treatment of peptic ulcer disease has been revolutionized by the discovery of *H. pylori* and its role in the aetiology of this condition; surgery is now reserved for complications that cannot be controlled pharmacologically and endoscopically. Because most peptic ulcers are caused by *H. pylori* or NSAIDs, a cause should always be sought. In *H. pylori*-negative non-NSAID-associated duodenal ulcers, *H. pylori* and NSAIDs are still the main aetiological causes, and they are still a common cause in apparently *H. pylori*-negative non-NSAID-associated gastric ulcers. It is thus important to ensure that *H. pylori* testing has been adequate (and if necessary, repeat it or use different tests such as serology if the patient is already taking a PPI), and to take a careful drug history (including over-the-counter medication) before investigating further. In confirmed *H. pylori*-negative, non-NSAID ulcers, more uncommon causes (Table 1) should be sought by biopsy and, where necessary, other tests.

Successful *H. pylori* eradication heals >90% of duodenal ulcers and virtually prevents ulcer relapse, whereas symptomatic relapse is common (50–80% at 1 year) if *H. pylori* is not treated. Although simple *H. pylori*-induced ulcers heal with *H. pylori* treatment alone, other ulcers and large or complicated *H. pylori* ulcers are usually treated with a longer course of acid suppression therapy. Both PPIs and H_2-receptor antagonists are effective, but PPIs are best in terms of healing rate and speed of action. It is usual to treat gastric ulcers with 1–2 months of PPI therapy as well as eradication of *H. pylori* as these are often slower to heal.

Gastric ulcers

Treatment involves taking a PPI for 6–8 weeks and removing the underlying cause, usually by treating *H. pylori* or stopping NSAIDs. Patients are traditionally re-endoscoped after 6–8 weeks to ensure the ulcer has healed and to rule out a gastric tumour masquerading as an ulcer. If the ulcer is still present, biopsies should be taken from the ulcer edge to exclude malignancy and other causes. The patient should be re-scoped after a further interval to check healing, and should continue taking the PPI until ulcer healing has been demonstrated endoscopically. The success of *H. pylori* treatment can be checked at endoscopy if there has been an opportunity to stop PPIs for 4 weeks before the endoscopy, or otherwise by UBT at least 4 weeks after PPIs have been stopped.

Duodenal ulcer

Helicobacter pylori-positive ulcers usually require a course of *H. pylori* eradication therapy, and then no further acid suppression unless the ulcer has been complicated (e.g. by GI bleeding); in this case, acid suppression should be continued until *H. pylori* eradication has been confirmed. Most gastroenterologists do not re-scope patients to check healing unless the patient has developed complications (e.g. gastric outflow obstruction) or remains symptomatic, as duodenal carcinoma is extremely rare.

Refractory peptic ulcer

Most ulcers heal using the above recommendations, but peptic ulcers that are failing to heal should prompt a number of questions:

- Is the patient compliant with prescribed treatment?
- Is this a simple peptic ulcer or something else, such as gastric cancer/lymphoma/Crohn's disease (see Table 1)? Take more biopsies from the ulcer edge.
- Has *H. pylori* eradication/testing been adequate? Consider taking biopsies from the proximal stomach (PPI use can promote proximal migration of *H. pylori*) or use a second method to test for *H. pylori*.

- Is there surreptitious or continuing NSAID use?
- Does the patient smoke? Smoking is associated with ulcer formation and impaired healing. Refer to smoking cessation services.
- Does the patient have a high body mass index (BMI)? High BMI can influence drug distribution and availability at gastric mucosal level, and weight loss should be encouraged.
- Could the patient have a hypersecretory state such as Zollinger–Ellison syndrome (particularly in those with duodenal ulcers when common causes have been ruled out)? Check fasting plasma gastrin and chromogranin A (remember than PPIs can cause hypergastrinaemia but not usually >2–3 times normal); also look for associated conditions (e.g. family history of multiple endocrine neoplasia type 1, gastrinoma).

Complicated peptic ulcer

Peptic ulcer can be complicated by bleeding and perforation, and this is dealt with in another article. Consider early *H. pylori* eradication in non-NSAID bleeding ulcers to reduce risk of poor compliance with the course of treatment. Gastric outflow obstruction resulting from pyloric stenosis can respond to prolonged acid suppression and *H. pylori* eradication. If it does not, endoscopic balloon dilatation or even surgery may be needed.

Who should be given *H. pylori* eradication therapy?[3]

The most clear-cut indications for eradication of *H. pylori* (if it is present) are:

- active gastric or duodenal ulcer
- history of previous gastric/duodenal ulcer (not treated for *H. pylori*)
- gastric MALT lymphoma
- history of resection of early gastric cancer.

Patients with GORD or complications of GORD are frequently tested for *H. pylori* on upper GI endoscopy, but there is no evidence that treating this group affects symptoms or treatment success. Most authorities and guidelines recommend treatment in *H. pylori*-infected people who are first-degree relatives of gastric cancer patients and who have atrophic gastritis (unless they are elderly). In NSAID-naive patients who are positive for *H. pylori*, eradication before commencing NSAIDs is associated with reduced risk of ulcers and their complications. In patients taking long or frequent intermittent courses of NSAIDs, especially where dyspeptic symptoms or previous ulcers have been observed, long-term PPI prophylaxis should be used. Our practice is also to eradicate *H. pylori* if present, because of the theoretically enhanced risk of *H. pylori*-associated gastric carcinoma in long-term PPI users.

Latest guidelines also suggest eradication in new users of aspirin, but evidence is less strong for low-dose aspirin. Some authorities advocate treatment of *H. pylori* in patients with iron deficiency anaemia in whom causes have been rigorously sought but not found (grade A recommendation). Eradication in iron deficiency anaemia has been associated with improvement in anaemia. There is also evidence supporting *H. pylori* eradication in patients (adults not children) with chronic idiopathic thrombocytopenic purpura, although this remains controversial.

Younger patients (age <55 years) presenting in the community with dyspepsia and lack of alarm symptoms are often tested for *H. pylori* and, if positive, given eradication therapy ('test-and-treat' strategy). This strategy is safe and avoids the need for endoscopy in a substantial number of patients. This strategy benefits those who have an ulcer underlying their symptoms and also 1 in about 14 of those with functional dyspepsia. However, a significant proportion of these patients have GORD or non-responsive NUD so will not benefit, other than through a still largely theoretical reduction in future gastric cancer risk. NICE guidelines on the referral of patients with suspected upper GI cancer advise that patients 55 years and older presenting with unexplained and persistent recent dyspepsia alone should be referred for urgent endoscopy.

Eradication of *H. pylori*[3]

Helicobacter pylori resistance rates to antibiotics are rising in most parts of the world. Once a decision has been made to eradicate *H. pylori*, a wide range of treatment options and regimens is available (Table 3).[3] Choice of regimen (and likelihood of success) depends on a number of variables, including host and bacterial sensitivity, previous antibiotic use and likely compliance with the prescribed regimen. Prescribers should follow local guidelines or liaise with microbiology departments if unclear on susceptibility. First-line treatment is governed by the level of clarithromycin resistance in a region. Clarithromycin resistance rates were 9% across Europe in 1998; however, by 2010 this had risen to >20% in most of Central, Western and Southern Europe. Rates remain low (<10%) in most of Northern Europe. Current UK recommendations from NICE are based on presumed low clarithromycin resistance rates.

Low clarithromycin resistance areas: first-line treatment remains triple combination therapy with twice-daily PPI, clarithromycin and amoxicillin or metronidazole for 1 or 2 weeks. It is successful in 70–85% of patients. Second-generation PPIs such as esomeprazole (or doubling the dose of conventional PPIs) can elevate eradication rates by up to 8–12%. Eradication rates have also been shown to be increased by about 5% if the duration of therapy is extended to 10–14 days. This is not associated with excess adverse effects, but the added cost should be considered. The most common reasons for failure are clarithromycin resistance and poor compliance with treatment.

Metronidazole resistance is also common, in particular among migrants from developing countries who have frequently had exposure to metronidazole and other nitroimidazoles. However, metronidazole resistance is only partial, and a recent meta-analysis of quadruple therapy (see below) has shown that metronidazole resistance has a limited effect on outcome when dosage and duration of therapy are adequate. Because of the inherent difficulties of eradicating the infection and the potential risks of treatment failure after re-treatment, patients should be counselled about the importance of good compliance; combination drug packs and written instructions can help.

If treatment failure is confirmed with UBT or stool antigen, second-line therapy with a bismuth-containing quadruple therapy or 10-day course of PPI, levofloxacin and amoxicillin is recommended (Table 3). Some specialists use quadruple therapy

Treatment regimens for eradication of *H. pylori*[3]

Low clarithromycin resistance (< 20%)	High clarithromycin resistance (≥20%)
First line	
7–14 days[a]	14 days
PPI 12-hourly[b]	PPI 20 mg 12-hourly
Clarithromycin 500 mg 12-hourly plus either:	Bismuth subcitrate 120 mg 6-hourly[d]
•Amoxicillin 1 g 12-hourly or	Tetracycline HCl 500 mg 6-hourly
•Metronidazole 400 mg 12-hourly[c]	Metronidazole 400 mg 8-hourly
Second line	
14 days	14 days
PPI 12-hourly	PPI 12-hourly
Bismuth subcitrate 120 mg 6-hourly	Amoxicillin 500 mg 12-hourly
Tetracycline HCl 500 mg 6-hourly	Metronidazole 400 mg 12-hourly
Metronidazole 400 mg 8-hourly	Clarithromycin 500 mg 12-hourly
or	*or*
	Sequential
10 days	5 days
PPI 12-hourly	PPI 12-hourly
Amoxicillin 1 g 12-hourly	Amoxicillin 1 g 12-hourly
Levofloxacin 500 mg 12-hourly	*followed by*
	5 days
	PPI 12-hourly
	Levofloxacin 500 mg 12-hourly
	Metronidazole 400 mg 8-hourly
Third line	
Based on susceptibility testing[e]	

[a] Extending treatment to 10–14 days improves eradication rates by approximately 5% and should be strongly considered.
[b] Choice of PPI may be determined by cost and also regional variation in metabolism of drug; for example, in Caucasian populations rabeprazole seems least metabolized by host cytochrome polymorphisms. In some regimens, doubling the dose of PPI increases eradication rates.
[c] Regimens with amoxicillin or metronidazole are equally effective.
[d] If metronidazole resistance is low, PPI–amoxicillin–metronidazole triple therapy can be as effective as bismuth-based therapy.
[e] Culture and antibiotic sensitivity testing can be used as an alternative to 'blind' treatment with second-line drugs. Other second- and third-line treatments are available but should usually be reserved for use by specialist units.

Table 3

as first line as success rates are very high – higher than triple therapy in many populations.

For third-line therapy, where there is a good reason to pursue *H. pylori* eradication, referral to a specialist centre that has facilities for culture and sensitivity-testing of *H. pylori* should be considered. However, some practitioners give 'blind' third-line therapy combinations, usually based around levofloxacin or rifabutin plus a PPI and an another antibiotic, usually amoxicillin. These regimens should not be used lightly. Rising rates of levofloxacin resistance should be taken into account and this might jeopardize its future efficacy. Where possible, it is recommended to test for levofloxacin susceptibility before prescribing it. Levofloxacin, like other quinolones, may be a risk factor for *Clostridium difficile* infection, particularly when used in combination with other broad-spectrum antibiotics. Rifabutin can cause cross-resistance to rifampicin for *Mycobacterium tuberculosis*, and bone marrow suppression is a rare but serious adverse effect.

High clarithromycin resistance areas: first-line therapy is bismuth-containing quadruple therapy, avoiding clarithromycin. If metronidazole resistance (if known) is low, PPI–amoxicillin–metronidazole triple therapy can be as effective. Where bismuth is not available, either non-bismuth-containing quadruple therapy or sequential therapy is recommended. Eradication rates with clarithromycin-resistant strains have been shown to be >89%. Second-line therapy is with a PPI–levofloxacin regimen. Third-line therapy should be guided by susceptibility testing, where possible in specialist centres.

It is important to confirm post-treatment eradication in those patients with an important indication for *H. pylori* treatment – this is best done by UBT or stool antigen test 4 weeks or more after treatment. For patients with uninvestigated dyspepsia, many practitioners do not routinely check for *H. pylori* treatment success unless symptoms recur or do not resolve.

Adverse events

Helicobacter pylori eradication is associated with adverse events in up to 50% of patients. These are usually antibiotic-associated diarrhoea or mild nausea, although serious adverse events such as *C. difficile*-associated colitis can rarely occur. Despite the frequency of adverse effects, <10% of patients stop treatment because of them.

Treatment of NSAID-induced dyspepsia and ulceration

- In primary care, NSAID-induced dyspepsia usually responds to stopping the drug and prescribing PPIs.
- In NSAID-naive patients who are at increased risk of GI adverse effects, *H. pylori* infection should be actively sought and eradicated before starting NSAIDs. Patients already taking NSAIDs should be treated with long-term PPIs to reduce the ulcer risk, as *H. pylori* eradication alone is not effective in reducing ulcer risk.
- NSAID- and aspirin-induced ulcers are best managed by stopping the drug, actively investigating for *H. pylori* infection (eradicating if present), and prescribing PPIs. In patients with previous NSAID-induced ulcers requiring continuing pain relief, non-NSAID analgesics should be substituted. If NSAIDs are necessary, they should be co-prescribed with PPIs. Specific COX-2 inhibitors can be prescribed in selected cases, keeping in mind their adverse cardiovascular risk profile. However, neither strategy entirely abolishes the risk of ulceration. Patients with NSAID-induced gastric ulcers should be followed up with repeated endoscopy and biopsy until the ulcers have completely healed.
- In patients with previous aspirin-induced ulcers who require continued antiplatelet therapy, eradication of *H. pylori* alone reduces but does not abolish the risk of further GI events. In high-risk cases, co-prescribing a PPI is a sensible additional strategy.

- If patients are unable to take PPIs, a twice-daily H_2-receptor antagonist or misoprostol is an alternative. PPIs are preferred and more effective, and misoprostol use is often limited by colic and/or diarrhoea.

Treatment of non-ulcer dyspepsia

NUD (also known as functional dyspepsia) is the presence of symptoms thought to originate in the gastroduodenal area in the absence of structural abnormalities. These symptoms (based on the Rome IV diagnostic criteria) are listed in Table 4. In clinical practice, diagnosis is on the basis of characteristic symptoms in the presence of a normal gastroscopy. However, it is important to take a careful history and consider alternative conditions, such as irritable bowel syndrome, gastroparesis and pancreatobiliary pathology, before concluding that the patient has NUD.

Unlike peptic ulcer disease, where treatment is pharmacological and usually straightforward, the management of NUD (as with all functional GI disorders) is more challenging and requires a careful dialogue between physician and patient. There is a high incidence of anxiety disorders, which should be addressed. Underlying pathophysiological disturbances are not fully understood but include impaired gastric accommodation (up to 40% of patients), delayed gastric emptying (25–40%) and visceral hypersensitivity (33%). Response to pharmacological treatments is often disappointing, and a significant placebo response (20–60%) is usually seen, as in other functional GI disorders. Most experts advocate a trial of PPI and/or *H. pylori* eradication (number-needed-to-treat 12), if present. Much of the benefit of these two treatments might result from the presence of unrecognized GORD, or peptic ulcers that had been missed at gastroscopy or had already remitted when it was carried out.

In patients troubled by symptoms that fail to respond to *H. pylori* eradication or a 4–8 week trial of PPI, reconsider the diagnosis before considering a trial of tricyclic antidepressant. A recent meta-analysis of antidepressants in the treatment of functional dyspepsia suggested an effectiveness of tricyclic antidepressants (but not selective serotonin reuptake inhibitors) compared with placebo, albeit with more adverse events. Most authorities previously recommended a trial of prokinetic agents such as domperidone, but recent guidance from the European Medicines Agency suggests this can carry an increased risk of cardiac abnormalities, particularly in individuals with a cardiac history and who are aged >60 years. For these reasons, domperidone is now recommended only for short-term use in low dosage (10 mg orally 8-hourly) for nausea and vomiting and is no longer licensed to treat other conditions such as bloating and heartburn. Limited data suggest benefit from bismuth, misoprostol, sucralfate and pirenzepine (an antimuscarinic), but most of these trials used small numbers of patients and firm recommendations cannot be made. Psychological studies have been performed using psychotherapy, cognitive therapy and hypnotherapy, with reported improvements in dyspepsia scores.

In clinical practice, the most cost-effective approach is to eradicate *H. pylori* if present. In *H. pylori*-negative patients and those who have failed to respond to eradication therapy, a 1-month trial of PPI or H_2-receptor antagonist therapy can be worthwhile, alongside reassurance and advice.

Diagnostic criteria for functional dyspepsia[5]

1. One or more of the following:
   - Bothersome postprandial fullness
   - Bothersome early satiation
   - Bothersome epigastric pain
   - Bothersome epigastric burning

and

2. No evidence (including at upper endoscopy) of structural disease that is likely to explain the symptoms

Subtypes

Postprandial distress syndrome (PDS):

- bothersome postprandial fullness and early satiation on >3 days/week

Epigastric pain syndrome (EPS):

- bothersome epigastric pain and burning on >1 day/week

Table 4

Prevention of ulcers, gastritis and gastric cancer

As discussed above, the prevalence of *H. pylori* is decreasing in developed countries, probably because of improvements in living standards and hygiene. *Helicobacter pylori*-associated peptic ulcer is also becoming less common, such that the major cause of peptic ulcer in some developed countries is now aspirin and NSAIDs. In developing countries, *H. pylori* is still very common, which affects the prevalence of ulcers and, more importantly, gastric cancer. *Helicobacter pylori* infection is a major risk factor for non-cardiac gastric cancer and is thought to increase the risk 2.5–5-fold.

The Maastricht expert group recommends that *H. pylori* eradication be undertaken in populations at high risk of gastric cancer. Mass eradication trials in Asia (Taiwan and China, with a high prevalence of gastric cancer) have reported excellent compliance, minor adverse events and low cost along with a 30–40% reduction in gastric cancer risk with successful eradication. However, this is considered controversial by some experts, due in part to the practicalities involved. Furthermore, it remains unclear whether *H. pylori* eradication can reduce the risk of gastric cancer in patients with gastric atrophy. In future, vaccination against *H. pylori* may become a potentially useful strategy in preventing ulcers and gastric cancer. There have been positive results in animal models and an early clinical trial in children in China, but the development of an effective vaccine in humans remains a challenge, partly because of the complex host-immune response. Further research is needed.

Challenging research suggests that *H. pylori* infection might confer some advantages for modern humans. There is good evidence that life-long infection reduces the severity of complications of gastro-oesophageal reflux, including reducing the incidence of oesophageal adenocarcinoma. (Treatment of *H. pylori* does not, however, increase this risk, so treatment should not be withheld for this reason.) There is also evidence that childhood *H. pylori* infection offers some protection against modern diseases such as asthma and allergy, possibly via the hygiene hypothesis. If this theory is upheld, it could in part explain the increasing incidence of these diseases, which could also increase in developing countries with mass *H. pylori*-prevention

programmes. However, the current view is that the number of lives saved from gastric cancer is likely to more than balance these risks.

Rational prescribing can reduce the incidence of NSAID-induced ulceration; in patients with increased risk of GI adverse effects (elderly, previous history of peptic ulcers), eradication of *H. pylori* (if detected), concomitant use of PPIs and prescribing the least gastrotoxic NSAIDs (e.g. ibuprofen) are recommended. ◆

KEY REFERENCES

1 Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut* 2015; **64:** 1353–67.

2 Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; **1:** 1273–5.

3 Malfertheiner P, Megraud F, O'Morain CA, et al. on behalf of the European Helicobacter and Microbiota Study Group and Consensus panel. Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. *Gut* 2017; **66:** 6–30.

4 Public Health England. *Helicobacter pylori* in dyspepsia: test and treat. 2017 (accessed Nov 2018), https://www.gov.uk/government/publications/helicobacter-pylori-diagnosis-and-treatment.

5 Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. *Gastroenterol* 2016; **150:** 1380–2.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 56-year-old man presented with a 6-week history of dyspepsia not responding to over-the-counter ranitidine. He had never smoked, was teetotal and had a history of hypertension, for which he was taking ramipril.

On clinical examination, his BMI was 34 kg/m^2, but otherwise nothing remarkable was detected.

Investigations

- Haemoglobin 130 g/litre (130–180)
- Sodium 139 mmol/litre (137–144)
- Urea 3.9 mmol/litre (2.5–7.0)
- Potassium 3.8 mmol/litre (3.5–4.9)
- Bilirubin 18 micromol/litre (1–22)
- Alanine aminotransferase 55 U/litre (5–35)
- Aspartate aminotransferase 60 U/litre (1–31)
- Alkaline phosphatase 140 U/litre (45–105)
- *Helicobacter pylori* serology was positive

What is the correct next step in his management?

A Trial of proton pump inhibitor
B *Helicobacter pylori* eradication therapy
C Urgent referral for gastroscopy
D Ultrasound scan of abdomen
E Urea breath test

Question 2

A 64-year-old woman presented with worsening joint pains. She had rheumatoid arthritis and was taking an anti-tumour necrosis factor biological agent and methotrexate. She had a history of hypertension and a duodenal ulcer caused by *Helicobacter pylori* and thought that she had undergone *H. pylori* eradication 10 years previously. She was asking if it was safe to take non-steroidal anti-inflammatory drugs (NSAIDs) to help her pain.

What is the best response?

A Allow NSAIDS but with co-prescription of a protein pump inhibitor (PPI)
B Check for successful *H. pylori* eradication and then allow NSAIDs with a PPI
C Prescribe a cyclooxygenase (COX)-2 inhibitor
D Avoid NSAIDs at all costs
E Allow NSAIDs with ranitidine

Question 3

A 72-year-old man presented with a persistent benign-looking gastric ulcer despite two courses of *Helicobacter pylori* eradication. He had a 40 pack–year smoking history, was a non-drinker and had no history of non-steroidal anti-inflammatory drug (NSAID)/aspirin use.

Investigation

- Biopsies from the ulcer edge showed chronic inflammation with *H. pylori* organisms and no evidence of dysplasia or malignancy

What is the best management?

A Prescribe bismuth-based quadruple therapy
B Refer for consideration of distal gastrectomy
C Repeat gastroscopy and biopsy of the ulcer edges
D Prescribe an oral proton pump inhibitory therapy (PPI) and refer him to smoking cessation services
E Repeat the gastroscopy, and culture specimens for *H. pylori* drug sensitivity