Helicobacter pylori infection and peptic ulcers

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Abstract

Nearly all peptic ulcers are caused either by *Helicobacter pylori* infection or by 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 bleeding. Only about 15% of *H. pylori*-infected people develop an ulcer in their lifetime; virulence of the *H. pylori* strain, host genetics and environment (particularly smoking) determine the risk. NSAID ulcers are largely the result of suppression of gastro-protective cyclo-oxygenase 1 (COX-1). The presence and type of ulcers cannot be predicted accurately from symptoms and the differential diagnosis is wide. Older dyspeptic patients and those with 'alarm' symptoms or signs require endoscopy to exclude upper gastrointestinal 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* treatment induces healing and prevents relapse. NSAID ulcers are treated by NSAID withdrawal and a PPI course; NSAID naïve users requiring ongoing treatment who are positive for *H. pylori* will need eradication, whereas others should be prescribed concomitant PPI or a selective COX-2 inhibitor. Treatment of functional dyspepsia is difficult and requires a multi-factorial approach.

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

What's new?

- In developing countries, *H. pylori* is becoming less common so, in some, NSAIDs and aspirin have become the most common causes of peptic ulceration
- Most guidelines suggest that younger patients (in the UK aged <55 years) with dyspepsia and no alarm signals should be managed either with non-invasive *H. pylori* testing and treatment if positive, or (particularly where community prevalence of *H. pylori* is <20%) with an empirical course of proton pump inhibitor (PPI)
- 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 is more convenient
- Proton pump inhibitors 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-naïve patients prior-testing and eradication of *H. pylori* is useful in reducing the risk.
- Despite their cardiovascular risks, selective COX-2 inhibitors may still have a place in occasional patients with severe NSAID-induced ulceration that persists despite PPI co-prescription or who cannot tolerate PPIs
- Domperidone should no longer be considered as a treatment option for non-ulcer dyspepsia due to concerns over cardiac safety and risk

A peptic ulcer is a breach in the gastric or duodenal mucosa down to the submucosa. Small or shallow breaches are termed 'erosions'; while sometimes insignificant, these may herald ulcers. Worldwide, the two most common causes of peptic ulceration are *Helicobacter pylori* infection and use of non-steroidal anti-inflammatory drugs (NSAIDs), which include 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 inflammation of the gastric mucosa. It is diagnosed and classified histologically because endoscopic appearances such as redness are often misleading, although magnification endoscopy can increase diagnostic accuracy. This gastritis is seldom, if ever, symptomatic, but can have important clinical sequelae in a minority of patients. These 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).

- *H. pylori* can cause either an antral-predominant gastritis (associated with increased meal-stimulated acid production), which predisposes to duodenal ulceration, or a corpus-predominant or pangastritis (associated with a 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 little inflammatory cell infiltration.
- Autoimmune gastritis is virtually confined to the corpus and is associated with anti-parietal cell and often intrinsic factor antibodies. It may result in vitamin B_{12} deficiency and pernicious anaemia, and, like *H. pylori* infection but

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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 ulcer)
- Idiopathic eosinophilic and lymphocytic gastritis
- Duodenal Crohn's disease
- Coeliac axis stenosis
- Hepatic artery chemotherapy
- Prescribed medicines including bisphosphonates, sirolimus, mycophenolate, corticosteroids (when combined with NSAIDs)
- Recreational drugs including crack cocaine

Table 1

unlike aspirin and NSAIDs, it is a risk factor for gastric adenocarcinoma.

H. pylori was first described by Barry Marshall and Robin Warren in 1983[1] 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.

Classification of gastritis

Type of gastritis	Aetiology
Non-atrophic	*Helicobacter pylori*
Atrophic	
• Autoimmune	Autoimmunity
• Multifocal atrophic	*H. pylori*, environmental insults
Special forms	
• Chemical	NSAIDs, bile?, other agents
• Radiation	Radiation injury
• Lymphocytic	Gluten (coeliac disease), *H. pylori*, idiopathic, drugs
• Non-infectious granulomatous	Crohn's disease, sarcoidosis, Wegener's granulomatosis and other vasculitides, foreign substances, idiopathic
• Eosinophilic	Food sensitivity?, other allergies
• Other infections	Bacteria other than *H. pylori* (other gastric helicobacters, mycobacteria and syphilis), viruses (cytomegalovirus), fungi (*Candida* spp., *Histoplasma capsulatum*, *Mucoraceae*)

Table 2

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 following initial infection, which usually occurs in childhood, it is able to persist lifelong 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 by far the most important cause of peptic ulcers and gastric adenocarcinoma. Its prevalence varies from more than 80% in developing countries to between 6% and 25% in developed countries, where prevalence is steadily falling owing to improved hygiene and sanitation, and possibly also to increased antibiotic use.

Epidemiology

Before the twentieth century, peptic ulcers were rare. Gastric ulcers and later duodenal ulcers were increasingly described in the late nineteenth century, the incidence of duodenal ulcers increasing progressively and reaching a peak in the 1950s. The cause of this rise 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, following a decrease in the prevalence of *H. pylori*. Hospitalization rates, too, have steadily declined with mortality resulting from peptic ulcers showing a significant reduction in the United States from 1993 to 2003.[3] *H. pylori* infection is present in about 25% of adults in most developed countries, and in a much smaller proportion in some.[4] It is 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 twentieth 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. *H. pylori* is acquired by human contact, usually by oro-oral rather than faeco-oral transmission. In developed countries it is usually acquired from the primary care-giver; in developing countries it is more often acquired from other children outside the family group. 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.[5] Concomitant use of gastro-protective agents (mainly PPIs and to some extent H_2-receptor antagonists) reduces the risk, although sub-optimal adherence to such treatment is also associated with an increased risk of upper gastrointestinal (GI) events.

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