Peptic ulcer disease

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Peptic ulcer disease had a tremendous effect on morbidity and mortality until the last decades of the 20th century, when epidemiological trends started to point to an impressive fall in its incidence. Two important developments are associated with the decrease in rates of peptic ulcer disease: the discovery of effective and potent acid suppressants, and of *Helicobacter pylori*. With the discovery of *H pylori* infection, the causes, pathogenesis, and treatment of peptic ulcer disease have been rewritten. We focus on this revolution of understanding and management of peptic ulcer disease over the past 25 years. Despite substantial advances, this disease remains an important clinical problem, largely because of the increasingly widespread use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin. We discuss the role of these agents in the causes of ulcer disease and therapeutic and preventive strategies for drug-induced ulcers. The rare but increasingly problematic *H pylori*-negative NSAID-negative ulcer is also examined.

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Introduction

Peptic ulcer disease embraces both gastric and duodenal ulcers and has been a major threat to the world's population over the past two centuries, with a high morbidity and substantial mortality. Epidemiological data for this disease and its complications have shown striking geographical variations in incidence and prevalence. Development of ulcer disease and death from it has been associated with the birth of urbanisation and was interpreted as a birth-cohort event with the peak of disease in those born during the late 19th century.[1,2] Our understanding of the disease changed greatly with the discovery of *Campylobacter pyloridis* (renamed *Helicobacter pylori* in 1989 because of a revised taxonomic classification) in 1982 by Warren and Marshall.[3,4] This discovery switched the notion from an acid-driven disease to an infectious disease, opening a huge area for intensive research that resulted in the reconciliation of previously suggested mechanisms of pathogenesis.

The fall of the acid dogma in peptic ulcer disease, which had found its undisputed acceptance during and after the introduction of histamine H_2-receptor antagonists, led to the present therapeutic principle. Maintenance acid-suppressive therapy for duodenal ulcer, which followed decades of dominance of surgical interventions (subtotal gastric resections, several forms of vagotomy), was replaced with a short-term antibiotic regimen targeting eradication of *H pylori* infection.[5,6] *H pylori* eradication as cure of peptic ulcer received its full recognition when the Nobel Prize for Medicine and Physiology was awarded to Warren and Marshall in 2005. This recognition has not, however, closed the chapter on peptic ulcers. The management of ulcer disease and its complications remains a clinical challenge. Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin are an increasingly important cause of ulcers and their complications even in *H pylori*-negative patients.[7,8] Other rare causes of ulcer disease in the absence of *H pylori*, NSAIDs, and aspirin also exist.

Search strategy and selection criteria

Because of the complexity of the topic and change in dogma after *H pylori* discovery, reference search pre-1990 was mainly through book chapters, monographs, and review articles, including selective search of original publications. For 1990–2008, the PubMed database was used to retrieve key articles on various and specific aspects of peptic ulcer disease. Search terms were "ulcer", "peptic ulcer", "gastric ulcer", "duodenal ulcer", "epidemiology", "ulcer pathogenesis", "*H pylori*", "*H pylori* eradication", "non-steroidal anti-inflammatory drugs", "aspirin", "cyclo-oxygenase-2", "ulcer complications", "bleeding", "proton-pump inhibitor", "misoprostol", "histamine-2-receptor antagonist", and "myocardial infarction". Selection of articles was based on individual and personal experience of the investigators with the intention to cover all major aspects of this specialty; only English language publications were included.

Clinical manifestations and diagnosis

The predominant symptom of uncomplicated peptic ulcer is epigastric pain, which can be accompanied by other dyspeptic symptoms such as fullness, bloating, early satiety, and nausea. In patients with duodenal ulcer, epigastric pain occurs typically during the fasting state or even during the night and is usually relieved by food intake or acid-neutralising agents. Roughly a third of these patients also have heartburn, mostly without erosive oesophagitis.[9] Chronic ulcers can be asymptomatic.[10] In particular, this absence of symptoms is seen in NSAID-induced ulcers, for which upper gastrointestinal bleeding or perforation might be the first clinical manifestation of disease. The most frequent and severe complication of peptic ulcers is bleeding, which is reported in 50–170 per 100 000, with the highest risk in people aged older than 60 years.[11–13] Perforation is less frequent than is bleeding, with an incidence of around seven to ten per 100 000.[14,15] Penetration of retroperitoneal organs is characterised by constant severe pain but fortunately is rare.[15] Gastric outlet obstruction due to ulcer-induced fibrosis is also rare, and should raise suspicion of underlying malignant disease.[15]

A peptic ulcer is diagnosed at endoscopy when there is a mucosal break of diameter 5 mm or larger, covered with fibrin; a mucosal break smaller than 5 mm is called an erosion. The 5 mm criterion is arbitrary, but is used in clinical trials. The extent to which this criterion relates to the pathological criterion of penetration of the muscularis mucosa is unclear. Peptic ulcers can be single or many. The typical location of the duodenal ulcer is in the bulb, where gastric contents enter the small intestine. The site of predilection for gastric ulcers is the angulus of the lesser curvature; however, they can occur at any location from the pylorus to the cardia. Occasionally, kissing ulcers are seen located face to face on the anterior and posterior walls of the duodenal bulb. If ulceration is seen in the more distal duodenum, then underlying Crohn's disease, ischaemia, or the rare Zollinger-Ellison syndrome should be considered. On endoscopic diagnosis of peptic ulcer, biopsy samples of the antral and body or fundus mucosa should be taken for detection of *H pylori* infection by rapid urease and histological tests.

In many developed countries, ulcer-like symptoms in patients aged up to 55 years are generally not investigated by endoscopic examination but by testing non-invasively for *H pylori* (^{13}C-urea breath test [UBT], stool antigen test) and treated with *H pylori* eradication if positive.[16,17] The rationale for this test-and-treat strategy is that symptoms in a proportion of patients will be due to underlying ulcer disease that will be cured by *H pylori* treatment. Moreover, malignant disease is rare in young people and in the absence of alarm symptoms such as loss of appetite, weight loss, anaemia, and vomiting.

***Panel 1:* Aetiological classification of peptic ulcers**

- Positive for *Helicobacter pylori* infection
- Drug (ie, non-steroidal anti-inflammatory drug [NSAID])-induced
- *H pylori* and NSAIDs positive
- *H pylori* and NSAIDs negative*
- Acid hypersecretory state (ie, Zollinger-Ellison syndrome)
- Anastomosis ulcer after subtotal gastric resection
- Tumours (ie, cancer, lymphoma)
- Rare specific causes
  - Crohn's disease of the stomach or duodenum
  - Eosinophilic gastroduodenitis
  - Systemic mastocytosis
  - Radiation damage
  - Viral infections (eg, cytomegalovirus or herpes simplex infection, in particular in immunocompromised patients)
  - Colonisation of stomach with *H heilmanii*
  - Severe systemic disease
- Cameron ulcer (gastric ulcer where a hiatus hernia passes through the diaphragmatic hiatus)
- True idiopathic ulcer

*Requires search for other specific causes.

Pathogenesis

Panel 1 shows an aetiological classification of peptic ulcers. The complex and multifactorial pathogenesis of peptic ulcer has been studied over several decades, and results from an imbalance of aggressive gastric luminal factors acid and pepsin and defensive mucosal barrier function. Several environmental and host factors contribute to ulcer formation by increasing gastric acid secretion or weakening the mucosal barrier.[18–20] Among environmental factors, smoking, excessive alcohol use, and drug use are most often quoted but none of them, apart from NSAID use, were identified as an individual ulcerogenic agent. Emotional stress and psychosocial factors are frequently identified as important contributors to ulcer pathogenesis.[21–23] Although stress cannot be neglected as a contributing factor, convincing evidence for it being the sole cause of duodenal ulcer is scarce.[24–26] A good example of stress as a contributory factor was the rise in bleeding gastric ulcers in elderly people after a severe earthquake in Japan.[27] The definition of stress ulcer should be restricted to bleeding ulcers in the context of severe organic illness, such as cerebral trauma, burning, and sepsis with multiorgan failure in intensive care units.[28,29]

H pylori-positive ulcer

Epidemiological studies revealed a very strong association between *H pylori* infection and duodenal and gastric ulcers. The ultimate proof of *H pylori* as the main cause of ulcer disease was the permanent cure of peptic ulcers by eradication of the infection.[30,31] More than 50% of the world's population has a chronic *H pylori* infection of the gastric mucosa, yet only 5–10% of those infected develop ulcers. Factors determining whether the infection will produce disease are the pattern of histological gastritis induced; changes in homeostasis of gastric hormones and acid secretion; gastric metaplasia in the duodenum; interaction of *H pylori* with the mucosal barrier and immunopathogenesis; ulcerogenic strains; and genetic factors (figure 1).

H pylori colonises the entire gastric epithelium, from the prepyloric antrum to the cardia. Clinical outcomes are dependent on the pattern of chronic mucosal inflammation induced.[32,33] In patients with duodenal ulcer, density of infection and severity of inflammation are greatest in the distal antral region with sparing of the acid-secreting body mucosa. After *H pylori* eradication, gastric mucosal changes are usually fully reversible. In gastric ulcer, inflammation affects the body and antral mucosa to a similar degree, although it varies dependent on ulcer location.[34] Unlike in duodenal ulcer, acid secretion in gastric ulcer can be decreased because of the more severe involvement of acid-secreting body mucosa. However, a crucial amount of acid production is always conserved.

In antrum-predominant non-atrophic *H pylori* gastritis both basal and stimulated gastric acid output is increased. This effect is most pronounced in patients with duodenal

ulcer.[35] Patients with duodenal ulcer and *H pylori* infection produce more acid than do infected people without ulcers in response to the same stimulation with gastrin. This finding is attributable to an impaired acid response to gastrin in infected people without ulcers, which is probably caused by the intense inflammation of their acid-secreting mucosa.[36] Patients with duodenal ulcers also have more acid-secreting parietal cells than do people without ulcers, and produce more acid in response to maximum gastrin stimulation.[36] Premorbid acid-secreting status might be a key factor determining the pattern of *H pylori* gastritis developed, and thus likelihood of development of duodenal ulceration. This suggestion arises from evidence that reduction of gastric acid secretion with proton-pump inhibitor (PPI) therapy increases the intensity of inflammation of the acid-secreting mucosa in *H pylori*-infected patients.[37] A high constitutive acid secretory capacity might therefore promote development of antral-predominant body-sparing gastritis, and thus duodenal ulceration.

H pylori infection impairs negative feedback regulation of gastrin release and thus acid secretion.[38,39] A low antral pH stimulates release of somatostatin from D cells in the antral glands, and this somatostatin exerts paracrine inhibitory control of gastrin release from adjacent G cells. *H pylori* has very high urease activity producing ammonia to protect the organism from its acidic gastric environment. Production of alkaline ammonia by bacteria on the surface epithelium and in the glands of the antrum prevents D cells in the glands from sensing the true level of acidity, leading to inappropriate release of somatostatin and an increase in gastrin, and consequently excess acid secretion.[40–42] The trophic effect of hypergastrinaemia induced by *H pylori* also induces hyperplasia of the enterochromaffin-like and acid-secreting parietal cells.

Neural pathways are also affected by *H pylori* (figure 2), with functional disruption of antral-fundic neural connections that downregulate acid production.[42] Impaired inhibitory neural control, in association with hypergastrinaemia, leads to further increase of acid output in patients with duodenal ulcers (figure 2).[43] Resolution of hypergastrinaemia in these patients after *H pylori* eradication is a common event and occurs much faster than does resolution of acid hypersecretion.[35,43,44]

Gastric acid hypersecretion and, more specifically, acid overload in the duodenum leads to development of metaplasia in the duodenal bulb.[45] Metaplasia is a prerequisite for *H pylori* colonisation of duodenal epithelium, because colonisation is specific and exclusive to gastric epithelial cells. After bacterial colonisation of islands of duodenal gastric metaplasia, the inflamed duodenal mucosa becomes more susceptible to peptic acid attack and ulceration (figure 1). After *H pylori* eradication, gastric metaplasia does not change substantially in prevalence and extent,[46] but with elimination of infection risk of ulcer recurrence is abolished.

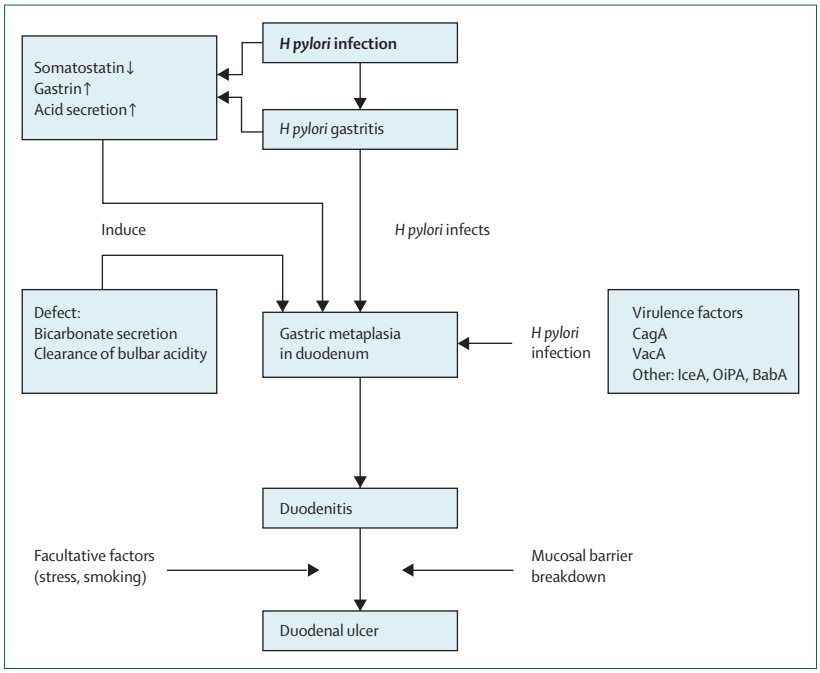

Figure 1: **Pathogenesis of *Helicobacter pylori*-positive duodenal ulcer**

H pylori causes an inflammatory response in gastric mucosa, with induction of epithelium-derived cytokines, predominantly interleukin 8 and interleukin 1β.[47,48] Influx of neutrophils and macrophages into the gastric mucosa with release of lysosomal enzymes, leukotrienes, and reactive oxygen species impairs mucosal defence and drives the immunopathogenetic process of ulcerogenesis.[49,50] T and B lymphocytes activated by bacterial antigens and proinflammatory cytokines regulate the local and systemic immune response with release of further cytokines (interleukins 1, 2, 6, 10, tumour necrosis factor α), and antibodies.[49,50] The type of T-cell response is crucial, with more mucosal damage resulting from a T-helper-1-predominant response, whereas a high regulatory T-cell response with interleukin-10 release confers protection.[51] As a result of the immunopathogenetic events, additional factors with ulcerogenic potential are released, including platelet-activating factor and components of the complement pathway.[52]

H pylori isolated from patients with ulcer disease carry a high virulence. Features of increased virulence include a strong adhesive property and increased production of enzymes with toxic potential. Strains from ulcer patients might produce higher amounts of urease than do those from people without ulcers. Urease catalyses production of ammonia, which in high concentrations is followed by formation of toxic complexes such as NH_4Cl.[53] Bacterial phospholipases A and C impair the phospholipid-rich layer in the mucosa that maintains mucosal hydrophobicity and integrity of the gastric epithelial barrier.[54–56]

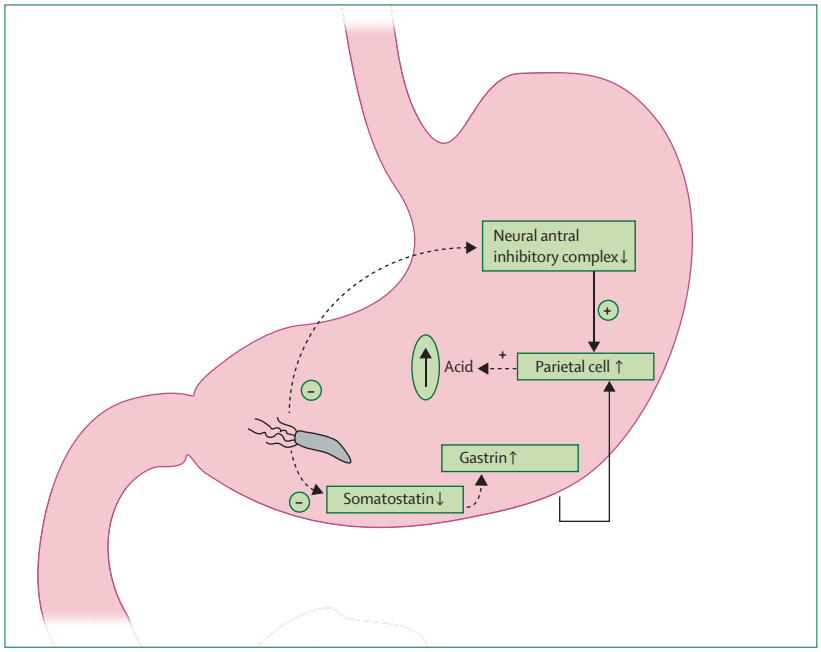

Figure 2: **Acid secretion in antrum-predominant *Helicobacter pylori* infection-associated gastritis***
*Phenotype typically seen in patients with duodenal ulcer.

Specific *H pylori* genotypes are associated with severe morbidity. The most prevalent *H pylori* genotypes in patients with peptic ulcerations are vacA-positive and cagA-positive.[57,58] *H pylori*-derived vacuolating cytotoxin (VacA), an 87-kDa protein, causes vacuolar degeneration in cultured gastric-cell preparations and gastric ulceration in laboratory animals. Although present in all *H pylori* strains, the *vacA* gene, dependent on its allelic form, is expressed in only 60%.[59] The cytotoxin-associated gene A (*cagA*), restricted to cytotoxin-producing strains of *H pylori*, is within an island of 31 genes defined as CagA pathogenicity island. *CagA* encodes a 120–160 kDa immunodominant protein that is a marker of increased virulence and enhances the local inflammatory response.[60–62] A series of other virulence genes with a higher prevalence in ulcer disease, such as the adhesion protein BabA[63] and the outer membrane inflammatory protein OipA,[64] are likely to play a rather modest part in pathogenesis.

A genetic predisposition to acquire *H pylori* has been shown in twins, with an increased affinity in monozygotes versus dizygotes.[65] Results of earlier studies suggested that people with blood group O carry a higher risk for ulcer disease than do those with other blood groups.[66] *H pylori* adhesion to gastric mucosa is increased in patients positive for Lewis b antigens, which are expressed on blood and gastric epithelial cells.[67] The pathogenetic importance of these findings is controversial, because the presence of these antigens is believed by some to contribute to more severe mucosal damage through increased adhesion, whereas others suggest that binding of *H pylori* to these antigens would help to eliminate *H pylori* by shedding of the surface gastric epithelial cells carrying the bacteria. Other ulcer-promoting factors have been proposed, for example NOD1 polymorphisms,[68] whereas interleukin-1β polymorphisms[69] and TLR4-gene polymorphisms[68] are negatively correlated with duodenal ulcer. Japanese working groups have reported that people with HLA type DQA 1301 have an increased prevalence of ulcer disease[70] and that the polymorphism of interleukin 8-251A/T increases risk of gastric ulcer and gastric cancer.[71]

H pylori–host interactions in ulcer pathogenesis are complex and aggravated by environmental risk factors. Pathogenesis of duodenal ulcer is heavily acid driven with immunopathogenetic components, whereas in gastric ulcer the immunopathogenetic response is likely to be the dominant aspect. *H pylori* eradication cures both gastric and duodenal ulcer and prevents relapses, which is lasting.[30,31,72,73] Additionally, healing is accelerated if antibiotics are given in addition to acid suppressants.[73,74] Finally, eradication prevents recurrence of ulcer bleeding and is better than maintenance acid-inhibitory therapy.[75–77] These findings led to the 1994 National Institutes of Health consensus statement, which said that antibiotic treatment in addition to antisecretory therapy is needed in all patients with *H pylori*-positive ulcers.[5] This statement was implemented in all subsequent guideline recommendations for therapy of peptic ulcer disease.[6]

NSAID-induced ulcer

Topical injury by ion trapping[78] and reduction of mucus gel hydrophobicity[79] was once thought to be an important mechanism of NSAID-induced gastric damage. Later, NSAIDs were shown to damage the stomach mainly by suppression of gastric prostaglandin synthesis.[80] The discovery of two isoforms of cyclo-oxygenase (COX), COX-1 and COX-2, sparked an enormous drive by the pharmaceutical industry to develop COX-2-selective NSAIDs as gastric-sparing anti-inflammatory analgesics. Now, good evidence exists that selective inhibition of COX-2 reduces but does not eliminate risk of gastroduodenal ulcers and their complications.[81]

Work in animals has shown that neutrophil adherence to gastric microcirculation plays a crucial part in initiation of NSAID injury.[82] Neutrophil adherence damages the mucosa by liberating oxygen free radicals, releasing proteases, and obstructing capillary blood flow. Inhibition of neutrophil adherence alleviates NSAID-induced damage in animal models.[82] Attention has focused on the role of nitric oxide (NO) and hydrogen sulphide (H_2S), in maintenance of gastric mucosal integrity. NO and H_2S increase mucosal blood flow, stimulate mucus secretion, and inhibit neutrophil adherence.[82] NO-releasing and H_2S-releasing derivatives of NSAIDs induce much less gastric damage than do their parent drugs.[83] Unlike animal ulcer models,

however, NSAID gastropathy in man is characterised by an absence of inflammatory cells unless *H pylori* infection is present. Whether neutrophils initiate NSAID injury in man is unknown.

Acid suppression has been the mainstay of management of NSAID-associated ulcer disease. Gastric acid probably exacerbates NSAID injury by converting superficial mucosal lesions to produce deeper injury,[84] interfering with platelet aggregation,[85] and impairing ulcer healing.[86] Patients taking NSAIDs have about a four-fold increase in risk of ulcer complications such as bleeding compared with non-users. Several risk factors have been identified in these patients, such as history of ulcer or ulcer complications, old age, comorbidities, use of high-dose NSAIDs, concomitant use of corticosteroids, aspirin, or anticoagulants, and *H pylori* infection.[87–90]

A history of ulcer complications is the most important predictor of future ulcer complications associated with NSAID use.[88] How past history increases risk is unclear. Indirect evidence exists that ulcers tend to recur at previous sites,[91,92] suggesting that local factors determining mucosal defence might play an important part in ulcerogenesis. Contrary to general belief, use of corticosteroids per se is not ulcerogenic.[93] However, both corticosteroids and anticoagulants substantially increase risk of ulcer bleeding when used concomitantly with NSAIDS.[88,93,94] Anticoagulants probably provoke bleeding from ulcers induced by NSAIDs in addition to causing generalised mucosal bleeding.

Does any interaction exist between *H pylori* and NSAIDs? There are data to suggest that *H pylori* increases, have no effect on, or decrease ulcer risk in NSAID users. Two systematic reviews have shown that *H pylori* infection substantially increases risk of peptic ulcer and ulcer bleeding in chronic NSAID users.[89,90] In one study, risk of ulcer bleeding was increased by a factor of 1·79 with *H pylori* infection, by 4·85 with NSAID usage, and by 6·13 in the presence of both NSAID use and *H pylori* infection.[90] In patients who are about to start NSAIDs, eradication of *H pylori* substantially reduces subsequent risk of endoscopic and complicated ulcers.[95,96] Two systematic reviews have shown that *H pylori* eradication was more effective than was placebo in primary prevention of peptic ulcers in regular NSAID users (relative risk 0·35, 95% CI 0·20–0·61).[97,98] Additionally, no difference is reported between *H pylori* eradication and co-therapy with a PPI in primary prevention of ulcers in regular NSAID users with average gastrointestinal risk.[99] However, eradication of *H pylori* alone is not sufficient to prevent ulcer bleeding in NSAID users with high gastrointestinal risk, such as a history of ulcer bleeding.[100]

Whether dyspepsia is a risk factor for ulcers in NSAID users is controversial.[88,94] However, in patients with a past history of ulcer bleeding, those who had breakthrough dyspepsia while on a COX-2 inhibitor or prophylaxis with a PPI had a significantly higher likelihood of recurrent ulcer than did those who remained asymptomatic (hazard ratio 5·3, 95% CI 2·6–10·8).[101] Thus, high-risk patients who develop breakthrough dyspepsia should have treatment withheld and undergo endoscopic assessment.

Use of low-dose aspirin increases risk of ulcer bleeding by two-fold to three-fold compared with risk in non-users.[102,103] Even use of very low-dose aspirin in people with low gastrointestinal risk is not risk free.[104] Growing evidence suggests that low-dose aspirin is not the same as non-aspirin NSAIDs in several important aspects. First, data from a large-scale randomised trial suggested that endoscopic ulcer is not a good predictor for upper gastrointestinal bleeding with low-dose aspirin.[105] The antiplatelet action of low-dose aspirin might be more important than its ulcerogenic effect in provoking upper gastrointestinal bleeding. Second, increasing age per se is not a risk factor for upper gastrointestinal bleeding with low-dose aspirin.[106] Third, research has consistently shown that *H pylori* infection is a risk factor for ulcer bleeding with low-dose aspirin.[107] In our opinion, low-dose aspirin may provoke bleeding from pre-existing *H pylori* ulcers. Eradication of *H pylori* heals ulcers and therefore reduces the risk of recurrent ulcer bleeding with low-dose aspirin.[108]

Management

Since Karl Schwarz's[109] dictum of no acid, no ulcer, development of medical therapies has targeted gastric acid secretion and mucosal defence mechanisms. Many drugs have been used to treat ulcers, but few early treatments stood the test of time (table 1). The most successful classes of drugs were those inhibiting gastric acid secretion. H_2-receptor antagonists revolutionised treatment of peptic ulcer, healing ulcers and keeping them in remission when given as maintenance therapy.[110,111] They were gradually replaced with the more potent class of acid-inhibitory drugs, the PPIs, which became available in 1989. PPIs selectively block the H^+K^+ ATPase of the parietal cell.[112] On the basis that speed of ulcer healing is associated with degree of acid suppression, PPIs became the hallmark in ulcer therapy. However, after the healing phase ulcers were usually seen to recur, and for years standard practice was to keep patients on maintenance acid suppression until the revolutionary introduction of *H pylori* eradication therapy.

A second group of drugs is directed at reinforcement of the mucosal barrier, and has found its major application in protection against NSAIDs and aspirin. Misoprostol, a prostaglandin analogue, has been the most widely used but its application is limited by abdominal side-effects, especially at higher doses.[113] Sucralfate and bismuth salts also promote ulcer healing by improving mucosal repair.[110] Sucralfate might also act partly by reducing acid secretion and suppressing *H pylori* infection.[114] Bismuth salts with some intrinsic anti-*H pylori* activity are used in ulcer therapy only in combination with antibiotics.[110] Cytoprotective drugs have been outdated by more

	Mechanisms	Use
H2-receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine, roxatidine)	Acid inhibition	*H pylori*-negative peptic ulcer; replaced by PPI because of inferiority in acid suppression
PPI (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole)	Most potent acid inhibition	Standard treatment for all *H pylori*-negative peptic ulcers; prevention of NSAID or aspirin ulcers; essential component in eradication regimen; given intravenously in bleeding ulcers
Prostaglandin analogues* (misoprostol)	Increase mucosal resistance; weak acid inhibition	*H pylori*-negative gastric ulcer; prevention of NSAID ulcers
H pylori eradication regimens (PPI plus two antibiotics)	Cure of *H pylori* infection	Standard therapy in all *H pylori*-positive ulcers
Bismuth salts (subcitrate, subsalicylate)	Weak antibacterial effect; increase of mucosal prostaglandin synthesis	In quadruple therapy for *H pylori* eradication

Several mucosal protectives used in some countries (ie, sucralfate, rebamipide, and others) do not have sufficient trial documentation to be included in the efficacy comparison with the listed standard therapies. PPI=proton-pump inhibitor. NSAID=non-steroidal anti-inflammatory drug. *Contraindicated in pregnancy.

Table 1: **Classes of drugs with proven effect on healing of peptic ulcer**

effective therapies. Current ulcer therapy consists of *H pylori* eradication in *H pylori*-positive peptic ulcer and PPI for healing and preventing peptic ulcers induced by gastrotoxic drugs. A small role exists for drugs enhancing mucosal resistance.

Treatment for *H pylori*-positive ulcer

Treatment for *H pylori*-associated ulcer disease is mainly directed at eradication of infection. Eradication is usually achieved with a combination of acid-inhibiting therapy and antibiotics. Antibacterial therapy alone does result in healing, but the process is accelerated by addition of acid suppressants (ie, PPIs).[74] The Maastricht Consensus Report provides recommendations on management of *H pylori* infection (panel 2).[6]

H pylori eradication is equally effective in both duodenal and gastric ulcers.[73,115] In duodenal ulcer, testing by non-invasive methods (^{13}C-UBT, stool antigen testing) is a validated surrogate marker to confirm healing.[6] However, in gastric ulcer, healing should be confirmed endoscopically and biopsies are mandatory to exclude malignant disease, even when the ulcer appears healed. For uncomplicated duodenal ulcer a 7–14 day eradication therapy does not need to be followed by PPIs, whereas for gastric ulcer PPIs should be continued beyond the eradication phase for 4–8 weeks.[116] If complications arise (ie, bleeding), PPI therapy should be continued until healing is confirmed endoscopically. In this circumstance, confirmation of eradication relies on histological examination of biopsy samples taken from both antral and body regions of the stomach, because PPI therapy can produce false-positive urease test results.

Eradication rates depend on several factors: (i) drug regimen; (ii) resistance rate to the antimicrobiotic used; (iii) compliance with the drug; (iv) duration of therapy; and (v) genetic variations in drug-metabolising enzymes. Two antimicrobials often used in eradication regimens are clarithromycin and metronidazole. *H pylori* can be resistant to either of these drugs, causing reduced eradication rates. Checking for antimicrobial sensitivity before treatment of *H pylori* is not routine. However, if a patient has previous exposure to these antimicrobials or lives in a region where these drugs are frequently prescribed, they are more likely to have a resistant strain and alternative antimicrobials should be given. Monitoring of eradication rates is important to detect emergence of resistant strains and alert to the need to modify the regimen. One should aim to maintain first-line eradication rates greater than 80%.[6]

The duration of eradication therapy remains controversial. In Europe, 1-week triple regimens are used, whereas US guidelines recommend 10 or even 14 days of therapy.[117] A meta-analysis showed that increasing the duration of triple therapy from 7 days to 10 days increased the eradication rate by 4% and from 7 days to 14 days by 5%.[118] Although these differences were statistically significant, the investigators questioned their clinical significance.[118] Quadruple therapies—PPI, tetracycline, metronidazole, and a bismuth salt—are alternative first-line therapies in areas of high prevalence of antibiotic resistance, and achieve excellent eradication rates as first-line treatment.[6,119] A first-line 10-day sequential therapy was better than was standard triple therapy in several studies done in Italy.[120] An intention-to-treat result of 84% for sequential therapy in one study from Spain[121] suggests that the greater efficacy achieved with this promising therapy than with triple therapies should be tested further before general recommendation.

The most effective treatment regimens fail in about 10–20% of patients. Bismuth-based quadruple therapy is the main option for second-line therapy if these compounds were not used as first-line treatment, with eradication rates of 57–95%.[122] However, since bismuth is not available in some countries because of putative toxic effects, triple therapies of various combinations have been tested as second-line options. PPI combined with amoxicillin and metronidazole are recommended as

Panel 2: *Helicobacter pylori* eradication regimens

First-line options (7–14 days)

- In populations with less than 15–20% clarithromycin resistance and greater than 40% metronidazole resistance: proton-pump inhibitor (PPI) standard dose, clarithromycin 2×500 mg, and amoxicillin 2×1000 mg, all given twice a day
- Less than 15–20% clarithromycin resistance and less than 40% metronidazole resistance: PPI standard dose, clarithromycin 500 mg, and metronidazole 400 mg or tinidazole 500 mg, all given twice a day
- In areas with high clarithromycin and metronidazole resistance: bismuth-containing quadruple therapy

Second-line option (10–14 days)

- Bismuth-containing quadruple therapy
- PPI plus metronidazole and amoxicillin, if clarithromycin was used in first-line treatment (in Latin America and China, furazolidone 2–4×100 mg is often preferred over metronidazole)

Rescue therapies (10–14 days)

- PPI twice a day plus amoxicillin 2×1000 mg with either levofloxacin 2×250 (500) mg, or with rifabutin 2×150 mg

second line if PPI, clarithromycin, and amoxicillin were used as first line.[6] Another combination with few data but a high eradication rate (91%) is PPI, tetracycline, and metronidazole.[123] Clarithromycin should be avoided in second line unless resistance tests confirm that the *H pylori* strain is susceptible.[124]

Patients who are not cured with two consecutive treatments, including clarithromycin and metronidazole, will have at least single and usually double resistance. No standard third-line therapy exists, and European guidelines recommend culture and susceptibility testing in these patients to select an eradication regimen according to microbial sensitivity to antibiotics. Classes of antibiotics that include either levofloxacin or rifabutin as a third component besides PPI and amoxicillin can be used for treatment of *H pylori* infection after failure. The eradication rate of levofloxacin-containing triple salvage therapies ranges from 63% to 94%.[125,126] Rifabutin combined with a PPI and amoxicillin given for more than 7 days is well tolerated and highly effective against double-resistant *H pylori* after failure of standard triple therapy.[127,128] However, rifabutin can select resistance in mycobacteria, and should therefore be used cautiously and never on a large scale. When a high prevalence of metronidazole resistance is suspected, this drug can be replaced by furazolidone; there is no potential for cross-resistance. In clinical trials, high eradication rates have been achieved when patients tolerated these drugs.[127] Moxifloxacin combined with metronidazole and omeprazole is reported to be as effective as are omeprazole, bismuth, metronidazole, and tetracycline in patients failing standard triple therapy, but experience is limited and needs further validation.[128]

Treatment for NSAID-induced ulcer

NSAIDs, including low-dose aspirin, are the most important cause of ulcer complications in developed countries where prevalence of *H pylori* infection is falling. In patients who develop uncomplicated peptic ulcers while on NSAIDs, more than 90% of gastric or duodenal ulcers heal with 8 weeks of standard-dose H_2-receptor antagonists (eg, ranitidine 150 mg twice a day), provided that NSAIDs are discontinued.[129] However, healing of gastric ulcers will be greatly impaired if patients continue to take NSAIDs. A descriptive review of head-to-head trials suggested that PPIs might be better than a standard dose of ranitidine in healing gastric ulcers in patients receiving continuous NSAIDs.[130] However, a recent large randomised trial did not show any difference in gastric ulcer healing between groups receiving esomeprazole 40 mg (85·7%), esomeprazole 20 mg (84·8%), and ranitidine (76·3%).[131] So far, high-dose PPI has not proved better than standard-dose PPI in healing gastric ulcers in patients receiving continuous NSAID therapy. Since *H pylori* ulcers cannot be differentiated from NSAID ulcers, testing for *H pylori* and eradication of the bacteria is essential. Current evidence suggests that *H pylori* eradication does not impair ulcer healing while patients are on NSAIDs.[132]

A systematic review of randomised trials found that double-dose H_2-receptor antagonists reduce risk of both gastric and duodenal ulcers. PPIs are better than are standard-dose H_2-receptor antagonists and misoprostol for prevention of duodenal ulcers. Misoprostol is better than standard-dose H_2-receptor antagonists in preventing gastric but not duodenal ulcers. PPIs have no advantage

	No gastrointestinal risk factors	One or two gastrointestinal risk factors	Many gastrointestinal risk factors or previous ulcer bleed
Low cardiovascular risk (low-dose aspirin not needed)	NSAID	NSAID plus PPI or misoprostol, or COX-2 inhibitor alone	COX-2 inhibitor plus PPI or misoprostol
High cardiovascular risk (low-dose aspirin needed)	Naproxen plus PPI or misoprostol	Naproxen plus PPI or misoprostol	Avoid NSAIDs and COX-2 inhibitors if possible*

NSAID=non-steroidal anti-inflammatory drug. PPI=proton-pump inhibitor. COX=cyclo-oxygenase. *Combination of low-dose aspirin, PPI or misoprostol, and naproxen or low-dose COX-2 inhibitor in selected cases (see text).

Table 2: **Recommendations on non-steroidal anti-inflammatory use according to gastrointestinal and cardiovascular risks**

over misoprostol in reducing the risk of gastric ulcers.[98] A note of caution is that effectiveness of PPIs for prevention of NSAID-associated ulcers was largely established by endoscopic and observational studies.[133–135] Only full-dose misoprostol (200 μg four times a day) prevented NSAID-associated ulcer complications in a large-scale trial.[113]

In a systematic review, COX-2 inhibitors induced significantly fewer gastroduodenal ulcers (relative risk 0·26, 95% CI 0·23–0·30), ulcer complications (relative risk 0·39, 95% CI 0·31–0·50), and treatment withdrawals due to gastrointestinal symptoms than did non-selective NSAIDs. Concomitant use of aspirin, however, negates the gastric-sparing effect of COX-2 inhibitors.[136] COX-2 inhibitors and non-selective NSAIDs both increase cardiothrombotic risk. The only probable exception is full-dose naproxen (500 mg twice daily).[137,138] The cardiovascular hazard of COX-2 inhibitors might be dose-dependent. In a pooled analysis of trials of celecoxib, there was a dose-dependent increase in cardiovascular hazard of this drug in patients with high baseline cardiovascular risk.[139] In another pooled analysis of observational studies, the excess cardiothrombotic risk associated with most NSAIDs and COX-2 inhibitors was not seen in patients receiving concomitant low-dose aspirin.[140] Large-scale, head-to-head randomised trials are underway to assess cardiothrombotic risk of NSAIDs and COX-2 inhibitors.

Because of the potential cardiovascular hazard of COX-2 inhibitors and non-selective NSAIDs, physicians should assess gastrointestinal and cardiovascular risk of individual patients before prescribing anti-inflammatory analgesics. In patients with low cardiovascular risk (absence of established or multiple risk factors for coronary artery disease), NSAIDs can be prescribed according to the number and nature of gastrointestinal risk factors (table 2). Patients with one or two gastrointestinal factors should receive a COX-2 inhibitor or an NSAID plus a PPI. This recommendation is based on randomised and observational studies that showed that a COX-2 inhibitor was similar to a non-selective NSAID plus a PPI in prevention of recurrent ulcer bleeding.[91,133] In patients with several gastrointestinal risk factors or a history of ulcer complications, neither of these treatments is adequate.[101] Combination of a PPI and a COX-2 inhibitor offers the best protection.[133,141]

Patients with high cardiovascular risk should start or continue to receive prophylactic low-dose aspirin, and full-dose naproxen is the preferred NSAID. Co-therapy with a PPI or misoprostol is recommended since naproxen plus low-dose aspirin will substantially increase risk of ulcer complications even without other gastrointestinal risk factors. Patients with high cardiovascular and gastrointestinal risk should avoid taking NSAIDs or COX-2 inhibitors. If anti-inflammatory analgesic therapy is judged necessary, the choice of therapy requires a trade-off between gastrointestinal and cardiovascular risks of individual patients. If a patient's cardiovascular risk is more serious (eg, recent myocardial infarction) than the gastrointestinal risk (eg, remote history of peptic ulcer), combination of a PPI or misoprostol, low-dose aspirin, and naproxen is preferred to keep cardiovascular toxic effects to a minumum. If gastrointestinal risk is more serious (eg, recent ulcer bleeding) than cardiovascular risk (eg, coronary heart disease well controlled with medical therapy), combination of a PPI or misoprostol, low-dose aspirin, and low-dose COX-2 inhibitor is preferred. This combination is based on the observation that the cardiovascular hazard of COX-2 inhibitors is dose dependent.[139] Furthermore, in patients receiving low-dose aspirin, COX-2 inhibitors probably carry a lower risk of gastrointestinal bleeding than do NSAIDs.[140]

For many years, the American Heart Association and the American College of Cardiology recommended the use of clopidogrel as an alternative to aspirin in patients with major gastrointestinal intolerance.[142] Whether clopidogrel has a lower risk of gastrointestinal bleeding than that of aspirin has yielded conflicting results in observational studies,[103,143] but in head-to-head randomised trials of patients with high gastroinestinal risk combination of aspirin and a PPI is better than is clopidogrel alone at prevention of ulcer bleeding.[92,144] An updated consensus report issued jointly by US cardiology and gastroenterology societies recommends co-therapy with a PPI instead of switching to clopidogrel in aspirin users with high gastrointestinal risk.[145] Additionally, the consensus recommends prophylactic PPI in patients receiving dual antiplatelet therapy. However, according to in-vitro studies some PPIs reduce the antiplatelet activity of clopidogrel by inhibiting CYP2C19, a hepatic cytochrome P450 enzyme.[146] The results of two observational studies showed a substantial increase in the risk of myocardial infarction in users of clopidogrel and PPIs.[147,148] So far, prospective data are not available. Patients with high gastrointestinal risk who receive dual antiplatelet therapy should not discontinue PPI cotherapy.

H pylori-negative NSAID-negative ulcer

Ulceration of the gastric or duodenal mucosa in the absence of *H pylori* infection and NSAID or aspirin usage is rare.[149–154] However, because of the falling prevalence of *H pylori* infection and resulting ulcers, the proportion of ulcers that are unrelated to this infection is likely to increase and several rare causes need specific attention. The most important consideration in a patient with gastric or duodenal ulcer, negative *H pylori* test, and negative NSAID or aspirin history is to check the validity of the test and history.[149] Furthermore, the sensitivity of any *H pylori* test is less than 100% and can lead to underdiagnosis of infection. Detection of *H pylori* infection is very important so that patients presenting with ulcers are not deprived of a permanent cure of this disease, especially since false-negative tests can result

from various medications frequently used by ulcer patients.[153] Before gastroduodenal ulceration is accepted to be truly negative for *H pylori*, endoscopic biopsy samples should be taken from both antrum and body of the stomach for histological examination and urease tests (including serology, urea breath test) should be done.

A detailed and careful history of the use of NSAIDs and aspirin is very important in any patient presenting with gastroduodenal ulceration in the absence of *H pylori* infection.[154] The patient might be unaware that several drugs obtainable over the counter as well as some herbal medications contain NSAIDs or aspirin. Surreptitious use of aspirin is also associated with *H pylori*-negative ulceration.[154]

Various rare conditions can be associated with ulcers of the stomach and duodenum in the absence of *H pylori* infection and NSAID or aspirin usage (panel 1).[149,155] To exclude these conditions, biopsy samples should be taken from the ulcer and surrounding mucosa even when the ulcer is situated in the duodenum. Gastric ulcers have also been documented after high-dose upper abdominal radiotherapy, although the *H pylori* status of the patients was not reported.[156] Zollinger-Ellison syndrome due to a gastrin-secreting tumour often causes diarrhoea and malabsorption and ulcers tend to be many, extending as far as the distal duodenum or proximal jejunum, and have a high risk of bleeding and perforation. Diagnosis is based on serum gastrin and its response to intravenous secretin and gastric secretion tests. Interpretation of these tests is difficult in patients taking PPI therapy, which nowadays includes most patients referred for investigation of upper gastrointestinal symptoms. Advanced imaging techniques are needed to identify the underlying gastrin-secreting tumour. High-dose PPI therapy has replaced total gastrectomy in management of the disorder and can be regarded as long term for patients in whom the tumour cannot be identified or fully resected.

Very few patients have truly idiopathic ulcers.[149] Early studies suggested that a proportion had increased gastrin and acid secretion resembling that associated with antral-predominant *H pylori* gastritis. However, some or all of these abnormalities might be related to rebound acid secretion after withdrawal of PPI therapy, which most ulcer patients receive.[157] Patients with idiopathic ulcers should be maintained on PPI therapy. Higher doses might be needed since the acid inhibitory effects of PPIs are less in patients without *H pylori* infection than in infected patients.[158] Due to their rarity, the natural history of idiopathic ulcers is unknown.

Stress ulcer, originally described by Cushing, is seen in patients with brain trauma and patients with severe burn sepsis with multiorgan failure and receiving mechanical ventilation.[28,159] Stress ulcer prophylaxis is done with either H_2-receptor antagonists or PPI, but a general consensus is not available because no clinical trial has shown a significant reduction in mortality or ultimate proof of a patient benefit.[159,160]

Contributors
Authors have worked jointly on the report.

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