

Seminar

Peptic-ulcer disease

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The discovery of *Helicobacter pylori* has greatly changed our approach to peptic ulcer disease. Bacterial, host, and environmental factors all have a role in peptic-ulcer disease. Although the prevalence of uncomplicated peptic ulcers is falling, hospital admissions for ulcer complications associated with non-steroidal anti-inflammatory drugs (NSAIDs) are rising. Evidence suggests that coprescription of NSAIDs with potent antiulcer agents and the use of highly selective cyclo-oxygenase-2 inhibitors reduce gastroduodenal ulceration. Whether these therapeutic advances will translate into clinical benefits remains to be seen. The interaction between *H pylori* and NSAIDs is one of the most controversial issues in peptic ulcer disease. With the fall in rates of *H pylori* infection, the proportion of ulcers not related to this organism and NSAIDs has risen, which will affect the management of peptic ulcer.

Introduction

For more than a century, peptic ulcer disease has been a major cause of morbidity and mortality. The pathophysiology of peptic ulcer disease has centred on an imbalance between aggressive and protective factors in the stomach. 20 years have elapsed since Marshall and Warren's discovery of the link between a bacterium called at that time *Campylobacter pylori* and peptic ulcer disease.¹ This finding was initially received with scepticism and disbelief. Now there is much evidence to support the idea that *Helicobacter pylori* infection is a prerequisite for duodenal and gastric ulcers.^{2,3} Nevertheless, much about the relation between *H pylori* and peptic ulcer remains to be learned. The rapid emergence of antimicrobial resistance has important implications for management of these ulcers.

Although hospital admissions for uncomplicated peptic ulcers in developed countries had begun to decrease by the 1950s,^{4,5} there was a striking rise in admissions for ulcer haemorrhage and perforation among elderly people.^{4,6} This increase has been attributed to the increased use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin.^{4,6} The widespread use of NSAIDs has led to an epidemic of ulcer complications. In the USA, prescribed NSAIDs account for about 25% of all reported adverse drug reactions. An estimated 16 500 patients with arthritis die from the gastrointestinal toxicity of NSAIDs every year.⁷ A better understanding of the mechanisms by which NSAIDs damage the stomach has led to the development of potent anti-ulcer agents and, recently, highly selective cyclo-oxygenase (COX)-2 inhibitors. Although there is evidence from large-scale clinical trials that these agents reduce the gastrointestinal toxicity of NSAIDs, whether these findings will translate into clinical benefits is unclear.

Researchers have previously identified several risk factors for the development of NSAID-associated ulcers.⁸ However, whether *H pylori* infection modifies the risk of

ulcer in patients taking NSAIDs has generated many conflicting data.⁹ With the reduction in frequency of uncomplicated peptic ulcers, the proportion of ulcers not related to *H pylori* or NSAIDs has increased. Recent data from the USA suggest that the association between *H pylori* and ulcer disease is not as strong as previously reported.¹⁰ The pendulum seems to swing from enthusiasm for the idea that peptic-ulcer disease is an infectious disease, to a more cautious view that *H pylori* has a causative role in peptic-ulcer disease. Ulcers not associated with *H pylori* or NSAIDs—ie, non-NSAID non-*H pylori* ulcers—have attracted considerable attention.

Pathophysiology of *H pylori* ulcers

Duodenal ulcers

Although there is much evidence to implicate *H pylori* in the development of duodenal ulcer, the underlying mechanisms remain unclear. The fact that duodenal ulcer can be effectively treated by acid suppression strongly suggests that duodenal ulcer is largely a disease of acid hypersecretion. However, the general view is that acid hypersecretion is only part of the equation in pathogenesis of duodenal ulcer; it is the imbalance between duodenal acid load and the buffering capacity of the duodenum that leads to duodenal ulcer formation.

Gastric acid secretion—Several groups have identified several gastric secretory abnormalities in patients with *H pylori*-associated duodenal ulcers. These abnormalities include increased basal and stimulated acid output,¹¹

Selection criteria and search strategy

We reviewed international publications printed in English before April, 2002. The pathophysiology of peptic ulcer is based on research work published in major scientific journals such as *Cell*, *Nature*, *Science*, *Gastroenterology*, and *Proc Natl Acad Sci USA*. The efficacy of eradication therapies is based on results of large-scale randomised trials. The recommended treatments for *H pylori* infection is based on the Maastricht-2 2000 Consensus Report. The management of NSAID-associated ulcers is based on work from The Cochrane Library and journals in medicine and gastroenterology such as *The Lancet*, *N Engl J Med*, *JAMA*, *Ann Intern Med*, *Arch Intern Med*, *Gastroenterology*, *Gut*, *Aliment Pharmacol Ther*, *Helicobacter*, and *Am J Gastroenterol*.

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reduced inhibitory effect of somatostatin on gastrin release,¹² and defective inhibition of acid secretion in response to antral distension.¹³ Levi and colleagues¹⁴ have proposed that the high ammonia concentration produced by *H pylori* urease activity prevents the antral D cells from sensing acidity in the antrum, and thus impairs the inhibitory control of gastrin release. However, direct evidence for this hypothesis is absent. Alternatively, *H pylori*-associated antral gastritis might affect D cells and G cells by stimulating the production of cytokines. Results from recent in-vitro studies show that some proinflammatory cytokines, such as interleukin-8 and TNF- α , affect the release of somatostatin and gastrin.^{15,16} The net result of these effects is an increase in acid production, and hence duodenal acid load. However, none of the gastric secretory abnormalities that we describe are specific to ulcer patients. Acid hypersecretion is present in virtually all patients with an antrum-predominant *H pylori* gastritis, so that there is a substantial overlap in acid output between patients with duodenal ulcer and controls. Thus, the abnormalities in acid secretion might be a secondary sign of *H pylori* infection rather than the sole cause of duodenal ulcer.¹⁷

Gastric metaplasia—Gastric metaplasia of the duodenal bulb develops in response to adverse stimuli, such as increased duodenal acid load, and is a prerequisite for *H pylori* colonisation. Wyatt and colleagues¹⁸ postulated that gastric metaplasia is essential for the development of duodenal ulceration. Indeed *H pylori* does colonise areas of gastric metaplasia in the duodenal bulb, leading to duodenitis and eventually to duodenal ulcer. However, there are inconsistent data for the correlation of intragastric pH with duodenal gastric metaplasia.^{19,20} Savarino and colleagues¹⁹ reported a significant correlation between acid output and gastric metaplasia, and a higher prevalence of gastric metaplasia in duodenal ulcer patients than in healthy controls. However, Hogan and coworkers²⁰ did not record any difference in the rate of gastric metaplasia between patients with duodenal ulcer and controls.

Duodenal bicarbonate secretion—Patients with duodenal ulcers have impaired bicarbonate secretion in the proximal duodenum in response to acidification of the duodenum.²¹ Unlike other pathophysiological defects, this impairment seems to be especially specific to duodenal ulcer patients. Eradication of *H pylori* will return duodenal bicarbonate secretion to normal in duodenal-ulcer patients.²⁰ The mechanism by which *H pylori* infection hampers duodenal bicarbonate secretion is not completely understood. One study in animals showed that *H pylori* inhibits bicarbonate response to acidification through interference with duodenal nitric oxide synthase activity.²²

Bacterial virulence factors—There has been much interest in a link between bacterial virulence factors and gastroduodenal diseases. Several supposed virulence factors of *H pylori* have been identified. Possession of the *cagA* gene, which encodes the immunodominant CagA protein, is one of the earliest risk factors identified.²³ Individuals infected with *cagA*+ strains have more intense inflammation in the stomach,²⁴ have higher amounts of mucosal interleukin (IL)-8,²⁵ and are more likely to have gastroduodenal ulceration than those who are CagA-.²³ The functions of CagA protein remained unknown until recently; several investigators have shown that this protein is delivered by *H pylori* into gastric epithelial cells, where it induces changes in the host cytoskeleton.^{26,27} Moreover,

Higashi and colleagues²⁸ showed that transfection of gastric epithelial cells with CagA protein results in the elongation and spread of these cells. Intuitively, the number and sequence of polymorphism of the CagA phosphorylation sites, which collectively determine the binding affinity of CagA to cytoplasmic tyrosine phosphatase SHP-2, might be important variables in the determination of the clinical outcome of infection by different *H pylori* strains.

Another widely examined virulence factor is the *vacA* gene that encodes the vacuolating cytotoxin. Allelic variants of the *vacA* gene in the middle region (m1 and m2) and the cleaved signal sequence (s1a, s1b, and s2) might account for the diverse cytotoxic activities of *H pylori*. Infection with s1a/m1 strains is associated with intense inflammation and duodenal ulceration.²⁹ However, inconsistent results were obtained when other investigators attempted to establish a correlation between *cagA* or *vacA* genotypes, or both, and duodenal ulcer in people from different geographical regions.³⁰

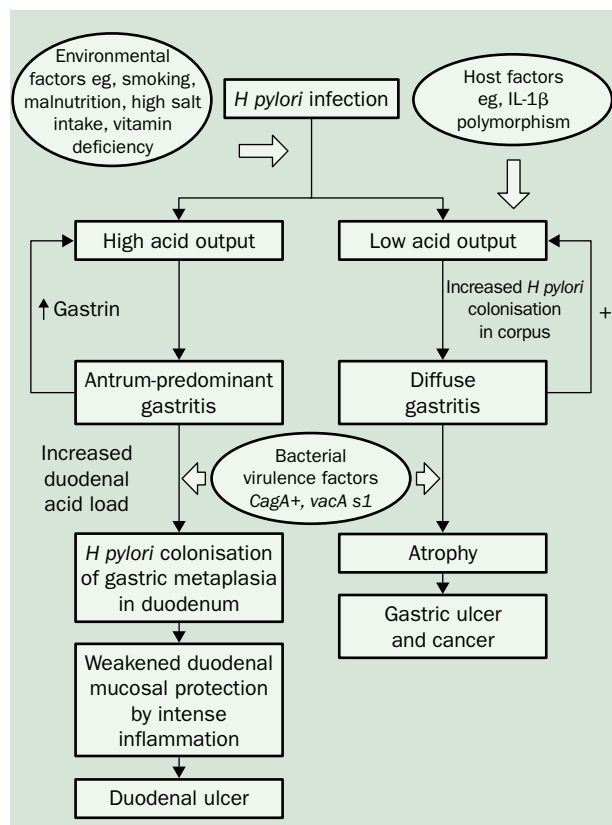
One factor that mediates the attachment of *H pylori* to gastric epithelial cells is the blood group antigen-binding adhesin (BabA) that targets human Lewis (b) surface epitopes. In a study from Germany, the presence of *babA2* genotype was significantly associated with duodenal ulcer and adenocarcinoma.³¹ However, the same association was not shown in the Japanese population.³²

Gastric ulcers

Long before the discovery of *H pylori*, patterns of gastritis associated with duodenal ulcers were known to be different from those associated with gastric ulcers.³³ Duodenal ulcer is associated with an antrum-predominant gastritis, whereas gastric ulcer is associated with a diffuse or a corpus-predominant gastritis.³⁴ This last gastric phenotype is linked with low acid output, gastric atrophy, and adenocarcinoma. This pattern is consistent with the negative association between duodenal ulcer and gastric cancer reported in epidemiological studies.³⁵

Gastric acid seems to have a key role in the distribution of *H pylori* colonisation. Logan and colleagues³⁶ showed that potent acid suppression with a proton pump inhibitor resulted in a proximal shift of *H pylori* in the stomach. This shift is accompanied by increased colonisation of *H pylori* in the corpus, leading to severe inflammation and further reduction of acid secretion.³⁷ Besides acid, environmental and host factors might also affect the distribution of *H pylori* in the stomach, and hence the pattern of gastritis. Environmental factors that affect parietal cell mass and acid secreting capacity, such as immaturity, concurrent infection, and malnutrition, are thought to be predisposing factors for the gastric-ulcer phenotype in response to *H pylori* infection.³⁸ El-Omar and colleagues³⁹ reported that the genetic make up of the host might also have a role. Polymorphism in the IL-1 β gene cluster, which has both proinflammatory and potent acid suppressive effects, is associated with an augmented cytokine response to *H pylori* infection that greatly increases the risk of gastric atrophy, gastric ulcer, and gastric cancer (figure).

Another intriguing finding for *H pylori*-associated gastric ulcers is their predilection for the antrum-corporum junction, also known as the transitional zone.⁴⁰ This area is where the antral-type mucosa abuts on the acid-secreting mucosa of the corpus, and is a region with dense colonisation of *H pylori*, maximum atrophy, and intestinal metaplasia, especially in patients with low acid output. Disruption of mucosal defence as a result of intense inflammation at the transitional zone might account for the preferential location of gastric ulcers at the antrum-corporum junction.



Proposed interactions between host, environment, and *H. pylori* infection in the development of gastric and duodenal ulcers

A two-way interaction might exist between *H. pylori* and gastric acid that determines pattern of gastritis and hence clinical outcome. Environmental factors such as smoking, malnutrition, high salt intake, and vitamin deficiency, and host factors are associated with low acid secretion status. These factors favour the colonisation of *H. pylori* in the corpus with intense inflammation and hence further reduction in acid secretion. The resultant hypochlorhydria promotes *H. pylori* colonisation, more intense corpus inflammation with subsequent development of gastric atrophy, gastric ulcer, and cancer. In patients with high gastric acid output, the gastritis will be predominantly antrum in distribution. This pattern of gastritis is associated with hypergastrinaemia and increased acid production. The resultant increase in duodenal acid load, *H. pylori* colonisation of gastric metaplasia, and loss of duodenal mucosal defence promote ulcer formation in the duodenum.

Treatment of *H. pylori* ulcers

Treatments for *H. pylori* infection have substantially evolved over the past two decades. Bismuth-based triple therapy, which consists of bismuth, metronidazole, and tetracycline, has been the conventional therapy.⁴¹ However, side-effects are common with this regimen, which often leads to poor compliance. First-line regimens that have proven efficacy consist of a proton pump inhibitor (PPI) or ranitidine bismuth citrate (RBC), and two antibiotics: amoxicillin and clarithromycin, metronidazole and clarithromycin, or amoxicillin and metronidazole, given twice daily for 7–14 days (table 1). Although data suggest that the efficacies of RBC-triple therapies and PPI-triple therapies are much the same,^{42–46} there might be a slight advantage for RBC-triple therapy in resistant *H. pylori*.⁴⁷ Meta-analysis of treatment trials is difficult to interpret because of the wide variation in prevalences of drug-resistant strains between populations. Additionally, pretreatment antimicrobial sensitivity testing was often not done.

The rapid emergence of antimicrobial resistance has substantially reduced the efficacies of the PPI-triple therapy or RBC-triple therapy. At present, up to 12% of

Trial	Drugs (mg)*	Cure rate (and 95% CI)
Lind ^{42†}	Ome 20 + Amo 1000 + Cla 500	91% (72–87%)
	Ome 20 + Met 400 + Cla 250	90% (84–95%)
Lind ^{43†}	Ome 20 + Amo 1000 + Cla 500	94% (88–97%)
	Omp 20 + Met 400 + Cla 250	87% (79–92%)
Sung ^{44‡}	RBC 400 + Amo 1000 + Cla 500	86% (79–93%)
	RBC 400 + Met 400 + Cla 500	90% (84–96%)
Misiewicz ^{45‡}	Lan 30 + Amo 1000 + Cla 250	86% (82–94%)
	Lan 30 + Cla 250 + Met 400	87% (83–95%)
Frevel ^{46†}	Pan 40 + Cla 500 + Met 500	90% (84–94%)
	Pan 40 + Amo 1000 + Cla 500	90% (84–94%)

ITT=intention to treat; Ome=omeprazole; Lan=lansoprazole; Pan=pantoprazole; RBC, ranitidine bismuth subcitrate; Amo=amoxicillin; Cla=clarithromycin; Met=metronidazole. *Twice daily dose. †Duodenal ulcer. ‡Ulcer or gastritis.

Table 1: Summary of major trials on the efficacy of 7-day PPI-triple therapies and RBC-triple therapies

H. pylori isolates in the USA are resistant to clarithromycin,⁴⁸ and this trend is still rising in most other developed countries. Resistance to clarithromycin is usually due to mutations in the ribosomal RNA of *H. pylori*.⁴⁹ On the other hand, metronidazole resistance is highly prevalent in developing countries where almost all *H. pylori* strains are resistant. In developed countries, about 10–50% of *H. pylori* strains are resistant to this drug.⁴⁸ Unlike clarithromycin resistance, metronidazole-resistant *H. pylori* shows a continuous spectrum of minimum inhibitory concentrations, which probably explains why high-dose metronidazole might overcome in-vitro resistance.⁵⁰ In view of the rising prevalence of antimicrobial resistance, post-treatment testing for *H. pylori* has been suggested by many, including in the latest Maastricht consensus.⁵¹ New data suggest that the stool antigen test is also useful in assessment of the outcome of treatment:⁵² a positive test done 7 days after completion of therapy will show that treatment has failed.

Information about salvage therapies is mostly anecdotal, or relies on data from studies that are poorly controlled. Generally, the pragmatic extension of treatment duration with PPI, amoxicillin, and clarithromycin is ineffective for clarithromycin-resistant strains. Switching between clarithromycin and metronidazole could be considered if repeated courses of PPI-triple therapies are used as second-line therapy in the absence of antimicrobial sensitivity testing.^{51,53} The Maastricht 2-2000 consensus report,⁵¹ recommends empirical quadruple therapy that includes bismuth, given for at least 1 week (panel 1). Early reports on new combinations, such as furazolidone-quadruple therapy and rifabutin-triple therapy also gave encouraging results.^{54,55}

NSAID-induced gastric injury

For the past three decades, investigators have been working on how NSAIDs damage the gastrointestinal tract. Some of these mechanisms have helped our understanding of the development of NSAIDs with lower ulcerogenic risk or prophylactic agents that reduce the toxicity of existing NSAIDs.

Topical injury

A study published in 1969 showed that aspirin induces topical injury in the dog stomach.⁵⁶ Subsequently, Fromm⁵⁷ reported that acidic NSAIDs can directly

Panel 1: Maastricht-2 2000 consensus report 51; recommended treatments for *H pylori* infection

First-line treatment	Duration
PPI twice daily or RBC 400 mg twice daily plus Clarithromycin 500 mg twice daily plus Amoxicillin 1000 mg twice daily or Metronidazole 500 mg twice daily	Minimum of 7 days
Second-line treatment	
<ul style="list-style-type: none"> Repeat PPI-triple therapy (switching between clarithromycin and metronidazole), or Quadruple therapy (PPI twice daily, bismuth subsalicylate/subcitrate 120 mg four times daily, metronidazole 500 mg thrice daily, tetracycline 500 mg four times daily) 	Minimum of 7 days
PPI (omeprazole 20 mg, esomeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg).	

damage the gastric epithelium by intracellular accumulation of these drugs in an ionised state, an occurrence known as ion trapping. However, the fact that enteric-coated formulation, pro-drugs, or systemic administration of NSAIDs did not reduce the frequency of gastroduodenal ulcerations implies a minor role for topical injury.⁵⁸ There might be other mechanisms by which NSAIDs induce topical injury. Lichtenberger and colleagues⁵⁹ showed that NSAIDs reduce the hydrophobicity of the mucus gel layer by changing the action of surface-active phospholipids. By preassociating an NSAID with zwitterionic phospholipids, the complex has proved to restore the mucus hydrophobicity and reduce acute gastric injury, without losing its effectiveness.⁵⁹

Suppression of prostaglandin synthesis

Since Vane's discovery⁶⁰ in 1971 that NSAIDs act by the inhibition of prostaglandin synthesis, there is substantial evidence that the ulcerogenic effect of an NSAID correlates well with its ability to suppress prostaglandin synthesis.^{61,62} Endogenous prostaglandins regulate mucosal blood flow, epithelial cell proliferation, epithelial restitution, mucosal immunocyte function, mucus and bicarbonate secretion, and basal acid secretion.⁶³ Inhibition of prostaglandin synthesis probably weakens the gastric mucosal defence to resist luminal irritants. Although inhibition of prostaglandin synthesis is a major mechanism in the ulcerogenic effect of NSAIDs, it is not the only factor. Mice with defective gastric prostaglandin synthesis did not spontaneously develop gastric ulceration.⁶⁴ Recent attention has focused on the role of nitric oxide (NO) in maintenance of gastric-mucosal blood flow. Like prostaglandins, NO has been shown to increase mucosal blood flow, stimulate mucus secretion, and inhibit neutrophil adherence.⁶⁵ In animals, NO-releasing NSAIDs produce less gastric damage than their parent drugs, and they even promote ulcer healing.⁶⁵

Neutrophil-mediated injury

Results from animal studies show strong evidence that neutrophil adherence to the endothelium of gastric microcirculation is critical in NSAID injury.⁶⁶ Neutrophil adherence damages the mucosa by liberating oxygen-free radicals, releasing proteases, and obstructing capillary blood flow. NSAIDs might induce the synthesis of tumour necrosis factor α (TNF- α) and leukotrienes,^{67,68}

and these inflammatory mediators stimulate neutrophil adherence by up-regulation of adhesion molecules.⁶⁹ Exogenous prostaglandins, NO, anti-TNF- α antibody, and leukotriene inhibitors block neutrophil adherence and alleviate the severity of NSAID damage in animal studies.^{67,70,71} Unlike acute ulcers in animals, NSAID gastropathy in human beings is characterised by a lack of inflammatory cells unless *H pylori* infection is present. Whether neutrophils initiate NSAID injury in humans is still unknown.

Role of acid

Gastric acid probably exacerbates NSAID injury by disrupting the basement membrane to produce deep injury,⁷² affecting platelet aggregation,⁷³ and impairing ulcer healing.⁷⁴ Indometacin has been shown to retard the proliferative response to epidermal growth factor at the ulcer edge and it inhibits angiogenesis in the granulation tissue of rat gastric ulcers. This inhibitory effect was partly reversed by coadministration of omeprazole with indometacin.⁷⁴ One important research issue is whether the combination of misoprostol and an acid suppressant would provide better gastric protection than either drug on its own.

Current issues in prevention of NSAID ulcers

Various prophylactic strategies to reduce the gastric toxicity of NSAIDs have been investigated. These strategies include concurrent treatment with histamine-2 receptor antagonists (H2RA), misoprostol, PPIs, and recently, substitution of conventional NSAIDs by selective COX-2 inhibitors. Although there are data showing that these agents reduce gastroduodenal ulceration, whether these findings would translate into clinical benefits deserves careful consideration (panel 2).

Endoscopic ulcer versus clinical outcomes

Endoscopy is often done to assess the efficacy of prophylactic agents in the prevention of mucosal damage induced by NSAIDs, on the assumption that ulcer detected during endoscopy is a surrogate endpoint for clinical outcomes. An ulcer has been arbitrarily defined as a circumscribed mucosal defect with a diameter of 5 mm or greater, and a perceivable depth.⁷⁵ However, in many studies this criterion is relaxed, and any flat mucosal break with a diameter of 3 mm or greater, is regarded as an ulcer. The distinction between small ulcers and erosions is arbitrary and prone to interobserver bias, especially in multicentre studies, and the clinical relevance of these minor endoscopic lesions is doubtful. Some of these endoscopic studies are further limited by inclusion of people at low risk, and therefore results cannot be extrapolated to those at high risk. One example is that low-dose misoprostol has been shown to reduce the frequency of gastroduodenal ulcers in individuals at low risk, but failed to prevent recurrent ulcer complications in patients with a history of ulcer bleeding.⁷⁶

Panel 2: Prevention of NSAID-associated ulcer: current opinions

- PPIs are better than standard-dose H2RAs, but no better than misoprostol in the prevention of gastric ulcer
- The efficacy of PPIs is affected by the proportion of patients infected with *H pylori*
- High-dose H2RAs afford only a slight reduction in the risk of gastric ulcer
- The gastric sparing effect of COX-2 inhibitors is offset by concomitant low-dose aspirin

In view of the limitations of endoscopy in assessing peptic ulcers, investigators have been encouraged to use clinical outcome as a study endpoint. Although measuring the efficacy of a treatment by clinically important events is appealing, not everyone agrees about how a clinically important event should be defined. The comparability of endpoints between studies remains uncertain. Published outcome studies include various events as clinical outcomes, ranging from serious conditions such as hospital admission for ulcer bleeding or perforation, to soft endpoints such as haem-positive stools, dyspepsia, or melaena without endoscopic confirmation of an ulcer. Thus, some outcome studies might lead to conclusions that seem more serious than they really are.

Prophylactic antiulcer agents

A meta-analysis of 33 randomised controlled clinical trials of misoprostol, H2RA, or PPIs for the prevention of gastroduodenal ulcers in chronic NSAID users published between 1996 and 2000,⁷⁷ showed that all doses of misoprostol significantly reduced the risk of endoscopic ulcers. High-dose misoprostol (800 µg daily) is the only prophylactic agent documented to reduce ulcer complications. Standard doses of H2RAs reduce the risk of duodenal but not gastric ulcers. Both double-dose H2RAs and PPIs are effective in reducing the risk of duodenal and gastric ulcers, and are better tolerated than misoprostol.

Although these prophylactic agents reduce the risk of NSAID-induced ulcers, effectiveness in clinical practice might not be as impressive as has been reported in clinical trials. First, high-dose misoprostol causes abdominal cramping and diarrhoea that often lead to withdrawal of treatment.⁷⁸ Although low-dose misoprostol (200 µg twice daily) is better tolerated, it does not prevent ulcer complications in high-risk NSAID users.⁷⁶ Second, the reported efficacy of double-dose H2RAs in the prevention of gastric ulcers was somewhat inconsistent. In one study, the rate of gastric ulcers at 24 weeks was 8% in patients who received famotidine 80 mg per day.⁷⁹ However, in another, 19% of patients who received high-dose famotidine developed gastric ulcers.⁸⁰ Third, there are unresolved issues about the effectiveness of PPIs in the prevention of NSAID-associated ulcers. In a large-scale investigation in which omeprazole 20 mg daily was compared with a standard-dose H2RA (ranitidine 150 mg twice daily), and low-dose misoprostol (200 µg twice daily), omeprazole was better than the other two drugs, with a composite endpoint of ulcers, erosions, and dyspepsia.^{81,82} However, when gastric ulcer was used as the endpoint, omeprazole was no better than low-dose misoprostol in the prevention of gastric ulcers (13% and 10% in the groups who received omeprazole and misoprostol, respectively).⁸² Furthermore, the efficacy of omeprazole is affected by the *H pylori* status of the study population. Among chronic NSAID users receiving omeprazole, the proportions of patients in remission at 24 weeks fell from about 75% in *H pylori*-positive patients, to less than 60% in uninfected patients.^{81,82} Recently, Graham and colleagues⁸³ compared high-dose misoprostol (200 µg four times daily), with two doses of lansoprazole (15 mg and 30 mg daily) for the prevention of ulcers in chronic NSAID users without *H pylori* infection who had a history of gastric ulcer. The proportion of patients who were free from gastric ulcers at 12 weeks was significantly higher in the misoprostol group (93%) than in the two groups treated with lansoprazole (80% and 82%, respectively). However, because of the higher withdrawal rate in the misoprostol group, there was no practical advantage of misoprostol over lansoprazole (success rate of 69% for each of the treatment groups).

COX-2 inhibitors

The molecular biology of cyclo-oxygenase (COX), the key enzyme that regulates prostaglandin synthesis, was elucidated with the identification of two distinct isoforms in the early 1990s.⁸⁴ Because COX-1 is constitutive and COX-2 is proinflammatory (the COX dogma), highly selective COX-2 inhibitors have been developed and marketed as effective anti-inflammatory agents with no gastric toxicity. Two large-scale studies have shown that highly selective COX-2 inhibitors, rofecoxib and celecoxib, reduce the risk of ulcer complications compared with non-selective NSAIDs.^{85,86}

Although there is much evidence that COX-2 inhibitors cause negligible gastric injury, several important issues remain unresolved. First, in the CLASS study, the therapeutic advantage of celecoxib was offset by the concurrent use of low-dose aspirin.⁸⁶ Acid-suppressive therapy would probably still be needed for arthritis patients who require aspirin prophylaxis. Second, data on the gastric safety of COX-2 inhibitors were largely derived from average-risk patients. The long-term outcome of the CLASS study presented at the US Food and Drug Administration hearings failed to show any advantage of celecoxib over diclofenac.⁸⁷ Whether COX-2 inhibitors and PPIs are of similar benefit for high-risk patients is being investigated. Third, in the VIGOR study, the frequency of acute myocardial events was significantly higher in the rofecoxib group than in the naproxen group.⁸⁵ This result has prompted the questions, do COX-2 inhibitors lack anti-platelet effect? Or do they increase cardiovascular risk because of unopposed COX-2 inhibition?

Fourth, the COX dogma has been challenged by results from recent work in animals. Wallace and colleagues⁸⁸ showed that selective inhibition of either COX-1 or COX-2 is not associated with gastrointestinal damage. Rather, it is the dual inhibition of COX-1 and COX-2 that is important. In rodents, COX-2, but not COX-1, is upregulated in gastric ulcers.⁸⁹ Selective inhibition of COX-2 delays healing of experimental ulcers, suggesting that COX-2 is important in restoring gastric epithelial integrity.⁸⁹ To and colleagues⁹⁰ showed that unlike ulcers in animals, both COX-1 and COX-2 are upregulated in human gastric ulcers. Whether selective inhibition of COX-2 has any clinical impact on ulcer healing remains unknown.

H pylori and NSAIDs: the end of the controversy?

Whether there is any interaction between *H pylori* and NSAIDs and the risk of ulcer disease is one of the most controversial issues in peptic ulcer research. There are data to suggest that *H pylori* increases, has no effect on, or decreases the ulcer risk in NSAID users.⁹ Several findings suggest that *H pylori* and NSAIDs are largely independent risk factors. First, the pathogenesis of *H pylori* ulcers differs from that of NSAID ulcers. Second, post-hoc analysis of some studies showed that *H pylori* infection was associated with a reduced risk of ulcers among chronic NSAID users who received omeprazole.^{81,82} This benefit was attributed to the augmentation of acid suppression by *H pylori*.⁹¹ Alternatively, *H pylori* infection might alleviate NSAID injury through stimulation of gastric prostaglandin synthesis.⁹² Third, NSAIDs can induce gastric ulceration in the absence of *H pylori* infection. Among chronic NSAID users who are infected with *H pylori*, curing the infection does not reduce mucosal injury⁹³ or prevent recurrent ulcer bleeding.⁹⁴

However, there is evidence that the interaction between *H pylori* and NSAIDs might not be that simplistic.⁹

Contrary to the notion that *H pylori* and NSAIDs damage the stomach by different mechanisms, neutrophil-induced mucosal injury might be a common pathogenetic pathway shared by these two factors. This hypothesis is consistent with the finding that *H pylori*-induced neutrophil infiltration was associated with an increased risk of ulcers in chronic NSAID users.⁹⁵ Although *H pylori* stimulates gastric prostaglandin synthesis, previous work has shown that this effect was completely offset by the administration of NSAIDs.^{92,96} Such a modest increase in prostaglandin synthesis is probably not sufficient to alleviate NSAID injury.

The issue of whether *H pylori* increases the risk of ulcer disease in NSAID users was recently addressed by a meta-analysis of 16 studies that included 1625 NSAID users.⁹⁷ *H pylori* infection increased the risk of ulcers in NSAID users to 3.53 times that of non-infected NSAID users. *H pylori* infection and NSAID use increased the risk of ulcer bleeding 1.79-fold and 4.85-fold, respectively. The risk of ulcer bleeding increased to 6.13 when both factors were present. However, this meta-analysis did not address the important issue of whether eradication of *H pylori* would reduce the risk of ulcers associated with NSAID use. Hawkey and colleagues⁹³ showed that curing *H pylori* infection did not reduce the risk of ulcer in chronic NSAID users. We have shown that the eradication of *H pylori* substantially reduced the risk of ulcer in NSAID-naive patients who are about to start NSAID treatment^{98,99} (table 2).

Why should the interaction between *H pylori* and NSAIDs be different between NSAID-naive patients and chronic NSAID users? The discrepancy could be reconciled if one postulated that *H pylori* contributes to an excessive ulcer risk in NSAID-naive patients, whereas NSAIDs cause most ulcers in chronic users, irrespective of *H pylori* status. Epidemiological studies have consistently shown that the risk of developing ulcers is substantially raised during the first few months of NSAID treatment.^{100,101} Initiation of NSAID treatment probably aggravates or precipitates ulcer disease in susceptible individuals. Exclusion of these patients will result in a group who can tolerate long-term NSAIDs, irrespective of their *H pylori* status. The *H pylori*-NSAID controversy is

	Chan et al ⁹⁸	Chan et al ⁹⁹	Hawkey et al ⁹³
Study population	NSAID naive	NSAID naive	Chronic users
Ulcer history	Excluded	Included	Included
Dyspepsia	Excluded	Included	Included
Definition of ulcer	≥5 mm	≥5 mm	≥3 mm
NSAIDs used	Naproxen	Diclofenac SR	Variable
Eradication regimen	1-week bismuth triple therapy	1-week omeprazole triple therapy	1-week omeprazole triple therapy
Follow-up	2 months	6 months	6 months
Eradication rate			
Intervention	89%	90%	66%
Control	0%	6%	14%
Endpoints	Primary: endoscopic ulcer	Primary: endoscopic ulcer secondary: complicated ulcer	Endoscopic ulcer or dyspepsia
Endoscopic ulcer (%)			
Intervention	7% (p=0.01)*	12% (p=0.0085)*	44%
Control	26%	34%	47%
Complicated ulcer (%)			
Intervention	2%	4% (p=0.0026)*	Not provided
Control	13%	27%	Not provided

*Intervention versus control.

Table 2: Major differences in the studies on *H pylori* eradication for the prevention of NSAID-associated ulcers

complicated further by the recent observation that eradication of *H pylori* is comparable with omeprazole in the prevention of recurrent ulcer bleeding associated with low-dose aspirin.⁹⁴ This finding suggests that *H pylori* might have a more important interaction with low-dose aspirin than with NSAIDs. Konturek and colleagues⁹⁶ showed that gastric adaptation to aspirin is impaired by *H pylori*, but is restored after the infection has been cured. Alternatively, low-dose aspirin might provoke bleeding from pre-existing *H pylori* ulcers by its antiplatelet effect. Cure of *H pylori* infection restores the mucosal barrier to resist aspirin-induced injury, however, whether eradication of *H pylori* will confer long-lasting protection against ulcer complications in high-risk aspirin users remains to be seen.

Non-NSAID, non-*H pylori* ulcers

The decline in prevalence of *H pylori* infection in developed countries has changed the pattern of peptic ulcer disease. In one retrospective study from the USA in ulcer patients who did not use NSAIDs, *H pylori*-negative ulcers were found in 47% of white patients and 22% of non-white patients.¹⁰² In a meta-analysis of duodenal ulcer trials in the USA, 20% of patients had ulcer recurrence within 6 months after the eradication of *H pylori*.¹⁰ This finding contrasts with results from Asia where the prevalence of *H pylori* is high, showing that ulcers not related to *H pylori* or NSAIDs (non-NSAID non-*H pylori* ulcers) are very rare.^{103,104} Graham and Large¹⁰⁵ proposed that the population prevalence of *H pylori* infection is the major factor that affects the frequency of non-NSAID non-*H pylori* ulcers. If the prevalence of *H pylori* is falling, and the number of ulcers from other causes remains stable, the total number of ulcers will decline, and a greater proportion of non-NSAID non-*H pylori* ulcers will be diagnosed clinically, which will have important implications for clinical management. For example, the *H pylori* test-and-treat strategy for dyspepsia might not

Panel 3: Unresolved issues about peptic ulcer

H pylori

- Why do only a few patients with *H pylori* antral gastritis develop duodenal ulcer?
- What are the factors governing the pattern of *H pylori* colonisation?
- What is the significance of CagA tyrosine phosphorylation?
- Is pretreatment antimicrobial sensitivity testing necessary?

NSAIDs

- Will PPIs and the new anti-inflammatory agents reduce hospital admissions for ulcer complications?
- Do COX-2 inhibitors retard ulcer healing in human beings?
- Can COX-2 inhibitors substitute anti-ulcer agents for high-risk patients?
- Prevention of aspirin-related ulcer complications: prophylactic therapy, NO-aspirin, other anti-platelet agents, or eradication of *H pylori*?

H pylori-NSAID interaction

- Is *H pylori* infection relevant in the era of COX-2 inhibitors?
- Will the eradication of *H pylori* confer long-term protection against aspirin-related ulcer complications in *H pylori*-infected individuals?

Acid-related disorders

- What effect will the widespread eradication of *H pylori* have on the incidence of gastro-oesophageal reflux disease?
- Is the incidence of non-NSAID, non-*H pylori* ulcers increasing?

longer be cost effective because the positive predictive value of serological testing of *H pylori* will fall. An increasing proportion of patients might require maintenance acid-suppressive therapy to prevent ulcer recurrence. A note of caution is that many of these reports were retrospective, used suboptimum methods to identify *H pylori* infection, and failed to reliably document NSAID use. In addition, other causes of peptic ulcer such as Zollinger-Ellison syndrome, Crohn's disease, and hyperparathyroidism had not been excluded. Are we overstating the role that *H pylori* has in peptic ulcer, or are we exaggerating the problem of non-NSAID, non-*H pylori* ulcers?

Although much has been learned about *H pylori* and peptic ulcers over the past 20 years, many important clinical and scientific questions remain unanswered (panel 3). With the rapid emergence of antimicrobial resistance in *H pylori*, cure cannot be assumed without confirmation. The ideal treatment for *H pylori* has yet to be identified. Despite the availability of effective prophylactic agents, ulcer complications associated with NSAID use continue to increase in elderly patients. Whether widespread use of COX-2 inhibitors in the future will reduce hospital admissions for NSAID-related gastrointestinal toxicity remains uncertain. Unlike NSAIDs, the problem of aspirin-related ulcer complications is expected to rise with the heightened use of low-dose aspirin for cardiovascular prophylaxis, and strategies to keep gastrointestinal toxicity of aspirin to a minimum require further investigation. Evidence suggests that *H pylori* is a risk factor for ulcers associated with NSAID and aspirin. The pattern of acid-related disorders is changing with the decreasing prevalence of *H pylori*. Gastro-oesophageal reflux disease has now become the most common acid-related disorder in many western countries. Non-NSAID, non-*H pylori* ulcer might also determine our approach to peptic ulcer disease in the future.

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Uses of error

An obstetric perspective

Deirdre J Murphy

Most obstetricians have experienced errors at some point in their career that contributed to the death or brain damage of a baby. These errors are too painful to contemplate and frequently result in litigation, but are fortunately uncommon. One of the greatest challenges in obstetrics relates to the delicate balance between patient safety, the fulfilment of high expectations, and maternal satisfaction with the birth experience. Errors occur more frequently when this balance is lost, usually in the small hours of the morning as a lone registrar on a busy delivery suite.

One night on-call I transferred a woman to theatre who had failed to progress in the second stage of labour with what appeared to be a large baby. The woman was very keen to avoid caesarean section and my clinical findings suggested that vaginal delivery was possible but unlikely. I did my best to fulfil her wishes and after three determined pulls delivered a very large head. With great difficulty and an extended episiotomy, I delivered the shoulders. There were cheers of joy from the onlookers while my heart sank. I passed a bruised baby with a brachial plexus injury to the paediatrician and began the job of repairing the extended perineal laceration that had divided the mother's anal sphincter. There was no doubt in my mind that I should have performed a caesarean section. I apologised to the mother for the injuries sustained but she was grateful that I had done my best and happy that she had avoided a caesarean section.

I examined the mother and her baby weekly for 6 weeks, more for my reassurance than hers, and fortunately they both made a slow but complete recovery.

On another occasion I saw a couple prior to an elective caesarean section for breech presentation. I noticed that the dates had been miscalculated and that the caesarean section had been booked 2 weeks earlier than was indicated. Earlier delivery carried an increased risk of respiratory complications for the baby and I proposed a rescheduled date. The couple were very angry and insisted on delivery that day as planned. I reluctantly agreed and sadly the baby was transferred to the intensive care unit and ventilated at 6 h of age. The baby was separated from the mother for a total of 5 days and none of us could look each other in the eye throughout her admission. I should never have agreed to their request.

My errors have taught me that obstetricians must maintain patient safety as the first priority and that it is not always possible to fulfil the high expectations placed on us. I share this important lesson with obstetrical trainees in the hope that some of them will avoid my mistakes. I share it with patients when they try to push me beyond the limits of safety. The margin for error in obstetrics has to be incredibly small. The consequences are that we are criticised for over-intervention, which is sometimes justified, and sued for late intervention, which is always regretted.

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