

HELICOBACTER PYLORI AND OTHER CAUSES OF GASTRIC ULCERATION

Management of peptic ulcer disease not related to *Helicobacter*

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Abstract Most peptic ulcers not due to *Helicobacter pylori* are caused by non-steroidal anti-inflammatory drugs (NSAID), among which an important subset are due to vascular protective ('low-dose') aspirin therapy. Non-steroidal anti-inflammatory drugs ulcers heal quite quickly when treated with a proton pump inhibitor (PPI), even though the NSAID is continued. If the NSAID can be stopped, the ulcers heal readily with either a PPI or a histamine H₂-receptor antagonist (H₂-RA). If anti-inflammatory treatment is still needed after ulcers are healed, prophylactic co-therapy with a PPI or misoprostol will reduce the risk of ulcer recurrence by about 60–80%. The alternative of switching to a highly selective cyclooxygenase-2 inhibitor has been shown to reduce the risk of a complicated ulcer by about 50–60%, unless low-dose aspirin treatment needs to be given as well for vascular disease. Idiopathic ulcers are becoming more frequent as *H. pylori* prevalence falls. Some may be sequelae of previous NSAID ulceration even though the NSAID has been ceased and the original ulcer had healed. These are best treated with an H₂-RA or a PPI, followed by long-term maintenance with either of these (often in half the healing dosage) to prevent recurrence. Ulcers due to Zollinger–Ellison syndrome and other hypergastrinemia syndromes are rare, and largely beyond the scope of this review.

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INTRODUCTION

Until just the last 25 years, the medical management of peptic ulcer disease was hampered by a very incomplete knowledge of the causes of ulcer and a paucity of effective therapeutic agents. The introduction of cimetidine in 1977 started the revolution in effective medical therapies. The recognition in the 1980s that *Helicobacter pylori* played a key role in the etiology of most peptic ulcers,¹ particularly duodenal ulcers, moved rational treatment to a higher plane.

However, it has been clear from the beginning that not all ulcers are caused by *H. pylori*, and there is evidence that the proportion of non-*H. pylori* ulcers is increasing. This article reviews the management of that group, subdivided according to the ulcer pathogenesis.

CAUSES OF NON-HELICOBACTER PYLORI ULCERS

The main cause of peptic ulcers in Western countries, apart from *H. pylori*, is treatment with non-steroidal

anti-inflammatory drugs (NSAID). Within this group, an increasingly important cause is the use of cardiovascular protective doses (low dose) of aspirin. Although the introduction of highly selective inhibitors of cyclooxygenase (COX)-2 will probably reduce the size of this problem, ulcers and ulcer complications still occur in patients treated with this new class. Collectively, ulcers caused by anti-inflammatory drugs and low-dose aspirin will be the main focus of this article. Rational management depends on an understanding of causation and risk groups, so this will be dealt with first.

Anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs

It has been known for about 70 years that aspirin ingestion is associated with bleeding acute lesions in the mammalian stomach. The first report that chronic ingestion of aspirin was an important risk factor for the development of gastric ulcer came from northern Queensland in Australia in 1961, when Douglas and Johnston noted an epidemic of gastric ulcer in mainly

middle-aged women who were regularly taking compound analgesics that contained aspirin.² Subsequently, long-term administration of pure aspirin produced gastric ulcers in rats, confirming that the etiological agent was aspirin itself.³

Ulcers are common in patients who take NSAID long term. The point prevalence in many studies where patients were endoscoped routinely, whether they had dyspeptic symptoms or not, has mostly ranged between about 15 and 30%.⁴⁻⁶ In keeping with this, case-control studies have found that NSAID increase the relative risk of patients presenting with ulcer bleeding and/or perforation by about four- to fivefold, and in some circumstances the increased risk has been as much as 20-fold.⁷⁻⁹

The case-control studies, as well as several large randomized controlled trials,¹⁰⁻¹² have identified a number of factors that increase the risk of NSAID ulcers or their complications. The most consistent of these have been:

- a history of peptic ulcer, whether taking NSAID or not at the time
- advancing age (there is no clear inflexion point, but the risk increases in an upwardly curvilinear fashion, becoming substantially increased in the 70s and older)
- use of NSAID in high dosage, or combination of two NSAIDs, including the combination of a NSAID with low-dose aspirin
- use of NSAID from the more damaging end of the spectrum
- co-administration of warfarin (marked increase in relative risk, often to >10)
- co-administration of corticosteroids (about a doubling of risk in some studies)
- cardiovascular disease.

Non-steroidal anti-inflammatory drugs that have been associated with a higher risk for ulcer complications include several of the longer acting drugs, although it is not always easy to make fair comparisons because some of these are marketed at relatively higher dosage. One meta-analysis, as well as a number of individual case-control studies, found that ibuprofen (in doses usually of 1600 mg/day or lower) and diclofenac were at the safer end of the spectrum for gastrointestinal (GI) risk.⁷⁻⁹ Both have quite short elimination half-lives.

Another important consideration when judging the risk of NSAID therapy is to estimate the patient's risk of mortality should they actually have an ulcer bleed. This is markedly increased in patients with severe comorbidities, for example, serious cardiovascular, respiratory or renal disease.

Low-dose aspirin

A large number of patients over the age of 60 are now taking aspirin for cardiovascular protection. The benefits of this, especially in high-risk patients such as those with unstable angina, are undoubted.¹³ However, even at the low doses used for the antiplatelet effect, there is a quite substantial ulcer incidence. One recent study, in patients scheduled for cardiac surgery and taking low-dose aspirin, showed that 29% had a gastric or duode-

nal ulcer when endoscopy was done routinely before surgery.¹⁴ Another study measuring the point prevalence of ulcers in a more representative population of low-dose aspirin users is nearly complete.

The risk of an ulcer hemorrhage in patients taking a daily dose of 75, 150 or 300 mg is increased about two-, three- and fourfold, respectively, compared to matched controls.¹⁵ In many hospitals, low-dose aspirin therapy is now the most common identifiable risk factor in older patients presenting with this emergency. The absolute risk of ulcer hemorrhage estimated from several large myocardial infarction and stroke prevention trials, appears to be about 0.1–0.3 per 100 patient years.¹³

Cyclooxygenase-2 inhibitors

The highly selective COX-2 inhibitors do appear to be realizing their promise of causing less gastroduodenal ulceration than non-selective NSAID. In several placebo-controlled studies, the number of patients developing an ulcer during 12 weeks treatment with rofecoxib or celecoxib was not significantly different than on placebo, and substantially less than in the comparator groups taking conventional NSAID.^{16,17}

However, ulcer complications do still occur in patients taking COX-2 inhibitors. In one large outcome study, which compared celecoxib with diclofenac and ibuprofen over 6 months¹¹ and 12 months,¹⁸ there was not a significant difference in the number of upper gastrointestinal bleeds and perforations between the NSAID and the COX-2 inhibitor arms. There was a reduction of about 50% in those patients taking celecoxib who were not also taking low-dose aspirin, indicating that aspirin abrogates the ulcer-sparing effect of at least this COX-2 inhibitor. Another large outcome study, which compared rofecoxib with naproxen and in which low-dose aspirin was forbidden, did show fewer ulcer complications in the rofecoxib-treated patients, but the reduction was only about 55%:¹² less benefit than would have been predicted from the earlier studies which used endoscopic ulcer as the end-point. Only some of the patients who developed ulcers while taking rofecoxib or celecoxib were infected with *H. pylori*.

Thus COX-2 inhibitors appear to not be devoid of ulcer risk, especially if combined with low-dose aspirin. In rats, COX-2 inhibitors have been found to inhibit healing of experimental ulcers,^{19,20} and COX-2 is known to be expressed in human gastric ulcers.²¹ So it is possible that there are some disadvantages to inhibiting COX-2 in the stomach, even though the risk seems to be less than with combined COX-1 and COX-2 inhibition.

Rare hypersecretory states

Multiple or recurrent ulcers in a patient who is not taking NSAID or aspirin and who is not infected with *H. pylori* should bring the rare acid-hypersecretion, hypergastrinemic syndromes to mind. The best known of these are, of course, the Zollinger–Ellison syndrome,

and the excluded antrum syndrome in patients who have had an incorrectly performed Billroth II style gastrectomy. These are largely outside the scope of the present article, because of their rarity, and are dealt with well elsewhere.²²

No cause for ulcer found

Despite the recognition of the importance of *H. pylori* and NSAID as the major causes of peptic ulcer, a proportion of ulcer patients appear to have neither factor. A few will actually be infected with *H. pylori*, but the organism has been missed because no test is 100% sensitive. Others will actually be taking NSAID, but the patient has concealed or forgotten this: not uncommonly because the NSAID or aspirin was obtained as a non-prescription drug.

However, recent studies in several countries have found that the proportion in whom neither causal agent is demonstrable may be quite substantial: about 20% of recurrent ulcers in a meta-analysis from the USA²³ and 22% of ulcers in a consecutive endoscopy series from Sydney, Australia.²⁴ Conversely, only 4.1% of a large group of patients presenting with GI bleeding in Hong Kong were both *H. pylori* negative and not taking NSAID.²⁵ It may be relevant that the USA and Australia are two countries where the proportion of the population who are infected with *H. pylori* has decreased markedly in recent years.

The mechanism of ulcerogenesis in these patients is not understood. There are some indications that patients who have had a prior NSAID ulcer have an ongoing increased risk for ulcer recurrence, even though the NSAID have been stopped. The best evidence for this comes from a case-control study by MacDonald *et al.*, who noted that even 12 months after ceasing NSAID treatment, the relative risk for presenting with an upper GI bleed was elevated approximately twofold.²⁶ Observations such as this may give some currency to the old notion that the site of a healed ulcer may have less resistance to acid and pepsin than entirely normal mucosa. Some very indirect support for this comes from our observation that ulcers in NSAID users are likely to recur in the same region of the stomach or duodenum as the original ulcer.²⁷

Non-steroidal anti-inflammatory drugs are not the only drugs that appear to be ulcerogenic. Esophageal injury is well recognized during treatment with bisphosphonates, but gastric erosions and ulceration have also been noted during treatment with these drugs in rats and humans.²⁸⁻³⁰ In view of their increasing use for osteoporosis, they may become increasingly important as a cause of gastric ulcers.

MANAGEMENT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ULCERS

This can be considered under two headings: (i) the healing of an ulcer that has developed during NSAID or

COX-2 inhibitor treatment; and (ii) strategies for preventing NSAID ulcers in patients who currently are ulcer free. The available evidence is virtually only for non-selective NSAID. There is almost no information to guide evidence-based decisions about how to manage or prevent ulcers during low-dose aspirin treatment at present. As aspirin is a non-selective COX-1 and COX-2 inhibitor, it is likely that the results of trials in patients taking other NSAID would apply to aspirin also, but there is some uncertainty about this because the mechanism of aspirin gastric damage is a little different. Randomized controlled trials in patients taking low-dose aspirin without other NSAID or COX-2 inhibitors are needed. Similarly, there are no reliable data to guide treatment or prevention of ulcers in patients taking COX-2 inhibitors. The best option is probably to again extrapolate from data from trials with non-selective NSAID.

Healing the established non-steroidal anti-inflammatory drugs-associated ulcer

If possible, the NSAID should be stopped, as healing with a histamine H₂-receptor antagonist (H₂-RA) will be faster than if the NSAID is continued.³¹ Alternatively, if the extra cost of using a proton pump inhibitor (PPI) is considered justified, continuing the NSAID may not be a disadvantage, according to one study with omeprazole in which patients were allowed to either stop or continue their NSAID.³²

Proton pump inhibitors have been shown in three randomized controlled trials to be more effective than ranitidine or misoprostol for healing NSAID ulcers when the NSAID is continued. The Astronaut study³³ compared ranitidine 150 mg twice daily with omeprazole 20 or 40 mg daily, and found gastroduodenal ulcer healing rates at 8 weeks of 87% and 71% on omeprazole 20 mg and ranitidine, respectively. In the Omnium study,³⁴ where misoprostol 200 µg four times daily was tested in place of ranitidine, the corresponding healing rates were 89% (omeprazole 20 mg) and 74% (misoprostol). The differences were statistically significant, and the higher dose of omeprazole conferred no extra benefit. A smaller study comparing lansoprazole 30 mg daily with ranitidine 150 mg twice daily again showed faster ulcer healing with the PPI (73% healed on lansoprazole compared to 53% on ranitidine at 8 weeks).³⁵

Reducing risk of non-steroidal anti-inflammatory drugs ulcers by choice of non-steroidal anti-inflammatory drugs

The strategy is simple. Choose, where possible, an NSAID from the less damaging end of the spectrum, and use it in the lowest dose that is effective. Highly selective COX-2 inhibitors fall into this category (so long as low-dose aspirin is not needed as well), and whether to use them instead of a largely non-selective NSAID such as diclofenac or ibuprofen requires judg-

ments about cost versus benefit for the individual patient. In low-risk patients such as young to middle-aged individuals without a past history of ulcer and with no hazard-increasing cotherapies (such as warfarin or steroids), the risk of using a non-selective NSAID is very small.

Preventing non-steroidal anti-inflammatory drugs ulcers with co-prescribed gastric protectants

It is very common for an H₂-RA to be prescribed with the aim of reducing the risk of NSAID ulcers, but there is not a firm evidence basis for risk reduction. Two large studies showed protection against duodenal ulcers but not gastric ulcers when the H₂-RA was used in standard dosage.^{36,37} The problem is that gastric ulcers are the more common problem in patients taking NSAID. In one study with double-dose famotidine, there was significant protection against gastric ulcers in low-risk patients,³⁸ but in higher risk patients (with recently healed ulcer) the protection against gastric ulcers re-developing was only 54% over 6 months.³⁹

Misoprostol is effective against NSAID ulcers, with a significant reduction (averaging about 60–70%) in the development of both gastric and duodenal ulcers in longer term studies.^{40,41} One large outcome study showed that the serious NSAID complications (gastrointestinal bleeding and perforation) were reduced when misoprostol was given concurrently for 12 months.⁴² Bleeding events were reduced by 40%, a little less than the protection seen in the previous studies that used endoscopic ulcers as the end-point.

Proton pump inhibitors have been found to give fairly substantial protection against the development of endoscopic ulcers in patients taking NSAID. Two placebo-controlled studies found a lowering of gastroduodenal ulcer incidence by 71% and 78% in patients given omeprazole 20 mg daily for 3–6 months.^{43,44}

Two large randomized controlled trials (Omnium and Astronaut) compared omeprazole 20 mg daily, misoprostol 200 µg twice daily, ranitidine 150 mg twice daily or placebo for 6 months in patients who took an NSAID continuously.^{33,34} They were a higher risk group, as most had an NSAID-associated ulcer (which first had to be healed) at the start of the study. Omeprazole (compared with placebo) reduced the rate of gastric and duodenal ulcers by about 70% and 75%, respectively (Fig. 1). It was substantially more effective than ranitidine against ulcers at both sites, comparable to misoprostol in protecting against gastric ulcers, and substantially superior to misoprostol in preventing duodenal ulcers. Misoprostol produced more diarrhea and abdominal pain than the PPI, even at the low dose used in the trial. A higher misoprostol dose might give better ulcer protection, although perhaps at the cost of increased side-effects.

A smaller study showed that lansoprazole 30 mg daily protected against NSAID ulcers to about the same extent as misoprostol.⁴⁶ Diarrhea was a problem in the misoprostol group, where 22% reported it as an adverse

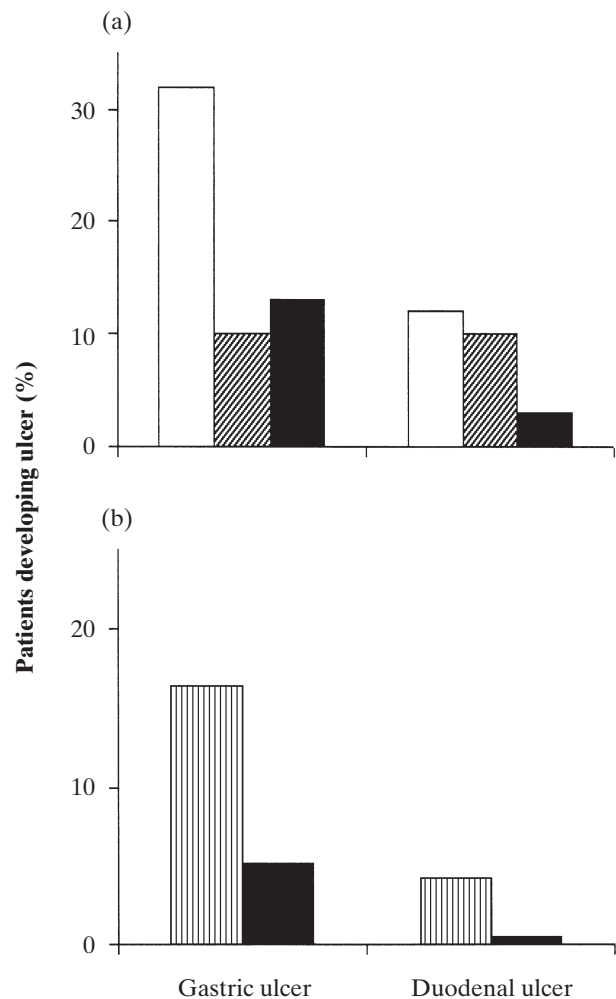


Figure 1 Reduction in non-steroidal anti-inflammatory drugs ulcer incidence during 6 months cotherapy with omeprazole 20 mg daily, misoprostol 200 µg twice daily, ranitidine 150 mg twice daily, or placebo. Data are from (a) Omnium study³⁴ and (b) Astronaut study.³³ (□) Placebo, (▨) misoprostol, (■) omeprazole, (▤) ranitidine. Reproduced by permission of the publishers.⁴⁵

event compared with 7% and 3% taking lansoprazole and placebo, respectively.

An algorithm that may guide management of NSAID ulcers is shown in Fig. 2.

MANAGEMENT OF NON-*HELICOBACTER PYLORI*, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ULCERS

Zollinger–Ellison syndrome

The aim for treating ulcers and preventing their recurrence is to keep gastric acid secretion adequately suppressed. This nearly always requires proton pump inhibitors in whatever dosage is needed to achieve this

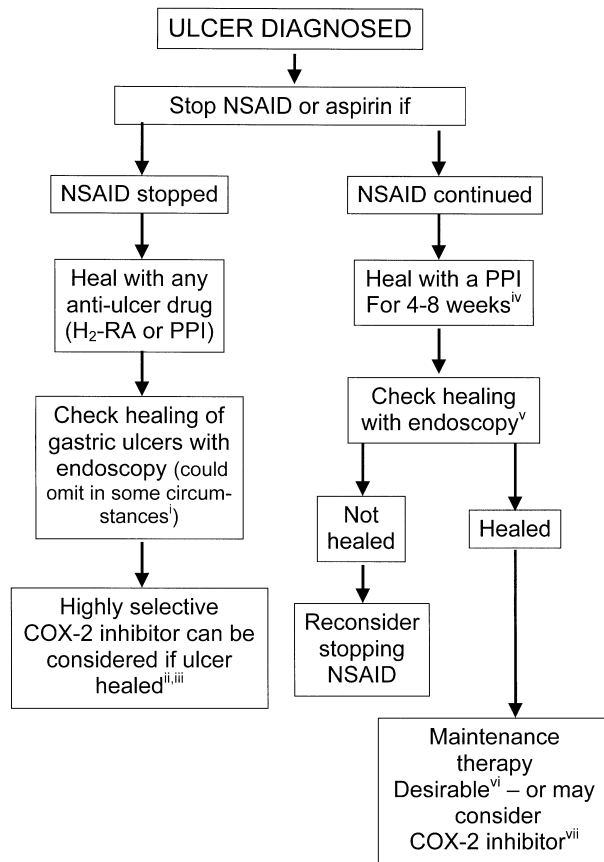


Figure 2 Algorithm to guide management of non-steroidal anti-inflammatory drugs (NSAID) ulcers. Because of great uncertainty about the role of *Helicobacter pylori* in NSAID ulcers, no guidance is given about *H. pylori* testing or treatment. ⁱReasonable exceptions may be small or multiple prepyloric ulcers (very likely to be NSAID induced) shown to be benign at initial endoscopy; ⁱⁱfor reasons given in the text, COX-2 inhibitors not recommended for patients with a current ulcer; ⁱⁱⁱif the ulcer developed while the patient was taking low-dose aspirin, an alternative antiplatelet drug may be considered; ^{iv}most data are with omeprazole 20 mg and lansoprazole 30 mg daily: allow longer for large ulcers; ^vadvisable if NSAID are to be continued since failure to heal would increase desirability of ceasing NSAID; ^{vi}omeprazole 20 mg/day or misoprostol 200 µg twice daily or three times daily; ^{vii}but there are no controlled trial data about safety of cyclooxygenase-2 inhibitors started immediately after ulcer healed. PPI, proton pump inhibitor. Reproduced with permission of the publisher.⁴⁷

goal. The mean dose of omeprazole required to achieve good acid control and prevent ulcers was 80 mg in one series.⁴⁸ High-dose H₂-RA have some efficacy in Zollinger–Ellison syndrome but escalating dosage is needed and control is eventually lost in many cases as the parietal cell becomes refractory to the H₂-RA inhibition. This may be because of upregulation of the H₂-receptor.⁴⁹ Of course, the preferred eventual solution is surgical removal of the gastrinoma if that is feasible. Another option that has been reported to control acid

secretion and leads sometimes to tumor regression is treatment with a somatostatin analog.⁵⁰

Idiopathic ulcers

When no cause for a peptic ulcer can be found, decisions about healing the ulcer and preventing its recurrence need to be made by analogy rather than based on specific evidence. A wealth of older literature, mostly from controlled trials that made NSAID ingestion an exclusion criterion for entry (hence most patients would have been infected with *H. pylori*), has shown that most duodenal and gastric ulcers can be healed in 6–8 weeks with an evening dose of an H₂-RA (e.g. 800 mg cimetidine, 300 mg ranitidine, 40 mg famotidine, 300 mg nizatidine).^{51–54} Proton pump inhibitors achieve healing in about half to two-thirds of this time.⁵⁵ Larger ulcers generally take longer, whichever treatment is used.

The same older literature showed that long-term maintenance treatment with an H₂-RA reduced ulcer recurrences to about 20–30% over 12 months, compared to background recurrence rates of around 70–90% per annum on placebo.^{56–58} For maintenance, also, PPIs have been shown to be more effective than H₂-RAs.⁵⁵ Whether to use an H₂-RA or a PPI, or even to consider ulcer-preventing gastric surgery, will be determined by the severity of the patient's idiopathic ulcer disease, and other factors such as whether ulcers have been dangerously complicated or breakthrough ulcer recurrence has occurred on less potent therapies.

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