Clinical Review

An Etiologic Approach to Management of Duodenal and Gastric Ulcers

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With rare exception, peptic ulcers can now be classified as either *Helicobacter pylori*–related, induced by nonsteroidal anti-inflammatory drugs (NSAIDs), or related to Zollinger-Ellison syndrome. *Helicobacter pylori*–related ulcers can be treated by eradication of *H pylori* or by traditional therapies, including antisecretory drugs or sucralfate. Successful eradication of *H pylori* requires compliance with a multidrug regimen. Therefore, candidates should demonstrate substantial motivation. In general, the greater the degree of ulcer recurrence or resistance, the stronger the indication for *H pylori* eradication. Sucralfate is effective in healing *H pylori*–related duodenal ulcers, and H_2 receptor antagonists heal *H pylori*–related duodenal and gastric ulcers. Omeprazole provides faster healing of *H pylori*–related ulcers, and is particularly useful in treating large gastric ulcers.

Dyspepsia induced by NSAIDs and NSAID-related endoscopic erosions are managed by stopping NSAID use or reducing the dosage; administering NSAIDs with meals; and administering H_2 receptor antagonists in full split-doses. NSAID-induced duodenal ulcers and small gastric ulcers can be healed with full split-doses of H_2 receptor antagonists, even while the NSAID is continued. Large (>5 mm) NSAID-induced gastric ulcers are most efficiently treated with omeprazole, particularly if the patient continues to take the NSAID.

Key words. Peptic ulcer; patient compliance; *Helicobacter pylori*; anti-inflammatory agents, non-steroidal; drug therapy, combination.
(*J Fam Pract 1994; 38:60-67*)

In the past decade, our understanding of peptic ulcer disease has changed dramatically. New concepts of peptic ulcer disease have been necessitated by the recognition and understanding of *Helicobacter pylori* (formerly *Campylobacter pylori*) infection and a large number of clinical studies of ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs). In this paper a system of understanding peptic ulcer disease is presented, which is clinically based and leads directly to a state-of-the-art therapeutic approach to "peptic ulcer."

Pathogenesis

A New Concept

For many years, the pathogenesis of peptic ulcer has been explained by the concept shown in Figure 1. Normally, the integrity of the gastric mucosa is maintained by a balance between aggressive factors, the most important of which are gastric acid and pepsin, and the normal defense mechanisms of the gastric and duodenal mucosa. These defense mechanisms include the normal secretion of mucus and bicarbonate, normal mucosal blood flow, and the ability of the mucosa to regenerate itself. This process is called "cell restitution." A patient with a peptic ulcer was believed to have developed an idiopathic imbalance between these aggressive and defensive factors. An idiopathic increase in aggressive factors or decrease in defensive factors led to the genesis of an ulcer.

The current concept of peptic ulcer employs the previous concept, but now we understand that idiopathic imbalances between aggressive and defensive factors do not occur. Rather, some external force acts to increase aggressive factors or decrease defensive factors. In the great majority of cases, this external force acts to disturb defense.

These external forces can be summarized as follows. On the aggressive side, there is the rare gastrin-secreting tumor that produces the Zollinger-Ellison syndrome

Submitted, revised, September 3, 1993.

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ISSN 0094-3509

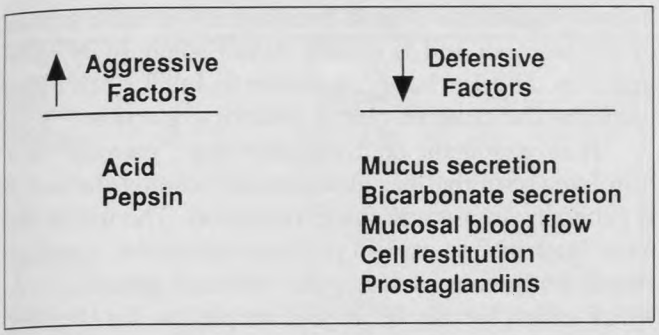

Figure 1. The figure depicts the previous concept of peptic ulcer disease. An ulcer develops when an imbalance develops, related to an idiopathic increase in aggressive factors, a decrease in defensive factors, or both.

(Figure 2). On the defensive side, there are two external factors. One is NSAID ingestion, and the other is infection with *H pylori*. These external factors are not necessarily additive. Thus, the prevalence of *H pylori* infection in patients with NSAID-induced gastric ulcers and in patients with Zollinger-Ellison ulcers is the same as in asymptomatic controls.[1–3] In the absence of NSAID ingestion or Zollinger-Ellison syndrome, however, everyone with a duodenal ulcer and almost everyone with a gastric ulcer has *H pylori* gastritis.[4–7] Actually, in the case of duodenal ulcer, *H pylori* is nearly always present, even in patients with a history of NSAID ingestion. Thus, there are three fundamental backgrounds for peptic ulcer, one of which must be present in order for an ulcer to occur. At this time, then, the use of the term "peptic" ulcer should decrease, since ulcer disease can now be discussed according to its true cause, ie, "*H pylori*–related," "NSAID-induced," or related to Zollinger-Ellison syndrome.

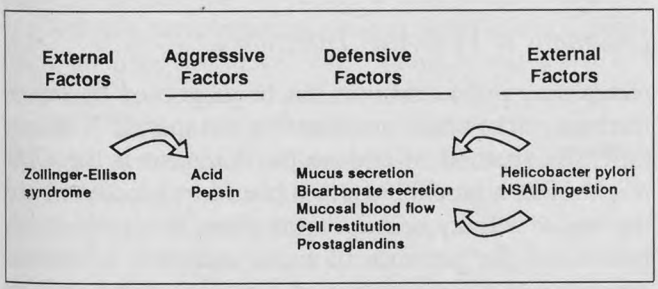

Figure 2. The current concept of peptic ulcer disease. An imbalance occurs between aggressive and defensive factors as a result of the influence of external factors. Zollinger-Ellison syndrome results in increased acid secretion. *Helicobacter pylori* infection results primarily in disturbed defense. NSAIDs disrupt defense.

Role of Acid

The clinical system of understanding ulcers described above allows clarification of the role of gastric acid in ulcer disease. It has long been known that acid is essential to the development of gastric and duodenal ulcers. This was described by Schwartz in 1910 in his dictum "no acid equals no ulcer." This adage is still true. However, acid is fundamentally causative to ulcers only in the Zollinger-Ellison syndrome. In ulcers resulting from *H pylori* infection or induced by ingestion of NSAIDs, acid should be thought of as an "essential permissive factor," as neither type of ulcer can develop without the presence of acid. Further, ulcers caused by *H pylori* or NSAIDs can be effectively healed with medications that reduce acid secretion.[8] This has been particularly confusing in the case of NSAID-induced ulcers, which are sometimes thought (incorrectly) not to be related to acid. In truth, NSAID-induced ulcers may require very little acid secretion to develop and continue. Therefore, very powerful antisecretory therapy may be needed to heal these ulcers, particularly if the NSAID is being continued during therapy. This is especially true of large NSAID-induced gastric ulcers.[8]

Other Factors

The influence of several epidemiologic factors on ulcer disease has been extensively studied. Of these factors, cigarette smoking is by far the most important. Cigarette smoking has a strong adverse influence on ulcers.[9–11] Thus, the prevalence of peptic ulcer is higher in smokers, and healing rates in heavy smokers (more than 1½ packs per day) are about one half the healing rates in nonsmokers after 8 weeks of therapy with an H_2 blocker. In addition, once ulcers have healed, nonsmokers not on maintenance therapy have an ulcer relapse rate at 1 year of 40% to 50%. Heavy smokers have a relapse rate of 100% at 3 months. Although cigarette smoking increases the risk of peptic ulcer disease in patients with *H pylori* infection, it is not one of the fundamental background factors previously discussed. Thus, if a heavy cigarette smoker with ulcer disease has *H pylori* infection eradicated, he will not have recurrent ulcers.[12] On the other hand, cessation of cigarette smoking in the face of persistent *H pylori* infection may or may not lead to resolution of ulcer disease.

There is still no evidence that certain diets or alcohol ingestion increase the risk of developing peptic ulcer disease.[13] Likewise, stress alone will not cause ulcers in the absence of one of the three background conditions. Whether emotional stress or certain personality types

increase the risk of ulcer disease remains controversial.[14–16]

H pylori–Related Ulcers

Classification of ulcers as *H pylori*–related, NSAID-related, or Zollinger-Ellison–related has certain clinical utility, since the management of the three ulcer types differs substantially. In this section, certain clinical features of *H pylori* infection and management of *H pylori*–related ulcers are reviewed. Zollinger-Ellison ulcers are relatively rare and usually managed by specialists; therefore, are not discussed further here.

Epidemiology

Infection with *H pylori* is the most common gastrointestinal infection in humans.[17] *H pylori* has been found in countries throughout the world. In Third World countries, *H pylori* infects almost everyone, and at an early age.[18,19] In industrialized nations, the prevalence of *H pylori* is also substantial. In the United States, about 10% of teenagers are infected, and the prevalence is about 1% higher for each year of age, so that more than half of elderly persons are infected.[20]

Helicobacter pylori lives only on gastric mucosa. It could therefore be found in the esophagus of a patient with Barrett's esophagus, but it has no role in the pathogenesis of gastroesophageal reflux disease. It is also found in the duodenal bulb of patients with duodenal ulcer.[21] The explanation is that these patients have metaplasia of the bulb, so that the lining is transformed from normal small-bowel epithelium to metaplastic gastric epithelium.

Helicobacter pylori produces urease, which splits urea into ammonia. Ammonia helps ensure the survival of *H pylori* by maintaining its local pH environment in the neutral range, and also helps to break down the gastric mucus layer. Tests for urease activity can be used to detect the presence of *H pylori*.[22,23]

The mode of transmission of *H pylori* is uncertain. Presumably, transmission is by close intimate contact, since infection tends to cluster within families.[24] However, contaminated drinking water has also been implicated.[25]

H pylori *and Gastroduodenal Disease*

The best established role for *H pylori* is in type B gastritis.[26] Of the several histologic types of gastritis, types A and B are the most common. Type A is associated with pernicious anemia and has no (or an inverse) association with *H pylori*. Type B is the most common form of histologic gastritis. Type B primarily involves the antrum of the stomach and is caused almost solely by *H pylori* infection. *H pylori* has been shown to fulfill Koch's postulates as the cause of type B histologic gastritis.[27,28]

It is important to remember that "gastritis" is a histologic term that has little clinical meaning. In fact, it is generally an asymptomatic condition. The use of the term "gastritis" to explain patients' symptoms, therefore should be discouraged. *H pylori*–induced gastritis, then, which affects literally billions of people, has for the most part no clinical manifestations.

An important question concerns whether *H pylori* causes the clinical syndrome of nonulcer dyspepsia. Nonulcer dyspepsia refers to the symptoms of a peptic ulcer, but no ulcer is detected by endoscopy. This entity is twice as prevalent as the combination of duodenal and gastric ulcer. The pathogenesis of nonulcer dyspepsia remains poorly understood. Gastric motor disturbances may account for most of the symptoms. The role of *H pylori* in nonulcer dyspepsia also remains controversial. Studies addressing the role of *H pylori* have not consistently found the prevalence of *H pylori* infection in patients with nonulcer dyspepsia to exceed that found in asymptomatic controls.[29] Furthermore, treatment of *H pylori* as a way of eliminating the symptoms of nonulcer dyspepsia has had mixed results.[30,31] Clinicians should, in general, resist the temptation to seek out or treat *H pylori* infection in patients with nonulcer dyspepsia.

As discussed above, *H pylori* can be one of the fundamental backgrounds in which peptic ulcer occurs. The strongest evidence comes from clinical studies showing that eradication of *H pylori* infection reduces the recurrence rate for duodenal ulcer to less than 10% at 1 year, and that recurrences correlate closely with successful eradication of *H pylori*.[12,32–34] The mechanisms by which *H pylori*–induced gastritis predisposes certain patients to ulcer formation are complex[35] and incompletely understood, and will not be discussed here.

Diagnosis of H pylori *Infection*

Helicobacter pylori infection can be diagnosed by several methods, all of which are sensitive and specific. The least expensive method of endoscopic diagnosis is the CLO test.[22] Here a biopsy sample is placed in a medium, and the urease activity causes the medium to change color, because of the presence of a pH indicator. Histologic staining is also commonly used. Giemsa's stain and Warthin-Starry-Faulkner's staining method are useful, but *H pylori* can generally be seen in tissue stained with hematoxylin and eosin.[36] Breath tests, touch cytology, and culture are also effective methods of detecting *H pylori*, but generally are not used. Serologic tests are available,[37]

Table. Traditional Management* of *Helicobacter pylori*–Related Duodenal Ulcer

Duodenal Ulcer Agent	Dosage	Usual Duration (wk)	Cost per Month† ($)	Cost per Treatment Course ($)
Cimetidine	800 mg hs	8	72.15	144.30
	400 mg bid	8	81.45	162.90
	300 mg qid	8	98.16	196.32
Ranitidine	300 mg hs	8	82.16	164.32
	150 mg bid	8	91.98	183.96
Famotidine	40 mg hs	8	79.89	159.78
	20 mg bid	8	82.70	165.40
Nizatidine	300 mg hs	8	80.56	161.12
	150 mg bid	8	83.27	166.54
Sucralfate	1 g qid	8	81.75	163.50
Omeprazole	20 mg qam	4	106.75	106.75

**Does not eliminate* Helicobacter pylori.
†1993 average wholesale price, source: 1993 RED BOOK. Montvale, NJ: Medical Economics Data.

and are sensitive and specific. However, most dyspeptic patients with a positive serologic test will have nonulcer dyspepsia and therefore would not benefit from treatment. If a patient has an endoscopically proven ulcer but a normal serum gastrin level and no history of NSAID ingestion, then by default he or she must have *H pylori* infection.

Therapy of H pylori–*Related Ulcers*

The most problematic aspect of *H pylori* eradication therapy is the need to administer multiple antibiotic medications. Successful eradication with bismuth requires concurrent administration of two antibiotics.[38] The optimal regimen is Pepto-Bismol (2 tablets or 30 cc 4 times daily), metronidazole (250 mg 3 or 4 times daily), and tetracycline (500 mg 4 times daily), all administered for 2 weeks.[38] Patients who take more than 60% of the prescribed medications have eradication rates greater than 90%, whereas those taking less than 60% of the prescribed doses have eradication rates of less than 60%.[39] Therefore, a critical factor in deciding whether to initiate therapy is the physician's estimate of how motivated the patient will be. There is little point in treating *H pylori* in a noncompliant patient, since this will often result in drug resistance. The organism has a marked propensity to develop resistance, particularly to metronidazole.[40] If the patient recalls previously taking metronidazole, it may be preferable to substitute amoxicillin 500 mg 4 times daily or erythromycin 500 mg 4 times daily. An alternative regimen employs omeprazole.[41] Omeprazole has anti–*H pylori* activity, and in high doses (20 mg twice daily) in combination with amoxicillin (500 mg 4 times daily) for 2 weeks, can eradicate the organism in more than 80% of patients. If this regimen is chosen, high efficacy requires that administration of *both* drugs begins on the same day.[41] *H pylori* therapy is at times associated with side effects such as nausea or diarrhea. For this reason, physicians should be available during therapy for counseling and encouraging patients to continue taking the drugs.

Antisecretory therapy also effectively heals ulcers caused by *H pylori* and is less toxic than antibiotic therapy. Since the principal advantage of antibiotic therapy for *H pylori* is to reduce or eliminate recurrence, a common recommendation has been to use antibiotic therapy for patients with documented recurrences or with resistant ulcers. However, it may be wise to initiate antibiotic therapy with the first episode in heavy smokers, since heavy smoking is the best predictor of ulcer recurrence. Some patients with first-time ulcer disease or infrequent recurrences can be given intermittent courses of antisecretory therapy. This approach is summarized in Figure 3. However, enthusiasm regarding anti–*H pylori* therapy for *H pylori*–related ulcers continues to grow, and in the foreseeable future, most or all *H pylori*–related ulcers will be treated by *H pylori* eradication. Certainly, it is perfectly acceptable to combine antisecretory therapy with antibiotic therapy. Indeed, this combination speeds the rate of ulcer healing.[42]

If antibiotic therapy is not used, then antisecretory therapy or sucralfate should be initiated. The drugs and their usual dosages for the treatment of duodenal ulcer are given in the Table. At 4 weeks, omeprazole is superior to H_2 blockers in the treatment of duodenal ulcer,[43,44] but 8 weeks of treatment with an H_2 blocker is equally effective. The amount of time each day during which the gastric pH is greater than 3.0 determines the speed of duodenal ulcer healing.[45] Sucralfate is effective for duodenal ulcers but less so for gastric ulcers, and has never been approved by the Food and Drug Administration for gastric ulcer. Sucralfate is marketed as more effective for smokers, but data to support this are inconclusive.[46] Sucralfate is often prescribed in combination with H_2 blockers for new or resistant ulcers, but there are *no* data to support this use.[47] Combination therapy with

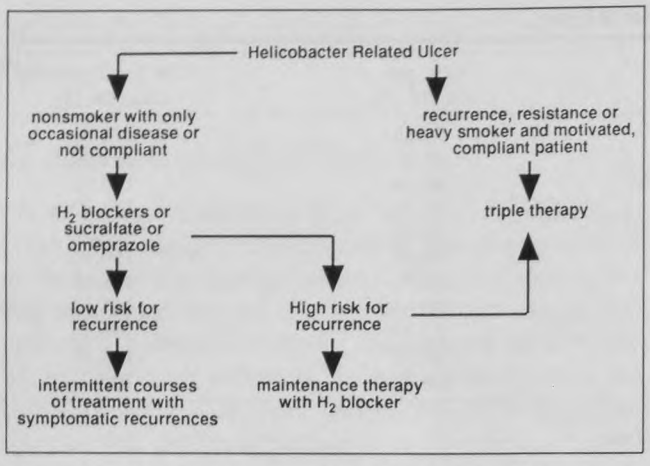

Figure 3. The decision to eradicate *Helicobacter pylori* should depend first on establishing that a *H pylori*–related ulcer is present. The presence or likelihood of recurrence or resistance and the motivation of the patient to comply with an aggressive treatment regimen determine whether to proceed with attempted eradication of *H pylori*. Patients given traditional antisecretory therapy can be treated later with anti–*H pylori* therapy, if desired.

sucralfate and H_2 blockers is not cost-effective. Likewise, the alarming and expensive practice of combining H_2 blockers with omeprazole is completely unjustified. Note that split-dose regimens of H_2 blockers are preferable for large gastric ulcers (Table 1). Overall, the results of many clinical trials indicate that for duodenal ulcers, the regimens in Table 1 may be considered equally effective. Each regimen will heal 80% to 95% of duodenal ulcers. The least expensive regimen is generally omeprazole 20 mg every morning for 4 weeks (Table 1).[48] Even reducing the duration of H_2 blocker therapy to 6 weeks will not bring the cost below that of omeprazole.

For gastric ulcer, H_2 antagonists are effective, and should usually be given in split doses. Omeprazole is not approved by the FDA for gastric ulcers, yet it is clearly superior to H_2 blockers for the treatment of large gastric ulcers.[8]

Resistant H pylori–*Related Ulcers*

Resistance to traditional therapy can be defined as failure to heal after a standard course of one of the medications shown in Table 1. Resistance to traditional therapy for *H pylori*–related ulcers can be predicted primarily in patients who are heavy cigarette smokers, who have large ulcers, and who are noncompliant.[49–52] Changing to or adding sucralfate is seldom effective. The most effective pharmacologic measures are to eradicate *H pylori*, change to omeprazole, or give H_2 blockers in higher doses.[49–52]

Preventing Recurrence of H pylori–*Related Ulcers*

The most effective way to prevent recurrence of an ulcer associated with *H pylori* is to eradicate the organism.[12,32–34] Traditional maintenance therapy is also effective, using either H_2 blockers (one half dose at bedtime) or sucralfate (1 g twice daily) if the ulcer is duodenal.[53,54] Omeprazole has no role in preventing recurrences except as part of an antibiotic regimen. Traditionally, candidates for maintenance have been those with documented recurrences or complicated ulcers, smokers, the elderly, and those with serious concomitant illness. These persons are at high risk for recurrence (Figure 3). Maintenance therapy with half-doses of H_2 blockers at bedtime has been widely touted for duodenal ulcer recurrence and is consistently much more effective than placebo in controlled trials. However, 20% to 30% of patients develop recurrent ulcers while on maintenance therapy.[53] Thus, maintenance therapy, often said to be effective, is really only partly effective. For this reason, smokers with duodenal ulcers and patients with gastric ulcers requiring maintenance therapy should be given full doses of H_2 blockers at bedtime.

NSAID-Induced Ulcer

Many clinicians, including gastroenterologists, do not clearly distinguish between NSAID *injury* and NSAID *prophylaxis*. Primary care physicians frequently engage in both prophylaxis and treatment of NSAID injury, and should have clearly in mind which they are doing in an individual patient. Thus, while there may be some role for misoprostol in prophylaxis, misoprostol (though effective) has virtually no role in the treatment of an established ulcer, even if the ulcer is NSAID-induced. Gastroenterologists primarily treat NSAID-induced injury, which is the focus of this discussion.

The overall morbidity, mortality, and economic burden of NSAID-induced gastrointestinal tract injury in the United States is high. Thus, although the risk of an NSAID-induced complication per patient or per prescription is low,[55] the extensive use of these agents has made NSAID-induced injury to the gastrointestinal (GI) tract quite common.[56,57] In the rheumatoid arthritis population alone, 2600 deaths per year have been attributed to NSAID-induced GI injury.[58] About one third of the cost of managing arthritis in the United States is consumed by managing the GI complications that result from NSAID therapy.[56]

Locations of NSAID Injury in the GI Tract

NSAIDs have been associated with esophagitis, esophageal stricture, gastric and duodenal ulcers,[59] small bowel ulceration, bleeding, perforation and stricture formation,[59,60] and colonic ulceration, bleeding, and perforation.[61] In addition, NSAIDs commonly cause GI bleeding from lesions that are not themselves NSAID-induced.[62] Since this paper addresses peptic ulcer disease, this review focuses on NSAID-induced injury in the stomach and duodenum.

Pathogenesis of NSAID Injury

NSAIDs may exert a direct toxic effect on the gastric mucosa after oral ingestion. This effect has been best described for aspirin.[63] However, NSAIDs also predispose the patient to gastric ulcerations through systemic inhibition of prostaglandin synthesis.[64] Thus, intrarectal and intravenous administration of NSAIDS has resulted in gastric ulceration as well.

Clinical Syndromes of NSAID Injury and Management

From a management perspective, it is useful to characterize three types of NSAID injury to the stomach and duodenum. These are (1) dyspepsia, (2) endoscopic erosions, and (3) ulceration.

NSAID-induced dyspepsia is the most common form of NSAID injury. It is particularly common in patients with previous dyspepsia. Importantly, in most patients with NSAID-induced dyspepsia, an ulcer cannot be detected by endoscopy. Therefore, NSAID-induced dyspepsia, in the absence of anemia, signs of GI bleeding, weight loss, or other worrisome associated symptoms, is not an indication for endoscopy. NSAID-induced dyspepsia is often managed by stopping or decreasing the drug dosage, taking the drug with food, or concomitantly administering H_2 blockers in full split-doses (Figure 4).[65] Doing nothing often works, since the symptoms tend to come and go while the patient continues the NSAID.[65]

For patients who do undergo endoscopy, the most common endoscopic abnormality is erosions.[65] These are more often in the stomach than in the duodenum. Erosions seldom cause clinically significant bleeding and are by definition insufficiently deep to cause perforation. They can be managed in a fashion similar to NSAID dyspepsia, including full split-doses of H_2 blockers (Figure 4).

The most important lesions induced by NSAIDs are ulcers, since they have the potential to bleed or perforate.

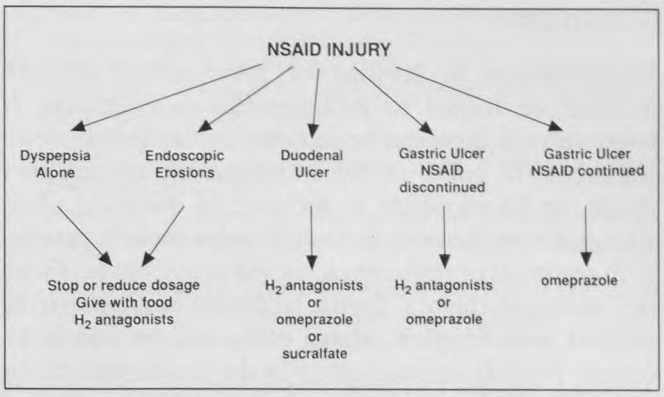

Figure 4. Management of injury caused by nonsteroidal anti-inflammatory drugs (NSAIDs). Simple dyspepsia can be treated empirically in many cases. Endoscopic erosions are managed in the same fashion as dyspepsia. Duodenal ulcers can be healed with several agents, even while the patient continues to take the NSAID. Eradication of *H pylori* may be appropriate in NSAID-induced duodenal ulcers. Large gastric ulcers or gastric ulcers in patients continuing to take the NSAID are best managed with omeprazole.

NSAID-induced ulcers are more common in the stomach than in the duodenum, but the incidence of NSAID complications is evenly divided between stomach and duodenum. NSAID-induced duodenal ulcers are relatively easy to heal, and can be treated with standard split-doses of H_2 blockers[66] or full doses of sucralfate[67] or omeprazole (Figure 4). In general, NSAID-induced duodenal ulcers can be healed even while the patient continues to take the NSAID.[66,67] NSAID-induced duodenal ulcers are generally accompanied by *H pylori* infection, and eradication may be appropriate.

NSAID-induced gastric ulcers are more difficult to heal, particularly if they are large (>5 mm) or if the patient continues taking the NSAID.[8,68] Healing of NSAID-induced gastric ulcers with H_2 blockers in standard doses can be markedly prolonged if the patient continues to take the NSAID, and there is little suggestion that sucralfate is effective. Large (>5 mm) NSAID-induced gastric ulcers are most efficiently treated with omeprazole.[8] Gastric ulcers in cases where the patient is continuing to take the NSAID should also be treated with omeprazole.[8] Misoprostol will heal NSAID-induced gastric ulcers even while the patient continues to take the NSAID.[69] However, a relatively low healing rate of 60% and the toxicity of the drug make it unacceptable for this use. Although this effectively summarizes NSAID injury and its management (Figure 4), an excellent and extensive review of all clinical aspects of NSAID injury (as well as prophylaxis) is available.[65]

Summary

Ulcers can now be classified as *H pylori*–related, NSAID-induced, or related to Zollinger-Ellison syndrome. *H pylori*–related ulcers can be successfully managed by eradication of *H pylori*, or by administering antisecretory drugs, or by sucralfate in the case of duodenal ulcer. Reasonable indications to treat *H pylori* include patients with recurrent or resistant ulcers and heavy smokers with new ulcers. In the near future, treatment of *H pylori* in all patients with *H pylori*–related ulcers will be widely accepted. NSAID-induced ulcers in the duodenum can be easily managed with antisecretory therapy or sucralfate while the patient continues to take the NSAID. NSAID-induced gastric ulcers are more difficult to heal, particularly if they are large or if the patient is continuing to take the NSAID. In these instances patients are more efficiently treated with omeprazole.

References

1. Fich A, Talley NJ, Shorter RG, Phillips SF. Zollinger-Ellison syndrome: relation to *Helicobacter pylori*–associated chronic gastritis and gastric acid secretion. Dig Dis Sci 1991; 36:10–4.
2. Saeed ZA, Evans DJ Jr, Evans DG, et al. *Helicobacter pylori* and Zollinger-Ellison syndrome. Dig Dis Sci 1991; 36:15–8.
3. Graham DY, Lidsky MD, Cox AM, et al. Long-term nonsteroidal anti-inflammatory drug use and *Helicobacter pylori* infection. Gastroenterology 1991; 100:1653–7.
4. Rauws EAJ, Langenberg W, Houthoff HJ, Zanen HC, Tytgat GNJ. *Campylobacter pyloridis*–associated chronic active antral gastritis. Gastroenterology 1988; 94:33–40.
5. O'Connor HJ, Axon ATR. *Campylobacter pylori*, gastric ulceration and the post-operative stomach. In: Rathbone BJ, Heatley RV, eds. *Campylobacter pylori* and gastroduodenal disease. Oxford: Blackwell Scientific Publications, 1989:125–38.
6. Laine L, Marin-Sorensen M, Weinstein WM. Nonsteroidal anti-inflammatory drug-associated gastric ulcers do not require *Helicobacter pylori* for their development. Am J Gastroenterol 1992; 87:1398–402.
7. Borody TJ, Brandl S, Andrews P, Jankiewicz E, Ostapowicz N. *Helicobacter pylori*–negative gastric ulcer. Am J Gastroenterol 1992; 87:1403–6.
8. Walan A, Bader J-P, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. N Engl J Med 1989; 320:69–75.
9. Piper DW, Nasiry R, McIntosh J, Shy CM, Pierce J, Byth K. Smoking, alcohol, analgesics, and chronic duodenal ulcer. Scand J Gastroenterol 1984; 19:1015–21.
10. Sonnenberg A, Müller-Lissner SA, Vogel E, et al. Predictors of duodenal ulcer healing and relapse. Gastroenterology 1981; 81: 1061–7.
11. Chiverton SG, Hunt RH. Smoking and duodenal ulcer disease. J Clin Gastroenterol 1989; 11(suppl 1):S29–S33.
12. Borody TJ, George LL, Brandl S, Andrews P, Jankiewicz E, Ostapowicz N. Smoking does not contribute to duodenal ulcer relapse after *Helicobacter pylori* eradication. Am J Gastroenterol 1992; 87:1390–3.
13. Friedman GD, Siegelaub AB, Seltzer CC. Cigarettes, alcohol, coffee, and peptic ulcer. N Engl J Med 1974; 290:469–73.
14. Walker P, Luther J, Samloff IM, Feldman M. Life events, stress, and psychosocial factors in men with peptic ulcer disease. Gastroenterology 1988; 94:323–30.
15. Talley NJ, Ellard K, Jones M, Tennant C, Piper DW. Suppressio of emotions in essential dyspepsia and chronic duodenal ulcer. case control study. Scand J Gastroenterol 1988; 23:337–46.
16. Adami H-O, Bergström R, Nyrén O, et al. Is duodenal ulcer reall a psychosomatic disease? A population-based case control study Scand J Gastroenterol 1987; 22:889–96.
17. Peterson WL. *Helicobacter pylori* and peptic ulcer disease. N Engl Med 1991; 324:1043–87.
18. Perez-Perez GI, Taylor DN, Bodhidatta L, et al. Seroprevalence o *Helicobacter pylori* infections in Thailand. J Infect Dis 1990; 161 1237–41.
19. Gastrointestinal Physiology Working Group. *Helicobacter pylo* and gastritis in Peruvian patients: relationship to socio-economi level, age, and sex. Am J Gastroenterol 1990; 85:819–23.
20. Dooley CP, Cohen H, Fitzgibbons PL, et al. Prevalence of *Heli cobacter pylori* infection and histologic gastritis in asymptomati persons. N Engl J Med 1989; 321:1562–6.
21. Axon AR. Duodenal ulcer: the villain unmasked? BMJ 1991 302:919–21.
22. Borromeo M, Lambert JR, Pinkard KJ. Evaluation of "CLO-test to detect *Campylobacter pyloridis* in gastric mucosa. J Clin Patho 1987; 40:462–8.
23. Graham DY, Klein PD, Evans DJ Jr, et al. *Campylobacter pylo* detected noninvasively by the ^{13}C-urea breath test. Lancet 1987 1:1174–7.
24. Drumm B, Perez-Perez GI, Blaser MJ, Sherman PM. Intrafamili clustering of *Helicobacter pylori* infection. N Engl J Med 1990 322:359–63.
25. Klein PD, Graham DY, Gaillour A, Opekun AR, Smith EO Water source as risk factor for *Helicobacter pylori* infection i Peruvian children. Gastrointestinal Physiology Working Group Lancet 1991; 337:1503–6.
26. Paull G, Yardley JH. Pathology of *C pylori*–associated gastric an esophageal lesions. In: Blaser MJ, ed. *Campylobacter pylori* in gas tritis and peptic ulcer disease. New York NY: Igaku-Shoin, 1989 73–97.
27. Marshall BJ, Armstrong JA, McGechie DO, Glancy RJ. Attemp to fulfill Koch's postulates for pyloric *Campylobacter*. Med J Aus 1985; 142:436–9.
28. Morris A, Nicholson G. Ingestion of *Campylobacter pyloridis* cause gastritis and raised fasting gastric pH. Am J Gastroenterol 1987 82:192–9.
29. Graham DY, Klein PD. *Campylobacter pyloridis* gastritis: the pas the present and speculations about the future. Am J Gastroenterol 1987; 82:283–6.
30. Rokkas T, Pursey C, Uzoechina E, et al. Non-ulcer dyspepsia an short term Denol therapy: a placebo controlled trial with particula reference to the role of *Campylobacter pylori*. Gut 1988; 29:1386 91.
31. Loffeld RJLF, Potters HVJP, Stobberingh E, Flendrig JA, Va Spreeuwel JP, Arends JW. *Campylobacter* associated gastritis i patients with non-ulcer dyspepsia: a double blind placebo con trolled trial with colloidal bismuth subcitrate. Gut 1989; 30 1206–12.
32. Hentschel E, Brandstatter G, Dragosics B, et al. Effect of ranitidin and amoxicillin plus metronidazole on the eradication of *Helico bacter pylori* and the recurrence of duodenal ulcer. N Engl J Me 1993; 328:308–12.
33. Graham DY, Lew GM, Klein PD, et al. Effect of treatment o *Helicobacter pylori* infection on the long-term recurrence of gastri or duodenal ulcer. Ann Intern Med 1992; 116:705–8.
34. George LL, Borody TJ, Andrews P, et al. Cure of duodenal ulce after eradication of *Helicobacter pylori*. Med J Aust 1990; 153 145–9.
35. Blaser MJ. Hypotheses on the pathogenesis and natural history o *Helicobacter pylori*–induced inflammation. Gastroenterology 1992 102:720–7.
36. Madan E, Kemp J, Westblom TU, Subik M, Sexton S, Cook Evaluation of staining methods for identifying *Campylobacter py lori*. Am J Clin Pathol 1988; 90:450–3.

37. Evans DJ Jr, Evans DG, Graham DY, Klein PD. A sensitive and specific serologic test for detection of *Campylobacter pylori* infection. Gastroenterology 1989;96:1004–8.
38. Chiba N, Rao BV, Rademaker JW, Hunt RH. Meta-analysis of the efficacy of antibiotic therapy in eradicating *Helicobacter pylori*. Am J Gastroenterol 1992; 87:1716–27.
39. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology 1992; 102:493–6.
40. Bell GD, Weil J, Powell K, et al. *Helicobacter pylori* treated with combinations of tripotassium dicitrato and metronidazole: efficacy of different treatment regimens and some observations on emergence of metronidazole resistance. Eur J Gastroenterol Hepatol 1991; 3:819–22.
41. Labenz J, Gyenes E, Rühl GH, Börsch G. Efficacy of omeprazole and amoxicillin to eradicate HP [abstract]. Am J Gastroenterol 1992; 87:1271.
42. Graham DY, Lew GM, Evans DG, et al. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. Ann Intern Med 1991; 115:266–9.
43. McFarland RJ, Bateson MC, Green JRB, et al. Omeprazole provides quicker symptom relief and duodenal ulcer healing than ranitidine. Gastroenterology 1990; 98:278–83.
44. Valenzuela JE, Berlin RG, Snape WJ, et al. US experience with omeprazole in duodenal ulcer. Dig Dis Sci 1991; 36:761–8.
45. Burget DW, Chiverton SG, Hunt RH. Is there an optimal degree of acid suppression for healing of duodenal ulcers? Gastroenterology 1990; 99:345–51.
46. Lam SK, Hui WM, Lau WY, et al. Sucralfate overcomes adverse effect of cigarette smoking on duodenal ulcer healing and prolongs subsequent remission. Gastroenterology 1987; 92:1193–1201.
47. VanDeventer GM, Schneidman D, Walsh J. Sucralfate and cimetidine as single agents and in combination for treatment of active duodenal ulcers. Am J Med 1985;79(suppl 2C):39–44.
48. Sintonen H, Alander V. Comparing the cost-effectiveness of drug regimens in the treatment of duodenal ulcers. J Health Econ 1990; 9:85–101.
49. Bardhan KD. Omeprazole in the management of refractory duodenal ulcer. Scand J Gastroenterol 1989; 24(suppl 166):63–73.
50. Collen MJ, Stanczak VJ, Ciarleglio CA. Refractory duodenal ulcers (nonhealing duodenal ulcers with standard doses of antisecretory medication). Dig Dis Sci 1989; 34:233–7.
51. Lam SK, Lee NW, Koo J, Hui WM, Fok KH, Ng M. Randomised crossover trial of tripotassium dicitrato bismuthate versus high dose cimetidine for duodenal ulcers resistant to standard dose of cimetidine. Gut 1984; 25:703–6.
52. Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. Lancet 1990; 355:1233–35.
53. Sontag SJ. ACG Committee on FDA-related matters. Current status of maintenance therapy in peptic ulcer disease. Am J Gastroenterol 1988; 83:607–17.
54. Bolin TD. Sucralfate maintenance therapy in duodenal ulcer diseases. Am J Med 1989; 86(suppl 6A):148–51.
55. Langman MJS. Epidemiologic evidence on the association between peptic ulceration and anti-inflammatory drug use. Gastroenterology 1989; 96:640–6.
56. Bloom BS. Risk and cost of gastrointestinal side effects associated with nonsteroidal anti-inflammatory drugs. Arch Intern Med 1989; 149:1019–22.
57. Armstrong CP, Blower AL. Nonsteroidal anti-inflammatory drugs and life-threatening complications of peptic ulceration. Gut 1987; 28:527–32.
58. Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA. Toward an epidemiology of gastropathy associated with nonsteroidal anti-inflammatory drug use. Gastroenterology 1989; 96: 647–55.
59. Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal anti-inflammatory drugs. N Engl J Med 1992; 327:749–54.
60. Levi S, deLacey G, Price AB, Gumpel MJ, Levi AJ, Bjarnason I. "Diaphragm-like" strictures of the small bowel in patients treated with nonsteroidal anti-inflammatory drugs. Br J Radiol 1990; 63:186–9.
61. Gibson GR, Whitacre EB, Ricotti CA. Colitis induced by nonsteroidal anti-inflammatory drugs. Arch Intern Med 1992; 152:625–32.
62. Lanas A, Sekar MC, Hirschowitz BI. Objective evidence of aspirin use in both ulcer and nonulcer upper and lower gastrointestinal bleeding. Gastroenterology 1992; 102:1647–53.
63. Hawkey CJ, Rampton DS. Prostaglandins and gastrointestinal mucosa: are they important in its function, disease or treatment? Gastroenterology 1985; 89:1162–4.
64. Konturek SJ, Obtulowicz W, Sito E, Oleksy J, Wilkon S, Kiec-Dembinska A. Distribution of protaglandins in gastric and duodenal mucosa of healthy subjects and duodenal ulcer patients: effects of aspirin and paracetamol. Gut 1981; 22:283–9.
65. Soll AH, Weinstein WM, Durata J, McCarthy D. Nonsteroidal anti-inflammatory drugs and peptic ulcer disease. Ann Intern Med 1991; 114:307–19.
66. McCarthy DM. Nonsteroidal anti-inflammatory drug-induced ulcers: management by traditional therapies. Gastroenterology 1989; 96:662–74.
67. Manniche C, Malchow-Møller A, Andersen JR, et al. Randomised study of the influence of nonsteroidal anti-inflammatory drugs on the treatment of peptic ulcer in patients with rheumatic disease. Gut 1987; 28:226–9.
68. O'Laughlin JC, Silvoso GK, Ivey KJ. Resistance to medical therapy of gastric ulcers in rheumatic disease patients taking aspirin—a double-blind study with cimetidine and follow-up. Dig Dis Sci 1982; 27:976–80.
69. Roth S, Agrawal N, Mahowald M, et al. Misoprostol heals gastroduodenal injury in patients with rheumatoid arthritis receiving aspirin. Arch Intern Med 1989; 149:775–9.