

How I Manage *H. Pylori*-Negative, NSAID/Aspirin-Negative Peptic Ulcers

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The first and most important action on encountering a patient with unexplained gastric or duodenal ulceration is to double check that they are truly *H. pylori* negative and also not taking any ulcerogenic medicines. Once the patient is confirmed to be *H. pylori* negative and NSAID negative, ensure that biopsies of the ulcer—whether gastric or duodenal—and of the surrounding gastric and duodenal mucosa are obtained to exclude underlying malignancy/lymphoma, Crohn's disease, and unusual infectious agents. If the etiology of the ulceration remains unexplained, an underlying gastrinoma should be considered and excluded. Patients with idiopathic ulcers should be maintained on proton pump inhibitor therapy, and higher doses may be required to control acid secretion and prevent ulcer relapse in these *H. pylori*-uninfected subjects.

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INTRODUCTION

Helicobacter pylori infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin are the major causes of ulceration of the stomach and duodenum (1–5). However, some ulcers are apparently unrelated to those risk factors and there is considerable variation in the reported proportion of such ulcers. Recent reports from North America suggest that up to 50% of ulcers are *H. pylori* negative (6–8) whereas in other parts of the world, the proportion of *H. pylori*-negative ulcers remains much lower at <4% (9–11). The prevalence of *H. pylori*-negative, NSAID/aspirin-negative ulcers depends upon the robustness of exclusion of *H. pylori* and NSAID/aspirin usage. It will also depend upon the background prevalence of *H. pylori* in the general population as *H. pylori*-negative ulcers will not exist if everyone has the infection. Such factors are likely to contribute to the variations in reported prevalence of *H. pylori*-negative ulcers.

It is unclear whether ulcers that persist after successful *H. pylori* eradication have a similar etiology to ulcers first presenting in the absence of the infection. Approximately 10% of ulcers remain unhealed despite eradication of *H. pylori* (12–14). Are these ulcers the same as *H. pylori*-negative ulcers with the infection merely having been an innocent bystander because of its high prevalence in the general population? Or, has the infection produced permanent changes to the structure and function of the stomach, which continues to predispose to mucosal ulceration after the organism has been eradicated? The fact that eradication of *H. pylori* infection cures the great majority of

patients with even severe ulcer disease, provided they are not NSAID or aspirin related, points against the infection causing a permanent ulcer diathesis. My own view is that ulcers recurring after *H. pylori* eradication are most probably equivalent to ulcers in patients without evidence of current or previous infection and should be managed in the same way.

When a patient who is not taking NSAIDs presents with chronic ulceration of the duodenum or the stomach and a negative *H. pylori* test, the first and most important consideration is that the result is a false negative. Several factors prevalent in dyspeptic patients are able to result in negative *H. pylori* test results in infected subjects. Suppression of gastric acidity by proton pump inhibitor therapy or high-dose H₂ antagonists markedly reduces the bacterium's urease activity and may produce false-negative urease tests including the breath test and urease strip test (15–17). Such therapy also reduces the density of colonization in both antrum and body (18,19). Though patients are advised to stop acid-suppressive medication 2–3 weeks before *H. pylori* testing, compliance with this advice is unreliable, particularly in symptomatic subjects. A variety of widely used antibiotics, as well as bismuth-containing preparations also suppress *H. pylori* infection and its urease activity. Even under optimal conditions, most individual *H. pylori* tests have a sensitivity less than 95% meaning that one in twenty infected subjects may be missed (20).

It is extremely important that *H. pylori* infection is not missed in patients with ulcer disease as this will deny them the chance of a long-term cure of the ulcer disease by eradicating

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the infection. In all patient with unexplained chronic gastric or duodenal ulceration, it is important to take biopsies from both the antrum and body region of the stomach for both histology and urease test and also to check *H. pylori* serology. A recent study has suggested that in some patients with duodenal ulceration, the infection is confined to the duodenal mucosa and eradicating it causes the ulcer disease (21). Consequently, in patients with duodenal ulceration and no evidence of *H. pylori* in the stomach, biopsies should also be taken from the duodenum.

The other common explanation for apparent *H. pylori*-negative, NSAID/aspirin-negative chronic peptic ulceration is unrecognized use of NSAIDs/aspirin. A careful history and examination of recent prescription records is important. Patients should also be carefully questioned about the use of over-the-counter medications and herbal medications, some of which contain salicylates. In some cases, urine and serum analysis to detect surreptitious use of these drugs may be appropriate (22).

Careful reassessment of *H. pylori* status and NSAID aspirin usage will reduce the number of unexplained ulcers. However, a small proportion of ulcers do occur in the absence of these well-established risk factors and may be related to a variety of other conditions. Several medications in addition to NSAIDs and aspirin may damage the gastroduodenal mucosa, including iron supplements, bisphosphonates, colchicines, and all medicines recently taken by patients should be scrutinized for any potential mucosal-damaging effects.

The one condition not to be missed in patients with unexplained gastric or duodenal ulceration is an underlying tumor. Though ulcers of the stomach are routinely biopsied to exclude cancer, this is not the practice for duodenal ulceration. However, in a patient with *H. pylori*-negative, NSAID-negative duodenal ulceration, the possibility of underlying carcinoma or lymphoma needs to be considered and this is one situation where biopsies should also be taken from the duodenal ulcer and surrounding duodenal mucosa.

Crohn's disease can cause ulceration anywhere in the gastrointestinal tract and should be considered in any patient with unexplained ulceration of the stomach and duodenum (5,23). The pattern of upper gastrointestinal ulceration associated with Crohn's disease is highly variable. Consequently, biopsies should be taken from both the duodenum and stomach in patients with unexplained ulcer disease.

Infections other than *H. pylori* are associated with ulceration of the upper gastrointestinal tract and should be excluded. Goddard *et al.* (24) reported duodenal ulceration associated with *Helicobacter heilmannii*. Treating the infection with quadruple therapy cured the ulcer disease (24). There are a number of case reports of chronic gastric ulcers associated with cytomegalovirus infection in immunocompromised patients (25,26). The typical inclusion bodies are seen in the gastric biopsies. These ulcers healed after treatment with ganciclovir (25,26). There is also a report of the presence of herpes simplex virus in *H. pylori*-negative ulcers though the nature of the association is unclear (27).

In 1986, Cameron and Higgins (28) reported ulceration of the proximal stomach in patients with hiatus hernia and occurring where the gastric mucosa passes through the diaphragmatic hiatus. These ulcers are usually associated with iron deficiency anemia, though the nature of the association is unclear. The etiology of the ulcer is also unclear but may be related to mucosal trauma or ischemia. The ulcers may be single or multiple. These Cameron ulcers were described before *H. pylori* infection is recognized and thus the role of the infection in these ulcers is unclear.

Gastric ulceration has also been reported following high-dose radiotherapy of the upper abdominal region (29). This seems likely to have been a direct complication of the therapy though the *H. pylori* status of the affected patients has not been documented (29). Ulcers may also occur in patients with severe systemic illness, for example, following extensive burns and these stress ulcers are likely to be independent of *H. pylori* status (30).

Most of the above causes of *H. pylori*-negative, NSAID/aspirin-negative ulcers can be detected by a careful clinical history and upper gastrointestinal endoscopy including taking adequate biopsies of the ulcer and surrounding tissue and including both the stomach and the duodenum. If this does not provide a satisfactory explanation for the mucosal ulceration, then one has to consider the possibility of the rare, but important, condition of the Zollinger–Ellison syndrome.

Patients with the Zollinger–Ellison syndrome usually have diarrhea accompanying the ulcer disease and which is responsive to acid-inhibitory therapy. There may also be a family history of endocrine tumors as the Zollinger–Ellison syndrome is sometimes part of a multiple endocrine neoplasia syndrome. Upper gastrointestinal ulceration resulting from a gastrinoma is usually severe, multiple and often extends into the more distal duodenum. Ulcer complications including perforation and bleeding are common and reflux esophagitis is often also present. However, it should be remembered that patients tend to be commenced on proton pump inhibitors early after development of possible ulcer symptoms and this may mitigate the features traditionally associated with underlying gastrinoma. Proton pump inhibitor therapy also makes the diagnosis of the Zollinger–Ellison syndrome by the traditional tests more complicated. It is often difficult, and probably unwise, to stop proton pump inhibitor therapy to perform tests of basal and maximal pentagastrin-stimulated acid output. Fasting gastrin may be difficult to interpret because of its increased concentration due to proton pump inhibitor therapy, which will overlap with values in patients with gastrinoma (31). The secretin test is probably the most discriminating (32,33). Following intravenous injection of secretin, the serum gastrin increases in patients with gastrinoma but not in control patients. A rise of more than 120 pg/ml is considered positive (33). This occurs due to the fact that gastrinomas have secretin receptors (34). I routinely perform tests to exclude the Zollinger–Ellison syndrome in patients with chronic ulcers unassociated with other recognized risk factors. **Table 1** summarizes conditions to

Table 1. Causes of “*H. pylori*, NSAID, aspirin negative” ulcers

Causes
Missed <i>H. pylori</i> infection
Unrecognized NSAID/aspirin usage
(1) Other medications
(2) Crohn's disease
(3) Neoplasm/lymphoma
(4) <i>H. heilmannii</i>
(5) Other infections
(6) Severe systemic disease
(7) Cameron ulcer
(8) Systemic mastocytosis
(9) Zollinger–Ellison syndrome

consider in patients with *H. pylori*-negative, NSAID/aspirin-negative ulcers and **Figure 1** provides flow chart for management of apparent *H. pylori*-negative, NSAID/aspirin-negative ulcers.

My experience is that the above investigations result in a very small proportion of patients remaining with apparently idiopathic ulcer disease (5). This attests to the remarkable ability of the normal upper gastrointestinal mucosa to withstand the highly acidic and proteolytic luminal environment to which it is exposed. We recently performed a series of gastric function tests in a small group of volunteers with idiopathic gastroduodenal ulceration and observed increased acid output, increased gastrin, and accelerated gastric emptying (5). Exaggerated gastrin response was also observed by Kamoda *et al.* (35) in three of nine idiopathic ulcers. We suggested that this may be contributing to the ulcer disease. However, recently we and others have recognized that discontinuation of proton pump inhibitor therapy can produce the same abnormalities (36–38). Consequently, it is unclear whether the abnormalities are the cause of the ulcer disease or the effect of its treatment.

The management of the small group of patients with truly idiopathic ulcers is unclear. The vast majority of studies of the value of acid inhibitor therapy in ulcer disease have been performed in patients with *H. pylori*-positive ulcers or with NSAID-associated ulcers. It is now recognized that the acid-suppressive effect of proton pump inhibitor therapy is greater in *H. pylori*-infected than -uninfected subjects (39,40). This is probably due to the fact that such therapy causes an increase in oxyntic mucosal gastritis that impairs gastric secretory function and augments the pharmacological effect of the drug. There are some reports that *H. pylori*-negative ulcers are more difficult to manage and more susceptible to complications than traditional ulcers (5,41). This might be related to their reduced response to acid-inhibitory therapy and using increased doses of proton

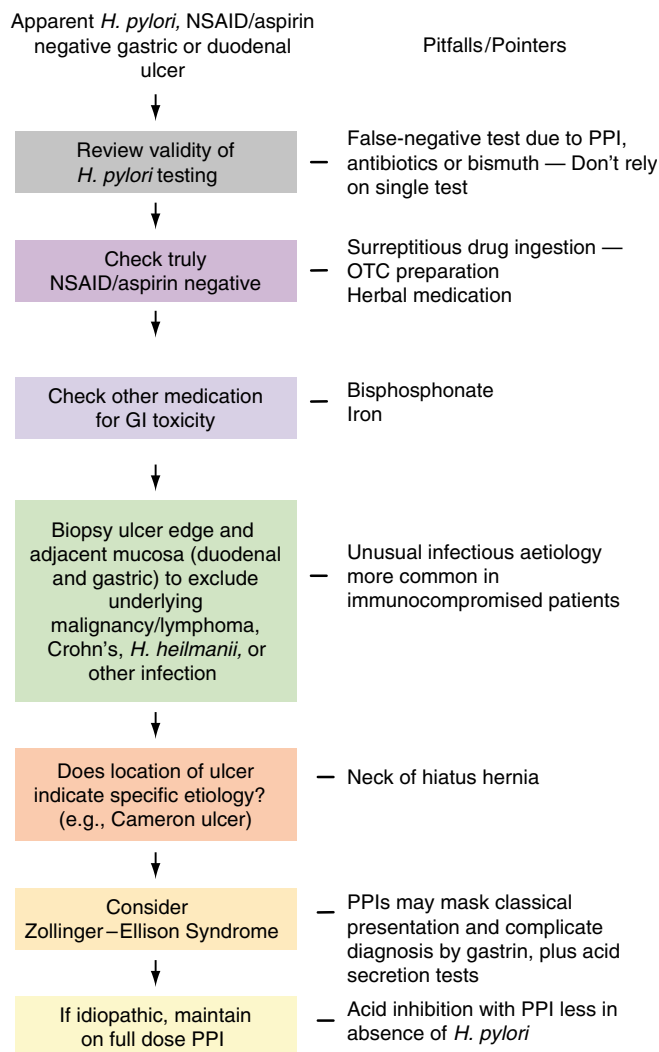


Figure 1. Flow chart for management of apparent *H. pylori*-negative, NSAID/aspirin-negative gastric or duodenal ulcer.

pump inhibitor therapy may be appropriate. The natural history of idiopathic ulcers is poorly documented due to the rarity.

In conclusion, the most important point about *H. pylori*-negative, NSAID/aspirin-negative ulcers is their rarity and the likelihood of patients presenting with such ulcers being due to these traditional risk factors being missed. A high index of suspicion for these factors is important. In patients confirmed to have genuine *H. pylori*-negative, NSAID/aspirin-negative ulceration, further investigations to exclude other causes should be performed. The Zollinger–Ellison syndrome should be considered remembering that proton pump inhibitor therapy will mitigate its classical clinical features.

CONFLICT OF INTEREST

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