

CHAPTER 5

Duodenal Ulcer Disease: Treatment by Surgery, Antibiotics, or Both

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The early scientific assessment of the pathophysiology of peptic ulcer disease (PUD), referring to both duodenal ulcer (DU) and gastric ulcer (GU), revolved around the role of gastric hydrochloric acid and pepsin secretion.¹ Gastric luminal proteolysis, a function of both forms of secretion, was thought to be the key. Patients with DU were shown to have statistically higher rates of gastric acid secretion than the non-DU population, a function of increased fundic parietal cell mass and, perhaps, a greater parietal cell sensitivity to circulating gastrin from the gastric antrum. Greater-than-normal rates of gastric emptying were demonstrated in patients with DU compared with non-DU subjects. The combination of increased rates of gastric acid secretion and increased rates of gastric emptying led investigators to conclude that the elevated acid load to which the duodenal mucosa was exposed per unit of time contributed to the formation of a DU. A number of patients with DU had normal or lower-than-normal rates of gastric acid secretion, suggesting that those patients may have abnormal endogenous gastric mucosal defense mechanisms.² Investigators found that patients with DU exhibited lower rates of duodenal mucosal and Brunner's gland bicarbonate secretion during luminal acidification compared with non-DU subjects, a defect that was thought to make the mucosa more susceptible to injury.

Studies in patients with GU demonstrated normal or subnormal rates of gastric acid secretion compared with non-GU subjects.

Whether there was some intrinsic defect in parietal cell function, or whether the chronic gastritis often seen in patients with GU contributed to this function was not clear. More investigative time was devoted to the study of abnormal defense mechanisms than intraluminal proteolytic mechanisms in patients with GU. Many patients with GU were shown to have abnormal forms of mucus overlying the epithelium and lower-than-normal rates of mucosal blood flow, particularly on the lesser curve at the junction of the antrum and fundus, where most benign GUs are located.

The dictum, "no acid-no ulcer" is still held to be valid. Thus, medical therapy has been directed toward neutralizing gastric luminal acid with antacids or inhibiting gastric parietal cell function with histamine H₂ receptor antagonists or proton pump inhibitors in patients with PUD. Acute ulcer healing, as observed endoscopically, can be achieved in 80% to 90% of patients receiving these forms of medical therapy. Unfortunately, when these medications are discontinued, recurrence rates are approximately 75% to 80%.³

Pharmacologic attempts at enhancing mucosal defense have had varying success. In the experimental laboratory, it is clear that exposure of the gastric lumen to prostaglandins of the E and I series inhibit gastric acid secretion while promoting the release of epithelial cell mucus and enhancing mucosal blood flow. In theory, all of these effects benefit mucosal defense. However, in randomized, prospective clinical trials, none of the synthetic prostanoids promoted acute DU healing compared with placebo. In addition, diarrhea from the enteropooling and headaches from the vasodilation caused by these medications made them poorly tolerated. Sucralfate, which has no acid neutralizing or secretory inhibitory effects, seems to be equally as effective as the antisecretory medications for acute ulcer healing. The mechanism(s) of action of sucralfate, although unknown, is thought to be related to defense enhancement. Recurrence rates after discontinuation of sucralfate also are approximately 75% to 80%. None of these observations in patients with PUD were stratified for the presence of *Helicobacter pylori* in the antral mucosa.

It was in 1984 that Marshall and Warren⁴ published their article, "Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration" in *The Lancet*. That flagellated, spiral organism that produces urease, initially referred to as *Campylobacter pyloridis*, is now known to be *H pylori*. It has spawned a plethora of published manuscripts in the scientific literature in which authors have attempted to better understand its role in PUD. In 1994, a National Institutes of Health (NIH)

Consensus Panel reviewed the available data on the relationship between the presence of *H pylori* antral mucosal colonization and PUD.⁵ A strong relationship between *H pylori* colonization and superficial gastritis was noted, but the relationship between *H pylori* colonization and PUD was more difficult to establish. There was no appropriate animal model to study. It was a fastidious organism that resisted culture and required special staining techniques to identify histologically. There was no unifying hypothesis with respect to its mechanism of pathogenicity. Perhaps the most compelling argument in favor of a causal relationship was (1) the frequency with which patients with PUD were colonized with the organism (95%) and (2) a dramatic reduction in recurrence rates from 75% before eradication of *H pylori* to 20% with the eradication of *H pylori*, in conjunction with standard antisecretory therapy. At that time, there were inadequate data to address the role of *H pylori* in patients who experienced the complications of PUD, such as bleeding, perforation, and obstruction.

OUR UNDERSTANDING OF *H PYLORI* IN THE NEW MILLENNIUM

Gastric luminal fluid, because of its acidic nature and the effect of peristalsis to prevent stasis, is normally sterile. *H pylori*, however, possesses endogenous characteristics that permit it to survive in this milieu. Although the location of the production of urease by *H pylori* is not known, the ammonia generated in the local environment of the bacterium as a result of urease activity neutralizes protons, resulting in a neutral local pH environment.⁶⁻⁸ It also provides a local nitrogen source for the metabolism of the bacterium (Table 1). The *H pylori* bacterium is flagellated, allowing for locomotion within the gastric mucus overlying the antral epithelium. Studies have demonstrated that this function is essential for colonization. Specific binding of the bacterium to the epithelial cells seems to be rare; however, it has been demonstrated by electron micrographs and is verified by the development of antibodies that can be detected systemically. This binding is specific for the epithelium of the gastric antrum and antral epithelial metaplasia of the postpyloric duodenum. The mechanism(s) involved in adhesion, although not well understood, may involve adhesins and ligands on the epithelial cell, lipid-binding adhesins, and an adhesin recognizing the Lewis blood group antigen.⁹

How does *H pylori* colonization cause inflammation? The systemic antibodies formed as a result of adhesion of the bacterium to the epithelium does not result in bacterial destruction. Perhaps this is because of the protection the mucus affords *H pylori* against

TABLE 1.

Putative Mediators of *H pylori*-Induced Gastroduodenal Epithelial Injury

Local effects

- elaboration of toxins

vacA

cagA

Effect on immune response

- elaboration of cytokines
- elaboration of IL-8
- recruitment of inflammatory cells
- release of inflammatory mediators
- production of immunoglobulins

Effect on acid secretion

- initial hypochlorhydria
- subsequent hyperchlorhydria
- elevated serum gastric levels
- reduced gastric antral somatostatin levels
- increased levels of gastric fundic N-methylhistamine
- hypergastrinemia may contribute to greater parietal cell mass

Effect on duodenal HCO₃⁻ secretion

- reduced secretion of duodenal HCO₃⁻ in patients colonized with *H pylori*

antibodies. Inflammatory cells such as T cells, plasma cells and macrophages accompany *H pylori*-induced gastritis.¹⁰ It is rare, however, to demonstrate bacterial invasion of the epithelium by either standard histologic techniques or electron microscopy. It is possible that as yet unidentified substances secreted by the bacterium lead to this inflammatory response. Contact between the *H pylori* bacterium and the antral epithelial cells induces cytokine release. Major histocompatibility complex (MHC) II antigens are expressed on the epithelial cells. The mucus overlying the bacterium-epithelial cell interface contains elevated levels of interleukin (IL)-1B, IL-2, IL-6, IL-8, and tumor necrosis factor (TNF), each of which can promote chemotaxis and activate neutrophils and T cells.¹¹⁻¹⁵ Of these cytokines, IL-8 has been the most extensively studied in this context and appears to play an important role in this inflammatory response.¹⁶⁻¹⁸

In addition to the inflammatory response described above, virulence factors, endogenous to specific strains of *H pylori*, also play

a role in the development of gastritis, ulceration, and neoplasia.¹⁹⁻²¹ The two primary gene products that come to bear on the gastric and duodenal mucosal detrimental effects of *H pylori*, to date, are vacA and cagA. The gene encoding the vacA cytotoxin is present in all *H pylori* isolates, yet not all *H pylori* bacteria are cytotoxic with respect to vacA. Recent data suggest that the *H pylori* strains associated with peptic ulceration possess an s1 signal sequence allele that appears to be associated with the production of cytotoxic vacA. This cytotoxin produces vacuolization of epithelial cell cytosol, but the mechanism of this effect has eluded investigators to date.^{22,23} The cagA protein has a 120-140 kDa molecular weight and is produced by about 60% of *H pylori* species.²⁴⁻²⁷ There is a strong correlation between *H pylori* cagA expression and epithelial cell cytosolic vacuolization. The genes for these two cytotoxins map to two distinct loci, so their expression is independent.²⁸⁻³⁰

H PYLORI COLONIZATION, GASTRIC ACID SECRETION, AND ULCER FORMATION

The gastric acid secretory response to *H pylori* colonization is variable. Early observations from volunteers' ingestion of the organism suggest that there is inhibition of acid secretion or a state of achlorhydria within 1 week.³¹ This was associated with dyspeptic symptoms and endoscopic evidence of gastritis. In one epidemiologic study in which *H pylori* was thought to be transmitted by a pH probe, 17 of 37 subjects who had acid secretory studies were achlorhydric. Evidence of gastritis is present before the development of achlorhydria.³² In most patients, the achlorhydric state subsides spontaneously; however, the pangastritis converts to antral gastritis. In most patients, a symbiotic relationship exists between the bacteria and mucosal integrity and function. Approximately 50% of adults in the United States are colonized with *H pylori*, yet only 15% to 20% of colonized patients will have PUD.

Those patients in whom DU develops have greater than normal rates of gastric acid secretion. The relationship between *H pylori* colonization and antral D-cell function results in attenuated somatostatin upon D-cell activation. As a paracrine agent, somatostatin from the D-cell diffuses in the extracellular fluid and binds to a receptor on the G-cell (gastrin) I in the antrum, inhibiting the release of the peptide. Thus, by interfering with D-cell function with *H pylori* colonization, after a meal, or with gastrin-releasing peptide (GRP) stimulation of the G-cell, an attenuated integrated gastrin response occurs in patients with DU compared to non-DU

subjects.^{33,34} This effect of *H pylori* on D-cell function may be related to alkalinization of the gastric antral mucosa from the *H pylori*-produced urease-induced release of amines derived from *H pylori* metabolism. It may also be the result of an increased expression of MHC II antigen expression on the epithelial cell resulting in increased cytokine release into the extracellular fluid surrounding the D-cell. It has been suggested that this chronic hypergastrinemia produces parietal cell hyperplasia, explaining the observation that patients with DU have a greater parietal cell mass than non-DU patients.³⁵ Gastrin secretion and stimulated gastric acid output may be reduced as much as 70% after successful eradication of *H pylori* colonization.³⁶

Fingerlike projections of antral epithelial metaplasia are frequently found in the postpyloric duodenum, thought to be caused by the acid hypersecretory state and chronic inflammation. *H pylori* only colonizes the mucus overlying antral mucosa; therefore, it is also found in the mucus and interacting with the metaplastic antral epithelium in the duodenum. The risk of developing a DU is increased fivefold in patients who exhibit this metaplasia of the duodenal bulb and 50-fold when this metaplastic epithelium is colonized by *H pylori*.³⁷

Another line of investigation regarding the role of *H pylori* and the hypersecretory state is the effect of the bacterium on histamine metabolism. Histamine, released from the enterochromaffinlike cell, is metabolized by N-histaminemethyl transferase (N-HMT) into an active metabolite, N-methylhistamine (N-MeHA), a potent acid secretagogue and inhibitor of antral D-cell somatostatin release. *H pylori* appears to possess N-HMT, shown in vitro and in vivo. High levels of N-MeHA and N-HMT were detected in cultured *H pylori*. Elevated levels of gastric mucosal N-MeHA and N-HMT were found in 13 patients colonized by *H pylori*, compared with 10 patients not colonized. This increased enzymatic activity probably contributes to the hypersecretory state in patients colonized with the bacterium.³⁸

Duodenal bicarbonate secretion from the epithelium and Brunner's glands is stimulated by luminal acidification and is considered to be an endogenous defense mechanism against the increased duodenal acid load observed in many patients with DU. Recent observations suggest that *H pylori* colonization causes an attenuation of this acid-stimulated bicarbonate response.³⁹ The mechanism involved is unknown, yet with eradication of *H pylori* colonization by antibiotics, this defect in duodenal bicarbonate secretion is ameliorated.

The stage is now set for a PUD thesis. With *H pylori* colonization, there is chronic antral and duodenal inflammation, antral metaplasia of the proximal duodenum, a hyper acid-secretory state, the release of cytotoxins vacA or cagA, increased mucosal cytokine release (particularly IL-8), and diminished duodenal bicarbonate response to luminal acidification. Why PUD develops in a low percentage of patients colonized with *H pylori* is a function of virulence factors endogenous to the *H pylori* species and host defense mechanisms.

ERADICATION OF *H PYLORI* AND TREATMENT OF PUD

The diagnosis of *H pylori* colonization can be made endoscopically or nonendoscopically. It should be remembered that, with the exception of serology, all the diagnostic tests for *H pylori* could be falsely negative in patients who have been treated recently with proton pump inhibitors, antibiotics, or bismuth-containing compounds. Endoscopically, in the acute phase of infection, pangastritis may be seen, whereas in the more chronic infection, inflammation may be limited to the antrum or duodenum. Biopsy and histologic demonstration of the organism using the Warthin-Starry stain is considered to be the "gold standard." The accuracy of this diagnosis is not 100% and interobserver variation has been demonstrated.⁴⁰ Biopsy of the antral mucosa also can be assessed for the presence of urease, commercially the CLO test, in which urea is converted to ammonia, bicarbonate and carbon dioxide, elevating the pH and causing a change in the colorimetric indicator.⁴¹ *H pylori* is a rather fastidious organism to culture, so it is not frequently used. Culture has been reported to be 100% specific and 80% to 90% sensitive.⁴²

The nonendoscopic tests include serology^{42,43} and the 13C or 14C urea breath test.^{44,45} In the former, standard kits for rapid analysis are available, as well as an enzyme-linked immunosorbent assay (ELISA). Serologic positivity suggests chronic infection; however, it may remain positive for many years, even after successful eradication of the organism. In the latter test, the patient ingests radiolabeled urea which, in the presence of urease from *H pylori*, is converted to ammonia and carbon dioxide. The radiolabeled carbon dioxide is excreted from the lungs. Air exhaled from the lungs is analyzed by either mass spectrometry or a scintillation counter. Soon, urea breath tests will be the primary assay to verify eradication of the organism after antibiotic therapy.

Optimal medical therapy for treating PUD includes both antisecretory and antimicrobial drugs. Historically, three drugs were

used to treat *H pylori*: bismuth, metronidazole, and tetracycline. With the addition of a histamine H-2 receptor antagonist for 4 weeks, a 70% to 90% successful eradication rate and 80% ulcer healing rate were observed.⁴⁶ A histamine H-2 receptor antagonist-based regimen consisting of ranitidine, bismuth citrate, and clarithromycin for 4 weeks is as effective as the metronidazole-containing regimen. Described more recently are proton pump inhibitor-based dual regimens consisting of omeprazole and clarithromycin or lansoprazole and amoxicillin, and a triple regimen of lansoprazole, amoxicillin, and clarithromycin.⁴⁷ Clarithromycin, in dual regimens, appears to be an effective alternative to metronidazole.^{48,49} All these regimens appear to have equal efficacy at eradication of *H pylori* and acute ulcer healing (Table 2). When determining an appropriate therapeutic regimen, efficacy, compliance, side effects, cost, and resistance should be taken into consideration.

INTRACTABLE DUODENAL ULCER

The general surgeon rarely sees the intractable duodenal ulcer. Most gastroenterologists treat the patient with symptomatic DU

TABLE 2.

Selected 2-Week Regimens for Treatment of *Helicobacter pylori* Colonization

Bismuth-based regimen	bismuth subsalicylate	525 mg q.i.d.
	metronidazole	250 mg q.i.d.
	tetracycline	500 mg q.i.d.
	H-2 receptor antagonist	as appropriate
Ranitidine bismuth citrate plus clarithromycin	ranitidine bismuth citrate	400 mg b.i.d.
	clarithromycin	500 mg b.i.d.
Proton pump inhibitor plus clarithromycin	omeprazole	40 mg q.d.
	clarithromycin	500 mg b.i.d.
Proton pump inhibitor triple therapy	omeprazole	20 mg b.i.d.
	or	
	lansoprazole	30 mg b.i.d.
	and	
	amoxicillin	1 g b.i.d.
	or	
	metronidazole	500 mg b.i.d.
	and	
	clarithromycin	500 mg b.i.d.

using one of the regimens mentioned above. Because all these regimens are usually successful in relieving symptoms, it is unusual for the patient with an asymptomatic DU, healed or unhealed as observed endoscopically, to be referred to a surgeon. In the patient with a symptomatic, nonhealing DU, the standard of care would be to recommend proximal gastric vagotomy. The patient would, in this instance, most likely have been treated with an antibiotic regimen that successfully eradicated *H pylori* colonization. Most surgeons would perform an esophagogastroduodenoscopy (EGD) to confirm the presence and location of the DU preoperatively. A biopsy of the antral mucosa then should be taken to test for the presence of urease. If *H pylori* is still present, depending on the intensity of the medical therapy the patient has received before being referred to the surgeon, a proximal gastric vagotomy may still be indicated.

On the other hand, the surgeon may wish to actually culture the organism for antibiotic sensitivity testing, as this is not routine in most institutions. If a strain is present that is resistant to the antibiotics the patient has received, a delay in operative intervention may be indicated so the *H pylori* colonization can be appropriately treated. If the reason for proceeding with proximal gastric vagotomy is compelling, the patient would be given the appropriate antibiotics postoperatively.

BLEEDING DU

When a DU bleeds, objective information regarding the presence of *H pylori* colonization is unlikely. In fact, in no published studies is the frequency of *H pylori* in patients with bleeding DUs clearly demonstrated. In some studies, however, the rate of recurrent bleeding fell from nearly 35% to 0% to 8% in patients appropriately treated with antibiotic therapy to eradicate *H pylori* colonization.⁵⁰⁻⁵² Although these studies were not specifically designed to address postoperative therapy, the data are profound enough to deduce that postoperative antibiotic therapy is as important a part of treatment as the operative procedure itself.

Bleeding is the complication of DU that carries the highest mortality, in part because of the frequency of rebleeding and need for additional surgery. In the acute, life-threatening situation with bleeding from the gastroduodenal artery at the base of a posterior DU, oversewing the ulcer base, with or without ligation of the gastroduodenal artery, combined with pyloroplasty and truncal vagotomy is the operation of choice. It may be possible to obtain a biopsy of the antral mucosa to assay for the presence of *H pylori*, but

antibiotic therapy should begin in the immediate postoperative period. The presence of urease in the specimen will verify the presence of *H pylori*, but a negative result is not an indication to stop already-initiated antibiotic therapy.

Patients who come to operation for recurrent episodes of non-life-threatening bleeding probably have had EGDs. The operation that carries the lowest recurrence rate, truncal vagotomy and antrectomy reconstructed with a gastroduodenostomy, is the procedure of choice in this setting. Unless the surgeon is confident that the patient has had *H pylori* successfully eradicated, appropriate antibiotic therapy should be an integral part of therapeutic intervention.

Given the low morbidity associated with antibiotic therapy, it seems reasonable to suggest that antibiotic therapy be used postoperatively in nearly all patients who require an operation for either acute or chronic DU bleeding. Recurrent postoperative bleeding—the nemesis of surgeons for years—will, hopefully, become nil.

PERFORATED DU

Most patients with acute duodenal ulcer perforation require operative intervention. When comorbid conditions preclude safe general anesthesia and a water-soluble contrast study confirms that the perforation has spontaneously sealed with omentum or against the liver, it may be reasonable to treat the patient nonoperatively, using nasogastric suction, a parenteral histamine H-2 receptor antagonist, and empiric antibiotics to eradicate *H pylori*.⁵³ Most surgeons consider the presence of comorbid conditions, more than 24 hours since the time of perforation, the presence of shock, and fewer than 3 months of symptoms to be a contraindication to definitive surgery at the time of closing the perforation operatively.⁵⁴ Omental patch closure of the duodenal wall defect, combined with parenteral histamine H-2 receptor antagonist therapy and antibiotics to treat peritoneal contamination and eradicate *H pylori* is the treatment of choice in this scenario.

Treatment for the patient who has had a perforated DU less than 24 hours, no comorbid conditions or shock, and a history of symptoms longer than 3 months is more controversial. Usually in this group, in addition to closing the perforation and treating with a parenteral histamine H-2 receptor antagonist, a definitive procedure—proximal gastric vagotomy—should be done. Published data suggest the following rates: .9% mortality, 4.5% morbidity, and 5% recurrence.⁵⁵ These data were not stratified for the presence of

H pylori colonization, and patients were not treated with antibiotics specifically designed to eradicate *H pylori* colonization.

A review of the available data indicates a wide range of *H pylori* colonization rates in patients with perforated DU. That reported rate is not universally more than 95% as with intractable DU; rather, it ranges from a high of 92% to a low of 0%.⁵⁶⁻⁵⁹ These reports use different assays to detect the presence of *H pylori*, have different inclusion and exclusion criteria, and do not report on a uniform patient population. No randomized, prospective studies have been published that address the best form of surgical therapy for these patients. A case can be made for simple omental patch closure with antibiotic therapy directed at *H pylori* alone, rather than adding proximal gastric vagotomy. Perhaps, at the very least, the indications for a definitive procedure in combination with omental patch closure should be less strict. Such decisions should be based on the surgeon's experience with proximal gastric vagotomy, the severity of the patient's preperforation symptoms, and knowledge of the patient's treatment with antibiotics to eradicate *H pylori* in the recent preperforation period.

SUMMARY

Peptic ulcer disease is a function of derangements in intraluminal aggressive factors and defects in endogenous defense mechanisms. Some of these previously described abnormalities may be caused by the presence of *H pylori* colonization of the antral mucosa and antral mucosal metaplasia of the proximal duodenum. In vivo and in vitro data are being accrued that support this concept, particularly with reference to the mechanisms of *H pylori*-induced aberrations in gastric and duodenal mucosal function.

Standard medical therapy for PUD includes antisecretory medications as well as antibiotics designed to eradicate *H pylori* colonization. It is rare for patients with an asymptomatic but nonhealed DU to come to surgical attention. Those who do, along with those with a symptomatic DU refractory to all forms of medical therapy, should be offered a proximal gastric vagotomy. Life-threatening bleeding from a DU requires secure suture ligation of the base of the ulcer combined with truncal vagotomy and pyloroplasty. Those patients with non-life-threatening hemorrhage most likely will have been treated with intensive medical therapy, including antibiotics, and should be treated with truncal vagotomy and antrectomy. If *H pylori* is still present histologically in the antral specimen, sensitivity testing of the bacteria should lead to the use of appropriate antibiotic therapy.

Both of these populations of patients with bleeding DU will likely have a lower rebleeding rate if *H pylori* is eradicated than if they are treated with surgery alone. Perforated DU should be treated with omental patch closure and antisecretory medications and antibiotics to eradicate *H pylori*, particularly when there are comorbid conditions such as shock, perforation for more than 24 hours, or if the patient has not had significant symptoms for 3 months preperforation. Those patients with perforated DU who are appropriate candidates for proximal gastric vagotomy in addition to omental patch closure and antibiotic therapy do well; however, the true benefit of proximal gastric vagotomy over omental patch closure with antibiotic therapy, in this population, has yet to be clearly demonstrated.

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