A Review of Recent Advances in the Treatment of Peptic Ulcer Disease & and Helicobacter Pylori Infection

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Abstract. Peptic ulcer disease (PUD) is common in the United States. PUD affects 10–15% of the population with 400,000 new cases diagnosed each year. Causes of PUD have been classified as entities that may increase acid production in the stomach and those that disrupt the mucosal barrier. Antacids, H-2 antagonists, proton pump inhibitors, and other drugs have been used in the treatment and represent the current course of therapy of PUD for the last decade. Nutritional aspects play a minor role in the cause and treatment of PUD. The discovery in 1983 of a bacteria in the gut of patients with gastritis and PUD has changed views in the medical community on how they should approach PUD. *Helicobacter pylori* is becoming more readily accepted as a cause of PUD. Treatment with bismuth and antibiotics together with an antisecretory drug is becoming front line treatment for the eradication of *H. pylori* and PUD. Reinfection rates after successful eradication of *H. pylori* are as low as 10% overall. A two-week "triple therapy" consisting of bismuth, metronidazole, and tetracycline or amoxicillin is a common regimen. Costs of triple therapy are considerably less than standard conventional therapy.

INTRODUCTION

Peptic ulcer disease (PUD) consists primarily of two common forms: duodenal ulcer (DU) and gastric ulcer (GU). It is estimated that PUD afflicts 10–15% of the population in the United States, that four to eight million people suffer from active or recurrent DU, and an additional 400,000 new cases are diagnosed annually.[1] Duodenal ulcer is the most common type of ulcer, and elderly people and women have a higher incidence of the disease.

Factors that have been implicated as causes of PUD are alcohol, caffeine, smoking, diet, stress, genetic diseases such as Zollinger-Ellison syndrome, potassium supplements, and certain drugs such as nonsteroidal anti-inflammatory drugs (NSAIDS).[2] In 1983 Warren and Marshall described what they termed an unidentified, curved bacteria on gastric epithelium in their patients with chronic gastritis.[3] Since that time *Helicobacter pylori* has been implicated as a risk factor for peptic ulcer disease. Significant research has been conducted to determine whether or not a bacteria such as this can live in the stomach and be the cause of ulcers.

For the last decade the conventional treatment for peptic ulcer disease has been with antacids and/or with histamine type-2 receptor antagonists (H-2 antagonists). A commonly accepted rationale for treating PUD with antacids is that ulcers are created as a result of excessive acid secretion from stomach parietal cells and that the antacid would neutralize this acid and protect the stomach from its corrosive effect. The mechanism of H-2 antagonists is to inhibit the action of histamine at the parietal histamine H-2 receptor, decreasing both basal and food-stimulated acid secretion.[4]

A new approach to treating PUD is to eradicate the organism that is believed to be causing the ulcer. Many regimens have been described in the literature and generally consist of an antibiotic and bismuth subsalicylate with or without an antisecretory drug.[1]

HELICOBACTER—A NEW GENUS IS DISCOVERED

In 1983 Warren described a corkscrew-shaped organism on gastric epithelial cells in patients with chronic gastritis.[3] A year later, a paper was published by Marshall and Warren that described the unidentified organism as having a connection with peptic ulceration.[5] They thought that this organism was a new species related to the *Campylobacter* genus. Though originally their work was met with much opposition and skepticism, Marshall was able to prove his theories.

Historically, bacteria were detected in the human stomach by Bottcher in 1874, and many investigators since then have given various descriptions of organisms in the stomach.[1,6] Three different descriptions were given of these organisms: spirochetes, streptococci, and *pseudomonas.* Marshall's description of the organism was the closest to the truth, and so in 1987 this organism was given the official name *Camphylobacter pylori.*

Ribosomal sequencing studies, analysis of the ultrastructure, determination of cellular fatty acid composition, growth characteristics, and the discovery that the organism had the ability to secrete urease led investigators to believe that this organism was from a new genus of microorganisms. A new genus was established in 1989 called *Helicobacter,* and the organism was give the official name *Helicobacter pylori.*[1,6] At the present time there are believed to be at least nine species of *Helicobacter,* four of which are considered to possess human pathogenic properties. Only one other species, *H. mustelae,* has been associated with gastroduodenal ulceration.[1]

Helicobacter pylori is a microaerophilic, gram-negative bacillus. It is present in about 10% of healthy people under the age of 30, 50% of people aged 50–65, and 75% of people aged 65 or older.[7] Patients infected with this organism may have asymptomatic gastritis or nonulcer dyspepsia or may develop peptic ulcer. *H. pylori* has been found in more than 90% of patients with DU and 70% of patients with GU.[5,7,8]

The mechanism of action by which *H. pylori* exerts its damage is not exactly known and remains controversial. Investigators have attempted to unfold the mystery; there are several theories. First, *H. pylori* reduces the hydrophobicity of the gastric mucosal through the destruction of the surface lipids by the lipases it secretes.[9] Second, *H. pylori* is thought to produce a chemoattractant substance or a chemotactic factor that attracts neutrophils and macrophages to the antral region during the development of gastritis.[10] Third, *H. pylori* inhibits somatostatin, which in turn will disinhibit the gastric secretions including gastrin.[11] Fourth, *H. pylori* produces urease, an enzyme that converts gastric urea to ammonia and carbon dioxide. This can be disruptive to the mucosal barrier.[1,12] It is known that *H. pylori* survives best in an acidic environment, but without the ability of urease to create an alkaline microenvironment, it is thought that the organism would not be able to survive.[1] *H. pylori* has mucolytic activity by secreting protease and lipase. Factors contributing to *H. pylori's* virulence usually deal with either colonization, which causes a direct damage of the mucosa by urease production, flagellar motility, cytotoxin production, parietal cell dysfunction, protease and phospholipase A-2 production, resistance to the body's immune response, and an antigen-mediated immune response.[1,6,7,13] Some studies have suggested a correlation between forms of gastric cancer and *H. pylori* infection.[14,15]

Transmission of *H. pylori* is either person to person or animal to person. In a recent review article by Ateshkadi, Lam, and Johnson,[1] the authors cited many studies that suggest a transmission from person to person. In one study 74% of parents and 84% of siblings of children with *H.pylori* infection also had the organism. This is in contrast to 24% of parents and 14% of siblings living with children who were *H. pylori* negative. In other studies, there were increased incidences of *H. pylori* in gastroenterologists who perform endoscopy, in veterinary surgeons, and in meat handlers. It has also been suggested that the organism can live in dental plaque, which could serve as a reservoir for repeated transmission and recurrent infection.

There have been many different methods developed to diagnose *H. pylori* infection. The organism can be isolated and identified in a culture. This requires a biopsy, which can easily be obtained during an endoscopy procedure. If a culture has been taken, a rapid urease test can also be performed. Serological testing is expensive and unreasonable for screening large populations. Breath tests can be used to detect urease activity. In the presence of the organism, labeled urea can be given to the patient and then the labeled CO_2 given off can be analyzed. This method is expensive and requires the use of a mass spectrometer or scintillation counter, but it is very reliable.[1,6]

TREATMENT OF PEPTIC ULCER DISEASE

Nutritional Aspects and Role of Diet in the Therapy of PUD

There is a paucity of information in the literature about nutritional aspects of treatment and cause of peptic ulcer disease. There seems to be little or no sound scientific evidence to support that diet contributes greatly to ulcerogenesis.[16] Reports have stated that a liquid diet may be more prone to cause ulcerogenesis than would a chewable, solid food diet.[17] The theory behind this is that when food is chewed, saliva is mixed with the food, and saliva contains an epidermal growth factor called urogastrone that is thought to inhibit acid secretion. Other foods or substances also have been shown to enhance ulcer formation.[18] These include cigarette smoking, coffee, tea, caffeine-containing soft drinks, and alcohol.

In the past, folklore ascribed to the use of a strict "peptic ulcer diet."[17] There was thought to be a special healing property in milk. Betram Sippy emphasized alkaline powders and mixtures of half milk and half cream to neutralize gastric acid.[17,18,19] Calcium came under attack in the 1960s when a concern about the "milk-alkali syndrome" surfaced in the medical community. This syndrome is characterized by hypercalcemia, alkalosis, azotemia without calcium in the urine, and calcification of the conjunctiva, cornea, and kidneys.[19] This, and a concern about acid rebound with calcium antacids, has removed calcium-containing antacids from being a primary source of treatment of PUD. Hade and Spiro have now challenged the acid rebound theory[19] and are investigating whether or not calcium-containing antacids should have a place in the treatment of PUD. They state that the evidence is questionable and possibly an unjustified "fall from grace of calcium carbonate" in the treatment of PUD.

With the effectiveness and potency of the H-2 antagonists, the role of diet in the therapy of peptic ulcer disease has been minor.[20] However, the role of food can not be overlooked in providing either pain or comfort to the patient with PUD. Foods such as orange juice, which have a pH of 3 or 4, and spicy foods, chili peppers, and other peppers should be avoided, so as not to contribute to the pain of PUD. Medical science has done away with some old customs in treating ulcer disease because of lack of rational evidence that they work, even though people still seem to get relief from home remedies.

It is true that certain nutrients when ingested have effects to turn on certain gastric hormones and enzymes that may set up for acid secretion.[21,22] In a study by Seidelin et al.,[23] dietary linoleic acid has been claimed to be responsible in part for the decline in peptic ulcer disease. Arachidonic acid, a metabolite of linoleic acid, is a precursor to certain prostaglandins that are cytoprotective and play a role in the mucosal barrier in the stomach lining. This study did not allow any judgments to be made regarding any causal relationship between unsaturated essential fatty acids and PUD. Omega-3 fatty acids have received much attention for their role in preventing cardiovascular disease.

It is apparently not important to have a specified diet when under therapy for peptic ulcer disease. This is largely due to the effectiveness and wide use of the H-2 antagonist drugs and other drugs that are used to control acid secretion and maintain the integrity of the gastric mucosa.

Pharmacological Aspects of Treatment of PUD

There are four main goals in the treatment of peptic ulcer disease: neutralizing existing acid, protecting stomach mucosa from existing acid, reducing secretion of new acid, and healing the ulcerated lesion. With the discovery of *H. pylori* as a causative agent in PUD, many treatment regimens have been described in the literature, most of which have been published since 1990. It now seems that it would be appropriate to add a fifth goal—eradication of *H. pylori* infection. The traditional way of treating PUD for the past decade and a half has been with the H-2 antagonist class of drug, antacids, drugs that act as proton pump inhibitors, and drugs that help maintain the integrity of the stomach lining.

1. Neutralizing Existing Acid. Antacids have been shown to be effective in neutralizing gastric acid and increasing the pH in the stomach, which may be their only role in treating PUD.[2,24] Antacids are commercially available as magnesium or aluminum hydroxide, calcium carbonate, and sodium bicarbonate and in many combinations of these agents. Side effects and numerous drug interactions with antacids may impair the absorption of some drugs. Aluminum-containing antacids may form insoluble complexes with phosphate, causing phosphate depletion. Magnesium and aluminum salts also cause diarrhea and constipation, respectively. As mentioned earlier, calcium is not used as much any more because of the potential for hypercalcemia and the fact that calcium is a potent stimulator of acid secretion. The effectiveness of antacids containing aluminum and magnesium are comparable to H-2 antagonists in promoting healing in duodenal ulcers.[2]

2. Protecting the Stomach Mucosa from Existing Acid or Drugs. Sucralfate (Carafate, MMD) is a sulfated aluminum hydroxide disaccharide that binds to ulcerated tissue, protecting it from further damage from the acidic environment in the stomach and duodenum. The drug is supplied in tablet form that can be swallowed whole, or the tablets can be placed in water, thus producing a liquid slurry that when ingested will coat the esophagus. The drug is not extensively absorbed from the gastrointestinal track, providing only local protection at the site of an ulcer or lesion. It can inhibit the absorption of some drugs and can inhibit the action of pepsin by absorbing to it. Sucralfate is indicated for use in the treatment of duodenal ulcers.[2,25]

Another drug that is used to protect the stomach mucosa is called misoprostol (Cytotec, Searle). Misoprostol is a synthetic prostaglandin E_1 analog. It possesses both antisecretory as well as mucosal protective properties. It reduces gastric acid secretion by direct action on the parietal cells. The drug can also increase mucous secretion, increase bicarbonate secretion from nonparietal cells, and stabilize mucosal membrane systems. The drug has been indicated for prevention of gastric ulcers in patients who are on NSAID therapy. Dose-related transient diarrhea is a common side effect. The drug is contraindicated for women who anticipate being or are pregnant. It is a powerful abortifacient.[2,25]

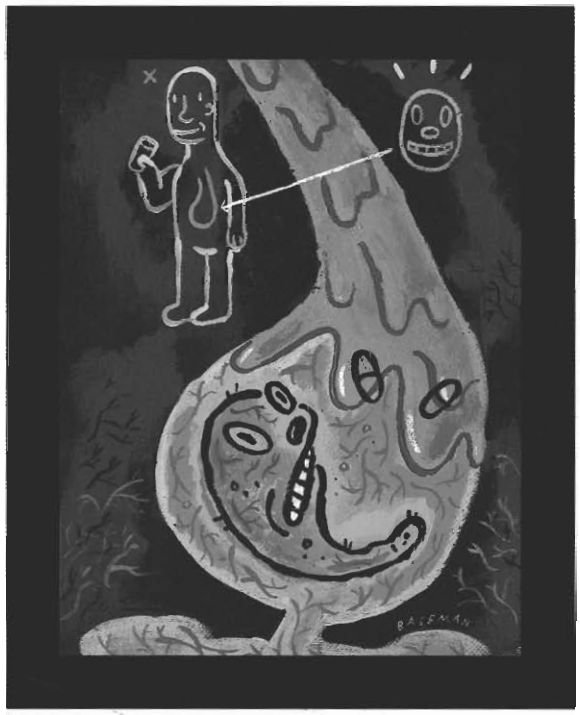
3. Reducing Secretion of New Acid. The synthesis of the first histamine type-2 receptor antagonist opened a new era in the treatment of gastroduodenal ulcer. The original work by Black[26] was so outstanding that he was awarded the Nobel prize in physiology and medicine in 1988.[26,27] There are currently four histamine type-2 receptor antagonist drugs approved for use in the United States: cimetidine (Tagamet, SK&B), ranitidine (Zantac, Glaxo), famotidine (Pepcid, MSD), and nizatidine (Axid, Lilly). The mechanism of action of these agents is to inhibit the action of histamine on the histamine type-2 receptors on the parietal cell. This action decreases gastric acid production and releases into the stomach. The drugs have also been used extensively in treating Zollinger-Ellison syndrome. Other uses include treatment of gastroesophageal reflux, upper GI bleeding, and various allergic and urticarial conditions in combination with an antihistamine (histamine type-1 antagonist). Cimetidine, ranitidine, and famotidine are also available in injectable form and are used in treating or preventing stress-related acid secretion due to iatrogenic illness or anxiety.

Severe adverse effects are not common with these drugs. However, mild side effects include headache, lethargy, confusion, and diarrhea. Hepatic metabolism is in some degree impaired because cimetidine and other H-2 antagonist drugs inhibit hepatic cytochrome P-450 enzyme systems. This can result in interference in the metabolism of certain drugs that are metabolized by the system (e.g., theophylline, coumadin macrolides).[2,25,27,26]

A new class of drugs was introduced recently. The first of these drugs, omeprazole (Prilosec, MSD) was approved for use in the U.S. for short-term treatment of peptic ulcer. The original trade name for omeprazole was Losec, but prescriptions written for Losec were often being misinterpreted for Lasix. Omeprazole controls acid

secretion by the inhibition of the gastric H+/K+ ATPase (the acid pump) enzyme involved in the final step of the secretion of H+ into the gastric lumen. The drug provides an effective means of controlling acid secretion regardless of the stimulus. There are minimal side effects, however; it can inhibit hepatic enzymes, causing interactions with other drugs. Gastrin levels that are two to four times the normal have been observed while the patient is taking omeprazole, but they return to normal after the drug is discontinued.[2,25,27,28]

4. Healing the Ulcerated Lesion. A combination of antacids, sucralfate, H-2 antagonists, and omeprazole is commonly used to treat peptic ulcer disease. The treatment is intended to be short term but often takes extended periods of time, months to years. This probably is not the result of failure of the treatment but a result of poor compliance on behalf of the patient. If the patient would follow the prescribed regimen exactly, theoretically the ulcer should be healed. This was believed to be true for many years and still is to some extent. With the discovery of *Helicobacter pylori,* however, the thinking has changed.



5. Eradication of *Helicobacter pylori.* There is extensive literature addressing the treatment of peptic ulcer disease caused by *H. pylori.* It is becoming widely accepted that the way to treat ulcer disease is to eradicate the causative organism. The subject is still controversial, but the trend seems to be treatment with bismuth compounds, namely bismuth subsalicylate (BSS) and colloidal bismuth subcitrate (CBS) as the cornerstone of treatment.[1,4,7] The use of BSS and CBS was shown to be fairly effective as monotherapy but would only suppress the growth of *H. pylori* and not completely eradicate it. The combination of bismuth compound with antibiotics has been widely investigated. However, there is little agreement on a regimen of choice. Bismuth has been shown to have some antimicrobial activity against *H. pylori.* Metronidazole (Flagyl), amoxicillin or tetracycline, and bismuth as a triple therapy seems to be the most widely accepted direction for treatment, although studies have compared different regimens.[29,30,31,32] Tucci et al. in a recent publication[33] suggested a one-day therapy of high dose amoxicillin, BSS, metronidazole, and omeprazole. They reported satisfactory results and concluded that this regimen provided an effective, safe, and inexpensive therapeutic approach. The problem is recurrence. The study was not designed to look at long-term recurrence of the infection. Many studies since then have suggested a longer duration of treatment and the standard seems to be triple therapy consisting of BSS, metronidazole, and amoxicillin or tetracycline for two to four weeks.[1,6,9,34,35]

In a recent study by Cutler and Schubert,[29] it was shown that eradication of *H. pylori* using a two-week triple therapy was very successful. Overall recurrence of the infection over a two-year period was 3.4%.

Cost of treatment for a traditional regimen of H-2 antagonists, combined with sucralfate and antacids could be more than $300 per month. Cost of a triple therapy for treatment of peptic ulcer caused by *H. pylori* based on a one-time regimen of two weeks could be as low as $40. Cost of medication is a factor worth considering. If reinfection occurred more than once a year and the patient had to be treated again and again, the savings would be in the thousands of dollars.

It is also important to consider the safety of the treatment. In the case of a triple therapy regimen, unless the patient has an allergic response or there is a direct contraindication for using the medication, triple therapy offers a safe and effective treatment for PUD.

CONCLUSION

Diet can play a role in the cause and in the treatment of PUD, but the role is minor because of the effectiveness of pharmacological agents that control acid secretion and protect the stomach. *H. pylori* has become an accepted cause of peptic ulcer disease in the research community but has not been completely accepted in practice by all physicians; however, it is evident that this new frontier will soon become the standard in practice.

Medical science has come a long way in its knowledge of treatment of various disease states. It is evident that continued research will uncover many new and innova-

tive therapeutic modalities. But these discoveries take time to be tested and accepted. It has been a decade since Warren and Marshall first identified the unknown organism that we now know as *Helicobacter pylori,* yet questions still remain about treating it. Many ideas surface only to be confounded by additional discovery. That is scientific progress.

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