The Pathophysiology and Pharmaceutical Treatment of Gastric Ulcers

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FACULTY:

J Dufton, M.D.

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Program Overview:

To provide participants with an understanding of pathophysiological and pharmaceutical treatments of gastric ulcers

OBJECTIVES:

After completing this program, participants will be able to:

- Understand the pathophysiology, incidence, and prevalence of gastric ulceration
- List primary symptoms of gastric ulceration
- List main risk factors of gastric ulceration
- Identify the most commonly used pharmaceuticals and their potential side effects
Pathophysiology

Peptic ulcers are open sores that develop on the inside mucosal lining of the digestive tract, specifically, the initial portion of the small intestine (duodenum), esophagus, and stomach. Peptic ulcers develop when the balance between the digestive acids and the protective mucosal layer is disrupted. In healthy individuals, the digestive tract is coated with a mucous membrane that protects the underlying tissue against the highly corrosive digestive acid; however, if the amount of acid is dramatically increased, or the pH of the acid is significantly reduced, or the mucus membrane layer becomes too thin or dry, the acid damages the tissue and ulceration ensues.¹ Thus, gastric ulcers are a type of peptic ulcer that affects the stomach lining due to an imbalance between gastric acid and the gastric mucosa.

Perhaps surprisingly, the most common type of peptic ulcer is not a gastric ulcer, but rather a duodenal ulcer. In the United States, approximately four-times as many duodenal ulcers are diagnosed each year compared to gastric ulcers.² The reasons for this are not completely understood, but may be related to the tissue of the stomach lining being more resilient to oxidation by strong acids compared to the tissue of the duodenum.

For many decades, peptic ulcer disease was thought to be primarily a result of emotional stress and diets rich in spicy foods. However, in the mid-1980s, *Helicobacter pylori* bacteria was discovered in the stomach of many patients with gastritis and peptic ulceration and recognized to be a significant causative agent.³ Acceptance of the bacteria-causing theory of gastric ulceration was initially very tentative, but it eventually became widely accepted, culminating in a Nobel Prize for medicine in 2005.⁴ Recent studies estimate that at least 70 percent, and possibly as high as 90 percent, of gastric ulcers are caused by *H. pylori* colonization, which results in antral mucosa erosion of the stomach, chronic inflammation, and ulcer formation.⁵ *H. pylori* infection is also involved in about 50 percent of gastric cancers.
*H. pylori* are corkscrew-shaped bacteria that commonly live and multiply within the mucous layer that covers and protects tissue lining the stomach and duodenum. The presence of *H. pylori* is usually benign and leads to no damage or negative consequences within the gastrointestinal tract. However, due to factors that are not entirely understood, *H. pylori* sometimes overgrows and is unable to be contained by the immune system despite the appearance of antibodies. The bacteria penetrate and disrupt the mucous layer and inflame the stomach lining, leading to chronic inflammation or gastritis. Chronic gastritis results in an inability to regulate gastrin, which is a peptide hormone that stimulates secretion of gastric acid (hydrochloric acid) by the parietal cells of the stomach and aids in gastric motility. Reduced regulation sometimes results in an increase of gastrin secretion, but in most cases, production is decreased, which results in either hypochlorhydria (low stomach acidity) or achlorhydria (no stomach acid). Normal plasma gastrin concentration should fluctuate between 0-200 pg/mL depending on food intake.

*H. pylori* infections that lead to increased gastrin production (up to 4,100 pg/mL in the plasma, but an average of about 1,500 pg/mL) can quickly erode the mucosal lining of the stomach and incite ulcer formation. On the other hand, chronically low production of gastrin leads to reduced digestive ability and its related sequelae, such as malabsorption, leaky gut syndrome, inflammatory reactions, and various gastrointestinal symptoms. It is not clear if transmitting *H. pylori* from person to person via saliva is a significant risk factor in developing gastric ulcers, or if a biochemical change in the bacteria’s host environment is the only causal factor. As noted above, the flora and fauna of every healthy gastrointestinal system includes *H. pylori* and numerous other types of bacteria, which normally coexist with the host symbiotically.

Another major cause of gastric ulceration is the regular use of non-steroidal anti-inflammatory drugs (NSAIDs), especially those that are classified as COX-1 inhibitors. The growth and maintenance of stomach mucus is stimulated by certain prostaglandins, which are blocked by most NSAIDs. Specifically, COX-1 inhibitors, such as aspirin, ibuprofen (Advil, Motrin), naproxen (Aleve) and ketoprofen, block the function of cyclooxygenase-1, which is essential for the production of prostaglandins needed to make the gastric mucosal lining. COX-2 selective
NSAIDs, such as celecoxib (Celebrex) or the since withdrawn rofecoxib (Vioxx), preferentially inhibit cyclooxygenase-2, which is less essential for the growth of gastric mucosa. As such, use of COX-2 inhibitors represent roughly half the risk of NSAID-related gastric ulceration when compared to COX-1 inhibitors.\textsuperscript{10} It has been predicted that as the prevalence of \textit{H. pylori}-caused ulceration declines in industrialized countries due to more appropriate medical treatment, a greater proportion of gastric ulcers will be due to increasing NSAID use among people with pain syndromes and arthritic conditions.\textsuperscript{11}

Even though it has been discovered and confirmed that bacterial infection plays a dominant role in the development of gastric and other peptic ulcers, emotional stress is still considered a significant causative factor.\textsuperscript{12} Most researchers agree that ulcers are not purely an infectious disease and that psychological factors do play an important role, although emotional stress is highly subjective and very difficult to quantify. Stress might promote \textit{H. pylori} infection and ulceration by causing an excess production of stomach acid which has been demonstrated in animal studies.\textsuperscript{13}

Other causes of gastric ulcers include conditions that can result in direct damage to the wall of the stomach lining such as alcoholism, radiation therapy, burns, and physical trauma to the abdomen. In addition to NSAIDs, over-use or misuse of virtually any oral pharmaceuticals can also precipitate gastric inflammation and ulceration, especially those medications used to treat osteoporosis called bisphosphonates (Actonel, Fosamax, others).\textsuperscript{14}

Risk factors that have been identified for gastric ulcers include tobacco smoking and chewing, moderate-to-high levels of alcohol consumption, moderate-to-high levels of coffee consumption, high-stress occupations, severe emotional trauma, long-term use of pharmaceutical medications, chronic pain, surgical procedures, advancing age, and heredity.\textsuperscript{15,16}
In terms of appearance, gastric ulcers are usually round or oval, between 2 and 4 cm in diameter, and located on the lesser curvature of the stomach. Gastric ulcers penetrate the muscularis mucosae and muscularis propria layers of the stomach by acid-pepsin aggression. The ulcer is usually smooth with regular and perpendicular borders. In contrast, irregular borders are often a sign of ulceration due to stomach cancer. During the active phase of gastric ulceration, the base of the ulcer consists of four zones: inflammatory exudate, fibrinoid necrosis, granulation tissue and fibrous tissue. The fibrous base of the ulcer may contain vessels with thickened walls or display thrombosis.

**Incidence and Prevalence**

The incidence of duodenal ulcers has dropped significantly during the last few decades, while the incidence of gastric ulcers has shown a small increase in recent years, which is mainly caused by the widespread use of NSAIDs. The two most important developments associated with the overall decreased rates of peptic ulcer disease are the discovery of effective and potent acid suppressants and the identification of *H. pylori* as the main causative agent. In essence, as the infectious cause of gastric ulceration is being successfully fought, a higher percentage of the U.S. population is succumbing to gastritis and ulceration from the chronic consumption of medication, primarily NSAIDs.

In most industrialized countries (including the U.S.), the prevalence of *H. pylori* infections leading to symptoms roughly matches age (i.e., 20 percent at age 20, 30 percent at age 30, 60 percent at age 60 etc.), although prevalence is even higher in third-world countries. Only a minority of cases of *H. pylori* infection will eventually lead to ulceration, but a large proportion will develop non-specific discomfort, abdominal pain and/or gastritis. Gastric ulcers are more common in males, especially those between the ages of 55 and 65. In the U.S., the lifetime risk for developing any type of peptic ulcer is roughly 10 percent, which means that about 20 million American adults will develop an ulcer during their life. Approximately 500,000 new cases of peptic ulcers are diagnosed yearly, with gastric varieties comprising about 16 percent of those.
As such, between 80,000 and 90,000 new cases of gastric ulceration are diagnosed yearly in the U.S. Despite duodenal ulcers being diagnosed nearly four-times more often than gastric ulcers, both types of peptic ulcers cause about 3,000 deaths each year in the U.S. Therefore, gastric ulcers are considered more life threatening due to their higher mortality rates.

**Signs and Symptoms**

Burning-type abdominal pain is the most common symptom of peptic ulcers. With gastric ulcers, the pain is felt predominantly in the middle of the abdomen, although it can be felt from the navel to the sternum and clavicles, and posteriorly in the thoracic region of the spine. The pain is caused by the tissue ulceration, which exposes nerve fibers, and aggravated by gastric acid coming in contact with the ulcerated area. The pain is typically worse with an empty stomach (about three hours after meals), although it may flare-up after eating spicy and acidic foods. Conversely, the burning pain may be temporarily relieved by eating certain foods or drinking beverages that buffer stomach acid, such as milk. The pain from gastric ulcers is rarely constant; rather, it fluctuates during the day, often flares up during the night, and might disappear for many days only to return again.

Gastric ulcers often bleed and produce distinctive signs and symptoms. Signs of bleeding in the upper digestive tract, including the stomach, are different than the signs from bleeding from the large intestine and bowel. Bleeding from gastric ulcers usually lead to black or tarry stool and vomit that looks like coffee grounds (if the blood is old and partially digested) or colored bright red (if the blood is fresh). Tarry stool from internal bleeding, known as melena, is especially foul-smelling due to the oxidized iron of the hemoglobin. In contrast, bleeding from ulceration in the lower gastrointestinal tract usually produces bright red blood in the feces, but no blood in the vomitus. In fact, vomiting is not a typical symptom of lower gastrointestinal bleeding.
In addition to intense pain and vomiting, other signs and symptoms of gastric ulcers include loss of appetite, unexplained weight loss, heartburn, indigestion, belching, bloating and nausea. Left untreated, peptic ulcers can result in anemia from loss of blood, infection (peritonitis) from tissue perforation, and scar tissue that can block passage of food through the digestive tract. Sudden, excessive bleeding can be life-threatening, especially if the ulcer erodes one of the blood vessels, such as the gastroduodenal artery. Stomach cancer is between three and six times more likely to develop from gastric ulceration caused by *H. pylori* infection. On the other hand, about four percent of stomach ulcers are actually caused by a malignant tumor, so sometimes stomach biopsies are needed to rule-out cancer.

**Diagnosing Gastric Ulcers**

The diagnosis of gastric ulceration is initially based on a physical exam; thorough history, which determines risk factors; and the presence of characteristic symptoms, which are dominated by burning stomach pain. The treating physician may then decide to test for the presence of *H. pylori*, which can be detected by a blood test, stool test, or breath test. The blood test measures antibody levels, although it is controversial whether a positive antibody test without confirming ulceration or inflammation via endoscopy is enough to warrant eradication therapy with antibiotics. A blood test is not always reliable for accurate peptic ulcer diagnosis because it cannot differentiate between past exposure to *H. pylori* and acute infection. Further, a false negative result is possible with a blood test if the patient has recently taken certain drugs, such as antibiotics or proton pump inhibitors. The stool test involves examining the feces in an attempt to find excessive numbers of *H. pylori* or antigens made against the bacteria. The breath test involves checking for *H. pylori* proliferation via radioactive carbon dioxide or urea. For radioactive carbon dioxide, the patient drinks a liquid containing radioactive carbon atoms, which are broken down by *H. pylori*. After an hour or so, the patient blows into a sealed bag and if an *H. pylori* infection is present, the breath sample will contain significant levels of radioactive carbon dioxide. This test provides the advantage of being able to monitor the response to treatment used to kill the bacteria. The urea breath test involves blowing into a bag or device and
measuring urea levels, which is an indication of urease activity by *H. pylori* proliferation. Breath tests are the least invasive and are about 95 percent accurate.

Confirmation of a gastric ulcer diagnosis is made with the help of additional tests such as endoscopies and barium contrast x-rays. The tests are typically ordered if the symptoms don’t resolve after a few weeks of treatment or when stomach pain appears in patients 45 years and older who also display unexplained weight loss, because these symptoms mimic those of stomach cancer. In patients older than 45 years, the possibility of malignancy as a cause of ulceration needs to be kept in mind. In addition to stomach cancer, other differential diagnoses for gastric ulcer include duodenal ulcer, non-ulcerative gastritis, gastroesophageal reflux disease, pancreatitis, liver congestion, cholecystitis, biliary colic, myocardial infarction, referred pain from pleurisy or pericarditis, and superior mesenteric artery syndrome.

An esophagastroduodenoscopy (EGD) is a form of endoscopy performed on patients in whom a peptic ulcer is suspected. With the patient under light sedation, the doctor inserts a thin tube with a tiny camera at the end (an endoscope) down the esophagus and into the stomach and duodenum. The endoscope allows for visual identification of the mucosal membranes of the gastrointestinal tract and lets the doctor take a sample of tissue to test for *H. pylori*. By direct visual identification, the location and severity of an ulcer can be described. If no ulcer is present, the EGD can often provide an alternative diagnosis. If a biopsy specimen is taken, histological examination and staining are undertaken and a culture is grown in order to confirm *H. pylori* infection. Further, direct detection of urease activity in a biopsy specimen is accomplished by a rapid urease test. In general, an EGD is more likely to be ordered if the patient is older, has signs of internal bleeding, or has experienced recent unexplained weight loss or significant difficulty eating and swallowing.
X-ray of the upper digestive tract can also be taken and are aided by the consumption of a chalky liquid containing barium. The barium coats the gastrointestinal tract and makes ulcers more visible on radiographs (the ulcers show up as concave depressions). The “barium swallow” series of x-rays creates images of the esophagus, stomach and small intestine. A chest x-ray can often determine if a peptic ulcer has perforated the tissue because air will leak from the inside of the gastrointestinal tract into the peritoneal cavity underneath the diaphragm, which is visualized on radiographs as darker areas. Air in the peritoneal cavity, shown on an erect chest x-ray or supine lateral abdominal x-ray, is an omen of perforated peptic ulcer disease.\textsuperscript{14}

If an ulcer is detected, it can be classified as one of five different types.\textsuperscript{17} Type-I gastric ulcers are the most common (representing about 60 percent of cases) and occur along the lesser curvature of the stomach, specifically at the incisura angularis along the locus minoris resistentiae. They ulcerate the fundic and antral mucosa regions of the stomach and often result because of hyposcretion of hydrochloric acid. Type-II gastric ulcers occur in the body of the stomach in conjunction with duodenal ulceration and are associated with hypersecretion of stomach acid. Type-III gastric ulcers are also fairly common (representing 20-25 percent of cases), occur along the pyloric channel within 3 cm of the pylorus, and are also associated with acid over-secretion. Type-IV gastric ulcers are located near the top of the stomach's lesser curvature at the proximal gastroesophageal region, occur usually because of hyposcretion of stomach acid, and respond especially well to antibiotics. Type-V gastric ulcers can occur throughout the stomach, but are associated primarily with chronic NSAID use.

**Prevention**

Prevention of gastric ulcers often involves reducing NSAID use and finding different medications or alternative approaches to relieve pain. For example, acetaminophen (Tylenol, others) has not been linked to peptic ulcers. If NSAIDs need to be taken long-term, H2 blockers or proton pump inhibitors may also be prescribed to prevent the development of peptic ulcers.
Patients may also receive a prescription for Misoprostol, a drug than can prevent NSAID-induced gastric ulcers.\textsuperscript{22}

Lifestyle is also important for reducing the risks of peptic ulcers. Doctors used to recommend eating bland foods, dairy products and small portions during meals, but newer recommendations include eating foods rich in fiber, especially fruits and vegetables. Fruits, vegetables and whole grains are also vitamin-rich, which may enhance the body’s ability to heal stomach irritation and prevent ulceration. Foods containing flavonoids, such as apples, cranberries, onions, garlic and tea may inhibit the growth of \textit{H. pylori}. Avoiding refined foods (white breads, pastas and sugar), eating less red meat and more cold-water fish, using healthy oils (olive oil or coconut oil), and reducing trans-fatty acids are all common dietary recommendations for reducing the risk of peptic ulcers.

Quitting smoking is also an important strategy because compounds in cigarettes interfere with the protective lining of the stomach, making it more susceptible to the development of ulcers. Smoking also increases stomach acid production. Reducing alcohol, coffee, and soda pop consumption can also help prevent ulcers as excessive use of these acidic beverages irritates and erodes the mucous lining of the stomach and intestines, leading to inflammation, ulceration and bleeding.\textsuperscript{25} Controlling stress and anxiety is also an important part of ulcer prevention, although not as vital as once thought. At the very least, stress may worsen the signs and symptoms of gastric ulcers. Relaxation techniques such as meditation, yoga, and tai chi are known to be able to reduce stress levels and impact peptic ulcer symptomatology.\textsuperscript{26}

\textbf{Natural Remedies}

A variety of nutritional strategies and dietary supplements have a positive impact on reducing the symptoms and retarding the development of gastric ulcers. Flavonoids and antioxidants such as anthocyanidins and resveratrol (found in blueberries, cherries, red grapes, and tomatoes) inhibit the growth of \textit{H. pylori}, which can have dramatic implications for gastric ulcer causality.\textsuperscript{27,28}
Probiotic supplements containing *Lactobacillus acidophilus* may help maintain a balance in the digestive system between beneficial and harmful bacteria, suppress *H. pylori* infection, and help reduce side effects from taking antibiotics.\(^\text{29}\) Vitamin C supplements (500 to 1,000 mg 1-3 times daily) deter the proliferation of *H. pylori* and are helpful in treating bleeding gastric ulcers caused by aspirin use.\(^\text{30}\)

Herbs have also proven helpful with treating gastric ulcers and can be taken fresh or as dried extracts or tinctures. Cranberry (*Vaccinium macrocarpon*), curcumin, enteric coated peppermint (*Mentha piperita*), black pepper (*Piper nigrum*), DGL-licorice (*Glycyrrhiza glabra*), green tea (*Camellia sinensis*) and mastic (*Pistacia lentiscus*) all help to inhibit *H. pylori* growth and protect the stomach against damage from NSAIDs.\(^\text{31,32,33}\)

Although few scientific studies have examined the effectiveness of specific homeopathic tinctures for gastric ulcers, many years of anecdotal reports suggests the following may be of help: *Argentum nitricum* (for bloating, belching and gastric pain), *Arsenicum album* (for ulcers with intense burning pain and nausea), *Kali bichromicum* (for burning or shooting abdominal pain that is worse in the night), *Lycopodium* (for bloating after eating), *Nitric acid* (for sharp, shooting pain that is worse at night), *Nux vomica* (for heartburn and indigestion), *Phosphorus* (for burning stomach pain that worsens at night), *Pulsatilla* (for symptoms that change abruptly).\(^\text{34}\)

Other natural therapies which may be of some benefit for those who suffer from gastric ulcers include acupuncture (used traditionally for a variety of conditions related to the digestive tract, including peptic ulcers) and chiropractic spinal manipulation.\(^\text{35,36}\) The nerves that innervate the stomach travel out from the thoracic spine, where they may become impinged and cause digestive dysfunction. Chiropractic spinal adjustments may take pressure off spinal nerves and restore normal organ function.
The Pharmaceutical Treatment of Gastric Ulcers

The modern history of peptic ulcer disease has followed a remarkable course and lead to widespread acceptance of the notion that the majority of gastric ulcers are caused by *H. pylori* and the institution of treatment protocols such as “triple therapy,” which has had dramatic effects (greater than 90 percent initial eradication rate and less than 10 percent re-infection rate at five years). Triple therapy is the use of a proton-pump inhibitor or H2 blocker (which both reduce gastric acid secretion) with either two different antibiotics or an antibiotic combined with bismuth salicylate (found in Pepto-Bismol). The discovery of effective and potent acid suppressants and the identification of the largely bacteria cause of peptic ulceration are the two most important developments that are associated with the overall decreased rates seen with peptic ulcer disease. Additionally, the morbidity associated with *H. pylori* infection has dramatically decreased from 1993 to present due mainly to triple therapy.

Although the overall rates of peptic ulcer disease have decreased, incidence of gastric ulceration has increased over the last few decades due to increased NSAID use. Thus, antibiotics or triple therapy are not given to patients with gastric ulcers caused by NSAIDs; rather, their pain medications are either reduced, eliminated or altered, and acid-reducing medications may be recommended for a few months to allow the ulceration to heal.

1) Proton-Pump Inhibitors

Proton-pump inhibitors are a group of drugs that display pronounced and long-lasting reduction of stomach acid production. They are among the most widely sold drugs in the world and are generally considered the most potent inhibitors of acid secretion, more so than an earlier class of inhibitors called H2-receptor antagonists (or simply H2 blockers). Proton-pump inhibitors act by irreversibly blocking the hydrogen / potassium adenosine triphosphatase enzyme system (commonly called the gastric proton pump) of the stomach’s parietal cells. The proton-pump is the final stage in stomach acid secretion, being directly responsible for secreting hydrogen ions into the gastric lumen and making it an ideal target for inhibiting acid secretion. Proton-pump
inhibitors reduce gastric acid secretion by up to 99 percent. Proton-pump inhibitors are given in an inactive form, which readily crosses cell membranes and enters into parietal cells, where they become activated by the acidic environment.

The lack of stomach acid aids in the healing of gastric ulcers and reduces the pain from indigestion and heartburn, but hydrochloric acid is required for the digestion of proteins and absorption of nutrients, especially vitamin B-12 and calcium. As such, hypochlorhydria (insufficient hydrochloric acid) can lead to a variety of side effects such as B-12 deficiency (which often mimics symptoms of Alzheimer’s), increased risk of bone fracture, increased risk of certain heart arrhythmias and interstitial nephritis, low serum magnesium levels (hypomagnesemia), headaches (the most commonly reported adverse effect), nausea, diarrhea, abdominal pain, flatulence, constipation, fatigue and dizziness. Furthermore, recent data suggests that there may be a rebound effect when proton-pump inhibitors are discontinued. In other words, stopping use can cause an increase in stomach acid production above that of normal levels that lasts for several weeks.

The most common clinically used proton-pump inhibitors include omeprazole (Losec, Prilosec, Zegerid, Lomac, Omepral, Omez), lansoprazole (Prevacid, Zoton, Monolitum, Inhibitol, Levant, Lupizole), dexlansoprazole (Kapidex, Dexilant), esomeprazole (Nexium, Esotrex), pantoprazole (Protonix, Somac, Pantoloc, Pantozol, Zurcal, Zentro, Controloc) and rabeprazole (Zechin, Rabecid, Nzole-D, Aciphex, Pariet, Rabeloc). The vast majority of these drugs are known as benzimidazole derivatives, but new research indicates that imidazopyridine derivatives may be a more effective means of treatment.

2) H2 Blockers

H2 blockers, also known as histamine blockers or H2-receptor antagonists, are competitive antagonists of histamine at the parietal cell H2-receptors in the stomach. H2 blockers suppress the secretion of hydrochloric acid by parietal cells by two mechanisms: histamine released by
enterochromaffin-like cells in the stomach is blocked from binding on parietal cell H2-receptors, which stimulate acid secretion; and as a consequence, other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H2-receptors are blocked. H2 blockers are still commonly used for the treatment of dyspepsia, but they have been surpassed in popularity by the more effective proton-pump inhibitors for the treatment of gastric ulcers.

In the U.S., all four FDA-approved members of the H2 blocker group (cimetidine, ranitidine, famotidine and nizatidine) are available over-the-counter in relatively low doses, or by prescription in larger doses. Brand names for these drugs include Tagamet (cimetidine), Zantac (ranitidine), Pepcid (famotidine) and Axid (nizatidine). Much like proton-pump inhibitors, H2 blockers are generally well-tolerated, with the exception of cimetidine (Tagamet), which was the first H2 blocker developed in the mid-to-late 1960s. Cimetidine became the first “blockbuster drug” (a drug generating more than one billion USD of revenue per year), but it was discovered to interfere with the body's mechanisms of drug metabolism and elimination through the liver cytochrome P450 pathway. As such, cimetidine use increases the risk of drug toxicity, and has also been linked to hypotension, gynecomastia in males, loss of libido, and impotence. Ranitidine (Zantac) was introduced in 1981 and was found to have a far better tolerability profile (fewer adverse drug reactions), longer-lasting action, and ten-times the biochemical activity of cimetidine. However, the most common side effects of H2 blockers can be similar to most proton-pump inhibitors because they too greatly reduce the production of hydrochloric acid, which is needed for healthy digestion and the absorption of vitamin B-12 and calcium. Due to their adverse effects on digestion and nutrient absorption, acid-reducing medications are only recommended for a consecutive duration of about two months.

3) Antibiotics

Antibiotics are prescribed to kill bacteria such as *H. pylori*, but due to resistance and adaptability, more than one type is often recommended to be taken at the same time. Antibiotic regimens are different throughout the world, but in the U.S., antibiotics prescribed for treating *H. pylori*
include amoxicillin, clarithromycin (Biaxin), metronidazole (Flagyl), furazolidone (Furoxone) and tetracycline. Antibiotics are usually prescribed for only two weeks at a time in order to avoid side effects. Relatively common side effects of antibiotic use include acquired resistance to antibiotic therapy, serious allergic reactions (including anaphylaxis), nausea, upset stomach, diarrhea, sun sensitivity, disruption of the intestinal flora and fauna, systemic overgrowth of pathogenic bacteria (such as Clostridium difficile) and yeast species (such as Candida albicans), and numerous potential interactions with other drugs.22

In the U.S., clarithromycin-based triple therapy (combined with a proton-pump inhibitor and either amoxicillin or metronidazole for 10-14 days) is considered the standard treatment for an ulcer caused by H. pylori; however, other protocols are also popular. Research shows higher cure rates with 14 days of treatment, although side effects become much more probable and severe beyond this time frame.38

At least four weeks after the initiation of antibiotic treatment, the patient is tested by the doctor using a breath or stool test to be sure the H. pylori infection has been eradicated. Blood tests are not useful after treatment because a patient's blood can test positive for H. pylori even after the bacteria have been eliminated. If the infection remains, another two-week round of triple therapy is usually recommended, but typically with a different combination of antibiotics to prevent resistance (although H. pylori resistance to amoxicillin is considered rare). Another strategy, called “salvage” or quadruple therapy, involves adding bismuth salicylate compounds to the treatment protocol.

4) Bismuth Salicylate

Medications that protect the lining of the stomach and small intestine from the damaging effects of acid are called cytoprotective agents and include the prescription medications sucralfate (Carafate) and misoprostol (Cytotec), and over-the-counter agents such as bismuth salicylate (Pepto-Bismol). Bismuth compounds may also directly kill H. pylori, although its antibacterial
actions should not be viewed as a replacement for conventional antibiotics. Bismuth salicylate, like all salicylates (especially aspirin), can cause serious bleeding problems when used alone in patients with bleeding ulcers. Bismuth quadruple therapy usually involves combining bismuth salicylate with a proton-pump inhibitor, tetracycline and metronidazole for 10-14 days.

The main reasons to add bismuth salicylate to a treatment regime for gastric ulcers is if the patient is still infected with *H. pylori* after a trial of triple therapy, or if the patient cannot take amoxicillin (a penicillin-like antibiotic) because of a penicillin allergy, or if the patient has been treated before with a macrolide antibiotic, such as clarithromycin. Side effects from bismuth salicylate are considered rare, but the most common are benign and include darkening of the stools and/or tongue, and a metallic taste in the mouth.

**Summary of Common Pharmaceutical Protocols:**

Proton-pump inhibitor / H2-blocker + clarithromycin + metronidazole / amoxicillin

Proton-pump inhibitor / H2-blocker + metronidazole + tetracycline / bismuth salicylate

Proton-pump inhibitor / H2-blocker + furazolidone + tetracycline / bismuth salicylate

**Antacids:**

Antacids are available over-the-counter. They neutralize existing stomach acid, which can provide relief of burning stomach pain, heartburn, and indigestion, but they are not considered as a treatment for gastric ulcers. Antacids do not kill *H. pylori* nor do they block the production of stomach acid. Commonly used antacids include aluminum hydroxide (Amphojel, AlternaGEL), magnesium hydroxide (Milk of Magnesia), aluminum hydroxide combined with magnesium hydroxide (Maalox, Mylanta), calcium carbonate (Rolaids, Titalac, Tums), and sodium bicarbonate (Alka-Seltzer). It is recommended to take antacids at least one hour before or two hours after taking other medications because antacids may block the medications from being
absorbed and effectively utilized.\textsuperscript{22} Other side effects can include constipation or diarrhea, depending on the main ingredients of the antacids.

**Ulcers that Fail to Heal:**

Peptic ulcers that don't heal with treatment are called refractory ulcers and may require surgery. Surgical procedures may involve a vagotomy or cauterization. Common reasons why ulcers fail to heal include: not taking medications according to directions, antibiotic resistant *H. pylori* population, patient’s use of tobacco or pain relievers that increase the risk of ulcers. Less often, refractory ulcers may be a result of extreme overproduction of stomach acid, which occurs in Zollinger-Ellison syndrome.
References:

22) PDR Medical Staff. PDR Guide to Drug Interactions, Side Effects and Indications; 2009 edition.