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Peptic Ulcers

WHAT ARE PEPTIC ULCERS?

A peptic ulcer is an open sore or raw area that tends to develop in one of two places:

- The lining of the stomach (called *gastric ulcers*), or
- The upper part of the small intestine--the *duodenum* (called *duodenal ulcers*). In the US, duodenal ulcers are three times more common than gastric ulcers.

Ulcers average between one-quarter and one-half inch in diameter. They develop when digestive juices produced in the stomach, intestines, and digestive glands damage the lining of the stomach or duodenum.

The two important digestive juices are *hydrochloric acid* and the enzyme *pepsin*. Both substances are critical in the breakdown and digestion of starch, fat, and proteins in food. They play different roles in ulcers:

- *Hydrochloric acid*. A common misbelief is that excess hydrochloric acid, which is secreted in the stomach, is solely responsible for producing ulcers. Acid output in patients with duodenal ulcers does tend to be higher than normal, but in most patients with gastric ulcers, acid production is usually normal or lower than normal. Some stomach acid, in fact, is important for protecting against *H. pylori*--the bacteria that has been the cause of most peptic ulcers. [Note: One exception is ulcers that occur in Zollinger-Ellison syndrome. This is a rare genetic condition in which very high levels of gastrin, a potent acid, is secreted by tumors in the pancreas or duodenum. See *Box Zollinger-Ellison Syndrome (ZES)*.]
- *Pepsin*. Pepsin is an enzyme that breaks down proteins in food. Since the stomach and duodenum are also composed of protein, however, they too are susceptible to the actions of pepsin. Pepsin is, then, also important in the formation of ulcers.

Fortunately, the body has provided a defense system to protect the stomach and intestine against these powerful substances:

- The *mucoous layer*, which coats the stomach and duodenum, forms the first line of defense.
- *Bicarbonate*, which the mucoous layer secretes, neutralizes the digestive acids.
- Hormone-like substances called *prostaglandins* help keep the blood vessels in the stomach dilated, ensuring good blood flow and protecting against injury. (Prostaglandins are also believed to stimulate bicarbonate and mucus production.)

Disrupting any of these defense mechanisms makes the stomach and intestine lining susceptible to the actions of acid and pepsin, increasing the risk for ulcers.

WHAT CAUSES PEPTIC ULCERS?

Helicobacter pylori (*H. pylori*)

Before the discovery of the bacterium *Helicobacter* (*H.*) *pylori*, the stomach was believed to be a sterile environment. Now, *H. pylori* is known to be a major cause of peptic ulcers. The bacteria appears to trigger ulcers in the following way:

- *H. pylori*'s corkscrew shape enables it to penetrate the mucoous layer of the stomach or duodenum so that it can attach itself to the lining.

- It survives its highly acidic environment by producing urease, an enzyme that generates ammonia and neutralizes the acid.
- *H. pylori* then produces a number of toxins and factors that in certain individuals cause inflammation and damage to the lining, leading to ulcers.
- It also alters certain immune factors that allow it to evade detection and cause persistent inflammation for a person's lifetime--even without invading the mucous membrane.

Even if ulcers do not develop, the bacterium is now considered to be a major cause of active chronic inflammation in the stomach (*gastritis*) and in the upper part of the small intestine (*duodenitis*).

It is also strongly linked to stomach (gastric) cancer and possibly other non-intestinal problems. [See discussions in How Serious Are Peptic Ulcers?]

Factors That Trigger Ulcers in H. pylori Carriers. It should be noted that *H. pylori* is found in about 25% of people who do *not* have peptic ulcers. The magnitude of *H. pylori* infection, particularly in older people, may not always predict the presence or absence of peptic ulcers. Other variables, then, need to be present to actually trigger ulcers. They may include the following:

- Genetic Factors. Some people harbor genetic strains of *H. pylori* that may make the bacteria more dangerous and increase the risk for ulcers in infected individuals. The most intensively investigated genetic factor is cytotoxin-associated gene A (CagA), which has been associated with both gastric and duodenal ulcers as well as with stomach cancer. Other genetic types that may also increase bacterial severity are called vacuolating cytotoxin (*vacA*) and antigen-binding adhesin (BabA) genotypes. Some of these genetic factors may be more or less important for development of ulcers depending on ethnicity.
- Immune Abnormalities. Some experts suggest that certain individuals have abnormalities in the immune response in the intestine that allow the bacteria to become injurious to the lining.
- Lifestyle Factors. Although lifestyle factors (e.g., chronic stress, coffee-drinking, smoking) were long believed to be the primary cause of ulcers, it is now thought they only increase susceptibility to them in some *H. pylori* carriers.

When *H. pylori* was first identified as the major cause of peptic ulcers, it was found in 90% of people with duodenal ulcers and in about 80% of people with gastric ulcers. As more people are being tested and treated for the bacteria, however, the rate of *H. pylori* associated ulcers has declined. For example, a 2001 study suggested that about half of ulcers are *not* caused by *H. pylori*. Instead, they tend to be due to regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin and other common pain relievers. Genetic factors, or, rarely, Crohn's disease or Zollinger-Ellison syndrome also cause ulcers. (see box).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) is the second most common cause of ulcers and the rate of NSAID-caused ulcers is increasing. About 20 million people take prescription NSAIDs regularly, and over 25 billion tablets of over-the-counter brands are sold each year in America. The most common NSAIDs are aspirin, ibuprofen (Advil), and naproxen (Aleve, Naprosyn), although many others are available.

Their damaging effects appears to rest primarily on actions that block an enzyme called cyclooxygenase (COX), which is involved in the production of prostaglandins. The COX enzyme has two forms:

- COX-2 causes intestinal contractions and inflammation. When NSAIDs block this enzyme, they help reduce pain and inflammation. This is their primary benefit.
- COX-1 also protects the stomach by its release of prostaglandins that protect the mucous layer, maintain normal bicarbonate levels, and keep blood flowing in the intestinal tract. When NSAIDs block COX-2, they expose the mucous lining to attack.

Standard NSAIDs block both COX-1 and COX-2. Even if an NSAID is injected intravenously, the drug will still inhibit prostaglandins in the stomach and duodenum. NSAIDs are mild acids and can cause some injury by direct exposure to the lining of the stomach. Their primary damaging effects, however, are from their actions against COX-1. Studies suggest the following risks:

- An analysis of controlled trials reported that about 1% of patients taking aspirin over a 28 month period will experience gastrointestinal bleeding. A significant risk existed even at low doses or with the use of modified-release formulations.
- Of further concern was a 1998 study indicating that taking NSAIDs for only six months posed a risk for symptomatic ulcers that was greater than 1%.

The risk for bleeding is continuous for as long as a patient is on these drugs and may even persist for about a year after taking them. Taking short courses of NSAIDs for temporary pain relief should not cause major problems

because the stomach has time to recover and repair any damage that has occurred.

Specific NSAIDs pose greater or lesser risks for ulcers and bleeding. No NSAIDs, however, even over-the-counter brands, should be used long-term except under a physician's direction.

[For additional discussions, see How Are NSAID-Induced Ulcers Prevented and Treated and Who Gets Peptic Ulcers?]

Ulcer Risk by Specific NSAIDs		
Lowest Risk	Medium Risk	Highest Risk
Nabumetone (Relafen)	Aspirin. Even low-dose aspirin (81 mg) used to protect the heart may pose some risk (although lower than standard doses).	Flurbiprofen (Ansaid) Piroxicam (Feldene) Fenoprofen Indomethacin (Indocin) Meclofenamate (Meclomen)
Etodolac (Lodine)	Ibuprofen (Motrin, Advil, Nuprin, Rufen)	Ketoprofen (Actron, Orudis KT) NOTE: Ketoprofen is often considered a medium-risk drug, but one study reported that taking the drug even one week at low doses causes significant GI injury.
Salsalate	Naproxen (Aleve, Naprosyn, Naprelan, Anaprox)	
Sulindac (Clinoril)	Diclofenac (Voltaren) Tolmetin (Tolectin)	
	NOTE: Drugs within the medium risk group vary in risk. For example, studies show that use of naproxen is twice as likely as ibuprofen to be associated with hospitalization from GI bleeding.	

Other Causes

The least common major cause of peptic ulcer disease is the Zollinger-Ellison syndrome (ZES).

Rarely, certain conditions may cause ulceration in the stomach or intestine, including:

- Radiation treatments.
- Bacterial or viral infections.
- Alcohol abuse.
- Physical injury.
- Burns.

Zollinger-Ellison Syndrome (ZES)

What is ZES?

The least common major cause of peptic ulcer disease is the Zollinger-Ellison syndrome (ZES). In this condition, gastrinomas (tumors in the pancreas and the duodenum) produce excessive amounts of gastrin, a hormone that stimulates gastric acid formation. These tumors are usually malignant, so proper and prompt management of the disease is essential.

Who Gets ZES?

The incidence of ZES in the United States is estimated at one case per million people per year, and at 0.1% to 1% among patients with peptic ulcers. The mean age at onset is 45 to 50 years, and men are affected more often than women.

How Is ZES Diagnosed?

ZES should be suspected in patients with ulcers who are not infected with *H. pylori* and have no history of NSAID use. Diarrhea may precede ulcer symptoms. Ulcers occurring in the second, third, or fourth portions of the duodenum or the jejunum (the middle section of the small intestine) are signs of the syndrome. Gastroesophageal reflux disease (backflow of the stomach's contents into the esophagus) is more prevalent and often more severe in patients with ZES, and can be complicated by ulcerations and strictures of the esophagus.

How Is ZES Treated?

Peptic ulcers associated with ZES are typically persistent and difficult to treat. Treatment consists of removing the tumors and suppressing acid with intravenous proton-pump inhibitors (Protonix). Proton-pump inhibitors block acid production and are a major advance for these patients. Previously, removing the stomach was the only option.

WHAT ARE THE SYMPTOMS OF PEPTIC ULCERS?

Dyspepsia and Common Symptoms of Ulcers

Dyspepsia. The most common symptoms of peptic ulcers are known collectively as *dyspepsia*. Peptic ulcers can occur without dyspepsia or any gastrointestinal symptoms, especially when caused by NSAIDs. Dyspepsia may be persistent or recurrent and can encompass a variety of problems in the upper abdomen, including the following:

- Pain or discomfort. [See *Ulcer Pain*, below, for more detailed description.]
- Bloating.
- A feeling of fullness. (People with severe dyspepsia are unable to drink as much water or other beverages as people with mild or no dyspepsia.)
- Hunger and an empty feeling in the stomach, often one to three hours after a meal.
- Mild nausea. (Vomiting, in fact, may relieve symptoms.)
- Regurgitation. (The sensation of acid backing up into the throat.)
- Belching.

Ulcer Pain. The pain of ulcers can be either localized in one place or diffuse. The pain has been described as burning, gnawing, or aching in the upper abdomen, or as a stabbing pain penetrating through the width of the gut. The symptoms may vary depending on the location of the ulcer:

- Duodenal ulcers often cause a gnawing pain in the upper stomach area several hours after a meal, and the pain is often relieved by eating a meal.
- Gastric ulcers may cause a dull, aching pain, often right after a meal; eating does not relieve the pain and may even worsen it. Pain may also occur at night.

Ulcer pain may be particularly confusing or disconcerting, however, since it may radiate to the back or to the chest behind the breastbone. In such cases it can be confused with other conditions--even a heart attack.

Symptoms of Anemia

Because ulcers can cause long-term hidden bleeding, patients may experience the symptoms of anemia, including fatigue and shortness of breath.

Emergency Symptoms

A sudden onset of severe symptoms may indicate intestinal obstruction, perforation, or hemorrhage, which are all emergency conditions. They may include one or more of the following:

- Tarry, black, or bloody stools.
- Severe vomiting, which may include one or more of the following: blood or a substance with the appearance of coffee grounds (a sign of a serious hemorrhage) or entire stomach contents (sign of intestinal obstruction).
- Severe abdominal pain with or without vomiting or evidence of blood.
- Persons who experience any of these symptoms should go to the emergency room immediately.

HOW SERIOUS ARE PEPTIC ULCERS AND H. PYLORI?

Impaired Quality of Life

Most people with severe ulcers experience significant pain and sleeplessness, which can have a dramatic and adverse impact on the quality of life.

Complications of Peptic Ulcers

Peptic ulcers from either *H. pylori* or NSAIDs can be very serious if they progress to the point of hemorrhage or perforation of the stomach or duodenum. Of the people who get ulcers, up to 15% will experience some degree of bleeding, which can be life threatening in some cases. Ulcers that form where the small intestine joins the stomach can swell and scar, resulting in a narrowing or closing of the intestinal opening. In such cases, a patient will vomit the entire contents of the stomach and emergency procedures are necessary.

Complications of peptic ulcers cause an estimated 6,500 deaths each year. These figures, however, do not reflect the high number of deaths associated with NSAID use. Ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs) are more likely to bleed than those caused by the bacteria *H. pylori*. NSAID-related bleeding and stomach problems may be responsible for 107,000 hospital admissions and 16,500 deaths each year.

Because there are usually no gastrointestinal symptoms from NSAIDs until bleeding begins, physicians cannot predict which patients taking these drugs will develop bleeding. The risk for a poor outcome is highest in people who have had long-term bleeding from NSAIDs, blood clotting disorders, low systolic blood pressure, mental instability, or the presence of another serious, unstable medical condition. Populations at greatest risk are elderly patients and those with other serious conditions, such as heart problems.

Stomach Cancer and Other Conditions Association with *H. pylori*

H. pylori is specifically strongly associated certain cancers. And, although evidence is inconsistent, some studies have also linked it to a number of non-gastrointestinal illnesses as well.

Stomach Cancers. Stomach cancer, also called *gastric* cancer, is the second most common cause of cancer worldwide. In developing countries where the rate of *H. pylori* is very high, the risk of stomach cancer is six times higher than in America. An important 2001 study strongly supported previous work that found a causal link between *H. pylori* infection and stomach cancer. In the study, uninfected people did not develop stomach cancer. However, the stomach cancer rates for *H. pylori*-associated conditions were: 4.7% for nonulcer dyspepsia, 3.4% for gastric ulcers, and 2.2% of stomach polyps. Experts now suggest that *H. pylori* may be as carcinogenic in the stomach as cigarette smoking is in the lungs.

The process most likely starts during childhood. Infection with *H. pylori* in early years promotes a precancerous condition called *atrophic gastritis*. This may lead to cancer through the following steps:

- With atrophic gastritis, the stomach becomes chronically inflamed and loses patches of glands that secrete protein and acid.
- Acid protects against carcinogens (substances that cause cancerous changes in cells).
- New cells replace those destroyed, but these new cells do not produce enough acid to protect against carcinogens.
- Over time, then, cancer cells in the stomach may develop and proliferate.

Onset of *H. pylori* infection in adulthood poses an even lower risk, since the development of atrophic gastritis takes years and the patient is likely to die of other causes first. Other factors, such as specific genetic strains and diets might also influence a higher risk for stomach cancer. For instance diets high in salt and low in fresh fruits and vegetables have been associated with a greater risk. Some but not all evidence suggests that the virulent *H. pylori* genetic strain called CagA may also be a particular risk factor for precancerous changes.

(Interestingly, people with duodenal ulcers caused by *H. pylori* appear to have a *lower* risk of stomach cancer, though scientists do not know why. It may be that different *H. pylori* strains affect the duodenum and the stomach. Or, the high levels of acid that affect the duodenum may help prevent the spread of the bacteria to critical areas of the stomach.)

Pancreatic Cancer. *H. pylori* has recently been linked to pancreatic cancer.

Heart Disease. Some research has reported a very high rate of *H. pylori* infection in men with coronary artery disease, but more recent work has found no relationship between the bacteria and heart disease. A 2001 study suggested that only relationship between the bacteria and heart disease may be that people with both tend to be in lower socioeconomic groups. Further studies are needed.

Other Diseases. *H. pylori* has also been weakly associated with other non-intestinal disorders including migraine, Raynaud's disease (marked by cold extremities), and some skin disorders, such as chronic hives.

WHO GETS PEPTIC ULCERS?

About 25 million American are expected to have peptic ulcers at some point in their lives. Peptic ulcer disease affects all age groups but is rare in children. Men have twice the risk for ulcers as women. The risk for duodenal ulcers tends to rise at around age 25 and continues until age 75; gastric ulcers peak in people between the ages of 55 and 65.

Risk Factors for *H. pylori*

H. pylori grows and colonizes only in the intestinal tracts of primates and in no other animals. The bacteria is most likely transmitted directly from person to person. Still, little is yet known about its transmission.

Who Harbors H. Pylori? About half of the world's adults are infected with *H. pylori*. The bacteria, however, are nearly always acquired during childhood and persist throughout life if not treated. The prevalence in children ranges from under 10% to over 80%, depending on where they live. The highest infection rates (3% to 10%) are in developing countries and the lowest (0.5%) are in industrialized nations, where the rates continue to decline. Even within industrialized countries, however, the infection rates in regions that have crowded unsanitary conditions are equal to those in developing countries.

How Does the Bacteria Pass from Person to Person? It is not entirely clear how the bacteria is transmitted. A 2001 Swedish study, for example, did not find that infected students posed any risk for their classmates. Transmission *within* families may be the most important route for *H. pylori*. A 2002 study reported that spouses of people with peptic ulcers are at significantly higher risk for ulcers, suggesting that the bacteria may be transmitted from intimate contact. Some evidence suggests that it is transmissible during gastrointestinal tract illness, particularly when vomiting occurs. The bacteria also may be passed in stools. Since *H. pylori* can live in water, but not apparently in food, then the bacteria may also be spread by sewage-contaminated water.

Who is at Risk for Ulcers from H. Pylori? Although *H. pylori* infection is very common, ulcers are very rare in children and only a minority of infected adults develops ulcers. Some known risk factors include smoking, being male, and the presence of the cytotoxin-associated gene A (CagA). Experts are unable to determine, however, any single factor or group of factors that could determine which infected patients are most likely to develop ulcers.

Risk Factors for NSAID-Induced Ulcers

Between 15% and 25% of patients who have taken NSAIDs regularly will have evidence of one or more ulcers, but in most cases they are very small. According to a 2000 study, 3.8% of regular NSAID users develop serious gastrointestinal conditions. Given the widespread use of these drugs, however, the total number of people with serious problems may be considerable. One medical center reported that between 50% and 80% of people who were hospitalized for gastrointestinal problems were taking NSAIDs.

High-Users of NSAIDs. Anyone who uses NSAIDs regularly is at risk for gastrointestinal problems. Even low-dose aspirin (81 mg) used to protect the heart may pose some risk (although lower than standard doses). In one study, over a four-year period, 4.5% of regular users were hospitalized for GI bleeding. The highest risks, however, are in people who require long-term use of very high doses, notably people who suffer from arthritis, particularly rheumatoid arthritis. Others that have a high intake of NSAIDs, include, but are not limited to, people with chronic low back pain, fibromyalgia, and repetitive stress injuries (such as carpal tunnel syndrome).

Contributing Factors. Certain factors add to the risk for ulcers in NSAID-users. They include the following:

- Those older than 65.
- Anyone with a history of peptic ulcers or upper gastrointestinal bleeding.
- Those with other serious ailments, such as heart disease or congestive heart failure.
- NSAID users who also take certain other medications, such as the anticoagulant warfarin (Coumadin), corticosteroids, or the osteoporosis drug alendronate (Fosamax).
- Alcohol abusers. Excessive alcohol use may intensify the risk of bleeding in those who also take NSAIDs. (Some studies have shown that alcohol may actually protect against *H. pylori*.) In any case, everyone should avoid excessive use of alcohol.
- People who take NSAIDs and are infected with the *H. pylori* bacteria. A 2002 study reported that the combination poses a 3.5-fold greater risk of ulcers than either one of these factors. (Not all studies report the higher risk in infected patients.)

Other Risk Factors for Ulcers from Either *H. Pylori* or NSAIDs

Stress and Psychological Factors. Although stress is no longer considered to play a causal role in ulcers, studies still suggest that stress may predispose someone to ulcers or help sustain existing ulcers. Some experts, in fact, estimate that social and psychological factors play a contributory role in 30% to 60% of peptic ulcer cases,

whether they are caused by *H. pylori* or NSAIDs. In any case, some experts believe that the anecdotal relationship between stress and ulcers is so strong that attention to psychological factors is still warranted.

Smoking. Smoking increases acid secretion, reduces prostaglandin and bicarbonate production, and decreases mucosal blood flow. Results of studies on the actual effect of smoking on ulcers, however, are mixed. Some evidence suggests that smoking delays the healing of gastric and duodenal ulcers. One study reported that after ulcers healed, about half of nonsmokers relapsed after a year, but that *all* heavy smokers relapsed after three months. Other studies have found no increased risk for ulcers in smokers. In any case, any impact of smoking on ulcers does not seem to be affected by the presence of *H. pylori*. This should not give smokers any comfort, however, given the other proven dangers from smoking.

HOW ARE PEPTIC ULCERS DIAGNOSED?

Peptic ulcers is always suspected in patients with persistent dyspepsia (e.g., bloating, belching, abdominal pain). Dyspepsia, however, occurs in 20% to 40% of people who live in industrialized nations, and only about 15% to 25% of these people actually have an ulcer. There are a number of steps needed to make an accurate diagnosis of ulcers.

Medical and Family History

The physician will ask for a thorough report of a patient's dyspepsia and other important symptoms, such as weight loss or fatigue, any present and past medication use (especially chronic use of NSAIDs), family members with ulcers, and drinking and smoking habits.

Ruling Out Other Disorders

In addition to peptic ulcers, a number of conditions, notably gastroesophageal reflux disease (GERD and irritable bowel syndrome), cause dyspepsia. In most cases, however, no cause can be determined. (In such cases, the symptoms are referred to collectively as functional dyspepsia.)

Peptic ulcer symptoms, notably abdominal and chest pain, may resemble those of other conditions, such as gallstones, or even the chest pain of heart attack. Certain features may help to distinguish these different conditions. However, symptoms often overlap, and it is impossible to make a diagnosis based on symptoms alone. A number of tests are needed. [See What Are the Symptoms of Peptic Ulcers?]

The following are some disorders that may be confused with peptic ulcers:

- **GERD.** About half of patients with gastroesophageal reflux disease (GERD) also have dyspepsia. With GERD or other problems in the esophagus (food pipe), however, the main symptom is usually heartburn, a burning pain that radiates up to the throat. It typically develops after meals and is often relieved by antacids. The patient may have difficulty swallowing, and there is often regurgitation or acid reflux. [See the *Well-Connected Report #85 Gastroesophageal Reflux Disease.*]
- **Heart Events.** Pain due to heart events, such as angina or a heart attack, is more likely to occur with exercise, and it may radiate to the neck, jaw, or arms. In addition, patients typically have distinct risk factors for heart disease, such as a family history, smoking, high blood pressure, obesity, and high cholesterol. [See the *Well-Connected Report #12 Heart Attack.*]
- **Gallstones.** The primary symptom in gallstones is typically a steady gripping or gnawing pain on the right side (under the rib cage), which can be quite severe and can radiate to the upper back. Some patients experience the pain behind the breast bone. The pain is often precipitated by a fatty or heavy meal, but gallstones almost never cause dyspepsia. [See the *Well-Connected Report #10 Gallstones and Gallbladder Disease.*]
- **Irritable Bowel Syndrome.** Irritable bowel syndrome can cause dyspepsia, nausea and vomiting, bloating, and abdominal pain. It occurs more often in women.

Dyspepsia may also occur with gastritis, stomach cancer, or as a side effect of certain drugs, including NSAIDs, antibiotics, iron, corticosteroids, theophylline, and calcium blockers used to treat high blood pressure.

Noninvasive Tests for Gastrointestinal (GI) Bleeding.

When ulcers are suspected, the physician administers tests to detect any bleeding. They include a rectal exam, a complete blood count, and a fecal occult blood test (FOBT). The FOBT tests for hidden (called *occult*) blood in stools. Typically, the patient is asked to supply up to six stool specimens in a specially prepared package. A small

quantity of feces is smeared on specially treated paper, which reacts to hydrogen peroxide. If blood is present, the paper turns blue.

Noninvasive Screening Tests for *H. Pylori*

Simple blood, breath, and stool tests can now detect *H. Pylori* with a fairly high degree of accuracy. It is not entirely clear, however, which individuals should be screened for *H. pylori*.

Candidates for Screening. Some physicians currently test for *H. pylori* only in individuals with dyspepsia who also have high-risk conditions, such as the following:

- Strong indications for ulcers, such as weight loss, anemia, or indications of bleeding.
- History of active ulcers.
- Risk factors for stomach cancer or other complications from ulcers.

Smokers and those who experience regular and persistent pain on an empty stomach may also be good candidates for screening tests. Some physicians argue that testing for *H. pylori* may be beneficial patients with dyspepsia who are regular NSAID users. In fact, given the possible risk for stomach cancer in *H. pylori* infected people with dyspepsia, some experts now recommend that *any* patient with dyspepsia that lasts longer than four weeks should be given blood tests for *H. pylori*. This is a subject of considerable debate, however.

Specific Screening Tests for H. Pylori. The following are the screening tests used or under investigation for *H. pylori*.

- **Breath Test.** A simple test called the carbon isotope-urea breath test (UBT) can identify up to 99% of people who harbor *H. pylori*. Up to two weeks before the test the patient must be off any antibiotics, bismuth-containing agents (such as Pepto Bismol), and proton-pump inhibitors. As part of the test, the patient swallows a special substance containing *urea* (a compound in mammals metabolized from nitrogen) that has been treated with carbon atoms. If present, the *H. pylori* bacteria convert the urea into carbon dioxide, which is detected and recorded in the patient's exhalation after ten minutes.
- **Blood Tests.** Blood tests are used to measure antibodies to *H. pylori*, with results available in minutes. Diagnostic accuracy is reported at 80% and 90%. One such important test is called enzyme-linked immunosorbent assay (ELISA). An ELISA test of the urine is also showing promise in children.
- **Stool Test.** A test to detect genetic fingerprints of *H. pylori* in the feces appears to be as accurate as the breath test for initial detection of the bacteria and for detecting recurrences after antibiotic therapy.

It should be noted that such tests are not as accurate as endoscopy, an invasive procedure, which is needed to confirm a diagnosis of *H. pylori*. The breath and stool tests, however, can be particularly useful after treatment to determine if patients are cured.

Managing the Test Results: Test and Treat . Depending on the results of the screening tests, some physicians take the following steps:

- **Approach for Non-Infected Individuals.** People who do not have evidence of *H. pylori* on a blood test or breath are typically given a four-week course of acid-suppressing medication, usually proton-pump inhibitors (PPIs), such as omeprazole (Prilosec).
- **Approach for *H-Pylori* Infected Individuals.** Patients who have evidence of bacterial infection are given antibiotics. If this does not relieve symptoms, they are given another six-week course of omeprazole (Prilosec). (Whether to give antibiotics to infected patients with non-ulcer dyspepsia is controversial, however, and discussed in the section What Are the Guidelines for Treating Peptic Ulcers Caused by *H. pylori*?)

If symptoms persist, then usually panendoscopy, also know simply as endoscopy, is performed. [See below.] This is an invasive procedure, but only endoscopy allows a biopsy of stomach tissue, making it the most accurate test.

Experts debate on whether endoscopy should be performed on *all* patients who do not respond to initial medication. It does not appear to add any useful information on treatment choices, however, unless there is evidence or suspicion of bleeding or serious complications. [See Panendoscopy, *below.*]

Panendoscopy

Panendoscopy (also called *gastroscopy* or, simply, *endoscopy*) is a procedure that evaluates the esophagus, stomach, and duodenum using an endoscope (a long thin tube containing a tiny video camera). When used with biopsy, panendoscopy is the most accurate procedure for detecting the presence of peptic ulcers, bleeding, and stomach cancer. It can also be used to confirm a diagnosis of *H. pylori*.

Appropriate Candidates for Panendoscopy. Panendoscopy is invasive and expensive and not suitable for everyone with dyspepsia. Most individuals with these symptoms are managed effectively after simple screening methods.

Panendoscopy is usually reserved for patients with dyspepsia who also have risk factors for ulcers, stomach cancer, or both. Such factors include the following:

- Having so-called "alarm" symptoms (unexplained weight loss, gastrointestinal bleeding, vomiting, difficulty in swallowing, or anemia).
- Being over 45 (when the risk for stomach cancer increases).

There is some debate over whether patients under 45 with persistent dyspepsia and no alarm symptoms should have endoscopy.

The Procedure. Panendoscopy may be performed either in a hospital or in a doctor's office and typically involves the following.

- The physician administers a local anesthetic using an oral spray and an intravenous sedative to suppress the gag reflex and to relax the patient.
- The physician then places an endoscope (a thin, flexible plastic tube) into the patient's mouth and down the esophagus (food pipe) into the stomach.
- A tiny camera in the endoscope allows the physician to see the surface of the esophagus, stomach, and duodenum and to search for abnormalities.
- The physician will take about ten small tissue samples (biopsies), which will be used to test for *H. pylori*.

Note: Some evidence suggests that in patients who are taking them, proton-pump inhibitors (PPIs) should be discontinued two weeks before an endoscopy. Their use may mask ulcers.

Capsule Endoscopy. Capsule endoscopy involves swallowing a capsule the size of a large vitamin, which contains tiny camera, light source, and a radio transmitter. The device takes and records pictures as it passes through the intestinal tract. At this point, its benefits are limited to the small intestine, so it is unlikely to play a role in the diagnosis of peptic or gastric ulcers. However, it has the potential to be an important tool for the diagnosis of obscure upper GI bleeding. Patients who have used it have usually found it painless and preferable to conventional endoscopy.

Upper GI Series

The upper GI (gastrointestinal) series was the standard diagnostic method for peptic ulcers until the introduction of adequate tests for detecting *H. pylori*. The patient drinks a solution containing barium. Then x-rays are taken, which may reveal inflammation, active ulcer craters, or deformities and scarring due to previous ulcers. Endoscopy is more accurate, although more invasive and expensive.

Other Laboratory Tests

Stool tests may show traces of blood that are not visible, and blood tests may reveal anemia in those who have bleeding ulcers. If Zollinger-Ellison syndrome is suspected, blood levels of gastrin should be measured.

WHAT ARE THE GUIDELINES FOR TREATING PEPTIC ULCERS CAUSED BY H. PYLORI?

Antibiotic regimens that eradicate *H. pylori* can cure peptic ulcers and are now the standard agents used for ulcers in infected individuals who are not taking NSAIDs. (Eliminating *H. pylori* can also cure the rare MALT lymphomas caused by this bacterium.) Other agents, such as proton-pump inhibitors or H₂ blockers, are useful for relieving ulcer symptoms.

[For details on these agents, see [What Are the Specific Drugs Used in Treating Peptic Ulcers?](#)]

Test and Treat: Candidates for Antibiotic Therapy and Elimination of *H. Pylori*

Patients with Clear Evidence of Ulcers. Antibiotics are clearly indicated for patients who have both ulcers and *H. pylori* infection. In spite of such clear indications, however, European and American studies continue to suggest that many physicians are still only treating symptoms and not curing the ulcers themselves. (Studies also suggest that most physicians are not counseling patients properly on the potential dangers of NSAIDs and other drugs that can cause ulcers.)

There is considerable debate about whether to test for *H. pylori* and then treat infected patients who have dyspepsia but who have no signs of ulcers.

Managing Patients with Dyspepsia and No Evidence of Ulcers

The best approach for treating dyspepsia is highly controversial. The options include the following:

- **Test and Treat.** This approach involves testing for *H. pylori* and eradicating the bacteria in infected patients.
- **Prescribing potent acid-suppressing agents.** This approach generally employs a trial of potent acid-suppression drugs called proton-pump inhibitors, such as omeprazole (Prilosec) or esomeprazole (Nexium).

In either case, endoscopy is usually performed if symptoms persist after four weeks. (Some evidence suggests that PPIs may mask ulcers, so patients taking these drugs may need to discontinue them for two weeks before endoscopy.)

Arguments for Testing and Treating Patients with Dyspepsia. The argument supporting testing and treating patients with non-ulcer dyspepsia are as follows:

- **Protection against ulcers.** Some evidence suggests that antibiotic treatments for infected patients with dyspepsia may prevent ulcers from developing. A study in 2002, for example, found that antibiotic regimens to eradicate *H. pylori* greatly decreased the likelihood of ulcers in infected patients with nonulcer dyspepsia who were also on long-term NSAIDs.
- **Protection against gastric cancer.** Some evidence suggests that eradicating *H. pylori* may prevent or delay the onset of stomach cancer in people with long-term dyspepsia who are infected with the bacteria. For example, a large 2001 study in Japan, where gastric cancer is especially common, found that such cancers developed in about 3% of infected patients with nonulcer dyspepsia. However, none occurred in dyspeptic patients who were treated with antibiotics for *H. pylori*.

Arguments Against Testing and Treating Patients with Dyspepsia. The arguments *against* testing and treating are as follows:

- **Lack of significant effect on symptoms.** Studies are mixed on whether antibiotics have much effect on dyspepsia symptoms. For example, in a 2003 study, overall symptom scores after a year were not significantly different between dyspeptic patients who were treated for *H. pylori* and patients who were maintained on PPIs.
- **Lower rates of *H. pylori* in the US.** The numbers of people with *H. pylori* infection is declining in the US, possibly making the test-and-treat approach too expensive considering the number of people it helps.
- **Increased risk for gastroesophageal reflux disease (GERD).** A number of studies suggest that *H. pylori* in the intestinal tract protects against gastroesophageal reflux disease (GERD), which in severe cases, can be a risk factor for cancer in the esophagus. Eliminating *H. pylori* may also have other adverse effects. [See Potential Adverse Effects from the Elimination of *H. pylori*, below.]
- **Overuse of antibiotics.** Concern that such treatments without clear evidence of ulcers will lead to unnecessary antibiotic prescriptions, increasing the risk for side effects. Overuse may also contribute to a growing public health problem--the emergence of bacteria that are resistant to antibiotics.

Antibiotic and Multidrug Regimens for Patients with Clear Evidence of Ulcers

The standard treatments for *H. pylori* include regimens that contain two or three antibiotics and a proton-pump inhibitor, usually omeprazole (Prilosec), which suppresses acid production. Cure rates after antibiotic treatment range from 70% to 90%.

A typical regimen contains three drugs for treating *H. pylori* and consists of the following:

- **A proton-pump inhibitor.** Omeprazole (Prilosec) is the standard proton-pump inhibitor. Others include lansoprazole (Prevacid), esomeprazole (Nexium), rabeprazole (Aciphex), and pantoprazole (Protonix). Proton-pump inhibitors are important for all types of peptic ulcers and a critical component of antibiotic regimens. They reduce the acidity in the intestinal tract, thereby increasing the effectiveness of the bacteria-fighting drugs used in regimens to treat *H. pylori* ulcers.

- Two antibiotics. Standard antibiotics are clarithromycin (Biaxin) and amoxicillin. (Some physicians substitute the antibiotic metronidazole (Flagyl) for clarithromycin or amoxicillin.)

This regimen is typically taken for at least 14 days. Many studies, however, are suggesting that it may be effective after only seven days in both adults and children.

Other regimens being used or investigated include the following:

- Quadruple (four-drug) combinations, some as short as five days, are proving to be very effective. Some contain two antibiotics, bismuth, and a proton-pump inhibitor. Of particular interest is Helicid (a new triple-drug capsule containing bismuth, metronidazole, and tetracycline), which is taken in combination with omeprazole. Clinical trials have been promising. The three-drug regimen is better tolerated, however.
- A less costly three-drug regimen uses omeprazole, bismuth (Pepto-Bismol), and tetracycline. It may be a good alternative, although it is less effective; side effects can be very distressing, and many patients cannot tolerate it.
- One potentially effective regimen uses clarithromycin (with or without amoxicillin) and Tritec, which combines ranitidine (an H₂ blocker) with bismuth citrate.
- Two-drug regimens are being developed. Some use omeprazole and one antibiotic and others use two antibiotics. So far, they are slightly less effective than taking three drugs and are not recommended.

Follow-Up. Follow-up testing for the bacteria should be conducted no sooner than four weeks after therapy is completed. Test results before that time may not be accurate.

In most cases, drug treatment relieves symptoms of ulcers. It should be noted, however, that symptom relief after treatment does not always indicate success, nor does persistence of dyspepsia necessarily mean that treatment has failed. Heartburn and other symptoms from gastroesophageal reflux disease (GERD), for example, sometimes worsen and require acid-suppression agents.

Failure. Treatment fails in about 15% of cases. Most often this is because patients fail to adhere to the regimen. Compliance with standard antibiotic regimens have been poor for the following reasons:

- The triple-drug regimens are complicated and require many pills. Helicid or two-drug combinations may help offset this problem.
- Side effects from the *H. pylori* regimens occur in up to 30% of patients. Gastrointestinal problems are very common, and cases of severe diarrhea have occurred during treatment.

Treatment may also fail if the patients harbor strains of *H. pylori* that are resistant to the antibiotics used. This is an increasing problem with some of the antibiotics used in the regimens. In such cases, different drugs will be tried.

Reinfection After Successful Treatment. Studies are indicating that, at least in developed countries, once the bacteria are eliminated, recurrence rates are low, well below 1% per year. Reinfection with the bacteria is possible, however, particularly in areas where the incidence of *H. pylori* is very high and sanitary conditions are poor. In such regions reinfection rates are between 6% and 15%.

Potential Adverse Effects from the Elimination of *H. pylori*

Weight Gain. Weight gain may be a problem in some cases.

Gastroesophageal Reflux Disease (GERD). Of ongoing interest are reports of a lower incidence of *H. pylori* in patients with gastroesophageal reflux disease (GERD). (GERD is inflammation in the esophagus, or food pipe, and the most common cause of heartburn.) There are some important unanswered questions associated with this issue:

- Is the lower incidence of *H. pylori* in GERD patients significant, and does the bacterium actually protect against GERD? Studies are still not conclusive in showing any significant risk for GERD in people who are *not* infected with *H. pylori*, except possibly in certain regions. In a 2003 study, for example, the absence of *H. pylori* infection in people with GERD was more pronounced in Asian patients compared to those in Europe and North American.
- Does eliminating the bacteria with antibiotic therapy actually produce GERD in some people? One study, for instance, observed that patients with cured infections of *H. pylori* were twice as likely to develop GERD as those who remained infected. However, a 2003 analysis of eight well-conducted studies reported no higher risk for GERD after antibiotic treatments. Nor was GERD any worse in patients who already had it. Seven of the eight studies, however, were conducted only eight weeks after antibiotic treatment. Longer follow-up studies are needed however to determine long-term consequences, if any.
- How should people who have GERD and are infected with *H. pylori* be managed? Patients with severe GERD usually require on-going proton-pump inhibitors (PPIs), such as omeprazole (Prilosec), which are

powerful acid-suppressors. Some evidence suggests that in such patients, the combination of *H. pylori* and chronic acid suppression may lead to atrophic gastritis--a precancerous condition in the stomach. Current guidelines then advocate eliminating the bacteria with antibiotics. There is some concern that once the bacteria is eliminated, however, GERD may worsen, which can pose a risk for Barrett's esophagus--also a precancerous condition. (On the encouraging side, however, evidence to date does not suggest any higher risk for more serious GERD complications after *H. pylori* is eliminated.)

Effects on Other Gastrointestinal Infections. Some evidence exists that *H. pylori* protects against *E. coli* and other gastrointestinal infections in children, particularly those that cause diarrhea. If true, then treating infected children for *H. pylori* should be undertaken very cautiously and only with evidence that the bacteria is causing harm.

WHAT ARE THE GUIDELINES FOR TREATING AND PREVENTING NSAID-INDUCED ULCERS?

General Approach for Preventing and Healing NSAID-Induced Ulcers

Preventing Ulcers or Rebleeding Induced by NSAIDs. If NSAID-induced ulcers or bleeding are identified, the first steps are the following:

- Test for *H. pylori* and if infected take antibiotic treatments.
- Try switching to alternative pain relievers. The first choice at this time are coxibs, usually celecoxib (Celebrex). It should be noted, however, that although they have a lower risk for ulcers and bleeding than standard NSAIDs, they are not entirely safe for the GI tract.

People who still need to take NSAIDs may try the following:

- Use the lowest NSAID dose possible.
- Try adding a proton-pump inhibitor (PPIs). Studies suggest they lower the risk for NSAID-induced ulcers but cannot completely prevent them. Brands include omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid), rabeprazole (Aciphex), and pantoprazole (Protonix).
- Try misoprostol or Arthrotec. If other agents are inappropriate, misoprostol protects against the major intestinal toxicity of NSAIDs. It was the first drug approved for preventing NSAID-induced ulcers. It is equally or even more effective than some of the PPIs, but it does not heal existing ulcers and has more side effects than PPIs. Patients tend to stop using it. Arthrotec is a combination of an ulcer protective agent called misoprostol and the NSAID diclofenac. One study found that patients taking Arthrotec had 65% to 80% fewer ulcers than those who took NSAIDs alone.
- One small study on animals suggested that taking L-arginine (an amino acid found in health stores) may help protect against damage from NSAIDs. As with all alternative agents, this product is not government regulated and more research is needed to confirm its benefits.

A 2002 study compared the coxib Celebrex with an NSAID (diclofenac) plus Prilosec in patients who had NSAID-induced bleeding. Unfortunately, there were no significant differences in rebleeding rates, which were high (about 5% within six months). Pain relief was about equal. More research is needed to determine whether other combinations may prove to be better for these patients.

Healing Existing Ulcers. For healing existing NSAID-induced ulcers, a number of agents are available. Treatment takes about two to six weeks. Proton-pump inhibitors are the most effective drugs. Others that may be beneficial include sucralfate or H2 blockers, such as famotidine (Pepcid AC), cimetidine (Tagamet), ranitidine (Zantac). Sucralfate may also help with dyspepsia caused by NSAIDs, but this agent plays no role in prevention. (Misoprostol, an effective agent used for prevention cannot heal existing ulcers.)

[For specific details on medications mentioned in this section, see [What Are the Specific Drugs Used in Treating Peptic Ulcers ?](#)]

Alternative Medications for People with Chronic Pain

COX-2 Inhibitors (Coxibs). Celecoxib (Celebrex), rofecoxib (Vioxx), and valdecoxib (Bextra) are known as COX-2 (cyclooxygenase-2) inhibitors, or coxibs. They inhibit an inflammation-promoting enzyme called COX-2. Others, such as etoricoxib, are under investigation. Meloxicam (Mobicox) is a related drug known as a COX-2 preferential.

Evidence is increasing that the coxibs are significantly less harmful to the gastrointestinal (GI) tract than common NSAIDs, but they still pose some risk. In an important 2003 study, Celebrex had a significantly better safety record

in the GI tract than NSAIDs and had lower rates of ulcers even in patients who needed to also take aspirin prevent heart attacks. Another 2003 study also suggested that rofecoxib was safer for the GI tract than NSAIDs. Some early evidence also suggests that, like NSAIDs, they may be partially protective against colon cancer and possibly even Alzheimer's disease.

In spite of their potential promise, some researchers believe that inhibiting COX-2 may have some negative side effects over the long term. The effects of these drugs on the heart particularly require clarification. The following are possible adverse effects or complications:

- They still pose a risk for gastrointestinal bleeding, although it is lower than with NSAIDs.
- Some studies have reported a higher incidence of heart attacks in patients taking Vioxx than in those taking NSAIDs. There were limitations to these studies, however, and 2003 study of 67,000 elderly patients found no higher risk compared to patients taking NSAIDs or any anti-inflammatory drug. Some (but not all evidence) suggests that the COX-2 inhibitors may increase the risk for blood clots. On the other hand, some studies have suggested that the anti-inflammatory effects, at least in Celebrex and meloxicam (Movicox), may have beneficial effects on blood vessels that would be heart protective.
- Celebrex or Vioxx can increase in blood pressure, with Vioxx having the greater effect.
- A few cases of neurologic side effects (hallucinations) have been observed with higher doses of Celebrex or Vioxx.
- Coxibs may have some adverse effects on kidney function, particularly in elderly people, which is similar to the effects of standard NSAIDs. Liver abnormalities, which are side effects of many drugs, have also been reported with coxibs and need further follow-up.
- They may have negative effects on pregnancy and fertility.
- Some severe allergic reactions have been reported in patients taking valdecoxib (Bextra). People allergic to sulfa drugs may be at particular risk. Anyone who develops a rash after taking these agents should stop taking them immediately.
- Patients who are sensitive to aspirin should discuss coxibs with their physician. Some may be safer for these individuals than others.

Coxibs can interfere with other drugs taken concurrently. Patients taking anticoagulant drugs such as warfarin may experience a higher risk for bleeding with the use of these agents. The use of coxibs can interfere with many other drugs taken concurrently, including lithium, methotrexate, and many others taken for heart disease, high blood pressure, or epilepsy. Patients should discuss all other medications with their physician.

COX-2 inhibitors are also significantly more expensive than traditional NSAIDs, costing about \$80 per month, compared to about \$15 for an NSAID like naproxen. Although they pose a lower risk for ulcers than NSAIDs, this risk is small for most NSAID users, so choosing coxibs may be justified only in patients with evidence of GI bleeding. More research is needed.

Capsaicin

Capsaicin is a component of hot red peppers and may bring pain relief when used as a skin cream (Zostrix). This is the only skin preparation that does more than just mask pain or reduce it temporarily. Capsaicin seems to reduce a substance in the body, known as substance P, which contributes both to inflammation and the delivery of pain impulses from the central nervous system. A small amount of capsaicin must be applied to the area of inflammation about four times a day. During the first few days of use, the patient will experience a warm, stinging sensation when the cream is applied. This sensation goes away, and pain relief usually begins within one to two weeks.

Arthrotec . Arthrotec is a combination of misoprostol [*see below*] and the NSAID diclofenac that may reduce the risk for gastrointestinal bleeding. One study found that patients taking Arthrotec had 65% to 80% fewer ulcers than those who took NSAIDs alone.

Acetaminophen . Acetaminophen (Tylenol, Anacin-3, Panadal, Phenaphen, Valadol, and other brands) is the most common alternative to NSAIDs. Acetaminophen is inexpensive and generally safe. It poses far less of a risk for gastrointestinal problems than NSAIDs and does not appear to pose a risk for miscarriage, as NSAIDs do, even when used regularly. It does have some adverse effects, however, and the daily dose should not exceed 4 grams (4000 mg). Patients who take high doses of this drug for long periods are at risk for liver damage, particularly if they drink alcohol and do not eat regularly. It may pose a small risk for serious kidney complications in people with preexisting kidney disease, although it is still the drug of choice for people with impaired kidney function. There is some evidence that taking even more than 2 grams (2000 mg) a day for the long term may confer a risk of ulcers and bleeding comparable to that of NSAIDs. This finding needs to be confirmed, however. It also may interact with certain medications, including the blood thinner warfarin.

Tramadol . Tramadol (Ultram) is a pain reliever that has been used as an alternative to opioids. It has opioid-like properties but is not as addictive. (Dependence and abuse have been reported, however.) It can cause nausea

but does not cause severe gastrointestinal problems, as NSAIDs can. Some patients experience severe itching. A combination of tramadol and acetaminophen (Ultracet) is now available and provides more rapid pain relief than tramadol alone and more durable relief than acetaminophen alone. Side effects are the same as for each of these agents.

Experimental Alternatives to COX-2s and NSAIDs. Possible safer alternatives to COX-2s and NSAIDs are also under investigation.

- NO-NSAIDs are drugs that combine NSAIDs and nitric oxide (NO), a substance that enhances blood flow to the stomach and increases levels of protective mucus and bicarbonate. These agents show particular promise in providing pain relief and reducing the risk for GI problems and warrant further investigation.
- Licofelone is drug that inhibits both the COX enzyme plus an inflammatory substance called Lipoxygenase 5. Early trials indicate they may be more effective and safer than either NSAIDs or COX-2 inhibitors, though further study is needed.

WHAT ARE THE DESCRIPTIONS OF THE SPECIFIC DRUGS USED WITH PEPTIC ULCERS?

The following drugs are sometimes used in the treatments of peptic ulcers caused by either NSAIDs or *H. pylori*. They are described in alphabetical order.

Antacids

Many antacids are available without prescription and are the first drugs recommended to relieve heartburn and mild dyspepsia. They play no major role in either prevention or healing of ulcers but help in the following ways:

- All of the many brands available rely on various combinations of three basic compounds, magnesium, calcium, or aluminum, which neutralize the acid in the stomach.
- They may also defend the stomach by increasing acid-buffering bicarbonate and mucus secretion.

It is generally believed that liquid antacids work faster and are more potent than tablets, although some evidence suggests that both forms work equally well.

Basic Salts Used in Antacids. There are three basic salts used in various antacids:

- Magnesium. Magnesium compounds are available in the form of magnesium carbonate, magnesium trisilicate, and, most commonly, magnesium hydroxide (Milk of Magnesia). The major side effect of these magnesium compounds is diarrhea.
- Calcium. Calcium carbonate (Tums, Titralac, and Alka-2) is a potent and rapid-acting antacid. It can cause constipation. There have been rare cases of hypercalcemia (elevated levels of calcium in the blood) in people taking calcium carbonate for long periods of time. This can lead to kidney failure and is very dangerous. None of the other antacids have this side effect.
- Aluminum. The most common side effect of antacids containing aluminum compounds (Amphogel, Alternagel) is constipation. Maalox and Mylanta are combinations of aluminum and magnesium, which balance the side effects of diarrhea and constipation. People who take large amounts of antacids that contain aluminum may also be at risk for calcium loss and osteoporosis. Long-term use also increases the risk for kidney stones. People who have recently experienced GI bleeding should not use aluminum compounds, if possible.

Interactions with Other Drugs. Antacids can interact with a number of drugs in the intestines and reduce their absorption. Conversely, some antacids increase the potency of certain drugs. The interactions can be avoided by taking these other drugs one hour before or three hours after the antacid.

Drug Interactions with Antacids (e.g., Maalox, Mylanta)	
Drugs that are less absorbed with antacids	Drugs that are made more potent with antacids
tetracycline	valproic acid
ciprofloxacin (Cipro)	sulfonylureas
propranolol (Inderal)	quinidine

captopril (Capoten)	levodopa
ranitidine (Zantac)	
famotidine (Pepcid AC)	

Antibiotics

H. pylori is usually highly sensitive to certain antibiotics, particularly amoxicillin or antibiotics such as clarithromycin that belong to the drug class known macrolides. Either type of agent serves effectively as a second antibiotic in a three-drug regimen. Others being used are tetracycline, metronidazole, and ciprofloxacin.

- Amoxicillin is the most common form of penicillin. It is inexpensive, but many people are allergic to it.
- Clarithromycin (Biaxin) is a macrolide and is the most expensive of the antibiotics used against *H. pylori*. It is also very effective, but there is growing bacterial resistance to this drug. Resistance rates tend to be higher in women and increase with age. Researchers fear that resistance will increase as the drug is used more and more against *H. pylori*.
- Tetracycline is effective, but tetracyclines have unique side effects among antibiotics, including skin reactions to sunlight, possible burning in the throat, and tooth discoloration. Pregnant women cannot take it.
- Ciprofloxacin (Cipro), known as a fluoroquinolone, is also sometimes used in ulcer regimens.
- Metronidazole (Flagyl) was the mainstay in initial combination regimens for *H. pylori*. As with clarithromycin, however, there continues to be growing bacterial resistance to the drug (about 25% to 35% of *H. pylori* bacteria).

Side Effects of Antibiotics.

- The most common side effects of nearly all antibiotics are gastrointestinal problems, including cramps, nausea, vomiting, and diarrhea.
- Allergic reactions can also occur with all antibiotics but are most common with medications derived from penicillin or sulfa. These reactions can range from mild skin rashes to rare but severe, even life-threatening anaphylactic shock.
- Some drugs, including certain over-the-counter medications, interact with antibiotics; patients should report to the physician all medications they are taking.
- They double the risk for vaginal infections in women.

Bismuth

Compounds that contain bismuth are often used in the three-drug antibiotic regimens. They destroy the cell walls of the *H. pylori* bacteria. The only bismuth compound available in the US has been bismuth subsalicylate (Pepto-Bismol), although a drug combination of the H2 blocker ranitidine and bismuth citrate (Tri-tec) has been released. High doses can cause vomiting and depression of the central nervous system, but the doses given for ulcer patients rarely cause side effects.

H2 Blockers

H2 blockers impede acid production by blocking the actions of histamine, a substance produced by the body that encourages acid secretion in the stomach. H2 blockers were the standard treatment for peptic ulcers until the development of antibiotic regimens against *H. pylori*. These drugs cannot cure ulcers, but in certain cases they are useful. They are effective only for duodenal ulcers, however, and have little effect on stomach (gastric) ulcers. Four H2 blockers are currently available over the counter in the US: famotidine (Pepcid AC), cimetidine (Tagamet), ranitidine (Zantac), and nizatidine (Axid). All have good safety profiles and few side effects. Each is discussed below. H2 blockers can interact with other drugs, so the physician should be made aware of any other drugs a patient is taking. There are some differences among these drugs.

• *Famotidine (Pepcid AC)*. Famotidine (Pepcid AC) is the most potent H2 blocker. The most common side effect of famotidine is headache, which occurs in 4.7% of people who take it. Famotidine is virtually free of drug interactions but it may have significant adverse effects in patients with kidney problems.

• *Cimetidine*. Cimetidine (Tagamet) has few side effects; approximately 1% of people taking cimetidine will experience mild temporary diarrhea, dizziness, rash, or headache. Cimetidine interacts with a number of commonly used medications, such as phenytoin, theophylline, and warfarin. Long term use of excessive doses (more than 3 grams a day) may cause impotence or breast enlargement in men; these problems resolve after the drug is discontinued.

• **Ranitidine.** Ranitidine (Zantac) interacts with very few drugs. In one study, ranitidine provided more pain relief and healed ulcers more quickly than cimetidine in people younger than 60, but there was no difference in older patients. A common side effect of ranitidine is headache, which occurs in about 3% of the people who take it.

• **Nizatidine.** Nizatidine (Axid) is a new H2 blocker. It is nearly free of side effects and drug interactions.

Long-Term Concerns. In most cases, these agents have good safety profiles and few side effects. H2 blockers can interact with other drugs, although some less so than other. In all cases, however, the physician should be made aware of any other drugs a patient is taking. There are also some concerns about possible long-term effects.

Also of concern are reports that long-term acid suppression with these drugs may cause cancerous changes in the stomach in patients who also have untreated *H. pylori* infections. More research is needed.

- Liver damage. (This is more likely with ranitidine than other H2 blockers, but is rare in any event.)
- Kidney-related complications. Adverse effects on the central nervous system in patients with even moderate renal (kidney) insufficiency have been reported with famotidine and may result in anxiety, depression, and mental disturbances.
- Increased risk for pneumonia in hospitalized patients.
- Ulcer complications (perforation, bleeding). Some experts are concerned that the use of acid-blocking drugs may actually increase the risk for serious complications from ulcers by masking their symptoms.

Misoprostol

Misoprostol (Cytotec) increases prostaglandin levels in the stomach lining, which protects against the major intestinal toxicity of NSAIDs.

Actions Against Ulcers. Misoprostol can reduce formation of ulcers in the upper small intestine by two-thirds and in the stomach by three quarters. It does not neutralize or reduce acid, so although the drug is helpful for preventing NSAID-induced ulcers, it is not useful in healing existing ulcers.

Side Effects.

- Diarrhea and other gastrointestinal problems are severe enough to cause 20% of patients to stop taking the drug. Taking misoprostol after meals should minimize these effects. One study indicated that taking the drug two or three times a day instead of the standard regimen of four times may prove to be just as effective and cause fewer side effects.
- Misoprostol can induce abortion or cause birth defects and should not be taken by pregnant women. If pregnancy occurs during treatment, the drug should be discontinued at once and the physician contacted immediately.

Proton-Pump Inhibitors (PPIs)

Actions Against Ulcers. Proton-pump inhibitors (PPIs) are the drugs of choice for managing patients with peptic ulcers from any cause. They suppress the production of stomach acid. These agents work by inhibiting the molecule in the stomach glands that is responsible for acid secretion, which is called the gastric acid pump.

PPIs can be used as part of a multi-drug regimen for *H. pylori* or used alone for preventing and healing NSAID-related ulcers. They are even useful in the treatment of ulcers caused by Zollinger-Ellison syndrome. (Of note, certain individuals carry a gene that regulates an enzyme called CYP2C19 that reduces the effectiveness of proton-pump inhibitors. This gene may be present in between 18% and 20% of Asians, who may not respond as well to these agents.)

Standard Brands. The standard PPI for ulcers has been omeprazole (Prilosec). In fact, it has been recommended for over-the-counter use. Other newer agents include lansoprazole (Prevacid), rabeprazole (Aciphex), esomeprazole (Nexium), and pantoprazole (Protonix). All are available orally. Pantoprazole is also available as an injection and lansoprazole as a suspension, which may be useful for patients who cannot take oral medications. In a comparison study of these agents, esomeprazole was superior in treating healing injuries in the esophagus that caused gastroesophageal reflux disease (GERD). It is not known yet, however, whether any individual PPI has superior advantages for treating ulcers.

Adverse Effects. Proton-pump inhibitors may pose the following concerns:

Side effects are uncommon but may include headache, diarrhea, constipation, nausea, and itching.

- Proton-pump inhibitors should be avoided by pregnant women and nursing mothers, although recent studies suggest that they do not pose an increased risk of birth defects.
- They may interact with certain drugs, such as antiseizure agents (e.g., phenytoin), anti-anxiety drugs (e.g., diazepam), and blood thinners (e.g., warfarin).
- Long-term use of high-dose PPIs may produce vitamin B12 deficiencies, but studies are needed to confirm any significance of this risk.
- The long-term use of proton-pump inhibitors by people with *H. pylori* may, in theory at least, reduce acid secretion enough to cause atrophic gastritis (chronic inflammation of the stomach). This condition, in turn, is a risk factor for stomach cancer. To compound concerns, long-term use of PPIs may mask symptoms of stomach cancer and so delay a diagnosis. To date, however, there have been no reports of an increased risk of stomach cancer with long-term use of these drugs.

Sucralfate

Sucralfate (Carafate) seems to work by adhering to the ulcer crater and protecting it from further damage by stomach acid and pepsin. It also promotes the defensive processes of the stomach. Sucralfate has an ulcer-healing rate similar to that of H₂ blockers. Other than constipation, which occurs in 2.2% of patients, the drug has few side effects. Sucralfate does interact with a wide variety of drugs, including warfarin, phenytoin, and tetracycline.

Experimental Agents

Ecabet is a unique anti-ulcer agent that is showing promise in early studies. It acts on the mucus lining of the stomach and has anti-bacterial activity.

HOW ARE BLEEDING ULCERS TREATED?

General Overview

When a patient comes to the hospital with bleeding ulcers, in most cases, endoscopy is performed. This procedure is critical for all phases of bleeding ulcers, including diagnosis, determination of treatment options, and treatment itself.

In high-risk patients or those with evidence of bleeding, options include watchful waiting with medical treatments or surgery. The first critical steps for massive bleeding is to stabilize the patient and support vital functions with fluid replacement and possibly blood transfusions. People on NSAIDs should discontinue them if possible.

Depending on the intensity of the bleeding, patients can be released from the hospital within a day or kept up to three days after endoscopy. Bleeding stops spontaneously in about 70% to 80% of people, but 30% of patients who come to the hospital for bleeding ulcers will need surgery. Endoscopy is the surgical procedure most often used for treating bleeding ulcers and for patients at high-risk for rebleeding. It is usually used in combination with medications, such as epinephrine and intravenous proton-pump inhibitors.

Between 10% to 20% of patients require more invasive procedures, usually major abdominal surgery. Such patients are usually bleeding.

Endoscopy for Treating or Preventing Bleeding Ulcers

Endoscopy is important for both diagnosing and treating bleeding ulcers. The physician first places an endoscope (a thin, flexible plastic tube) into the patient's mouth and down the esophagus (food pipe) into the stomach.

Endoscopy Used for Diagnosing Bleeding Ulcers and Determining Risk for Rebleeding. Physicians are able to detect the signs of bleeding such as active spurting or oozing of blood from arteries. Endoscopy can also detect specific features in the ulcers referred to as *stigmata*, which indicate a higher or lower risk for rebleeding.

Such features include the following:

- Low-risk (5% to 15%) for bleeding: flat dot; a clean or white base.
- High-risk (30% to 50%) for bleeding. Swollen but nonbleeding blood vessels; blood clots that adhere to ulcers.
- According to one study, if patients with these high-risk features are untreated, their risk for rebleeding after endoscopy ranges from about 10% in the first day after endoscopy to about 3% by the third day. Identifying

and treating patients with high-risk features in the ulcers (referred to as stigmata) can reduce these risks. (Other factors that increase the risk for rebleeding include have bleeding disorders, very low blood pressure, other serious medical conditions, and bleeding that started after hospitalization.)

Endoscopy as Treatment. Endoscopy is usually employed to treat bleeding from ulcers with visible blood vessels that are less than 2 mm in diameter. This approach also appears to be very effective in preventing rebleeding in patients whose ulcers are not bleeding but have high-risk features (swollen blood vessels or clots adhering to ulcers).

The following is a typical endoscopy procedure in many patients:

- The surgeon passes a probe through an endoscopic tube and applies electricity, heat, or small clips to coagulate the blood and stop the bleeding. It also causes fluid build-up that helps to compress the blood vessels.
- In high-risk cases, the physician may inject epinephrine (commonly known as adrenaline) directly into the ulcer to enhance the effects of the heating process. Epinephrine activates the process leading to blood coagulation, narrows the arteries, and enhances blood clotting.
- Intravenous (IV) administration of a proton-pump inhibitor--most likely omeprazole or the newer PPI pantoprazole--significantly prevents rebleeding and appears to be cost effective. In one major study, the use of IV proton-pump inhibitors reduced the risk for bleeding from 23% without the agent to 7% with a PPI. (Oral PPIs are also effective, but studies are needed to compare their effectiveness with IV PPIs. A proton-pump inhibitor may also be useful alone for initial bleeding episodes if endoscopy is unsuccessful, inappropriate, or unavailable.)

Intravenous H₂ blockers are often used, but a major analysis reported no benefits from their use in bleeding duodenal ulcers--although they may be useful for gastric ulcers.

Endoscopy is effective in controlling bleeding in more than 85% of appropriate candidates. If rebleeding occurs, a repeat endoscopy performed by experienced doctors may be effective in about 75% of cases. Those who fail to respond require major abdominal surgery. The most serious complication from endoscopy is perforation of the stomach or intestinal wall, which occurred in about 1.4% of patients in one large 2002 study.

Other Medical Considerations. Certain agents may be warranted after endoscopy:

- Patients who harbor the *H. pylori* bacteria, even if NSAIDs caused the bleeding, should be treated with antibiotic therapy to eradicate the bacteria. Triple therapy, including antibiotics, to eradicate *H. pylori* immediately after endoscopy is warranted in most patients infected with the bacteria.
- Somatostatin (a hormone used to prevent bleeding in cirrhosis) is also useful for reducing persistent peptic ulcer bleeding or the risk of recurrence. Researchers are investigating adding other therapies, such as fibrin glue, a blood clotting factor. To date none are more effective than the current therapies.

Major Abdominal Surgery

Major abdominal surgery for bleeding ulcers is now generally performed only when endoscopy fails or is not appropriate. Certain emergencies may require surgical repair, such as when an ulcer perforates the wall of the stomach or intestine, causing sudden intense pain and life-threatening infection.

Surgical Approaches. The standard major surgical approach uses a wide abdominal incision and standard surgical instruments (called open surgery). Laparoscopic techniques employ small abdominal incisions and the insertion of tubes that contain miniature viewing tubes and instrument. They are increasingly being used for perforated ulcers. Surgery is not effective for upper GI ulceration caused by chronic NSAID use.

Major Surgical Procedures. There are a number of surgical procedures aimed at long-term relief of ulcer complications.

- Vagotomy cuts the vagus nerve and interrupts messages from the brain that stimulate acid secretion in the stomach. This surgery may impair stomach emptying; a recent variation that cuts only parts of the nerve may reduce this complication.
- Antrectomy removes the lower part of the stomach, which manufactures the hormone responsible for stimulation of digestive juices.
- Pyloroplasty enlarges the opening into the small intestine so that stomach contents can pass into it more easily.

Antrectomy and pyloroplasty are usually performed with vagotomy.

WHAT LIFESTYLE CHANGES ARE RECOMMENDED FOR PEPTIC ULCERS AND DYSPEPSIA?

Diet

It was common in the past to restrict people suffering from peptic ulcers to frequent intake of small amounts of bland foods and milk. Exhaustive research conducted since then has shown that a bland diet is not effective in reducing the incidence or recurrence of ulcers, and that frequent small meals throughout the day are no more effective than consumption of three meals per day. Large amounts of food should still be avoided because stretching or swelling of the stomach can result in painful symptoms.

Fruits and Vegetables. The good news is that a diet rich in fiber may cut the risk of developing ulcers in half and speed healing of existing ones. Fiber found in fruits and vegetables is particularly protective; vitamin A contained in many of these foods may increase the benefit. Some studies on associations between specific food chemicals and ulcers are as follows:

- In one study, apples and yams appeared to be especially helpful.
- Apples, celery, cranberries, onions, red wine, and green and black tea are also high in natural chemicals known as flavonoids that appear to inhibit *H. pylori* growth and have many other health benefits. In fact, cranberry juice specifically may have properties that help prevent *H. pylori* from infecting the intestinal lining.
- Of great interest are laboratory experiments suggesting that a compound found in broccoli and broccoli sprouts called sulforaphane may also be lethal to *H. pylori*, even drug-resistant strains. Additional testing is under way.
- Tea has chemicals that may help protect against cancers in the stomach and esophagus.

Milk. Milk actually encourages the production of acid in the stomach, although moderate amounts (two to three cups a day) can be drunk without harm.

Coffee and Carbonated Beverages. Coffee (both caffeinated and decaffeinated), soft drinks, and fruit juices with citric acid increase stomach acid production. Although no studies have proven that any of these drinks contribute to ulcers, consuming more than three cups of coffee per day may increase susceptibility to *H. pylori* infection.

Spices and Peppers. Studies conducted on spices and peppers have yielded conflicting results. The rule of thumb is to use these substances moderately, and to avoid them if they irritate the stomach.

Garlic. Some studies suggest that high amounts of garlic may have some protective properties against stomach cancer, although a recent study concluded that it offered no benefits against *H. pylori* itself and, in high amounts, causes considerable gastrointestinal distress.

Vitamins. Although no vitamins have been shown to protect against ulcers, *H. pylori* appears to impair absorption of vitamin C, which may play a role in the higher risk of stomach cancer.

Exercise

Some evidence exists that exercise may help reduce the risk for ulcers in some people. In one 2000 study, exercise was associated with a lower risk for duodenal (but not gastric) ulcers in men. In this study, exercise appeared to have no effect on ulcer development in women.

Stress Relief

Stress relief programs have not been shown to promote ulcer healing, but they may have other health benefits.

Alternative Treatments

Melatonin is a hormone found in the brain that is normally associated with its role in sleep. Researchers have also observed that gastrointestinal tract is rich in melatonin, and that the hormone may have properties that help prevent ulcers, reduce acid secretion, and improve blood flow. It is not known whether this would benefit peptic ulcers, but it appears to warrant some research. Melatonin is a powerful hormone that can have major effects on all parts of the body. Doses of melatonin over 0.3 can disrupt the body's natural clock in the brain and long-term consequences are unknown. High doses have been associated with the following adverse events:

- Mental impairment.
- Severe headaches.
- Nightmares.

Interactions with other drugs are not completely known. It should be stressed that melatonin is currently classified as a dietary supplement and not as a drug, so its quality and effectiveness is uncontrolled in the US. (The United States is the only developed nation that does not regulate this agent.) The bottom line is that at this time, people who take melatonin are experimenting on themselves.

WHERE ELSE CAN INFORMATION ABOUT PEPTIC ULCERS BE OBTAINED?

National Digestive Diseases Information Clearinghouse (www.niddk.nih.gov). Call 301-654-3810.

American Gastroenterological Association (www.gastro.org). Call 800-NO-ULCER.

American Society for Gastrointestinal Endoscopy (www.asge.org). Call 978-526-8330.

American College of Gastroenterology (www.acg.gi.org). Call 703-820-7400.

Helicobacter pylori Foundation (www.helico.com .

Centers for Disease Control and Prevention (www.cdc.gov). Call 800-311-3435.

Find an Endoscopist at www.asge.org.

Find a Gastroenterologist at www.acg.gi.org/acg-dev/patientinfo/frame_phylocator.html.

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