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THE ROLE OF AN AGGRESSIVE FACTOR IN PEPTIC ULCER DISEASE (PUD)

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Abstract

The stomach is the expanded part of the digestive tract between the esophagus and the small intestine. It acts as a reservoir and has chief function in enzymatic digestion. Several types of glands provide different types of secretions in the alimentary tract most of which act as lubricant and to protect the stomach mucosa from excoriation. The pathophysiology of peptic ulcer disease (PUD) is often described as an imbalance between aggressive factors and mucosal protective mechanisms. *Helicobacter pylori*, a gram-negative organism that has been identified as a potential causative agent in the pathogenesis of peptic ulcer disease, which is diagnosed by invasive or non-invasive methods. Three classes of drugs have been shown to have a direct effect on *Helicobacter pylori*: antibiotics, bismuth salts, and proton pump inhibitors. Because *Helicobacter pylori* is difficult to eradicate, most treatment regimes combine agents from two or even all three of these cases. In all of them, patients with active peptic disease should also receive a total of 6 weeks of acid suppression with an H_2-receptor antagonist. The discovery of *Helicobacter pylori* as a gastrointestinal pathogen has had a profound effect on current concepts of the pathogenesis and treatment of peptic ulcer disease.

Key words: peptic ulcer disease, *Helicobacter pylori*, H_2-receptor antagonist, pathophysiology

List of Abbreviations

ADF	American Digestive Health Foundation
CagA	Cytotoxin-associated gene- A
CDC	Center for Disease Control and Prevention
GERD	Gastro-Esophageal Reflux Disease
H-gated	Hydrogen ion-gated
H_2O_2	Hydrogen peroxide
H_2-receptor	Histamine-2-Receptor Antagonists
NIH	National Institutes of Health
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
PUD	Peptic Ulcer Disease
VacA	Vacuolating cytotoxin- A

Introduction

The alimentary tract provides the body with a continual supply of water, electrolytes, and nutrients. To achieve this requires: movement of food through the alimentary tract; secretion of digestive juices and digestion of food; absorption of the digested products, water, and the various electrolytes; circulation of blood through the gastrointestinal organs to carry away the absorbed substances; and control of all these functions by the nervous and hormonal systems (Guyton and Hall, 2006). The lining of the gastrointestinal tract constitutes the body's largest surface area facing the external environment. The integrity of the mucosa depends on the balance between aggressive luminal factors and mucosal defense mechanisms. Changes in this balance may lead to gastrointestinal disorders or diseases. The complex mechanism by which this tube, almost nine meters long in humans, maintains its integrity has challenged and fascinated physiologists for centuries. One of the characteristic features of the gastric mucosa, in common with other epithelia tissues of the gastrointestinal tract, is a continuous layer of mucus covering its entire surface (Guyton and Hall, 2006).

The Role of an Aggressive Factor in Peptic Ulcer Disease (PUD)

The pathophysiology of peptic ulcer disease can be seen as an imbalance between mucosal aggressive factors (e.g., acid and pepsin) and mucosal protective factors (e.g. mucous production, bicarbonate secretion and blood flow) (Decross and Marshall, 1993). *Helicobacter pylori* is a gram-negative organism that has been identified as a potential causative agent in the pathogenesis of peptic ulcer disease.

Alterations in mucosal protective factors induced by *Helicobacter pylori* are significant cofactors in the formation of peptic ulcer disease. Cigarette smoking, alcohol use and NSAIDs are also factors that impair mucosal protective factors.

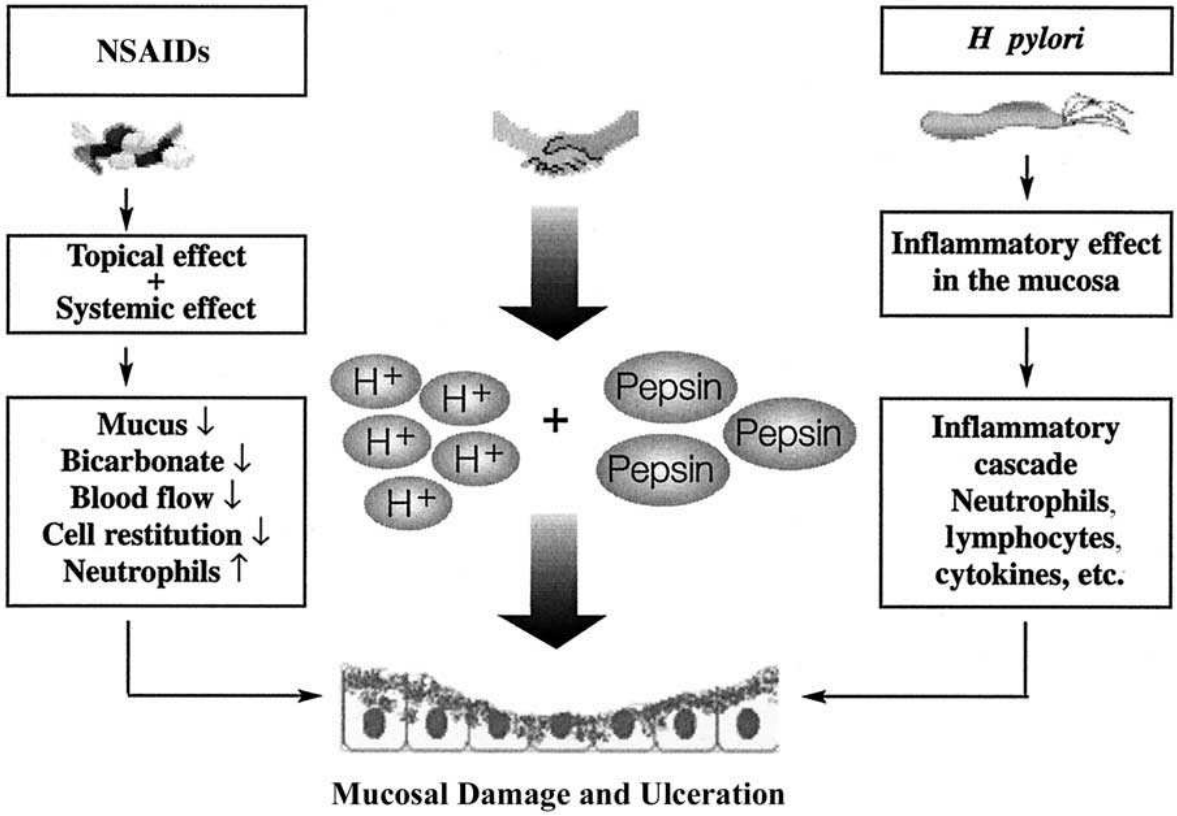

Figure 1: Nonsteroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* infection: injurious effects on the gastric mucosa (Byrd et al., 2000).

Helicobacter pylori has a number of colonization factors that allow it to survive in the harsh gastric environment and cause tissue injury. The organism is spiral shaped and its flagella allows it to penetrate the cell mucous layer, where it adheres to surface epithelia by adherence pedestals, which prevents the organism from being shed during cell turnover and mucus or gastric motility (Berardi, 1999).

One of the key survival mechanisms of *Helicobacter pylori* in the acidic gastric environment is the urease activity. Urease is a surface bond enzyme that cleaves urea to form ammonia and carbon dioxide, making the environment surrounding *Helicobacter pylori* relatively alkaline (Decross and Marshall, 1993). This permits the bacterium to buffer its micro environment and facilitates its survival when it is exposed to low pH in the gastric lumen (Falk, 2000). Furthermore the ammonia generated by urease has been proposed as a gastric irritant and causes mucosal injury (Bourke et al., 1996). Most urease is found in the bacterial cytoplasm. *Helicobacter pylori* expresses a unique protein called urel that serves as an H-gated channel. Urea transport through urel allows *Helicobacter pylori* to survive in the acidic environment of the stomach. Initiation of urel prevents *Helicobacter pylori* urease activity, presenting a means of eradicating the organism in the stomach acidity without the use of antibiotics (Weeks et al., 2000). *Helicobacter pylori* also produces catalase, an enzyme that protect against the damaging effects of oxygen metabolites, especially hydrogen peroxide (H_2O_2) release from leukocytes (Decross and Marshall, 1993). Additionally, *Helicobacter pylori* produces proteases, lipases and phospholipases, which hydrolyze the surface mucous layer and facilitate penetration into the mucus coat (Huang et al., 2002). Weakening of the mucosal barrier results in more tissue injury from luminal contents such as gastric acid and microbes (Decross and Marshall, 1993).

Approximately 90% of *Helicobacter pylori* strains produce a cytotoxin that causes cell vacuolization. All strains express the VacA gene, but only about 50% express the mature cytotoxin. Another protein associated with the vacuolating cytotoxin is the CagA gene, which is present in 60% of patients (Rave, 1999). Its gene product is of unknown functions, but has been associated with more severe gastritis, duodenal ulcer disease and gastric cancer (Berardi, 1999). *Helicobacter pylori* also releases chemo tactic proteins, such as lipopolysaccharide, that attract large numbers of lymphocytes and neutrophils that may contribute to mucosal injury.

Within a few days of infection with *Helicobacter pylori* a patient infected may develop dyspepsia, epigastric pain, nausea and vomiting. Shortly thereafter, there is a period of hypochlorhydria that persists for a few months, after which the intra-gastric pH returns to normal levels (Rave, 1999). This transient reduction in activity could weaken the first line of defense against pathogenic organisms and could make the host more susceptible to enteric infections (Falk, 2000). Many gastroenterologists now consider the eradication of *Helicobacter pylori* as the first line goal of ulcer therapy. However, some specialists still hesitate to treat when gastro-esophageal reflux (GERD) is also present because of potential protective benefits Helicobacter has on the esophagus, and the fact that *Helicobacter pylori* infection increases prostaglandin release, protecting from NSAID-induced ulcers. Data is emerging supporting the eradication of *Helicobacter pylori* in all patients, regardless of their use of NSAIDs or presence of GERD (Huang et al., 2002; El-Omar et al., 2000).

Poor sanitation conditions and contamination of water result in a higher incidence of *Helicobacter pylori* prevalence. Lower socio-economic groups who are more likely to experience these conditions are at a higher risk for contracting.

Close contact with a *Helicobacter pylori* infected individuals has been observed to result in transmission. This transmission has been observed, particularly in the case of spouses and individuals in close contact with individuals being treated for *Helicobacter pylori* (CDC, 2002).

Prevalence

It is estimated that 10% of the population have peptic ulcer disease. Approximately two third of the World's population is infected with *Helicobacter pylori* (CDC, 2002). In the United States, it is estimated that 20% of individuals under age 40 are infected and half of individuals over age 60 are infected (NIH, 2002).

Individuals with type "O" blood have a higher incidence of *Helicobacter pylori* infection than do persons with other blood types. Research has shown that this is due to the presence of an antigen in type O blood which facilitates adherence of the *Helicobacter pylori* organism to the gastric mucosa (ADF, 2000).

Helicobacter pylori is one of the most common chronic bacterial infections of humans, affecting more than 50% of World population, but the majority of those infected remain a symptomatic throughout life. About 20% of infected adult manifest one of many different outcomes, such as duodenal ulcer, gastric ulcer disease, gastric cancers or lymphoma (IARC, 1994 and NIH Consensus Conf., 1994).

Diagnosis of Peptic Ulcer Disease

The only laboratory tests useful for diagnosis of peptic ulcer disease are those that detect *Helicobacter pylori* infection (Peterson and Graham, 1999).

Diagnosis tests for *Helicobacter pylori* are categorized as either direct (invasive) tests (endoscopy) or indirect (non invasive) tests (e.g. serology test and carbon labeled urea breath test) (Hopkins and Morris, 1994). Direct tests are invasive and use endoscope biopsy of the gastric mucosa to determine the presence of *Helicobacter pylori*. Indirect tests are non- invasive and direct either an immune response (e.g. antibodies against *Helicobacter pylori*) or metabolic products of *Helicobacter pylori* (e.g. urease activity) (Holtman and Talley, 1995). The type of diagnostic test used depends on the clinical situation (Decross and Marshall, 1993 and Cutler, 1999).

Table 1: Diagnostic Tests for *Helicobacter pylori* Infections

Diagnostic Test Application	**Method of Organisms Identification**	**Advantages**
Invasive Rapid Urease Test Histology Culture	Indirect by urease production Indirect by morphological features Direct by biochemical properties	Diagnostic test of choice when endoscopy is done. Evaluates degree of inflammation in gastric tissue. Used to determine antimicrobial susceptibility of *Helicobacter pylori*.
Non-Invasive Serology Urea Breath Test	Indirect by immunological features Indirect by urease production	Used for initial diagnosis in physician's office. Preferred test for evaluating *Helicobacter pylori* eradiation after treatment.

Adapted from Decross and Marshall, 1993 and Cutler, 1999.

Complications of Peptic Ulcer Disease

The most common complications of ulcers are bleeding complications and perforation (i.e. when the ulcer erodes through the wall of the stomach or duodenum causing a hole). Bleeding can be gradual or abrupt, in the latter case it is often associated with black, tarry loose stools (called melena), and a drop in blood pressure. Most ulcer bleedings can be controlled by endoscopy, during which the ulcer is cauterized or injected (with necrotizing factor) to stop the bleeding. Only about 2 to 5 percent of people with a peptic ulcer require surgery. Perforation is associated with sudden severe abdominal pain and usually requires surgery (Graham, 1996).

Treatment Regimens for Peptic Ulcer Disease

Three classes of drugs have been shown to have a direct effect on *Helicobacter pylori*: antibiotics, bismuth salts, and proton pump inhibitors. Because *Helicobacter pylori* is difficult to eradicate, most treatment regimes combine agents from two or even all three of these cases. In all of them, patients with active peptic disease should also receive a total of 6 weeks of acid suppression with an H_2 receptor antagonist.

Refractory Ulcers

Ulcer recurrences after *Helicobacter pylori* therapy suggest smoking, non compliance with treatment regimen, NSAID use, persistent *Helicobacter pylori* infection or Zollinger- Ellison syndrome. The most common cause of ulcer recurrence after *Helicobacter pylori* antibiotic therapy is failure to achieve successful *Helicobacter pylori* eradication. Successful eradication should reduce the ulcer recurrence rate to less than 10% (Berardi, 1999).

In cases of eradication failure, it is recommended to culture *Helicobacter pylori* from biopsy specimens and susceptibility testing before starting a second treatment regimen (Guay and Gilberstadt, 2000). The selection of second line treatment depends on which treatment was used originally; the same combination of agents should not be used twice. Maintenance therapy with low dose proton pump inhibitors or histamine$_2$-receptor antagonists are indicated for high risk patients who fail *Helicobacter pylori* eradication or have symptomatic ulcer recurrences to 20% to 25% in one year (Berardi, 1999). Prevention of ulcer recurrence lasts as long as maintenance therapy is contained.

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