The Role of *Helicobacter pylori* in Peptic Ulcer Disease

By

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Research Article

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ABSTRACT

The link between Helicobacter pylori (H. Pylori) infection and peptic ulceration is now well established: presence of infection is a strong risk factor for later ulcer development and ulcers rarely occur in the absence of H. pylori or the other main risk factor, non steroidal anti-inflammatory drugs (NSAIDs). The role of H pylori in peptic ulceration in human is presented in this paper. A peptic ulcer is an excoriated area of stomach or intestinal mucosa caused principally by the digestive action of gastric juice. The two most common factors that predispose to ulcers are chronic gastric infection with H. pylori and ingestion of non-steroidal anti-inflammatory drugs. An effective first-line therapy for uncomplicated cases of h. pylori infection would be Amoxicillin + Metronidazole + Pentoprazole. Treatment of H. pylori usually leads to clearing of infection, relief of symptoms and eventual healing of ulcers.

Keywords: Helicobacter pylori, peptic ulcer, stomach.

INTRODUCTION

Helicobacter pylori was rediscovered in 1982 by two Australian scientists, Robin Warren and Barry J Marshall as a causative agent for peptic ulcer (Marshall, 1983). Prior to this, peptic ulcer was regarded as a disease closely associated with stress or spicy food. However in their original paper, Marshall and Warren (1984) contended that most peptic ulcers and gastritis were caused by colonization with this bacterium, not by stress or spicy food as had been assumed before. Earlier, John Lykoudis, a general practitioner in Greece, treated patient for peptic ulcer disease (PUD) with antibiotics, beginning in 1958, long before it was commonly recognized that bacteria were a dominant cause for the disease (Rigas and Papavasiliou, 2002). Things have remarkably changed since then. The link between H. pylori infection and peptic ulceration is now well established: presence of infection is a strong risk factor for later ulcer development and ulcers rarely occur in the absence of H. pylori or the main risk factor NSAIDs. Peptic ulcers (duodenal type) recur in infected subjects, but the eradication of H. pylori with antimicrobial therapy virtually eliminates further recurrence (Patchett et al.,1992;Valle et al.,1991). Even when ulcers are not present, H. pylori infection invariably causes a histologic gastritis (Atherton and Blaser, 1997).

H. pylori is a short, spiral gram-negative microaerophilic bacterium with unusual-appearing sheathed polar flagella (Dunn et al.,1997). It is slow growing in vitro and requires complex media. After prolonged culture it assumes a coccoid morphology that is slowly metabolizing and resistant to adverse conditions (Bode et al.,1993;Nilius et al.,1993). The metabolic pathways of H. pylori, including its main energy source, are poorly characterized but three enzymes are uniformly present and useful for laboratory identification: oxidase, catalase and urease. Urease activity is especially intense compared with other urease – producing bacteria and form the basis of several diagnostic tests.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antral gastritis (type B)</td>
<td>99</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>80</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>50-60</td>
</tr>
<tr>
<td>Non-ulcer dyspepsia</td>
<td>50</td>
</tr>
<tr>
<td>Aged-matched controls</td>
<td>50</td>
</tr>
</tbody>
</table>

PATHOGENESIS

There now is extensive evidence implicating H. pylori in the pathogenesis of chronic superficial gastritis. Voluntary ingestion of the bacterium by two human volunteers resulted in acute or chronic gastritis (Marshal et al., 1985; Morris and Nicholson, 1987). Both urease activity and motility are important for H. pylori colonization of the human stomach. Urea hydrolysis generates an alkaline environment that may protect the bacterium from acid and motility is important for passage through the gastric mucus. Urease creates an alkaline micro-environment by hydrolyzing urea to ammonia. Urea is a waste product of protein catabolism by the body's cells and is normally present in the gastric juices.

Once the bacteria reach the mucus that coats the stomach or duodenal lining, they use their flagella to corkscrew through the mucus to the epithelia cells. In this location, the pH of mucus is nearly neutral and the bacteria attach to the mucus-secreting epithelium or multiply adjacent to it. Bacteria products incite an inflammatory response in the wall of the stomach and mucus production decreases. Once infection occurs it persists for years, often for life. From 10% to 20% of infected persons develop ulcers, 65% to 80% of patients with gastric ulcers and 95% of those with duodenal ulcers are infected with H. pylori. The thinning of the protective mucus layer at the site of infection probably accounts for the development of peptic ulcers of the stomach and duodenum. A small percentage of individuals infected with H. pylori develop cancer of the stomach but more than 90% of those with stomach cancer are infected by the bacterium (Nester et al., 2004). Virulent H. pylori strains produce a protein CagA, which they inject into host cells resulting in changes in shape and surface characteristics of the cells. These changes represent a prelude to malignancy. Another bacterial product, VacA, acts on mucosal cells to promote flow of urea into the stomach.

H. pylori induces the synthesis of reactive oxygen species (ROS) in gastric mucosa in vivo. There is positive association between the amount of ROS present, the infective load of H. pylori and the extent of gastric mucosal injury (Davies et al., 1994). Levels of 9-hydroxydeoxyguanosine, a marker for oxygen free radical induced DNA damage, are increased in individuals infected with H. pylori compared with uninfected individuals (Baik et al., 1996), further demonstrating that H. pylori infection is associated with ROS production.

H. pylori appears to induce programmed cell death (apoptosis) of gastric epithelial cells (Mannick et al., 1996; Moss et al., 1996) and to stimulate oxidative DNA damage in infected human gastric mucosa (Baik et al., 1996). In addition, H. pylori appears to inhibit gastric epithelial cell migration and proliferation (Ricci et al., 1996). Thus, H. pylori infection can induce gastric mucosal injury both directly and indirectly.

HISTOPATHOLOGY OF H. PYLORI

Classification of histologic gastritis previously had not been uniform from center to center. This has now been standardized and updated (Dixon et al., 1996). H. pylori is most commonly associated with chronic superficial gastritis. This is characterized by mononuclear inflammatory cell infiltration associated with neutrophilic infiltration of the epithelium and is specifically associated with metaplastic change, granuloma, or fundus gland atrophy (Dixon, 1995). The amount of inflammation may be highly variable, ranging from minimal infiltration of the lamina propria with intact glandular architecture to severe dense inflammation with microabscess formation and reactive epithelial atypia (Genta et al., 1996). Concomitantly, there often are degenerative changes of the epithelial cells including mucin depletion, cytoplasmic vacuolization, and disorganization of mucosal glands. After eradication of H. pylori infection by antimicrobial agents, most of these features disappear rapidly (Dixon, 1995); however mononuclear cells may persist for several months.

DIAGNOSIS

Diagnostic tests for H. pylori can be divided into those performed on gastric biopsy specimens (and therefore requiring upper gastrointestinal endoscopy) and non-invasive tests.

Invasive

1. Endoscopy: At present, for initial diagnosis, endoscopy-based tests are preferred, because endoscopy can also establish whether there is an indication to treat the infection.
2. Histology with special stains: e.g. modified Giemsa, Gimenez or Warthin – Starry stains. This is the most established test and is widely available and accurate.

3. Biopsy urease test: It involves placing a biopsy specimen in the medium containing urea and a pH indicator, with a color change occurring if urease is present. It is cheaper and more rapid than the other tests but may be inaccurate in some situations e.g. in patients with achlorhydria where bacteria overgrowth may give false-positive results.

Non-invasive

1. Serology: Is cheap, convenient and accurate but cannot be used to check early treatment success because reliable falls in antibody levels from the pretreatment baseline do not occur for 6 months.

2. Urea breath test: This test uses radioactive carbon atom to detect H. pylori. It reliably reflects treatment success or failure 1 month after stopping treatment.

3. Anti-H. pylori IgG and anti CagA antibodies using commercial Enzyme-linked Immunoassay(ELISA) and Western blot are non-invasive methods for detection of H. pylori infection (Mahmood and Hamid, 2010; Burucoa et al., 2013). Rapid Urease Test(RUT) & histology have higher accuracy than non-invasive tests(ELISA & Western blot) (Mahmood and Hamid, 2010).

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>60-95</td>
<td>100</td>
</tr>
<tr>
<td>Histology</td>
<td>70-95</td>
<td>100</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>95-98</td>
<td>95-98</td>
</tr>
<tr>
<td>Biopsy urease test</td>
<td>90-95</td>
<td>98-100</td>
</tr>
<tr>
<td>Serology</td>
<td>95</td>
<td>95</td>
</tr>
</tbody>
</table>


PEPTIC ULCER DISEASE (PUD)

A peptic ulcer is an excoriated area of stomach or intestinal mucosa caused principally by the digestive action of gastric juice or upper small intestinal secretions (Guyton and Hall, 2006). Peptic ulcers are defects in the gastrointestinal (GI) mucosa that extend through the submucosa into the muscle layer. They require the presence of acid and pepsin for their formation and, therefore are classified as acid peptic disorders. Ulcers are rarely due simply to excessive secretion of acid. Most cases represent an imbalance between acid, pepsin and other potentially damaging agents and factors that act to protect mucosal integrity. The different types of PUD include: duodenal ulcer, gastric ulcer, Meckel's diverticulum ulcer, esophageal ulcer.

The two most common factors that predispose to ulcers are chronic gastric infection with H. pylori and ingestion of NSAIDs. Other factors that predispose to ulcers include: smoking, alcohol poor secretion of mucus. Symptoms include: abdominal pain, bloating and abdominal fullness; loss of appetite and weight loss; hematemesis; anemia, melena; hematochezia, vomiting, nausea, heartburn, waterbrash.

ULCER PATHOPHYSIOLOGY

Ulcers are formed when the mucosa of the stomach or duodenum can not resist the corrosive effects of acid on its surface. The primary defect may not reflect any abnormality in acid secretion, instead, impaired mucosal defense mechanisms may be of primary importance. Exogenous factors including infection with H. pylori contribute to the formation of ulcers. In H. pylori colonization responses to increased gastrin, the increase in acid can contribute, to the erosion of the mucosa and therefore ulcer formation. Studies in the varying occurrence of ulcers in some developing countries despite high H. pylori colonization rates suggest dietary factors play a role in the pathogenesis of the disease (Ma, 2011).

The inflammatory response to H. pylori in children differs somewhat from that in adults. Endoscopy may reveal a finely granular or nodular mucosal surface, which microscopically corresponds to lymphnodular hyperplasia, especially in the antrum (Genta et al., 1993. Such lymphoid aggregates often contain activated germinal centers. In addition, the quantity of neutrophils may be smaller than that seen in adults.
There must be periodic or intermittent changes in both the aggressive factors and the defensive factors to account for the intermittent formation and spontaneous healing of many ulcers. Complications include bleeding, perforation and penetration, gastric outlet obstruction (Walsh and Fass, 1997).

**DIAGNOSIS OF PUD**

**Physical Examination:** Midepigastric tenderness is a common but non-specific finding. The physical examination is useful to exclude other potential causes for epigastric pain, such as musculo-skeletal tenderness, neuropathy and abdominal masses.

**Laboratory Studies:** Semen or plasma gastric measurement is the most specific method for identifying or excluding gastrinoma. Stool guaiac or occult blood examinations are used to detect GI blood loss. A similar test (Gastroccult) may be used to detect blood in gastric aspirates in acute bleeding.

**Endoscopy:** Fiberoptic endoscopic instruments permit direct visual examination of the esophageal, gastric and proximal duodenal mucosa. Ulcers are seen as depression with white or yellow bases surrounded by normal gastric or duodenal mucosa often with erythematous or edematous edges.

**Radiographic Examination:** Most gastric ulcers and many duodenal ulcers can be diagnosed by ordinary barium radiographic examinations. Radiography is especially useful for identifying infiltrative disease such as lymphoma and extrinsic compression of the stomach and duodenum by mass lesions.

**Acid Secretory Studies:** Measurements of basal and stimulated gastric secretory function can be made directly by nasogastric intubation and pentagastrin stimulation. Absence of acid after stimulation virtually excludes the diagnosis of peptic ulcer.

**Treatment**

Most patients with PUD can be treated effectively by two measures: use of antibiotics along with other agents to kill infectious bacteria and administration of an acid-suppressant drug.

1. Antacids
2. Ranitidine and famotidine, which are both H2 antagonists provide relief of peptic ulcers, heartburn, indigestion and excess stomach acid and prevention of these symptoms associated with excessive consumption of food and drink.
3. Sucralfate (Carafate) has also been a successful treatment of peptic ulcers.
4. Perforated peptic ulcer is a surgical emergency and requires surgical repair of the perforation.
5. Patients who are taking NSAIDs may also be prescribed a prostaglandin analogue (Misoprostol) in order to help prevent peptic ulcers, which are a side-effect of NSAIDs.

**Treatment of H. pylori**

Treatment regimens for *H. pylori* infection have been evolving since the early 1990s. Antimicrobial therapy for this infection is a complex issue and the following drugs are currently used in combination regimens: Proton-pump inhibitors and/or bismuth, metronidazole, clarithromycin, amoxicillin (Malferttheiner et al., 2002). Tetracycline is used in rescue therapy (Gisbert and Pajares, 2001). An effective first-line therapy for uncomplicated cases would be Amoxicillin + Metronidazole + Pentoprazole (a PPI). Treatment of *H. pylori* usually leads to clearing of infection, relief of symptoms and eventual healing of ulcers. Recurrence of infection can occur and treatment may be required, if necessary with other antibiotics.

However, there are concerns about the emergence of resistant strains in Nigeria (Aboderin et al., 2007). From other parts of the world strains resistant to metronidazole (Jenks and Edward, 2002); clarithromycin (Osato et al., 2001); amoxicillin (Wu et al., 2000) have been documented. The resistance problem with *H. pylori* shows that treatment regimens will continue to evolve as the search continues for effective treatment eradication protocols.
REFERENCES


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