Helicobacter pylori Gastritis, Peptic Ulcer, and Gastric Cancer: Clinical and Molecular Aspects

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Helicobacter pylori causes specific ultrastructural changes to the gastric mucosa. In developing countries a high percentage of infants acquire this infection, which initially causes a transient drop in stomach acid and thus allows transit of lower bowel pathogens, with consequent diarrhea and malnutrition. When infection occurs at an early age, the acid-producing cells of the stomach are involved in the inflammation, and the lifelong reduced acid output means a duodenal ulcer rarely develops. However, lifelong gastric inflammation leads in due course to atrophy, and in the presence of other factors gastric cancer may develop. People infected with H. pylori on average are of shorter stature than uninfected people. Adherence of H. pylori to the gastric mucosa is a prerequisite for infection, and a new binary model of adherence has been shown recently. Chaperonins of H. pylori induce macrophages to secrete cytokines, which leads to an immunologic cascade and inflammation.

Helicobacter pylori Gastritis

Helicobacter pylori gastritis is not endoscopically diagnosed because red gastric mucosa frequently is found to be histologically normal; however, gastritis is histologic inflammation, which can occur in normal-looking mucosa. When H. pylori infection starts early in life, in subsequent years the chronic inflammation may be remarkably asymptomatic. However, the ultrastructural damage of the mucosa by H. pylori is specific and significant, and it includes loss of intercellular junctions between the mucosal cells. The mucosal cells bulge and lose their normal shape; microvilli are effaced, and the cytoskeleton is lost. The mucus content of the mucosal cells is greatly decreased; and there is close adherence of H. pylori to the mucosal cells, with formation of adherence pedestals [1].

Age of Acquisition: Duodenal Ulcer and Gastric Cancer

When the age at first infection with H. pylori is ≤5 years, the inflammation usually occurs throughout the stomach (pan-gastritis), with damage to the acid-producing cells [2]. Thus there will be a permanent reduction in acid output by the stomach, and the low acid level will be insufficient for the formation of a duodenal ulcer (DU) [3]. However, the chronic inflammation, which persists for decades, may be coupled with genetic or inflammatory instability of potential oncogenes, and these together can result in gastric cancer later in life ([2, 4] and see below).

When the age at acquisition of H. pylori is >5 years, the acid-producing cells have matured and are not inflamed. If gastric metaplasia occurs in the duodenum, then H. pylori can infect this tissue and cause duodenitis [2, 5]. Acid and pepsin can then cause a DU [5]. In patients with DUs, the paucity of somatostatin and lack of suppression of acid secretion are the result of H. pylori infection [6]. The other major cause of peptic ulcer is ingestion of nonsteroidal antiinflammatory drugs (NSAIDs). In patients who did not ingest NSAIDs, recurrent bleeding in DUs resolved after their H. pylori infection was cured [7].

Nonulcer Dyspepsia

In developed countries, only 50% of patients with nonulcer dyspepsia (NUD) have H. pylori infection, so the causes of dyspepsia in the uninfected could be the causes in many of the infected. Whether H. pylori infection in NUD should be treated will remain controversial until clinical or histopathological features are identified that predict benefit from cure of the infection. If NUD symptoms originate from gastric inflammation, it would not be expected that loss of symptoms would occur until 9 months after cure, because that length of time is required for histology to revert to normal in cured patients. Thus, long-term prospective studies are the only way to detect satisfactorily whether cure of H. pylori infection relieves upper gut symptoms.

Among 24 patients cured of H. pylori infection whose cases were reviewed after 1 year, the mean dyspepsia score was only 1.4, compared with a score of 5.2 among 38 patients who were not cured of H. pylori infection [8]. Those whose infection had not been cured (34 of 37 patients) received additional medication in comparison with those whose infection had been cured (4 of 37 patients) [8].

NUD is common in children; those with ulcer-like dyspepsia and some with severe central abdominal pain may experience dramatic relief of symptoms after their H. pylori infection is cured [9].
**H. pylori Infection and Gastric Cancer**

High titers of antibody to *H. pylori* have been found in populations from many parts of the world where cancer is highly prevalent—China, Wales, North and South America, and many European countries [10]. There is also a high rate of *H. pylori* infection among children in such areas, and gastric atrophy and intestinal metaplasia are more common as well. These conditions follow *H. pylori* infection [2]. A low intake of fruit and vegetables (antioxidants) and a high intake of salt, nitrates, and nitrites have been postulated as being of importance. However, this type of diet is not found consistently in populations at high risk for cancer [11].

DNA damage is caused by neutrophil products that are present in *H. pylori* inflammation, which can lead to inactivation of suppressor genes and expression of oncogenes [4]. Intestinal metaplasia in the stomach is most frequent when there is both *H. pylori* infection and bile reflux [12]. Among 29,300 patients with gastric ulcers, the risk of gastric cancer was 1.8 and remained high during the review period of 24 years, but among 30,000 with DU this risk of gastric cancer was only 0.6 [13].

Thus, *H. pylori* “starts the avalanche” that can lead eventually to gastric cancer. When gastric atrophy is present in the stomach, *H. pylori* infection is not found in these atrophic areas; therefore, *H. pylori* as a precursor of gastric atrophy has been underestimated. However, better serological tests than for pepsinogen A are required to detect those who are at greatest risk of gastric cancer among the many patients who are infected with *H. pylori*.

**H. pylori Infection in Children in Developing Countries**

In developing countries the prevalence of *H. pylori* in children with persistent diarrhea and malnutrition was found to be double the prevalence in healthy children [14]. In addition, the age-related increasing prevalence of *H. pylori* correlated with an increasing prevalence of diarrhea and malnutrition in children. In Gambian infants the age-related point prevalence of *H. pylori* at 6 months was 40%; 9 months, 60%; 12 months, 70%; and 21 months, 80%. In infants, urine acid output following a feeding indicates the acidity of the stomach; in the first 6 months of life a drop in urine acid output was significantly related to the presence of acute *H. pylori* infection [15].

Thus, primary *H. pylori* infection could allow lower-gut pathogens to gain access to the gut and cause diarrhea and malnutrition. IgM to *H. pylori* is more frequent in infected symptomatic children, which suggests that primary infection with *H. pylori* in children who have IgM to the pathogen is followed by the asymptomatic phase when the IgM is no longer found. Babies of *H. pylori*—positive mothers have IgG for 3 months and do not have a higher rate of infection than controls during the first year [16].

**Systemic Effects of H. pylori Infection**

In an economically poor area of the United Kingdom, 11-year-old girls found to be infected with *H. pylori* by a salivary antibody test were shorter than uninfected 11-year-old girls [17]. In the same area, men with *H. pylori* infection were 1.1 cm shorter than uninfected controls, and women were 1.9 cm shorter than uninfected women [18]. *H. pylori* infection has also been found to be a risk factor for coronary heart disease in some studies [19] but not in others.

**Chaperonins of H. pylori**

*Hp*cpn60 is a 14-mer protein with a molecular weight of 58.2 kD that occurs as cylindrical stacks of 4–5 rings; such stacks were seen on the wall of *H. pylori* in 1990 [20]. *Hp*cpn60 is readily isolated extracellularly. *Hp*cpn10 has a molecular weight of 13 kD [21]. The genes *Hp*cpn10 and *Hp*cpn60 are on a bicistronic operon and thus are more accurately defined as *Hp*cpn10-1 and *Hp*cpn60-1 [21]. A second *Hp*cpn10 gene has also been found that is more correctly defined as *Hp*cpn10-2. *Hp*cpn10 protein has nickel-binding properties and activates the urease enzyme of *H. pylori* [21].

It has been postulated that *H. pylori* gastritis could be due to antibodies against *Hp*cpns, which are then directed against human chaperonin homologues in gastric cells, but there is no evidence in animal models of such autoimmune inflammation. In preimmunized rats mycobacterial cpn60 induced arthritis, but when mice were immunized with macrophages that expressed Mcpn60-2 they were protected against challenge with *Mycobacterium tuberculosis*. In addition, *Yersinia enterocolitica* cpn60 reactive T cells protected mice against challenge with *Y. enterocolitica*. However, *H. pylori* chaperonins will induce macrophages to secrete cytokines (TNF and IL-1) and will stimulate T cells and other cells, leading to an “immunologic cascade.”

The DNA that encodes the A-domain of *Hp*cpn10-1 has been found to be conserved in all of 25 isolates studied, but the DNA that encodes the B-domain shows polymorphism [22]. Therefore, *Hp*cpn10-1 should be a good immunogen.

**Adherence of H. pylori to the Gastric Mucosa—a New Binary Model**

Adherence of *H. pylori* to the gastric mucosa is a prerequisite for infection. To study the adherence of *H. pylori* to mucosal cells, binding experiments must be done under the same microaerophilic conditions that are present in the stomach and are required for the culture of *H. pylori* [23]. Glycolipid recognition is a common mechanism for bacterial adhesion to host cells. Lingwood et al. [24] have shown that at neutral pH *H. pylori* specifically recognizes gangliotetraosylceramide (Gg4), gangliotetrasylceramide (Gg3), and phosphatidylethanolamine (PE), but it insignificantly recognizes sulfoglycolipid (SGC). However, when *H. pylori* is exposed to pH 2 or pH 2.5 for 5 minutes, followed by neutralization, the major glycolipid recognized is SGC, which is present in the stomach [23].

Expression of *H. pylori* heat-shock proteins or chaperonins such as *Hp*cpn60 increases after exposure of *H. pylori* to 42°C.
for 5 minutes or to acidic conditions, and Hpcpn60 specifically recognizes SGC. Thus, in the stomach the increased expression of Hpcpn60 is coupled with a change in H. pylori binding specificity to SGC [23]. This binding of H. pylori to SGC was prevented by antibiotics that inhibit protein synthesis, such as erythromycin and chloramphenicol, or by pretreatment with anti-Hpcpn60 antibodies, but the binding of H. pylori to PE was not affected.

The acid-induced change in binding specificity was maintained in the presence of 5 mM of urea, which shows that urea does not protect H. pylori from an acidic pH response. In conclusion, Hpcpn60 can act as an adhesin to mediate SGC recognition under acidic conditions. A binary receptor model of H. pylori binding has been proposed by Huesca et al. [23] and depends on whether the bacteria bind under the mucus where the pH is neutral to Gg4, Gg3, and PE, or bind at an acidic pH to SGC.

The cagA Gene

The synthesis of cagA protein is correlated with more severe gastritis, both types of peptic ulcer, and gastric cancer [25]. H. pylori “type I” strains have the cagA gene and express the vacuolating cytotoxin, while “type II” strains do not have the cagA gene and do not express cytotoxin. While the cagA gene is more common in peptic ulcer strains than in isolates from asymptomatic controls in most countries, such as the Netherlands [26] and Hong Kong [27], in Korea 98.3% of all strains have the cagA gene [28]. H. pylori strains with the picB gene induce the cytokine IL-8, which causes inflammation and mucosal injury [29].

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References