

Helicobacter Pylori Infection and Hyperemesis Gravidarum

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Introduction

In 1983, Warren and Marshall proposed the possible association of *Helicobacter pylori* (HP) with peptic ulcer disease and gastric cancer². Two years later, such an association was confirmed in 1985 by Marshall in 114 infected patients in Fremantle Hospital³. Meanwhile, the Royal Perth Hospital team produced evidence to justify the creation of a new genus and in 1989 they renamed the organism HP⁴. Since then, 18 other HP species have been found, one in man and the remainder in animals including birds⁵.

Morphology of HP

Helicobacter pylori is a curved or s-shaped gram-negative, non-capsulated, non-spore forming bacillus with a length of about 3 μm and a width of about 0.5 μm (figure 1). HP is surrounded with cytoplasmic membrane which in turn is covered by an outer membrane. Both the outer and inner face of the membranes is covered with dot-like structures presumably corresponding to incorporated proteinacious structures. HP is predominantly an extracellular organism but intracellular penetration can rarely occur⁸.

Helicobacter pylori is oxidase and catalase positive and hippurate negative⁹. It is actively motile by hanging drop preparation with 4 to 6 lophotrichous sheathed flagella which are the most distinguishing structural characteristic of HP¹⁰.

Helicobacter pylori is very similar to *Campylobacter jejuni* but is different in being urease positive while *Campylobacter jejuni* is urease negative. *Campylobacter jejuni* is motile with one polar flagellum while HP has multiple polar flagella (Figure 2)¹¹.

Helicobacter pylori is primarily found in the antrum of the stomach but is also seen in the duodenum within areas of gastric metaplasia. The antral and duodenal organisms are associated with mucosal inflammation but fungal bacteria may be observed adjacent to endoscopically and histologically normal mucosa. The spiral form, flagella, and flexibility of the bacterium HP reflect a unique predilection for gastric mucosa.

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Figure 1. False-color transmission electron micrograph (TEM) of the bacterium *Helicobacter pylori*



Figure 2. False-color transmission electron micrograph of the bacterium *Campylobacter jejuni*

They allow the organism to corkscrew or swim through mucosa in a manner impossible for rod-shaped bacteria. The organism has also been observed to burrow into the intracellular spaces and the protection offered by this relative isolation could explain the difficulty in complete eradication of the organism by active surface agents as bismuth preparations. The organism was found to avoid contact with gastric acid presumably because of its susceptibility to a pH less than 3.5¹².

Association between HP and HG

The hypothesis that infection with HP is associated with HG was tested in a prospective study. The results obtained showed that positive serum IgG concentrations were found in 95 of the 105 hyperemesis patients (90.5%) compared with

60 of 129 controls (46.5%). The investigators concluded that infection with HP may cause HG²¹.

More recently, in a matched case-control study, the incidence of HP infection in patients with HG in comparison with non-HG pregnant women was studied; moreover, the correlation between positive serology for HP IgG and the time of onset and duration of HG symptoms was investigated. The results obtained revealed that positive serum HP IgG antibody was detected in 88.9% of the patients in the experimental group versus 40.7% of the controls. The investigators concluded that, although more patients with HG were seropositive for HP infection than controls, we are not able to demonstrate correlation between seropositivity for HP and the time of onset or duration of HG symptoms. Moreover, although HP infection may be an important factor in exacerbating HG, it may not represent the sole cause of the disease²⁴.

Epidemiology

Prevalence

Infection with HP is very common throughout the world occurring in 40-50% of the population in developed countries and 80-90% of the population in developing regions.¹³ In all infected individuals, HP causes active chronic gastric inflammation which progresses in 10-20% of affected persons to peptic ulcer disease, mucosa associated lymphoid tissue (MALT) lymphoma, or gastric adenocarcinoma which is the second leading cause of cancer-related worldwide^{14,15}. HP has been classified as a grade I carcinogen because intestinal-type gastric carcinoma occurs after HP gastritis which leads to atrophy and intestinal metaplasia; the diffuse type is also associated with HP infection. Prospective serological studies have correlated prior HP infection with subsequent gastric cancer¹⁶. MALT is not found in normal gastric mucosa but may develop after HP infection¹⁷. HP was found in 92% of 100 patients with gastric lymphoma and the lymphomas regressed after eradication of the infection¹⁸.

Mode of Transmission

Iatrogenic transmission of HP following endoscopy is the only proven mode²⁶. For the general population, the most likely mode of transmission is from person to person by either the oral-oral route (through vomitus or possibly saliva) or perhaps the fecal-oral route. The person-to-person mode of transmission is supported by the higher incidence of infection among institutionalized children and adults and the clustering of HP infection within families

One of the most important points to consider in

HP infection in pregnancy is its transmission to the fetus (i.e. transplacental transmission)^{11,21}. Therefore, it might be reasonable to treat the HG with suitable medication for eradication of HP²².

Table 1. Diagnostic tests for Helicobacter pylori.

<i>Non-invasive</i>	<i>Invasive</i>
Urea Breath Test (UBT)	Upper GI endoscopy and biopsy
<ul style="list-style-type: none"> • C¹³ UBT is very sensitive for diagnosis and follow-up. • It measures the urease enzyme associated with HP infection. • It can't be used in pregnancy or pediatric cases due to the radioactivity. 	Biopsy taken by endoscopy for: <ul style="list-style-type: none"> • Histopathology • Microbiology • Rapid urease test • PCR testing Needs multiple biopsies because infection is patchy. Affected by treatment with bismuth or proton pump inhibitors.
Serological evaluation	
<ul style="list-style-type: none"> • Serum Ig G based test. • Less specific because it remains positive for months following a recent infection. 	
Fecal antigen detection	
Useful in screening or follow up of treatment.	

Eradication of HP

Inadequate sanitary practices, low social class, crowded living conditions have high prevalence of HP infection. While adequate nutritional status (vegetables – fruits – vit. C) protect against HP infection. Surprisingly tobacco and alcohol don't increase the risk of infection

Current guidelines recommend that treatment of HP infection should take the form of triple therapy comprising a proton pump inhibitor and two antimicrobials chosen from clarithromycin, a nitroimidazole (metronidazole or tinidazole), and amoxicillin^{62,63}. This is the standard treatment because of its high tolerability and simplicity of administration. The rates of successful eradication vary widely; however, ranging from 70% to 95%. Treatment failure occurs because of poor patient compliance or bacterial resistance⁶⁴⁻⁶⁶.

PPI-based triple therapies using clathromycin in combination with either amoxicillin or metronidazole are at present the most commonly used first line therapies for HP infection with pooled eradication rates of approximately 90%⁶⁷⁻⁶⁹. The largest experience has been gained with regimens using omeprazole⁷⁰⁻⁷². Recent European

Consensus authorities recommended that PPI-based triple therapy containing clarithromycin and amoxicillin should be preferred to clarithromycin combined with metronidazole⁷³. However, the latter combination is still clinically useful, for example, in the case of known intolerance to amoxicillin⁵⁶.

A proton pump inhibitor and clarithromycin plus tinidazole are usually taken twice daily and the other drugs (e.g. metronidazole, amoxicillin) usually thrice daily. Whether clarithromycin should be given as 250 mg or 500 mg is unclear as there have been reports of high eradication rates with 250 mg and high eradication values with 7 or 10 days treatment. Studies with large numbers of patients, which may give more guidance, have indicated better results with 10 days treatment rather than 7 days^{74,75}.

Esomeprazole, the S isomer of omeprazole, is the first proton pump inhibitor to be developed as an optical isomer for the treatment of acid related disorders. It provides a greater inhibition of acid secretion than omeprazole and all other proton pump inhibitors^{76,77} and has recently also been introduced in the treatment of HP infection. Several multicenter trials have shown that esomeprazole in combination with clarithromycin and amoxicillin is effective as first line treatment of HP infection^{78,79}.

Because of its unique pharmacokinetic properties, azithromycin may be an attractive component of drug combinations for HP eradication. This antimicrobial agent represents a new generation macrolide of the azalide class. Trials have been conducted to evaluate short-term regimens (3 to 6 days) of azithromycin in combination with a PPI and amoxicillin, metronidazole, or tinidazole; results were conflicting with eradication rates ranging from 57% to 93%^{58,80,81}.

Definition of HP Cure

For documentation of successful treatment of HP infection, at least two negative biopsy-based tests were required (either histology and culture or histology and rapid urease test). If one of the performed tests was positive for HP, the patient was defined as treatment failure. For patients who refused follow-up endoscopy, a validated ¹³C-urea breath test was accepted to confirm cure of HP infection⁵⁶.

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