CURRENT ISSUES REGARDING Helicobacter pylori: From 1875 to Nobel prize 2005

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Helicobacter pylori is a Gram-negative bacterium that infects the lining of the stomach and duodenum. It is the only known microorganisms that can thrive in the highly acidic environment of the stomach. Its helical shape (from which its name is derived) is thought to have evolved to penetrate and colonize the mucus lining. (Samuel Baron, 1996)
The stomach is protected from its own gastric juice by a thick layer of mucus that covers the stomach lining. Once H. pylori is safely ensconced in the mucus, it is able to fight the stomach acid that does reach it with an enzyme it possesses called **urease** that converts urea, of which there is an abundant supply in the stomach (from saliva and gastric juices), into bicarbonate and ammonia, which are strong bases. This creates a cloud of acid neutralizing chemicals around the H. pylori, protecting it from the acid in the stomach. The reaction of urea hydrolysis is important for diagnosis of H. pylori by the breath test.
History of discovery
In 1875, German scientists found helical shaped bacteria in the lining of the human stomach. The bacteria could not be grown in culture and the results were eventually forgotten (Blaser, 2005).

The bacterium was rediscovered in 1979 by Australian pathologist Robin Warren, who did further research on it with Barry Marshall beginning in 1981; they isolated the organisms from mucosal specimens from human stomachs and were the first to successfully culture them (Marshall, 2006). In their original paper, Warren and Marshall contended that most stomach ulcers and gastritis were caused by infection by this bacterium and not by stress or spicy food as had been assumed before (Marshall and Warren, 1984).
In 1985, Marshall drank a Petri dish of *H. pylori*, (1 million bacteria) developed gastritis, and the bacteria were recovered from his stomach lining, thereby satisfying three out of the four Koch's postulates. The fourth was satisfied after a second endoscopy ten days after inoculation revealed signs of gastritis and the presence of "H. pylori". Marshall was then able to treat himself using a fourteen day dual therapy with bismuth salts and metronidazole. Marshall and Warren went on to show that antibiotics are effective in the treatment of many cases of gastritis.

In 2005, Warren and Marshall were awarded the Nobel Prize in Medicine for their work on *H. pylori*. 
EPIDEMIOLOGY
In Western countries, H. pylori affects about 20% of persons below the age of 40 years, and 50% of those above the age of 60 years.

- H. pylori is uncommon in young children.
- Low socio-economic status predicts H. pylori infection.
- Immigration is responsible for isolated areas of high prevalence in some Western countries.

In developing countries most adults are infected.

H. pylori infection begins in early childhood, with up to 50% of children being infected before the age of ten, and 80–90% of the population being infected by adulthood (Naficy et al., 2000).
Epidemiological studies suggest person-to-person transmission, by either faecal-oral or oral-oral routes, to be the major mechanism. In developing countries, there is evidence for both food- and water-borne transmission of *H. pylori*. Intrafamilial spread appears to play a central role in transmission of the infection in both developing and developed countries (Sinha et al., 2004). Iatrogenic transmission can occur, in which tubes, endoscopes, or specimens in contact with the gastric mucosa from one person are introduced to another person (Akamatsu et al., 1996). Occupationally acquired infections (laboratorians) also have been reported (Sobala et al., 1991).
It was generally believed that following acquisition of *H. pylori*, and in the absence of treatment, *infection would persist throughout life*. However, based on seroepidemiological studies in adults and children from both developing and developed countries, it appears that the spontaneous elimination of *H. pylori* infection may occur, aided by the administration of antibiotics for other reasons (Xia and Talley, 1997).
DIAGNOSIS

BREATHE TEST
BLOOD TEST
ENDOSCOPY
BREATH TESTS:
It is very important that prior to any breath testing for *H. pylori*, you have to instruct the patient not to take any antibiotics for one month, PPIs for one week, H2 receptor antagonists for 24 hours.
The patient drinks ¹³C- or ¹⁴C-labelled urea, which the bacterium metabolizes producing labelled carbon dioxide that can be detected in the breath. In the C14-urea breath test, the breath sample is read in a scintillation counter. In the C13-urea breath test the breath sample is read in a mass spectrometer.
ANTIBODY TESTS: should be used only as screening tests. Two fingerstick tests, Flexsure HP and QuickVue One Step, have received FDA approval. They are relatively inexpensive, rapid and simple to use (Moayyedi et al., 1997).

If positive, it means a current infection OR a past infection (3y).

A new rapid flow microparticle immunofluorescence assay (FMIA) was developed to detect H. pylori antibodies and antibodies against virulence factors (Buhling et al., 2004).

PCR TESTS

Detection of H. pylori DNA (PCR) in materials obtained non-invasively (e.g: non gastric fluids such as saliva and stool) is of great value because this would not only allow for diagnosis but also for genotyping, susceptibility testing, detection of virulence markers and also provide an easier approach to investigate routes of transmission (Makristathis et al., 2004).
The most reliable method for detecting *H. pylori* infection is a biopsy check during endoscopy with a rapid urease test, histological examination (by Gram stain, Giemsa stain or silver stain), and microbial culture.

Except for the biopsy check, none of the test methods are completely accurate.

Biopsy specimens taken from the angularis of the stomach are 100% sensitive (Sobala et al., 1991). Remember to stop all antibiotics (1 month), cytoprotective drugs as sucrulfate (1 w), H2-receptor antagonists, and PPIs (1 day) before endoscopy.
The CLO test, developed by Marshall, was the first of the commercially available biopsy urease tests designed specifically for H. pylori detection. It consists of an agar gel containing phenol red and urea; in the presence of urease, the urea is hydrolyzed, leading to a pH (and hence a color) change of the indicator. The test is interpreted up to 24 h after placement of the gastric biopsy sample onto the agar gel (Cutler et al., 1995)

The Biohit Helicobacter pylori Quick test is a novel rapid (1-2 min.) biopsy urease test (Makristathis et al., 2004).
Immunohistochemical staining of *H. pylori* from a gastric biopsy.
A bactéria Helicobacter pylori
CLINICAL PRESENTATION
It is estimated that up to 70% of infection is asymptomatic and that about 2/3 of the world population are infected by the bacterium, making it the most widespread infection in the world (Goodman and Cockburn 2001).
GASTROINTESTINAL MANIFESTATIONS

ACUTE GASTRITIS
DUODENAL ULCERS
GASTRIC ULCERS
CHRONIC SUPERFICIAL GASTRITIS
CHRONIC ATROPHIC GASTRITIS
HYPOCHLORHYDRIA
MALT LYMPHOMAS
GASTRIC CANCER
NON ULCER DYSPEPSIA
EXTRADIGESTIVE DISEASES:

· Hematologic diseases: IDA, ITP, lymphoma, pernicious anemia.....

· Vascular diseases Ischaemic heart disease, primary Raynaud's phenomenon, primary headache.....

· Autoimmune diseases Sjogren's syndrome, autoimmune thyroiditis, autoimmune thrombocytopenia, and Henoch-Schoenlein purpura ...

· Respiratory diseases Chronic bronchitis, pulmonary tuberculosis, bronchiectasis, lung cancer, bronchial asthma...

· Skin diseases Idiopathic chronic urticaria and alopecia areata....

· Other diseases Liver cirrhosis, growth retardation, chronic idiopathic sideropenia, sudden infant death, diabetes mellitus (higher HbA1c level among infected patients with type 2 diabetes)
H. pylori was described to impair cytochrome P450 liver activity in anti-HCV positive cirrhotic patients (Giannini et al., 2003); interestingly, H. pylori was detectable in hepatocarcinoma tissue from 13 out of 15 patients, and not in nontumor tissue (Ito et al., 2004). This suggests a potential role for H. pylori in liver disease and ultimately in hepatocarcinogenesis (Ponzetto et al., 2003). H. pylori may play a role in the formation of intrahepatic stones and the induction of biliary epithelial inflammation (Avenaud et al., 2000).

H. pylori may play a role in the induction of hyperammonemiam and the subsequent development of hepatic encephalopathy in patients with cirrhosis and chronic liver disease (Miyagi et al., 1997).
Gastric cancer association

Gastric cancer and gastric MALT lymphoma have been associated with \textit{H. pylori}, and the bacterium has been categorized as a group I carcinogen by the International Agency for Research.

It has been proposed that \textit{H. pylori} induces inflammation and locally high levels of TNF-alpha and/or interleukin \( \gamma \). According to the proposed perigenetic mechanism, inflammation-associated signaling molecules such as TNF-alpha can alter gastric epithelial cell adhesion and lead to the dispersion and migration of mutated epithelial cells without the need for additional mutations in tumor suppressor genes such as genes that code for cell adhesion proteins (Tsuji et al., 2003).
Acid reflux and esophageal cancer

The infection rate with *H. pylori* has been decreasing in developing countries, presumably because of improved hygiene and increased use of antibiotics. Accordingly, the incidence of gastric cancer in the U.S. has fallen by 80 percent from 1900 to 2000. However, gastroesophageal reflux disease and esophageal cancer have increased dramatically during the same period.

In 1997, Blaser put forward the theory that *H. pylori* might also have a beneficial effect: by regulating the acidity of the stomach contents, it lowers the impact of regurgitation of stomach acids into the esophagus (Blaser, 2005).
TREATMENT
Asymptomatic Patients

Routine antibiotic treatment of asymptomatic patients is not recommended. The exceptions are patients who are
(1) relatives of persons with gastric cancer
(2) patients in whom intestinal metaplasia has been detected on gastric biopsy
The standard first-line therapy is a one week triple-therapy. The Sydney gastroenterologist Thomas Borody invented the first triple therapy in \(1987\) (Thomas, 1989).

Today the standard triple therapy is the combinations of one antisecretory agent with two antimicrobial agents for 7 to 14 days and several regimens have been FDA approved. Amoxicillin, clarithromycin and a proton pump inhibitor such as omeprazole (Mirbagheri et al., 2006) (Meyer et al., 2002) are used in place of amoxicillin in those allergic to penicillin (European Helicobacter Pylori Study Group, 2000).

Triple therapy for two weeks, consisting of furazolidone [100mg qid], amoxicillin, and bismuth, was successful in 86 percent of cases (Coelho et al., 2000).
Other FDA-approved regimens are the dual therapies consisting of clarithromycin (500 mg tds) together with either omeprazole (40 mg once daily) (cure rate, 74%) or ranitidine bismuth citrate (RBC) (400 mg bid) (cure rate, 82%) for 14 days (Peterson et al., 1996). But dual therapy is not recommended as a primary therapy as the eradication rate is less than that of triple therapy (Soll, 1996).
Second-Line Therapies
Eradication is more difficult when a first treatment attempt has failed, usually because of either poor patient compliance or the development of antibiotic resistance. Therefore, a 10-to-14-day treatment course is advocated for second-line therapies (Suerbaum and Michetti, 2002).

Rifabutin, given in association with amoxicillin and pantoprazole for 10 days, achieved an 86% rate of cure, even in patients with resistant strains (Perri et al., 2001).
Third-Line Quadruple "Salvage Therapy" (Marshall Therapy)

Ciprofloxacin 500mg bid
Rifabutin 150mg bid
Omeprazole 40mg tds (six times the normal dose)
Amoxycillin 1000mg tds

This regimen is indicated for primary therapeutic failure.
Resistant Infections

Unfortunately, an increasing number of infected individuals are found to harbour antibiotic-resistant bacteria. This results in initial treatment failure and requires additional rounds of antibiotics. For resistant cases, a quadruple therapy may be used.

Resistance is common with metronidazole.

For the treatment of clarithromycin-resistant strains of *H. pylori* the use of levofloxacin as part of the therapy has been recommended.

Endoscopy and biopsy with C&S of the *H. pylori* strain can be done in some resistant cases.
Alternative Treatments

A preliminary human study suggests high-dose vitamin C may be capable of inhibiting H. pylori in selected cases (Zhang et al., 1997).

Polyunsaturated Fatty Acids, alpha-linolenic acid, linoleic acid, and gamma-linolenic acid (Frieri et al., 2000).

Mastic gum is suggested to have a bacteriostatic effect is seen at concentrations as low as 0.0075 mg/ml (Huwez et al., 1998).

Garlic, was found to inhibit the growth of H. pylori in vitro, with a minimum inhibitory concentration of 40 mcg of thiosulfinate per ml (Aydin et al., 2000).

Regular consumption of broccoli sprouts might eradicate H. pylori (Galan et al., August).

A study done on Mongolian gerbils indicates that green tea extract can suppress H. pylori growth (Matsubara et al., ).
**TOPICAL THERAPY**

Drugs are kept in the stomach for a few hours. For 2 days before the therapy, patients were given lansoprazole 30 mg OD for preventing the decrease of antimicrobial activity of drugs in the low pH condition, and pronase 20,000 units bid for removal of the surface mucus. A tube is inserted into the duodenum, and a balloon is inflated with air and lodged post-bulbarly. Then the 100 ml of 7% sodium bicarbonate solution including drugs (ABM: amoxicillin 4.0 g, bismuth subnitrate 4.0 g and metronidazole 2.0g, and the other regimen is CM: clarithromycin 1.6g and metronidazole 2.0g. ) is introduced into the stomach through the biopsy channel of the endoscope.
Endoscope is pulled out and the solution is kept in the stomach for a couple of hours. Finally, a solution is suctioned out through the tube.

The cure rate of ABM was 77% (37/48), and that of CM was 81% (21/26). (Kimura, et al. 1995)

**Advantage of topical therapy:**
- It requires much less time than oral medication
- Well tolerated
- Few side effects by antibiotics absorbed from intestine
- Drugs do not reach the stomach by way of the bloodstream.
Prophylactic and therapeutic vaccination against Helicobacter infection have been successful in a variety of animal models (Blanchard and Czinn, 2000). Intranasal delivery of antigen with CpG-oligodeoxynucleotide induced a strong systemic immune response and a mucosal immunoglobulin A (IgA) response (Helicobacter, 2005). Further studies are necessary to determine the efficacy of such vaccines in prevention of H.pylori infections.
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