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RESEARCH ARTICLE

Helicobacter pylori: Gastric ulcer and cancer causing bug

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Abstract

Helicobacter pylori (*H. pylori*) are the bacteria that are notorious today in medical microbiology for causing gastric ulcer and cancer. Apart from this, it also plays a significant role in serious stomach inflammation (chronic gastritis). The pathogen generally weakens the protective coating of the stomach, thus allowing digestive juices to irritate the sensitive stomach lining. It is estimated that half of the world's population is infected with *H. pylori*. Those living in developing countries or crowded, unsanitary conditions are most likely the factors to catch this bacterium, which is passed from person to person. *H. pylorus* loves to grow in the stomach, and it is believed probably contracted during childhood. Chief symptoms include; abdominal pain, bloating and fullness, dyspepsia or indigestion, feeling hunger and mild nausea. Simple blood, breath, and stool tests can determine *H. pylori* infection. The most accurate way to diagnose *H. pylori* is through upper endoscopy of the esophagus, stomach, and duodenum. As, this procedure is invasive, it is generally only done on people suspected to have an ulcer, or who are at high risk for ulcers or other complications from *H. pylori*, such as stomach cancer. Treatment must be taken for 10 to 14 days. Medications may include: Two different antibiotics, such as clarithromycin, amoxicillin, tetracycline, or metronidazole. Proton-pump inhibitors, such as omeprazole, lansoprazole, or esomeprazole. Bismuth subsalicylate (Pepto-Bismol), in some cases .Once the *H. pylori* bacteria are gone from your body, the chance of being infected again is very low. *H. pylori* infection is linked to stomach cancer and ulcer disease as now proven medically and scientifically. A clean and germ-free environment may help in decreasing the bioburden of *H. pylori* infection.

Brief introduction:

H. pylori, a gastric organism was first identified more than 100 years ago and its association with gastritis has been acknowledged since the 1970s (Marshall, 1989). *Helicobacter pylori* are Gram-negative, spiral-shaped, flagellated bacteria found in the stomach (Logan & Walker, 2001). It was identified in 1982 by Barry Marshall and Robin Warren, who found that its presence in patients with chronic gastritis and gastric ulcers. It is also associated to the development of duodenal ulcers and stomach cancer (Blaser. 2006). More than 50% of the world's population harbor *H. pylori* in their upper gastrointestinal tract (Mertz & Walsh, 1991); while most individuals are asymptomatic, a significant number of patients develop serious gastrointestinal disease. Infection is more prevalent in developing countries, and cases of incidence are declining at a faster rate in Western countries. *H. pylori*'s helix shape is thought to have evolved to penetrate the mucoid lining of the stomach (Yamaoka. 2008; Brown. 2000).

Historical view:

Helicobacter pylori were first discovered in the stomach of patients with gastritis and stomach ulcers in 1982 by Dr. Barry Marshall and Dr. Robin Warren of Perth, Western Australia (Blaser. 2006).

German scientists found spiral-shaped bacteria in the lining of the human stomach in 1875, but they were unable to culture it, and the results were eventually forgotten (Blaser, 2005). Interest in understanding the role of bacteria in stomach diseases was renewed in the 1970s, with the visualization of bacteria in the stomach of gastric ulcer patients (Steer, 1975). The bacterium had also been observed in 1979, by Australian pathologist Robin Warren, who did additional research on it with Australian physician Barry Marshall beginning in 1981. They finally succeeded in visualizing colonies in 1982, when they unintentionally left their petri dishes incubating for 5 days over the Easter weekend (Marshall et al. 1984).

Epidemiology at a glance:

At least half the world's population is infected by the bacterium, making it the most extensive infection in the world (Pounder *et al*., 1995). The age at which this bacterium is acquired seems to persuade the possible pathologic outcome of the infection: people infected with it at an early age are likely to develop more intense inflammation that may be followed by atrophic gastritis with a higher subsequent risk of gastric ulcer, gastric cancer or both. Acquirement at an older age brings different gastric changes more likely to lead to duodenal ulcer (Brown, 2000). However, the infection rate of children in developing nations is higher than in industrialized nations, probably due to poor sanitary conditions. The higher prevalence among the elderly reflects higher infection rates when they were children rather than infection at later ages (Kusters *et al*., 2006). The lower rate of infection in the West is largely attributed to higher hygiene standards and widespread use of antibiotics. Despite high rates of infection in certain areas of the world, the overall frequency of *H. pylori* infection is declining (Malaty, 2007). *H. pylori* are contagious, although the exact route of transmission is not known (Mégraud, 1995; Cave, 1996). Person-to-person transmission by either the oral-oral or fecal-oral route is most likely. Consistent with these transmission routes, the bacteria have been isolated from feces, saliva and dental plaque of some infected people. Findings suggest that H. pylori are more simply transmitted via gastric mucus than via saliva (Brown. 2000). Transmission occurs mainly within families in developed nations yet can also be acquired from the community in developing countries (Delport et *al*., 2007). *H. pylori* may also be transmitted orally by means of fecal matter through the ingestion of waste-tainted water, so a hygienic environment could help decrease the risk of *H. pylori* infection (Brown. 2000).

Signs and symptoms:

Over 80% of people infected with *H. pylori* show no symptoms (Boyanova, 2011). Acute infection may appear as an acute gastritis with stomach ache or nausea (Butcher *et al*., 2003). Where this develops into chronic gastritis, the symptoms, if present, are often those of non-ulcer dyspepsia: stomach pains, nausea, belching, bloating and vomiting or black stool (Ryan, 2010). Individuals infected with *H. pylori* have a 10 to 20 % life time risk of developing peptic ulcers and a 1 to 2 % risk of acquiring stomach cancer (Kusters *et al*., 2006). Inflammation of the pyloric antrum is more likely to lead to duodenal ulcers, while inflammation of the corpus is more likely to lead to gastric ulcers and gastric carcinoma (Suerbaum *et al*., 2002). However, it is possible that *H. pylori* play a role only in the first stage that guides to common chronic inflammation, but not in further stages leading to carcinogenesis (Brown. 2000).

Microbiology perspective:

H.pylori are a helix-shaped, Gram-negative bacterium about 3 µm long with a diameter of about 0.5 µm. It is microaerophilic, but at lower concentration than is found in the atmosphere. It contains a hydrogenase which can be used to get energy by oxidizing molecular hydrogen produced by intestinal bacteria (Olson *et al*., 2002). It produces oxidase, catalase, and urease. It is capable of forming biofilms (Stark *et al*., 1999) and can convert from spiral to a possibly viable but non culturable coccoid form (Chan *et al*., 1994), both likely to favor its survival and be factors in the epidemiology of the bacterium.

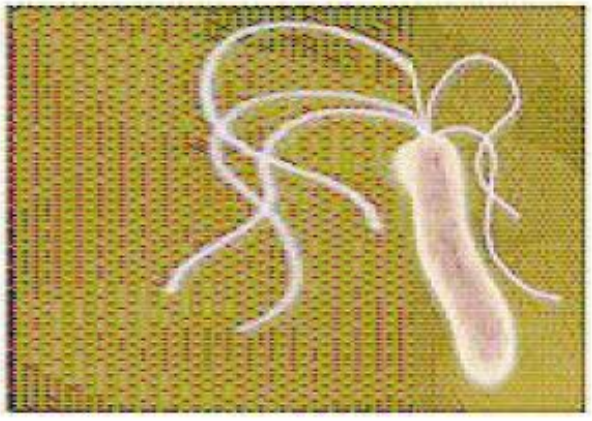

Figure 1: Helicobacter pylori

Pathophysiology:

For the sake of colonization of the stomach, *H. pylori* stays alive the acidic pH of the lumen and use its flagella to burrow into the mucus to reach its niche, close to the stomach's epithelial cell layer (Amieva *et al*., 2008). Many bacteria can be found deep in the mucus, which is continuously secreted by mucus-secreting cells and removed on the luminal side. To avoid being carried into the lumen, *H. pylori* adopts a unique way as it senses the pH gradient within the mucus layer by chemotaxis and then swims away from the acidic contents of the lumen towards the more neutral pH environment of the epithelial cell surface (Schreiber *et al.*, 2004). *H. pylori* are also found on the inner surface of the stomach epithelial cells and rarely inside epithelial cells (Petersen *et al*., 2003). It produces adhesions which bind to membrane-associated lipids and carbohydrates and help it stick to epithelial cells. The survival of *H. pylori* in the acidic stomach is dependent on urease. The ammonia produced is toxic to the epithelial cells, and, with the other products of *H. pylori* including proteases, vacuolating cytotoxin A (VacA), and certain phospholipases, damages those cells (Smoot, 1997). Inflammatory processes of *H. pylori* infections are also mediated by highly disulfide-bridged proteins. Helicobacter cysteine-rich proteins (Hcp), particularly HcpA (hp0211), trigger an immune response all the way throughout the differentiation of human myeloid Thp1 monocytes intomacrophages (Dumrese *et al*., 2009). Colonization of the stomach by *H. pylori* ultimately results in chronic gastritis, an inflammation of the stomach lining. The severity of the inflammation is likely to underlie *H. pylori* related diseases (Shiotani *et al*., 2002). The type of ulcer that develops depends on the location of chronic gastritis, which occurs at the site of *H. pylori* colonization (Dixon. 2000). The acidity within the stomach lumen channel affects the colonization pattern of *H. pylori*, and therefore at last determines whether a duodenal or gastric ulcer will develop or not (Kusters *et al*., 2006). The inflammatory response to the bacteria induces G cells in the antrum to secrete the hormone gastrin, which travels through the bloodstream to the corpus (Blaser *et al*., 2004). Gastrin activates the parietal cells in the corpus to secrete even more acid into the stomach lumen. The exorbitantly increased acid load damages the duodenum, and ulceration may eventually result (Schubert *et al*., 2008). Pathogenic strains of *H. pylori* have been shown to activate the epidermal growth factor receptor (EGFR). Activation of the EGFR by *H. pylori* is associated with altered signal transduction and gene expression in host epithelial cells that may contribute to pathogenesis (Baldwin *et al*., 2007; Broutet *et al*., 2001). A number of past research reports also indicated that absolute eradication of *H. pylori* prevents ulcer relapse as well as rebleeding in both duodenal and gastric ulcer thus improves ulcer healing and normalizes histology and acid secretion from chronic gastritis (Kandulski *et al*., 2009).

Diagnostic options:

Colonization with *H. pylori* is not a disease in and of itself but a condition associated with a number of disorders of the upper gastrointestinal tract (Kusters *et al*., 2006). Testing for *H. pylori* is recommended if there is peptic ulcer disease, low grade gastric MALT lymphoma, after endoscopic resection of early gastric cancer, if there are first degree relatives with gastric cancer, and in positive cases of dyspepsia. One can test noninvasively for *H. pylori* infection with a blood antibody test, stool antigen test, or with the carbon urea breath test (Stenström *et al*., 2008). However, the most consistent method for detecting *H. pylori* infection is a biopsy check during endoscopy with a rapid urease test, histological examination, and microbial culture. There is also a urine ELISA test with 96 % sensitivity and 79% specificity (Logan et al. 2001). Some studies pointed out that duodenal ulcer is common as compared to gastric ulcer its prevalence being 4:1 in USA (Ellashoff & Grossman, 1980) and U.K (Coggon *et al*., 1981) 5:1 in Pakistan (Ahmed *et al*., 1990) and very high prevalence 32:1 in certain parts of India (Chen *et al*., 2007)

Genome in focus:

H. pylori consists strains having diverse genomic makeup (Oh *et al*., 2006). Among them, the genomes of three have been completely sequenced with great success (Baldwin *et al*., 2007).The attempt of whole genome sequencing was done to understand the pathogenesis mechanism. *Helicobacter pylori* strain 26695 has a circular genome of 1,667,867 base pairs and 1,590 possible predicted coding sequences (Tomb *et al*., 1997). Studies indicated that approximately 29% of the loci have been revealed in the "pathogenesis" category of the genome database. In this regard, two of sequenced strains have approximately 40-kb-long Cag pathogenicity island (a common gene sequence that is believed to be involved in causation and mainly play role in pathogenesis) that is actually a stretch of 40 genes (Broutet *et al*., 2001). This pathogenicity island is usually not observed from *H. pylori* strains isolated

from humans who are merely carriers of *H. pylori* but they remain asymptomatic.

Prevention:

H. pylori are a major reason of some diseases of the upper gastrointestinal tract. Rising antibiotic resistance increases the search for different new therapeutic options; this might include prevention by means of vaccination (Logan *et al*. 2001).

Treatment Strategies:

Once *H. pylori* are detected in a person with a peptic ulcer, the normal procedure is to eradicate it and let the ulcer to heal. The standard first-line therapy is a one week "triple therapy" consisting of proton pump inhibitors such as omeprazole and the antibiotics clarithromycin and amoxicillin (Malfertheiner *et al*., 2012). Variations of the triple therapy have been developed over the years, such as using a different proton pump inhibitor, as with pantoprazole or rabeprazole, or replacing amoxicillin with metronidazole for people who are allergic topenicillin (Malfertheiner *et al*. 2007). An increasing number of infected individuals are found to harbor antibiotic-resistant bacteria. This results in initial treatment failure and requires additional rounds of antibiotic therapy or alternative strategies, such as a quadruple therapy, which adds a bismuth colloid, such as bismuth subsalicylate (Stenström *et al*., 2008; Fischbach *et al*., 2007; Graham et al. 2008). For the treatment of clarithromycin-resistant strains of *H. pylori*, the use of levofloxacin as part of the therapy has been suggested (Perna *et al*., 2007; Hsu *et al*., 2008). An intramuscular vaccine against *H. pylori* infection is undergoing Phase I clinical trials and has shown an antibody response against the bacterium (Megraud, 1998).

Herbal treatment: An alternative approach:

In a recent study, anti-Helicobacter pylori activity of 50 commonly used Unani medicine plants from Pakistan that are broadly utilized for the cure of gastrointestinal disorders to discover the natural source for direct compounds against *H. pylori* (Huang *et al*., 1997). Curcumin contains many powerful antioxidants and anti-inflammatory compounds, which have been shown to maintain colon health, a healthy cardiovascular system, and brain health. Dozens of studies have shown that it is a chemo-preventative, and more recently it has been shown to apply a strong antibacterial effect against *H. pylori* (Chiba *et al*., 1996).

Prognosis in Brief:

H. pylori colonize the stomach and induce chronic gastritis, a long-lasting inflammation of the stomach. The bacterium persists in the stomach for decades in most people. Most individuals infected by *H. pylori* will never experience clinical symptoms despite having chronic gastritis. Approximately 10–20 % of those colonized by *H. pylori* will ultimately develop gastric and duodenal ulcers. *H. pylori* infection is also associated with a 1–2 % lifetime risk of stomach cancer and a less than 1 % risk of gastric MALT lymphoma (Kusters *et al*., 2006). In the absence of treatment, *H. pylori* infection once established in its gastric niche is widely believed to persist for life (Brown, 2000). In the elderly, however, it is likely infection can disappear as the stomach's mucosa becomes increasingly atrophic and inhospitable to colonization. Mounting evidence suggests that *H. pylori* have an important role in protecting from some diseases. The incidence of acid reflux disease, Barrett's esophagus, and esophageal cancer have been rising noticeably at the same time as *H. pylori*'s presence decreases (Blaser, 2005).

Vaccines: A hopeful approach:

Vaccines; no doubt provide longer immunity than other options. In this regard, the first tremendous work has been carried out by making murine model in the early 1990s provided a clear vision that vaccination against *H. pylori* infection could provide immunity (Hardin & Wright, 2002). However the mechanism of protective immunity when studied thoroughly against the organism established by means of stimulation of T-helper type 2 phenotype cells, which are induced by the production of interleukins 4 and 10 and not by antibody production (Sutton, 2001). Several such trials in past have been conducted. Different agents, like cholera toxin and an *Escherichia coli* heat labile toxin, have been used in combination with specific
H. pylori antigens (eg, urease) (Douce et *al*., 1997).In the same way, attenuated live vaccines,
like strains of *Salmonella*, used in combination with *H. pylori* antigens have shown a bit success but not absolutely (Michetti *et al*., 1999). Clinical trials are underway with the goal of producing an in expensive, safe, and effective vaccine seeming to be within reach.

Conclusion:

In conclusion, a number of researches conducted in the past decades have confirmed causal relationship between *H. pylori* infection and gastritis, duodenal, gastric ulcer and cancer thus have broken the idols of traditional medical notions. In this way, the discovery of *Helicobacter pylori* has utterly revolutionized the pathological, physiological and clinical view regarding gastric and duodenal ulcer. Moreover, there is very high load of this infection among developing countries due to a number of risk factors as well as rapid increase in antibiotic resistance. There is a dire need that the concerning authorities should make stringent steps for control and prevention of this infection which is probably the contaminated food and water.

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