H. pylori: Scientific basis to patient cure

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The journey on the road of discovery of *Helicobacter pylori* (Hp) to cure of infection associated conditions ended in Stockholm on December 10, 2005 when Barry Marshall and Robin Warren received the Nobel Prize in Physiology or Medicine. All who have traveled this road, both patients and physicians, should celebrate this journey with them. It was not an easy journey, at least not initially, since skeptics lined the path jeering travelers with chants that infectious ulcer disease and cancer lacked any scientific basis. Now at journeys end the skeptics are gone and the scientific world has embraced the clinical importance of *H. pylori* and is clamoring to capitalize on the opportunities presented by Marshall's and Warren's discovery. While prevalence of infection is declining, it's clinical and scientific influence will remain prominent for decades.

Hp infection causes varied clinical outcomes presumably due to variable intensity and distribution of gastritis and altered gastric acid physiology among infected individuals. Most pathogenic bacterial strains contain a specific cluster of genes know as the "*cag* pathogenicity island" which encodes for CagA protein and processes responsible for it's translocation into host cells. Intercellular CagA induces pro-inflammatory cytokine production, interleukin-1β (IL-1 β) and interleukin-8 (IL-8), which activate and recruit acute inflammatory cells to the mucosa causing intense gastritis and modifying gastric acid secretion. Specific polymorphisms of the IL-1β gene cluster increase risk for stomach cancer. Presumably more severe gastric inflammation leads to repeated epithelial injury and repair, eventual mitotic errors, proliferation of chromosomally altered cells, and finally cancer. An alternative explanation for *H. pylori* associated gastric cancer proposes that the inflammatory milieu of the infected stomach promotes homing and engraftment of pluripotent bone marrow derived cells which in their foreign inhospitable environment exhibit altered growth and differentiation such that epithelial cancer develops.

While *H. pylori* can cause gastric cancer, does eradication of infection reduce subsequent cancer risk? Uemura followed more than 1,000 Hp infected Japanese patients with endoscopically resected early gastric cancer. Within 8 years 3% of those not receiving treatment for their infection developed subsequent early stage cancers while no cancers developed when infection was cured. He also performed periodic endoscopy on 1,500 Japanese patients during a mean period of 7.8 years. Gastric cancer developed in 4% of those in whom infection persisted while no individual who was uninfected or received Hp treatment acquired cancer. Individuals with severe atrophy, corpus-predominant gastritis, and intestinal metaplasia were at greatest risk for developing subsequent gastric cancer. Are such pre-malignant mucosal changes reversible or is there a "point of no return" after which cure of infection no longer prevents malignant transformation? In a trial by Wong, Hp treatment did not prevent subsequent gastric cancer in the group as a whole, but in those with no baseline atrophy, metaplasia or dysplasia antibiotics did significantly prevent gastric malignancy. Gastric acid secretion normalizes in most individuals after curing infection, but in those with severe histological change, physiologic abnormalities are irreversible. As a whole these data suggest that eradication of *H. pylori* can modify gastric physiology, histology and cancer risk but there is likely a point at which conditions are so advanced that treatment is futile. Thus to be most successful, Hp therapy should be initiated as early as possible.

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is also linked to *H. pylori* infection particularly strains that produce a truncated flavodoxin protein, FldA. Bacterial infection causes mucosal B-cell proliferation which when sustained, leads to monoclonal malignant transformation through acquisition of genetic abnormalities such as trisomy 3 or microsatellite instability. Transformed B-cell clones with the genetic translocation t(1;18)(q21;q21) expand independent of persistent *H. pylori* and respond poorly to bacterial eradication. Past treatment of MALT lymphoma involved chemotherapy, radiotherapy, and surgical resection but now Hp eradication has emerged as first-line therapy. Cure of infection achieves complete remission in the majority of early low-grade stage E1 (limited to mucosa and submucosa) tumors. More advanced tumors develop genetic alterations involving the BCL-10 gene and

inactivated tumor suppressor genes, p53 and p16 which promote high-grade transformation, independent growth and treatment resistance. Careful staging using endosonography to judge tumor depth, immunohistochemical analysis, and genetic analysis (if available) are important in the diagnosis and management of MALT lymphoma. Monoclonal B cells can be detected by molecular techniques long after successful treatment so long-term surveillance for recurrence remains important even in those who achieve apparent complete endoscopic and histological remission.

Marshall and Warren's major contribution was linking *H. pylori* to ulcer disease and determining that cure of infection reduced ulcer recurrence. Host genetics and bacterial virulence play key roles in ulcer disease. In ulcer patients gastritis is more intense and often confined to the antrum which leads to up regulation of gastrin and down regulation of somatostatin, the net effect being increased acid secretion especially following a meal. In some individuals the acid produced is sufficient to overwhelm mucosal defense and cause an ulcer. But when infection is cured, acid secretion returns to normal, which explains why ulcers do not recur. In most areas of the world *H. pylori* still causes most ulcers but in the United States, less than 50% of ulcers are infectious so curing the infection does not prevent all recurrences.

The relationship between *H. pylori* and GERD remains controversial. In Asia despite a high prevalence of infection, individuals with reflux have lower infection rates. In this region CagA strains are common, host genetics favor corpus-predominant gastritis and lower acid results from infection. Thus infection could lessen acid reflux while those not infected with *H. pylori* would be more prone to GERD. In Western countries the same histological and physiological response to infection that promotes duodenal ulcer might also promote GERD, making clinical differences between infected and non infected individuals less striking.

In a similar vein, whether treatment of infection is harmful or beneficial in GERD patients depends on infection-related histology and physiology. Normalizing acid secretion by curing *H. pylori* infection in someone with hypochlorhydria could initiate reflux symptoms de novo or complicate treatment of existing symptoms. On the other hand, when infection related histology and physiology favor hyperchlorhydia eliminating infection could actually improve reflux symptoms and Hp status would not affect treatment response.

How to test for *H. pylori* is as important as whom to test. In older individuals or those with alarm features that could indicate an ulcer or cancer, endoscopic testing is preferable while non-invasive testing is appropriate for others. Serology is the most common non-invasive technique used in the US although it is inaccurate when the prevalence of infection is low. Also primary care physicians often use serology inappropriately to monitor success of treatment despite availability of better non-invasive tests. Outside the US, physicians are more likely to use more accurate tests but even these "better" tests (urea breath test, stool antigen test) are not perfect; their results are affected by concomitant acid suppressive medication.

Efficacy, cost, side effects, ease of administration and prevalence of antibiotic resistance should guide *H. pylori* treatment. No single antibiotic can cure infection and no single therapeutic regimen has emerged as ideal. Current treatment options are complicated and include combinations of acid suppressive medications and two or more antibiotics dosed several times daily for one to two weeks. Side effects of therapy are frequent so patient compliance can be a problem. Primary antibiotic resistance is more common than previously thought and secondary resistance invariably develops when initial treatment fails. Simplifying regimens or shortening treatment duration usually reduces effectiveness. Although treatment success varies among countries, available regimens are generally effective in over 75% of individuals.

A PPI together with amoxicillin (1 gram) and clarithromycin (500 mg) each dosed twice daily for 7-14 days has emerged as the first line treatment of choice. If a patient is allergic to penicillin, metronidazole 500 mg can be substituted for amoxicillin but efficacy is less since imidizole resistance is common. If initial treatment fails, re-treatment with 2 weeks of bismuth-based quadruple therapy with high dose metronidazole (500 mg) is a reasonable option but this complicated regimen fosters non compliance. A simpler regimen, a PPI together with amoxicillin (1 gram) and levofloxacin (250 mg or 500 mg) each twice daily for 7-14 days, is now the "rescue" treatment of choice The recent observation that glycans normally found in the stomach can inhibit *H. pylori* could lead to novel "pylori specific" treatments. This and an effective *H. pylori* vaccination could control and possibly eliminate the most common world-wide bacterial infection.

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