Helicobacter pylori: past, present and future

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ABSTRACT

Helicobacter pylori is an organism that is a worldwide cause of significant morbidity and mortality. There has been a sea change in our understanding and hence diagnosis and treatment of this ubiquitous bacterium over the last few years and more is in the offing. Though it still affects over half the world's population, there has been an identification of genes and epigenetic motifs which can modify disease expression and cancer occurrence with *Helicobacter* infection. Newer diagnostic modalities like urine antibody analysis, immune-chromatographic culture methods, pepsinogen assays and micro-RNA detection promise earlier identification of more virulent forms. Advances in endoscopy have also incorporated Chromo-endoscopy, Narrow Band Imaging, Confocal endo-microscopy and Raman spectroscopy for diagnosis of *H. pylori* infections with greater accuracy. Advent of genotype drug resistance assays and newer therapeutic regimens have afforded greater efficacy in eradicating this infection. An interesting area of research is novel drug delivery systems, like the gastro-retentive systems, which have increased efficacy of existing drugs against *Helicobacter*. Vaccine development is also underway with ongoing animal trials on EPIVAC vaccine among others, showing some benefits. Though there is still a long way to go, all these newer modalities hold out hope for the possibility of a reduction in the burden associated with this wide spread infection.

Keywords: Diagnostic modalities, Endoscopy, *Helicobacter pylori*, Treatment strategies

Helicobacter pylori is a bacterium that has transcended centuries, unchanged and thriving. From its first discovery in 1982 by Warren and Marshall, there has been a slow but steady change in the management and diagnosis of the infection. It still continues to colonize more than half of the world's populace and more than 60% of India's population.[1]

Most of the people with this infection develop some form of the disease. The degree of the manifestation differs from person-to-person depending on the host susceptibility genes, virulence factors and environmental factors. The disease manifests as chronic gastritis after infection via the feco-oral route. The bacterium is an obligate pathogen of the human stomach causing a form of superficial gastritis. The cytotoxin associated gene A (cagA) is an important inductor of inflammation and is an important marker for complications. There is marked variability in the manifestation of *H. pylori*, mainly due to the variations in the epigenetic EPIYA C motifs.[2] The presence of two or more of these motifs predisposes to a greater risk of atrophic gastritis and gastric carcinoma. The disease caused by the organism ranging from atrophic gastritis to gastric cancer is a continuous spectrum of the manifestations. The disease merits such global importance, because of its association with gastric cancer. Seventy five percent of all gastric lymphomas and all gastric MALTomas are attributable to *H. pylori* infection.[3]

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An important recent discovery in the pathogenesis of *H. pylori* is the FOXD3 mRNA and gene. The mRNA of the gene acts as a promoter for a tumor suppressor gene. It has been found that patients with intestinal metaplasia and, more so, those with gastric cancer have a lower FOXD3 mRNA level in their blood.[4] This may be a future diagnostic or therapeutic target. One important point to note in the pathogenesis of *H. pylori* gastric cancer is that the extent, severity and the atrophy correlates with the presence of gastric cancer and is almost always preceded by a period of chronic gastritis where diagnosis and intervention can be yielding and preventive.

There is a cohort of patients in whom *H. pylori* detection and eradication should be actively pursued. According to the Maastricht IV guidelines,[5] this population includes – first degree relatives of gastric cancer patients, past carcinoma of stomach, severe pangastritis or atrophy, chronic acid inhibition therapy (>1 year), environmental risk factors like smoking and if the patient fears carcinoma of the stomach. There have been reports of association of the infection with many extraintestinal manifestations. To name a few, they are coronary artery disease, iron deficiency anemia, Idiopathic Thrombocytopenic Purpura, B12 deficiency, Alzheimer's disease, Parkinsonism, migraine, alopecia, urticaria, Raynaud's phenomenon, Sjogren's autoimmune thyroiditis and hyperemesis gravidarum.[6]

There have been a few diagnostic modalities in use for *H. pylori* over the last few decades, each with its own set of advantages and disadvantages. All, except IgG serology, require stopping of acid suppressants for at least 2 weeks prior to application of the method. The current strategy advocated is to "Test and Treat" which means, to treat only those patients who test positive for *H. pylori*.[5] This precludes any empirical therapy. After *H. pylori* eradication, current consensus is to test a select cohort for eradication. That cohort includes patients with persistent symptoms after four weeks, associated ulcers, MALTomas and early gastric cancer.[7] The investigative techniques in use traditionally include rapid urease test, urea breath test, stool and urine antigen tests, histopathology and culture.

With rapidly changing technology, newer tests are now either being used, or are in the pipeline. Immunohistochemistry based techniques of staining improve sensitivity and specificity of biopsy specimens. Urine antibody tests are a new method which can be done either by the immunoassay or the immuno-chromatographic method.[8] Serum Cag A antibodies have been found to correlate with gastric cancer in a meta analysis, though its significance in India has not been found to be as much.[9] Serum pepsinogen assays have been called "serological biopsy" and the ratio of Pepsinogen I/II is a new marker for presence of gastric atrophy.[10] The ratio is lower in the presence of *H. pylori*. The Japanese classify their patients into four groups on the basis of *H. pylori* and Pepsinogen status. The risk of gastric cancer varies in each group, with group D (*H. pylori* negative but Pepsinogen positive) denoting the highest risk of gastric cancer.[11] This screening tool cannot be used in India as the Pepsinogen levels are lower and, hence, fallacious.[12] Serum miRNA levels can also be used for detecting early gastric cancer in *H. pylori* infection, namely the miR–187, miR–371-5p and miR-378. There is also interest in the CYP2C19 polymorphism, which though does not aid in diagnosis, has important therapeutic implications as the patients with the said polymorphism are resistant to eradication therapies which are based on Omeprazole, Lansoprazole or Levofloxacin.

With the focus on newer endoscopic techniques in all areas of gastroenterology, really, *Helicobacter* detection cannot be left behind. Endoscopy is basically a surrogate for definitive tissue diagnosis of *Helicobacter*, but with newer techniques, that line has become blurred. Presence of a non bleeding duodenal ulcer itself has more than 90% positive predictive value for *H. pylori* presence. Presence of antral nodularity(chicken skin appearance) has a specificity of 96% for *Helicobacter* but is only 32% sensitive. Conversely, presence of star fish like appearance of the gastric mucosa, also known as RAC (regular arrangement of collecting venules) has a high negative predictive value for *H. pylori* infection.[13] Extent of chromoendoscopic staining with 0.1% phenol red solution also correlates with urea breath test and *H. pylori* density on histology.[14] The use of magnifying endoscopy for *H. pylori* has also been recently validated. Yagi *et al*[15] classified the appearance of *H. pylori* infected gastric mucosa visible on magnifying endoscopy into 4 patterns, - Z0, Z1, Z2 and Z3. The Z0 pattern has 93.8%

sensitivity and a 96.2% specificity for predicting normal gastric mucosa. Z1, Z2 and Z3 correspond with *H. pylori* infection.[15] Narrow band imaging endoscopy has also classified *H. pylori* infections into three types depending on pit pattern and vessel architecture with around 95% sensitivity and 82% specificity.[16] Infrared Raman Spectroscopy has a near 100% specificity at 1542/cm frequency for detecting *H. pylori* infection as a result of differential Porphyrin concentration. [17] Confocal Laser Endomicroscopy can also be used to detect *H. pylori* infection by visualizing organisms, neutrophils and microabscesses.

Not just diagnostic protocols but treatment strategies are also showing a slow but steady change. Various therapeutic regimes are now in use including the Sequential, Concomitant, probiotic based therapies and Hybrid regimen in addition to the standard Quadruple and Bismuth based therapies. The standard triple regimen uses 10 to 14 days of proton pump inhibitor along with clarithromycin and amoxicillin. The sequential therapy employs the use of 5 to 7 days of simultaneous PPI and amoxicillin followed by 5 to 7 days of PPI with clarithromycin and metronidazole. The concomitant therapy has treatment with 10 to 14 days of simultaneous PPI, clarithromycin, amoxicillin and metronidazole. The probiotic based regimen adds a probiotic to the standard triple regimen. The hybrid regimen is similar to the sequential therapy with the difference of continuing amoxicillin with clarithromycin and metronidazole even in the second half of the course of therapy.

When evaluated for side effects and overall efficacy, it was found in a recent meta-analysis, that the 14 day sequential regimen has overall good tolerance and efficacy, and is a good compromise on both while neither being the most efficacious, nor the best tolerated.[18] With rising antimicrobial drug resistance, there is a need to evaluate the bacterium for the presence of the same. Conventional anti microbial susceptibility testing techniques depend on culture and is cumbersome as well as time consuming. An alternative to culture techniques are molecular assays which, though expensive and research based at present, may be useful adjuncts to therapy in the near future. The GenoType HelicoDR assay determines resistance patterns to Clarithromycin and quinolones.[19] The sensitivity for Clarithromycin resistance is nearly 100% while being around 85% for quinolones.

With the development of advances in imaging, diagnostic and treatment methods, drug delivery systems are an interesting area of development. Gastroretentive drug delivery systems increase the time of contact of drugs against *H. pylori* as the drugs are site specific.[20] Floating systems cause the drug to float on the stomach contents till they are passed out. A disadvantage of this system is that the drug is not available specifically at the intended site.[21] Bio-adhesive systems adhere to the mucosa and offer promising results in increasing drug contact and efficacy with a disadvantage of being dependent on gastric emptying and turnover. Dual systems, in development, combine the advantages of both systems and may be the drug delivery system of the future, improving the efficacy of antibacterial therapy.

While all these measures aim to diagnose and treat *H. pylori* infection, there is a need for thrust in the development of a vaccine to prevent the disease all together. The three parts of a vaccine are the antigen, the adjuvant and the vector system. Various adjuvants have been tried but animal tests show the highest efficacy for alkyl hydroperoxide reductase and alum based vaccines.[22] Attenuated *Salmonella* and Poliovirus have been evaluated as vector delivery systems. The antigen for immunogenicity showing best outcomes is EPIVAC, a fusion protein of CD4+ T cell epitopes from HpA, UreB amd Cag A antigens. All these have shown some degree of effectiveness in animal studies and human studies are pending. A recombinant urease antigen vaccine is currently undergoing human studies. The problem with developing a vaccine for *H. pylori* is the fact that it is an excellent parasite because it behaves more like a commensal. All human vaccination trials have never shown vaccine induced clearance. The question facing researchers at the moment is the right choice of antigen and adjuvant for the development of the vaccine.

H. pylori is an infection that has spanned centuries, unchanged in virulence yet adapting for survival. With all the new armaments in our arsenal, it seems the time may have come to finally banish, if not eradicate this scourge of humanity.

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