

38 years Journey of *Helicobacter pylori*: Where it is now?

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Helicobacter pylori (*H. pylori*), previously named *Campylobacter pylori*, was first isolated in 1982 from patients with chronic gastritis or gastric ulcers in Western Australia. Barry J. Marshall and Robin Warren, two Australian researchers, have been awarded Nobel Prize in Physiology or Medicine for this Nobel discovery.¹ It is also linked to the development of duodenal ulcers and stomach cancer. *Helicobacter pylori* is a gram-negative bacterium that colonizes human stomach and now is an established cause of chronic superficial gastritis, chronic active gastritis, peptic ulcer disease and gastric adenocarcinoma. Before this discovery, it was a belief that stress and lifestyle factors were the two major causes of peptic ulcer disease. Marshall and Warren braked that dogma, and it was soon clear that *H. pylori*, causes more than 90% of duodenal ulcers and up to 80% of gastric ulcers.²

A recent meta-analysis on the global prevalence of *H. pylori* infection has shown an overall prevalence of 44.3%, and estimated prevalence are as high as 89.7% in Nigeria and as low as 10.0% in Indonesia and 8.9% in Yemen.³ In the United States, the presence of *H. pylori* infection in patients carries a lifetime risk of developing peptic ulcer of at least 16% and a 1%–3% risk of developing gastric cancer.² Socio-economic status, level of urbanization and sanitation conditions, likely reüects the differences of *H. pylori* prevalence from country to country. This infection is fast decline in most of the western countries, due to the success of therapeutic regimens and improved personal and community hygiene that prevents re-infection. The eradication in some of the countries has been quite promising. However, the situation is exactly opposite in many of the developing countries like Bangladesh due to failure of treatment and emergence of drug resistance.

The exact route of this *H. pylori* transmission is unclear; however, evidence supports person-to-person transmission via oral–oral or fecal–oral route between family members. After it has been transited to the gastric lumen, *H. pylori* localizes to specific locations like;

antrum and corpus. Where it adapted to survive in acidic conditions and establish persistent infection. Once persistent infection is established, several gastro-duodenal complications such as gastritis, gastric ulcer, duodenal ulcer, dyspeptic symptoms, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) B-cell lymphoma may develop. In addition to its association with gastro-duodenal complications, in recent years it has been reported to cause several extra-gastric complications such as ischemic heart disease, neurodegenerative diseases, and hematological disorders (iron deficiency anemia, immune thrombocytopenic purpura, and vitamin B12 deficiency).⁴ In a study Rahman A, et al (2020) show that, *H. pylori* infection was significantly associated with decrease in serum ferritin, MCV, MCH. Though in his study, *H. pylori* were not significantly associated with iron deficiency anemia, but it was significantly associated with iron deficiency. Based on the above findings, *H. pylori* infection may be sought for and treated in patients with unexplained iron deficiency anemia.⁵

Currently, the diagnosis of *H. pylori* infection is carried out by invasive (for example, endoscopy and endoscopic biopsy for histopathology, culture, and rapid urease test) and non-invasive (for example, urea breath tests, stool antigen test, and serological tests) methods. The guidelines of the Japanese Society for Helicobacter Research recommended that the diagnosis of infection is performed by using at least one of several invasive; however, increased accuracy is obtained by using multiple diagnostic tests. But endoscopy-based diagnostic methods are not recommended for screening purposes and this is because of their invasiveness, high cost, and unavailability.⁶ The urea breath test is currently recommended as the best approach for the screening of *H. pylori* infection because of its non-invasiveness and high sensitivity but it is relatively expensive.⁶ However, we can use noninvasive screening tests in younger patients and endoscopy-based methods in elderly patients (usually over 60 years, or over 45 years in some

European countries). Currently, the novel polymerase chain reaction (PCR)-based approach is sensitive for the detection of *H. pylori* DNA in stool samples. So, the preference of diagnostic tests depends on many factors like; patient's choice, test's accuracy, availability as well as its cost-effectiveness.

Eradication therapy for *H. pylori* significantly decreases the risk of developing gastric cancer if given before the onset of pre-cancerous lesions (atrophy, intestinal metaplasia, and dysplasia) and has proven to be the only effective strategy for reducing the development of gastric cancer.⁶ The Kyoto global consensus report involving members of the Japanese Society of Gastroenterology, the European Helicobacter Study Group, the Asian Pacific Association of Gastroenterology, the Healthy Stomach Initiative, and the working group members of gastroenterology for International Classification of Diseases-11th revision (ICD-11) recommended screening for *H. pylori* gastritis after the age of 12 years and proposed that all positive cases to be treated with eradication therapy even if they have no related symptoms or conditions.⁷

Careful selection of first-line eradication therapy plays a key role in the cure of *H. pylori* infections. This should be based on the local resistance pattern of the antibiotic sensitivity. Clarithromycin (a macrolide)-based triple drugs therapy with Proton Pump Inhibitor (PPI), Clarithromycin, and Amoxicillin (or Metronidazole where its resistance rate is low) is now recommended as the first-line eradication therapy only when clarithromycin resistance is below 15%. However, if Clarithromycin resistance exceeds 15%, Bismuth quadruple therapy (Bismuth, PPI, Tetracycline, and Metronidazole) or non-bismuth quadruple therapy (PPI, Amoxicillin, Clarithromycin, and Metronidazole; also known as concomitant therapy) may be consider for 10–14 days as an alternative to first-line triple therapy.⁶

In most of the ASEAN countries, metronidazole resistance is high, and an increasing rate of clarithromycin resistance in recent years causes difficulty in eradication of *H. pylori* by clarithromycin and metronidazole based therapy. A meta-analysis on primary antibiotic resistance conducted in the Asia-Pacific region in 2017 reported an increasing pattern of clarithromycin resistance rate in recent years, whereas metronidazole resistance rates were as high as 75% in

Vietnam, 84% in Bangladesh, and 88% in Nepal. However, in most areas, amoxicillin resistance is rare (below 5%), and in some parts clarithromycin resistance is also lower than 15%; therefore, PPI-clarithromycin-based triple therapy for 14 days is most effective.⁸ In most regions, the frequent use of antibiotics is the main contributor to drug resistance and decreasing efficacy of eradication therapies.⁹

Person to person transmission and re-infection among the family members can be prevented by “mass eradication” strategy. If any family member being offered *H. pylori* eradication therapy for some clinical symptoms, the other members (>12 years) of the family should be screened and eradication therapy should be offered together to all who are positive for *H. pylori* infection. In this way, re-infection from asymptomatic family members can be avoided.⁶

How long humans carried *H. pylori* is still a debatable issue. However, it has colonized humans possibly for many thousands of years and successfully presence in human stomach for such a long period. Eradication of *H. pylori* infection has been proven to reduce the incidence of gastric cancer. But the eradication treatment become more difficult day by day because of antibiotic resistance. Worldwide clarithromycin or metronidazole containing regimens are no longer suitable for empiric use in most of the countries because of inadequate eradication rates (<80%). The efficacy of available alternatives (such as quadruple, sequential, concomitant, and levofloxacin-containing triple regimens) has varied greatly.¹⁰ Therefore, local and national surveillance networks are required to select effective eradication regimens for each individual region. Consequently we can limit the malignant and nonmalignant burden of *H. pylori* chronic infection.

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