

## Growing Multidrug Resistance of *Helicobacter pylori* to Antibiotics: an Alarm to Gastric Health

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**Received:** June 28, 2018; **Published:** July 05, 2018

Barry J. Marshall and Robin Warren, two Australian researchers established the identity of *Helicobacter pylori* (*H. pylori*) from the biopsies of human subjects suffering from chronic gastritis and gastric ulcers [1]. The discovery of this gram-negative, microaerophilic bacterium opened a new window in the mainstream of gastrointestinal research and made a paradigm shift in approaches of studying the gastrointestinal diseases. At least half the world's population is infected by *H. pylori*, grading it one of the most widespread infection in the world. Over 50% of the world's population have *H. pylori* infection in their upper gastrointestinal tract which perhaps may be associated with significant role in the gastric niche. Dramatically, over 80% of infected individuals remain asymptomatic. In general, the incidence of *H. pylori* infection is more common in developing countries than Western countries [2].

Interestingly, until the discovery of *H. pylori*, gastritis and gastric ulcers were not believed to have a microbial cause owing to the conventional thinking that no bacterium can sustain in the acidic environment of the human stomach. After discovery of this bacterium, a long debate continued about its identity and patho-physiological roles. Of note, to demonstrate the *H. pylori* as a causative agent of gastritis, Marshall drank a *H. pylori* containing solution, as result he became sick with symptoms like nausea and vomiting several days later. After 10 days inoculation, he underwent endoscopy analysis which revealed the signs of gastritis and the presence of *H. pylori*. Over two decades research of these two crazy researchers awarded the Nobel Prize of 2005 in Physiology or Medicine.

Impressive repertoire of chemotactic and metabolic adaptive mechanisms has been identified in *H. pylori* for its survival abilities in acidic environment of stomach [3,4]. In the present state of the art, sizable preclinical and clinical literature has accumulated in the recent past linking the role of *H. pylori* in the development of duodenal ulcers and stomach cancer. Besides having a scope for further investigation, to a greater extent, it has now been partly accepted that *H. pylori* infection is the most important risk factor for the development of non-cardia gastric cancer [5]. More precisely, the transition from normal mucosa to non-atrophic gastritis is primarily induced by *H. pylori* infection which results into formation of precancerous lesions which may then advances to development of atrophic gastritis and intestinal metaplasia. However, further developments leading to gastric cancer are generally believed to be independent of *H. pylori* [6]. Besides the causing of gastritis and gastric ulcer, perhaps the link of *H. pylori* in progression of gastric cancer has accelerated the *H. pylori* research.

Eradication of *H. pylori* infection has become a global concern, especially the developing countries needs novel therapeutic modalities for the management of *H. pylori* infection owing to the growing incidence of *H. pylori* infection. The most commonly employed first line anti-*H. pylori* therapeutic regimen comprises a combination of proton pump inhibitors (PPI: Omeprazole, pantoprazole, rabeprazole etc) and any two antibiotics like amoxicillin, clarithromycin, metronidazole, levofloxacin, fluoroquinolones, rifabutin or tetracycline. In general, the most commonly prescribed first-line therapy is a one-week "triple therapy" comprising of PPI like omeprazole and the antibiotics like clarithromycin and amoxicillin [7]. In general, resistances to antimicrobial agent's is evolving all over the world and clinical preclinical reports describe the dramatic decrease in the efficacy of antibiotics while treating variety of infectious diseases, and *H. pylori* is not an exceptional to this evolutionary trend of developing resistance against antibiotics [8].

Although *H. pylori* are sensitive to many antibiotics *in vitro*, however, only few antibiotics are effective in the clinic. Of note, increasing number of infected individuals is frequently found to harbour antibiotic-resistant *H. pylori* strain all over the world [9]. For example there is worldwide increase in *H. pylori* resistant strains to metronidazole and clarithromycin. *H. pylori* antibiotic resistance to clarithromycin and levofloxacin has increased significantly during the last 6 years all over the world. Series of preclinical and clinical reports across the world clearly shows the emerging resistance of *H. pylori* against series of antibiotics like metronidazole, amoxicillin, rifabutin, tetracycline, levofloxacin and furazolidon [10,11]. In the most populated country like China, prevalence of *H. pylori* resistance to clarithromycin has increased remarkably from 20% to 50% in the past two decades. In general, the reports describes that the global frequency rate of resistance is high in Africa and the most sensitive drug is rifabutin, while the lowest sensitive has been observed with metronidazole in the world [10]. Metronidazole is the most frequently prescribed antibiotic for the management of *H. pylori* infection. *H. pylori* strains from almost all over the world have demonstrated resistance in metronidazole. The worldwide percentage of metronidazole resistance in Africa is 75.02%, South America 52.85%, Asia 46.57%, Europe 31.19%, to 30.5% in North America. Interestingly, in developed countries about 30% of the *H. pylori* strains are metronidazole resistant, whereas in developing countries, the occurrence of resistance is very high [10]. The Physicians usually extend the time of antibiotic treatment or employ additional rounds of antibiotic therapy to curb the infections; however, such practice may also result in increasing the probability of selecting more aggressive antibiotic resistant *H. pylori* strains.

The research window of 'role of gut microbiota in brain functioning' has gained momentum recently [12]. Sizable literature has accumulated in the recent years linking the pathogenesis of *H. pylori* with brain-gut axis. Although the direct and immediate effect of *H. pylori* infection on the brain-gut axis is yet to evolve, but there is logical possibility that *H. pylori* infection might induce abnormalities indirectly by affecting the brain-gut axis. For example, the treatment of *H. pylori* ameliorates the disturbances in the upper and lower digestive tract. It is speculated that *H. pylori* may have direct neurotoxic effects that might alter the brain-gut axis via activation of neurogenic inflammatory processes, or by depleting the microelement reserve in the digestive tract [13]. It is this concern of *H. pylori* infections which warrants the implementation of worldwide *H. pylori* eradication programmes using a battery of novel and effective antibiotics.

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**Volume 5 Issue 8 August 2018**

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