Singh *et al. J Pure Appl Microbiol,* **13**(**2**), 715-723 | June 2019
Article 5531 | https://dx.doi.org/10.22207/JPAM.13.2.07

Print ISSN: 0973-7510; E-ISSN: 2581-690X

REVIEW ARTICLE OPEN ACCESS

Helicobacter pylori Infection: Challenges in India

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Abstract

***Helicobacter pylori (H. pylori)* is a very common infection In India. Nevertheless there remain a lot of challenges with relation to this infection in this country. The lack of good clinical studies and absence of guidelines pertaining to the Indian sub continent makes dealing with this infection difficult. There is a lot of confusion whether to "test and treat" for *H. pylori* even in patients of peptic ulcer disease (PUD), un investigated dyspepsia, and those with high risk for gastric malignancy. Invasive and costly methods such as gastroscopy, rapid urease test (RUT) and biopsy are used to test *H. pylori*. The non-invasive and cheap diagnostic tools such as breath tests and stool tests are not easily available in India. Once the diagnosis of *H. pylori* infection is made, the next challenge is to determine the most effective antibiotic regimen in Indian context. Issues of antibiotic resistance and re infection make the management even more difficult. The Indian enigma of high *H. pylori* infection and low gastric cancer(GC) rates makes the case against eradication even more strong. It is also important to consider the genetic diversity of *H. pylori* in India. More long term prospective studies are required from India before we can take the eradication at community levels. Improvement of hygiene and sanitation and providing proper drinking water is a challenge that needs to be taken up by the health administration to deal with the *H. pylori* problem.**

Keywords: *Helicobacter pylori*, dyspepsia, diagnosis; eradication; antibiotic resistance.

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(Received: 23 March 2019; accepted: 10 June 2019)

Citation: Ayaskanta Singh, Jimmy Narayan and Shivaram Prasad Singh, *Helicobacter pylori* Infection: Challenges in India, *J Pure Appl Microbiol*., 2019; **13**(**2**): 715-723. doi: 10.22207/JPAM.13.2.07

INTRODUCTION

Helicobacter pylori (H. pylori) is a gram negative bacterium. It colonises the mucosal lining of the human digestive tract. It has special affinity for stomach and duodenum[1]. Right from its discovery by Warren and Hastings in the early eighties; research on *H. pylori* is voluminous[3,4]. It is considered to be one of the most common chronic bacterial infections which affect almost two thirds of the worldwide population[5]. The transmission of this bacteria is from person to person and through contaminated water. It causes inflammation in the gut especially in the stomach and duodenum[1]. Most of these inflammatory changes are silent and clinical manifestations occur in around one-fifth of the patients after a long latent period[6]. *H. pylori* causes chronic active gastritis as a rule in almost all the patients. Studies have shown that this infection has a role in causing peptic ulcer disease(PUD), atrophic gastritis, gastric neoplasm, and "mucosa-associated lymphoid tissue(MALT)" lymphoma[1,7,8].

There is a steady decline in the incidence of *H. pylori* infection. This has been attributed to the facts that there has been improvement in hygiene and sanitation and also due to development of antibiotic regimens which can successfully eradicate the infection. Nonetheless in a country like India; a lot of challenges remain. The need of the hour is to consider *H. pylori* is a serious transmissible infectious disease, to discuss the pros and cons of treating this infection as a whole or in a select group of patients. It is pertinent to consider the genomic profile and variants of *H. pylori* in India. Focus should be on the regional data on antibiotic resistance profile and the effectiveness of the various antibiotic regimens in eradicating the bacterium. The unawareness of general physicians regarding the infection; the apathy of the health care system and the absence of guidelines especially from India makes it more challenging to deal with this infectious disease.

H. pylori and its significance in India

H. pylori is a very common infection. It's sero prevalence varies from 5-10% in developed countries to 80-90% in the developing countries[9]. The story is no different in the Indian subcontinent. Most of the cases are exposed to the infection in childhood and approximately eighty per cent of the general population is infected when they reach adulthood[9]. Various epidemiological surveys indicate a "sero prevalence of 20%-50% in children under the age of five, increasing to 80%-90% by the age of twenty, and remaining constant thereafter"[8-11]. This infection is transmitted by feco oral route. Contaminated water is often the culprit in causing this infection especially in the rural areas[12,13]. Hygiene plays a major role in the prevalence of this infection. This has been reflected in the fact that in developed countries and in societies with improved sanitation; there has been notable drop in the prevalence of this infection[8]. The reasons behind the commonness of this infection and lower age of acquisition in India are poverty, overcrowding, poor sanitation and contaminated water supply. This is a massive challenge from the administrative point of view to improve the general health; hygiene and sanitation and provide good drinking water in order to prevent this infection.

The infection primarily causes inflammation of the mucosa of stomach and duodenum. The inflammation may have acute changes such as gastritis; yet the most clinical significant manifestations are usually long standing. It may cause numerous manifestations such as atrophic gastritis; intestinal metaplasia; PUD; gastric lymphoma and neoplasms[1,7-8]. The infection has also been implicated to cause iron deficiency anemia; idiopathic thrombocytopenia and vitamin B12 deficiency[14-16]. However many clinicians also consider *H. pylori* as an innocent bystander whose eradication may cause more harm than good.

The most significant outcome of *H. pylori* infection is gastric neoplasm[2-3]. There is a lot of research papers including meta analysis which established that *H. pylori* is an important cause for gastric neoplasm[2-3]. However in some regions of the world [Africa and Indian sub continent]; there is very high infection rates of *H. pylori*; yet fortunately the prevalence of gastric malignancy is low. On the other hand, the prevalence of *H. pylori* related peptic ulcer disease and its complications are quite high in these regions.

Should *H. pylori* be eradicated in Indian setting?

Although the clinical implication of this infection is huge; the most significant being gastric malignancies; yet it is improbable to screen and eradicate *H. pylori* on mass population especially in

a country like India. Ramakrishna BS in an excellent review article has discussed elaborately the points why *H. pylori* infection should not be eradicated in India[17].

"Maastricht V/Florence Consensus Report" recommend that "*H. pylori* eradication for gastric cancer prevention is cost-effective in communities with a high risk for gastric cancer"[18]. The "Second Asia–Pacific consensus guidelines for *H. pylori* infection" also advocates similar strategy of universal eradication of *H. pylori* at community levels[19]. These recommendations are based on the community based economic studies that have evaluated the cost-effectiveness of "screen-and-treat" policies in general population for the prevention of gastric neoplasms[20]. This approach will benefit those communities, who have a high prevalence of gastric cancer(GC). Almost all the randomized trials favoring mass eradication were conducted in these areas. However in countries like India where the prevalence of GC is low; long term longitudinal studies are required to gauge the cost effectiveness of such a strategy of mass eradication. Indian authors argue that adopting such a practice in India is challenging and not viable[17,20].

The estimated population of the country is just about 1. 3 billion people. If we keep the *H. pylori* prevalence at 60%, roughly around 8 hundred million individuals will have *H. pylori* infection[21]. The enormity of the task of treating this infection at community levels is discouraging and might dissuade doctors and the government from aggressively managing the infection. Nonetheless, when one considers it on an individual case basis, it becomes much simpler to deal with the problem.

There is another aspect of *H. pylori* infection. The *H. pylori* strains are genetically variable, and there are certain known markers of virulence in *H. pylori.* The virulence factors, which have been recognized are the "*cag* pathogenicity island (cag PAI)", the "vacuolating cytotoxin (VacA)" and the "outer inflammatory protein (Oip A)". It is likely that all individuals do not have infection with the virulent strains of *H. pylori*. Host genetic predisposition and environmental factors plays an important role in the expression of various manifestations of *H. pylori.* This probably can explain low prevalence of gastric carcinoma in Indian sub continent. However the challenge is to identify the various virulent strains of *H. pylori* in India and treat accordingly. Some authors consider *H. pylori* a normal commensal rather than a pathogen in human beings. They consider *H pylori* to be protective against certain immunological and autoimmune diseases like asthma and Crohn's disease[22]. Any indiscriminate eradication may do more harm than good. Thus the biggest question is that whether *H pylori* infection needs eradication and who are the patient groups who should be treated.

The American College of Gastroenterology (ACG) guideline says that "*all patients with a positive test of active infection with H. pylori should be offered treatment*"[23]. Thus the crucial issue is to identify the patients who should be tested? Hence the following specific conditions are discussed in detail.

Peptic ulcer disease [PUD]

One important indication for treatment of *H. pylori* infection is PUD. Studies from various parts of the country have shown a strong association of this bacteria with duodenal and gastric ulcers[24-25]. Many papers from the West showed that treatment of this infection not only caused ulcer healing, but also prevented ulcer recurrenc[26-27]. However peptic ulcer can occur again if there was recurrence (either recrudescence or re-infection). Marshall et al in their landmark paper concluded that "*H. pylori* eradication resulted in greater peptic ulcer healing rate (92% vs. 61%) and lower 12-month relapse rate (21% vs. 84%) than non-eradication"[26]. A meta-analysis which included thirty four studies involving around four thousand patients, eradication therapy with antibiotics was superior to proton pump inhibitors alone in healing duodenal ulcer and better to placebo in avoidance of ulcer recurrence[27].

Indian studies also show a good duodenal ulcer healing [75%-90%] with antibiotic therapy intended to treat *H. pylori* infection[28-29]. However the problem in India is that the relapse rates of peptic ulcer after eradication therapy is higher than those reported in studies reported from the West. Nanivadekar *et al* had followed up patients with healed duodenal ulcer for three years. They

found that ulcer relapse was seen around 10% of cases without recurrence of *H. pylori* infection and in 63% cases with recurrence of *H. pylori* infection[30] .

Non-ulcer dyspepsia [NUD] and un investigated dyspepsia

H. pylori gastritis is considered to be a cause of dyspepsia. However the majority of studies on functional dyspepsia have not shown any benefit after eradication of *H. pylori* infection. A Cochrane Database review of seventeen randomized controlled trials that looked into over three thousand patients concluded that "there was an 8% relative risk reduction in dyspeptic symptoms after *H. pylori* eradication"[31]. Thus there is very small benefit in treating dyspepsia with antibiotics. The few studies from India also echo similar results. Different studies from the country showed that treatment of *H. pylori* is not that effective as compared to PPI s; sucralfate or anti depressants in providing symptomatic relief in NUD patients[32-33].

Several guidelines on *H. pylori* now advocate a "test-and treat" in primary care without doing a gastroscopy[18-19,23]. The recommendations suggest that those patients who are under the age of fifty and without any alarm symptoms; should be tested and treated if positive for *H. pylori*; rather than doing invasive procedure like an endoscopy[23]. However the evidences from India are not substantial enough for adapting such a practice. Even a Cochrane Database systematic review concluded that such a test and treat approach is not cost effective in primary care setting and also does not provide symptomatic relief in dyspeptic patients[31].

Gastric Carcinoma and the Indian Enigma

H. pylori is being recognized as Type I carcinogen for GC and primary gastric lymphoma(GL). There is substantial evidence in form of meta analyses of case control studies which suggest *H pylori* can cause both GC and GL[34-36]. However most of the data supporting this have come from case control studies from countries like Japan and China where there is a high prevalence of gastric neoplasm. In Asian countries like India and similar tropical countries from Africa there exists incongruence between the *H. pylori* infection rates and gastric malignancies. In our country even if there is a very high frequency of *H. pylori* infection; yet incidence of gastric neoplasm is relatively low. Probably other factors apart from the infection, play a role in the etiopathogenesis of GC. Indian diet may also act as a protective factor against the dreaded malignancy. Even within the country there is great regional variation with respect to infection and the prevalence of GC. There is a lack of good studies from India. There are few case control studies and unexpectedly they failed to show an association between *H. pylori* infection and GC. Kate V et al have done case control study where 50 patients with gastric neoplasms and 50 controls with non-ulcer dyspepsia (NUD) were enrolled. They found that *H. pylori* infection was detected less commonly in GC (38%) than those with NUD (68%)[37]. Another study from South India showed that 64. 7% patients with gastric adenocarcinoma and 74. 4% patients with NUD tested positive for *H. pylori*[38]. However these studies had very small sample size and the results cannot be extrapolated to the general Indian population. Another limitation of the above cited studies is that gastroscopy based rapid urease tests (RUT) were used to diagnose *H. pylori* infection. The problem with these endoscopy-based tests is that in patients with GC due to presence of underlying gastric atrophy and intestinal metaplasia, the tests can be false negative. Another case control study from Lucknow had taken a better sample size of 279 cases with gastric neoplasms(263 GCs and 16 GLs) and 456 healthy controls. This study also failed to demonstrate that *H. pylori* infection was more common in patients with gastric neoplasm as compared to the controls[39]. Thus research from India on this infection and its association with gastric neoplasm and its premalignant conditions like intestinal metaplasia and atrophic gastritis is really scarce to derive any definitive conclusion.

Diagnosis of *H. pylori* infection: Difficulties faced in India

The initial stage in the management is to establish the diagnosis of *H. pylori* infection. The challenges that doctors face in India are issues of accessibility and expenditure with regards to the diagnostic tests of *H. pylori* infection. Worldwide, non invasive tests for active infection are preferred (*e.g.*, "urea breath test" or "stool antigen test") over tests that require endoscopy. Although, the 14C-urea breath test is probably the cheapest test, yet it is not readily available. Endoscopy is available

at tertiary care centers, but is high-priced. The cost can range from Rs 300 at a government hospital or medical college to between Rs 500 and Rs 5000 at corporate hospitals and diagnostic centers[40]. The advantage of endoscopy is that patients can be evaluated for mucosal disease such as peptic ulcers, gastritis and early malignancy. Endoscopy also allows one to take biopsy specimens that can be examined by histopathology, "rapid urease test (RUT)", or culture for antibiotic sensitivity. RUTs are inexpensive, accurate and easily available. Saksena *et al* showed that "the rapid urease test (RUT) and brush cytology had the highest degree of agreement whereas histology was the most specific diagnostic test"[41]. Another major issue with endoscopy is that most of the hospitals and diagnostic centres do not follow the standard protocol of disinfection of the endoscope. Essentially, the endoscope, the biopsy forceps, and other parts of the endoscopy system can easily become infected with *H. pylori* and can spread the infection. Thus it is essential to maintain high-level disinfection of all endoscopic equipments in order to prevent the iatrogenic spread of the infection.

Serologic testing for *H. pylori* antibodies has > 80 per cent sensitivity and > 90 per cent specificity. This test is easily available but is costly. Another limitation of the test is that even after successful eradication of H pylori, it can remain positive for many years. All the recommendations do not advocate serologic testing for diagnosing this infection.

Challenges faced in *H. pylori* eradication in India

There are two important reasons why *H. pylori* treatment is a challenge in the Indian sub continent. First, the surroundings and water is contaminated and the gut infections are very widespread. This may make the task of eradication of this infection futile if there is going to be reinfection with the same bacteria sooner or later. Secondly, antibiotic use is widely prevalent. In India, antibiotics are easily available, even without a prescription and this easy access can lead to overuse or misuse. Even doctors are sometimes at fault as antibiotics are commonly misprescribed or dispensed erroneously due to lack of apt awareness, desire to meet patient demands and maybe for economic incentives. This results in high frequency of antibiotic resistance.

Table 1 shows the high percentage of antibiotic resistance from various studies from India. This implies that the standard antibiotics regimens for *H. pylori* infection may not be effective in India. Fixed dose combinations(FDC) of proton pump inhibitors [PPIs] and antibiotics which are cost effective and easy to prescribe, are widely available in India. One such FDC of PPI with amoxicillin and tinidazole is very popular and widely prescribed by Indian doctors. However; in these FDCs, the dose of amoxicillin is suboptimal, being 750 mg BID rather than 1 g BID as recommended. In a large Indian multicentre study by Thyagarajan et al, two fifty nine isolates of *H. pylori* were tested for susceptibility to antibiotics in vitro. They found

Table 1. *H. pylori* antibiotic resistance in India

Antibiotic	Study	Number of patients	Resistance rate (%)
1. Clarithromycin	Thyagarajan[42]	259	45
	Mhaskar[48]	15	91
	Abraham[49]	7	100
2. Amoxicillin	Thyagarajan[42]	259	33
	Devarbhavi[50]	~	40
	Mhaskar[48]	15	73
3. Tetracycline	Datta[43]	67	8
	Mhaskar[48]	15	27
4. Metronidazole	Datta[43]	67	85
	Bhatia[45]	31	42
	Thyagarajan[42]	259	78
	Mukhopadhyay	~	90
	Devarbhavi[50]	~	16

that "around 80% had resistance to metronidazole, 45% to clarithromycin, and 33% to amoxicillin"[42]. In another study from West Bengal, 80% and 8% of the bacteria were resistant to metronidazole and tetracycline respectively[43]. In a similar study from Gujrat, around 80% *H. pylori* isolates were resistant to metronidazole, around 60% were resistant to Clarithromycin and around 70% were resistant to Amoxicillin, 50% to Ciprofloxacin and 50% to tetracycline[44]. Thus the fixed-drug combinations used to eradicate the infection may be less useful in view of such high antibiotic resistance in India.

The effectiveness of various antibiotic regimens in treating *H. pylori* needs to be determined in Indian setting. The few clinical studies from India which have been done on the eradication rate of the bacteria are discussed in Table 2. The problem with many of these trials is that they used a single test (RUT) to establish the clearance of *H. pylori* bacteria. When rigorous criteria (i.e., "a combination of negative urease test, negative histology and negative urea breath test") were applied; the eradication rate was significantly lower. In a clinical trial done by Bhatia *et al.* around 150 patients were randomized either to receive lansoprazole, amoxicillin and tinidazole or lansoprazole, amoxicillin and clarithromycin. Surprisingly it was found that "only 31% and 46% of patients receiving the above combinations respectively had eradication of *H. pylori* infection"[45].

Table 2. Eradication Rates of *H. pylori* in India

	Number of patients	Location	Treatment regimen	Duration	Eradication Rates	Tests used
Valooran *et al.*[51]	73	Pondicherry	Omeprazole; Clarithromycin Amoxicillin	10 days	81%	RUT; Histology
Chaudhary *et al.*[52]	20	New Delhi	Lansoprazole; Amoxicillin Tinidazole	14 days	80 %	RUT
Bhatia *et al.*[45]	70	Mumbai	Lansoprazole; Amoxicillin Tinidazole	14 days	42%	RUT; UBT; Histology
Bhasin *et al.*[53]	20	Chandigarh	Omeprazole; Clarithromycin Amoxicillin	14 days	70%	RUT;
Bhasin *et al.*[54]	24	Chandigarh	Lansoprazole; Amoxicillin Clarithromycin	14 days	96%	RUT

It is a major challenge to diagnose complete *H. pylori* eradication. All the guidelines suggest H2 breath test as the gold standard test to look for *H. pylori* eradication. However limited availability of the breath test makes it a Herculean task. On the other hand, it is very difficult to convince a patient to undergo a costly and invasive test such as gastroscopy and RUT test for the second time.

Another point to consider is that it is likely that the rates of recurrence of the infection, after successful treatment, may be very high in India. Studies from the West show that re-infection rates are very low (< 0. 5 per patient year) after successful eradication[46]. However there are only few papers on *H. pylori* recurrence rates after successful eradication from India. In one study of forty five patients who were followed up for one year following successful eradication of *H. pylori*, it was seen that recurrence of infection was observed in only one case (2. 4%)[47]. However, the study by Nanivadekar et al from India show that recurrence of *H. Pylori* occurs in around 60% of patients within 3 years[30].

CONCLUSION

There remain a lot of challenges with relation to *H. pylori* infection in India. There is lack of good clinical studies from India and absence of guidelines pertaining to the Indian sub continent. There is a lot of confusion whether to "test and treat" for *H. pylori* even in patients of peptic ulcer disease, un investigated dyspepsia, and those with high risk for gastric malignancy. Invasive and costly methods such as gastroscopy and RUT and biopsy are used to test *H. pylori*. The non invasive and cheap diagnostic tools such as breath tests and stool tests are not easily available in India. Once the identification of *H. pylori* infection is made, the next challenge is to determine the most effective antibiotic regimen in Indian context. Issues of antibiotic resistance and re infection make the management even more difficult. The Indian enigma of high *H. pylori* infection and low incidence of GC makes the case against eradication of *H. pylori* even more strong. As *H. pylori* strains are genetically diverse, it is unlikely that most infected persons in the community have virulent strains. More long term prospective studies are required from India before we can take the eradication at community levels. Improvement of hygiene and sanitation and providing proper drinking water is a challenge that needs to be taken up by the health administration to deal with the *H. pylori* problem.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The authors declares that there is no conflict of interest.

AUTHORS' CONTRIBUTION

AS and JN drafted the manuscript. JN gathered information from the literature. AS compiled information from the literature, and designed the figures and tables. SP supervised and reviewed the manuscript.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in this review.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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