Review Article

# *Helicobacter pylori* in humans: Where are we now?

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## Abstract

*Helicobacter pylori* has been associated with colonization of gastro duodenal mucosa of humans from millions of years. The main burden of the disese is in the developing countries, due to overcrowding and poor hygiene. If left untreated it leads to lot of sequlae from minor to sinister diseases over a period of time. The main challenges that remain are prevention of *H. pylori*-related diseases by effective treatment and screening procedures and development of a vaccine, which can address all these issues including beneficial aspects of *H. pylori*. The literature pertaining to different aspects of *H. pylori* were scrutinized from Pubmed. Material on clinical behavior, complications of chronic gastric involvement, and prevention besides role of *H. pylori* in nongastric diseases and the latest trends of management was collected for research and review. We continue to face many challenges.The prevention of cancer of the stomach, a worst sequlae of *H. pylori* continues to be a big challenge despite population screening and prevention surveys being underway in many countries. On the other hand continued scientific work has now unfolded involvement of *H. pylori* in extragastric diseases like cerebrovascular, cardiovascular, idiopathic thrombocytopenia, sideroblastic anemia, mental diseases, and collagen vascular diseases. In contrast, the beneficial effects of *H. pylori* with respect to allergic diseases and obesity are now clear. Moreover, problem of drug resistance for eradication of *H. pylori* has arisen for which novel treatments are being tried. *Lactobacillus reuteri* having anti *H. pylori* action is emerging as one of the promising treatment.

**Key Words:** Beneficial aspects, extra gastric diseases, gastric-cancer and its prevention, *H. pylori, lactobacillus reuteri*, novel clinical behavior, research questions, treatment challenges, vaccination

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## INTRODUCTION

*Helicobacter pylori*, a gram negative bacillus has naturally colonized humans for at least tens of thousands of years. The main burden of the disease is in developing countries, which can be ascribed to overcrowding and poor hygiene.[1] Infection due to *H. pylori* is very common in developing nations and the basic research continues to expand also along with new challenges.[1,2] The prevalence of infection ranges from 20% in the developed/industrialized countries to more than 90% in the developing world.[2,3] We will be addressing these issues in the context of latest scientific research under the following subheadings:

- Gastro duodenal involvement and clinical issues.
- Extra gastric diseases and *H. pylori*-Culprit or innocent bystander.

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- Beneficial aspects of *H. pylori*/other face of the bug.
- Treatment issues/upcoming remedies.
- Comprehensive need-based research.

## Gastric involvement: Clinical issues

The gastric inflammation due to *H. pylori* may be antral-predominant gastritis, which is most closely associated with duodenal ulceration, whereas pangastritis is linked to gastric ulceration and adenocarcinoma.[2,3] It is also a risk factor for mucosa-associated lymphoid tissue (MALT) lymphoma.[1-3] *H. pylori* infection is etiologically associated with a number of gastro-duodenal disorders. Acute infection causes neutrophilic gastritis with transient hypochlorhydria and subjects complain of epigastric pain and nausea. Chronic infection causes a wide variety of gastritis including chronic superficial gastritis, nodular gastritis, and chronic atrophic corpus gastritis with metaplasia. *H. pylori* infection is strongly associated with peptic ulceration of duodenum and stomach. Chronic corpus atrophic gastritis with intestinal metaplasia caused by *H. pylori* infection is an initiating event in most cases of intestinal type adenocarcinomas stomach. In fact *H. pylori* infection is associated with both diffuse-type and intestinal-type gastric adenocarcinoma. Another entity gastric MALT lymphoma evolves through *H. pylori* gastritis with MALT, lymphoepithelial lesions, low grade B cell lymphoma, and finally diffuse large B cell lymphoma.[3,4] *H. pylori* has increasingly been recognized in other gastric pathologies like autoimmune gastritis and pernicious anemia.[2,3]

### *Evolving/novel clinical behaviour: A matter of concern*

Recently new pattern of duodenal involvement in the form of diffuse duodenum nodular lymphoid hyperplasia (DDNLH) has been reported from Kashmir, India. It has been ascribed to specific strain of *H. pylori*. In this condition hundreds to thousands of nodules appear in second, third, and fourth part of duodenum and in few centimeters of jejunum. If not diagnosed and treated immediately (by anti *H. pylori* antibiotics) it may prove detrimental.[4] The disease is regarded to be due to immune deficiency and if left untreated it can lead to dreaded complications. All these patients were heavily infected with *H. pylori*, were very sick clinically, and were having deficiency of many vitamins. Few patients with resistant *H. pylori* infection showed no significant relief or reduction of nodular lesions. The association of *H. pylori* infection with DDNLH had never been reported earlier. The disease has many important features, which medical practitioners need to recognize. First the disease affects young persons and causes intractable severe illness. Second it is associated with *H. pylori* infection and is potentially treatable. Third there is a regional distribution in Kashmir and this may be related to specific nature of *H. pylori* infection prevalent in Kashmir. Lastly if untreated, the disease in some of these patients may transform to lymphoma (cancer of lymphoid disease). The patients with DDNLH presented with epigastric pain and vomiting suggesting gastric stasis and obstruction. Weight loss, diarrhea, gastric symptoms, iron defeciency anemia, and hypoalbuminemia were caused by selective and dominant involvement of the duodenal mucosa. Histology of these lesions demonstrated hyperplasic lymphoid follicles with mitotically active germinal centers and abnormalities in immunoglobulins. The new entity is being routinely missed, so high emphasis should be put on its early recognition and treatment.[4]

### *Can we prevent cancer of stomach?*

*H. pylori* eradication holds the key to prevent gastric cancer, which in turn needs population-based primary screening. However, there are differences in the incidence of *H. pylori* in populations, which depend on different *H. pylori* Cag A status and dietary habits apart from host genetic factors. Advanced research has focused on serological tests to identify the patients at risk for gastric cancer development much before the onset.[1,2,4,5] Population-based screening has been implemented in countries with high risk such as Japan. Thus the eradication therapy is most likely to be effective prior to the development of precancerous changes in the form of atrophy or metaplasia, as is evident from basic sciences. However, in our clinical practice (authors of this review) we have seen even metaplasia disappearing after anti *H. pylori* treatment. In a study in China, screening and treatment in individuals at the age of 20 years resulted in adequate reduction in the life time risk for gastric cancer (14.5% in males and 26.6% in females).[3,5-8] Several studies have shown conflicting results whether preneoplastic changes might return to normal, remain invariant, or show progress.[8-11] There is point of no return, which is critical for prevention. However, in Japan, for the prediction of gastric cancer and atrophic gastritis serological testing with a combination of pepsinogen 1 and pepsinogen 11, gastrin and antibodies to *H. pylori* are done, which yields accurate results with high specificity.[10-12] Again there are variable results with decreased pepsinogen as early marker for same.[13,14] By and large serological testing for *H. pylori* and atrophic gastritis is a promising way to detect the risk of gastric cancer.[12-15] However, there are no proper guidelines, which is a burning issue and needs to be addressed as early as possible.

## *H. pylori* and extragastric diseases: Culprit or innocent bystander?

The establishment of casual link between *H. pylori* and extragastric diseases has added new dimensions to this chapter. A possible association between *H. pylori* infection and extragastric diseases like neurological diseases, ischemic diseases, cardiovascular diseases, skin diseases, cirrhosis, and mental diseases including Parkinsonism cannot be ruled out. However, the strength of these associations is reduced if confounding factors are taken into consideration.[1-3,5,16] Therefore further studies/trials are needed to find the real association.

In two extragastric diseases, namely idiopathic thrombocytopenic purpura (ITP) and iron deficiency anemia (IDA), a convincing evidence of association with *H. pylori* has been found in both children and adults. In both these conditions treatment with anti *H. pylori* results in marked clinical improvement.[16,17] The current recommendations in ITP are to see the status of *H. pylori* and eradicate the same in positive cases. In IDA, recommendations are to rule out gastro-intestinal bleed and attempt anti *H. pylori* treatment along with iron administration, if *H. pylori* is present.[16-20]

## Beneficial aspects/other face of *H. pylori* infection

- In esophageal disorders like gastro-oesophageal reflux disease (GERD) and adenocarcinoma of esophagus and gastric cardia, *h.pylori* seems to have a protective role. Falling prevalence of *H. pylori* colonization and a rising incidence of these conditions depict this effect. In most studies cagA + strains is significantly lower among these patients of esophageal disorders than among controls.[1,21]
- Allergic disorders, asthma and atopic diseases seem to have negative relationship with *H. pylori*, that is, *H. pylori* is having a protective role.[1,22,23] The acquisition of infection in childhood is associated with reduced risk of allergic diseases and obesity. Furthermore neutrophil activating protein (NAP) has been identified to play role in this process. Based on this, NAP was identified as material/substance for vaccination. The introduction of vaccine in experimental setting for the prevention of *H. pylori* could theoretically provide a protective role in allergic diseases.[24,25]

In obesity *H. pylori* again seems to have a positive role. Ghrelin is an important factor in appetite and satiety regulation. The eradication of *H. pylori* restores normal number of ghrelin producing cells in the gastric mucosa and normal leptin in gastric mucosa, which leads to increased appetite. In developed countries dietary habits and negative *H. pylori* have been proposed to play a role in obesity.[22,25] Future course of research should explore the use of *H. pylori* vaccine for the purpose of reducing obesity. Keeping in view the above beneficial effects of *H. pylori*, it can be regarded as a double edged sword and whether to eradicate it or not is again an issue that needs a balanced answer.

## Treatment issues/upcoming remedies

Due to problem of antibiotic resistance to clarithromycin, amoxicillin (A) and metronidazole, other treatment combinations for *H. pylori* infection are needed. In addition, efficacy of protein-pump inhibitors (PPI) is a question.[1,26,27] Now levofloxacin (L) is being tried, replacing clarithromycin (PPI-A, L). Sequential double therapy initially by one antibiotics and PPIS (5 days) and then other antibiotic and PPI (5 days) to effect different strains is tried in Japan and Korea. Quadruple therapy ofloxcin, bismuth, metrindazole and tetracycline (OBMT) in which bismuth potassium is incorporated is more promising.[28,29] Molecular tests now allow easy detection and monitoring of antibiotic resistance.[30]

### *Can Lactobacillus/normal gut flora combat H. pylori?*

*Lactobacillus reuteri*, a promising form of treatment for *H. pylori* was discovered in 1980. Its anti *H. pylori* property was reproduced in multiple trials.[31] A substance called reuterin is secreted by the lactobacillus, which has antibacterial action on the growth of some harmful gram negative and gram positive bacteria along with yeast, fungi, and protozoa besides *H. pylori*. In one of the studies it was found that adding reuteri to omeprazole dramatically increased the cure rate from 0% to 60% of *H. pylori* infected patients compared with the use of drug alone.[32] Likewise other studies also showed that it definitely suppresses the growth of *H. pylori* in stomach and gut.[32,33] *L. reuteri* is found naturally in humans, however, it is not found in all individuals. Therefore dietary supplementation is needed to introduce and maintain high levels of *L. reuteri* in some people. Since reuterin inhibits the growth of some harmful gram positive and gram negative bacteria along with yeast, fungi, and protozoa, a gut organism capable of fighting other harmful gut organisms has naturally generated a great interest. Researchers have found that reuterin has desired antimicrobial side effects. *L. reuteri* is also found in breast milk. It has been tested for tolerance in children, healthy adults, and immunosuppressed patients like human immunodeficiency virus (HIV). No adverse effects except flatulence in healthy adults and mild nausea in HIV patients have been observed. Research has shown that several different strains of *L. reuteri* have positive effect on health, including various types of gastrointestinal disorders and oral health. In the

1980s, when the bacterium was discovered, *L. reuteri* was detected naturally in the bodies of 30-40% of the population. Today it is found only in 10-20% of the population.s[34] This drop has been ascribed to changes in lifestyle.[33,34] We do not eat fermented foods, such as sauerkraut, to the same extent as before and also use preservatives, which kill bacteria in the food and in the body.[35] Today Lactobacillus is freely available as sachets/capsules in Indian markets under the trade name Apylori for use. Further research is needed to find the strength of association between use of *L. reuteri* and its anti *H. pylori* action.

*Vaccine for H. pylori–dream or reality*

Because the colonization of *H. pylori* has far-reaching health consequences, it represents a significant public health challenge. Current treatment modalities include use of multiple antibiotics in combination with acid suppression medications. Historically, efforts to develop a vaccine for prevention and treatment of *H. pylori* infection began in earnest in the early 1990s. Later when it became clear that the prevalence of *H. pylori* was declining in developed countries, and with it the prevalence of peptic ulcer and especially gastric cancer, some questioned whether a vaccine was necessary or not. Due to aftermath of antibiotic resistance, it is difficult to eliminate *H. pylori*, and the development of a vaccine as an alternative therapy is of increased interest.[36] A new study led by researchers at Rhode Island Hospital in collaboration with the University of Rhode Island (URI) and EpiVax has identified a potential vaccine capable of reducing colonization of *H. pylori*. This has generated a lot of interest in researchers and hopefully vaccine for *H. pylori* will become a reality very soon. These encouraging, though preliminary, results suggest that further development of an epitope-based mucosal vaccine against *H. pylori* can potentially lead to a novel approach to prevent *H. pylori*-associated diseases in humans. However, the current best understanding is that even in the United States and presumably other developed countries, vaccination of infants to prevent *H. pylori* infection would be cost effective.[36,37] This would be especially true in industrialized countries such as Japan, which has a particularly high prevalence of gastric cancer, not to mention developing countries where the prevalence of *H. pylori* infection is high and gastric cancer is common. The efficacy of antibiotic treatment is limited by frequent reinfection. Immunization against *H. pylori*, once thought to be impossible, is now widely considered the only practical approach to large-scale elimination of the bacterium from susceptible populations. In many studies, immunization not only prevented new *H. pylori* infection but also cured animals of ongoing infection, paving the way for design of both prophylactic and therapeutic vaccines.[36-38] Various approaches including whole cell vaccines, recombinant antigens (e.g., urease A/B subunits, CagA, VacA, Nap A, catalase, or heat shock proteins) in combination with bacterial toxins or other adjuvants have been successfully tested.[39-41] An important aspect of *H. pylori* vaccine is the selection of antigen. Vaccination trials exploiting the antigenic properties of some proteins such as urease, the vacuolating toxin (Vac A), the cytotoxin-associated antigen (CagA), the blood-group antigen-binding adhesin (BabA), and the NAP have been done. The method of vaccine delivery has also been a matter of debate. It was initially argued that oral vaccination would probably be the best route because *H. pylori* is noninvasive pathogen and effective mucosal immunity would be the key to eradication. The problems encountered with this vaccine were instability in acidic PH requiring larger multiple doses and inavailability of suitable adjuvant. For oral immunization cholera toxin and *Escherichia coli* labile toxin (LT) has generated a lot of interest. Another approach is to use other mucosal routes such as the nasal mucosa and the rectal mucosa for effective immunization. The search for effective immunization route is ongoing. The mucosal immunity can be induced by oral, intranasal, or rectal routes. In nasal routes of administration less adjuvant is required. It, however, has shortcoming as it leads inflammation of olfactory bulb and causes paralysis of facial nerve. Other modalities of administering vaccines such as intraperitoneal and subcutaneous routes are also being pursued. Pilot studies in humans have been conducted using oral vaccines containing either 180, 60, or 20 mg of urease with 5 μg LT given in 4 weekly oral doses. The vaccine lead to a significant increase in IgA antiurease antibody ($P = 0.018$) and decrease in *H. pylori* bacterial overload. It is obvious that infections caused by microorganisms that gain access to the body via the mucosal membranes are best prevented by mucosal vaccination. The advantages of mucosal vaccination are numerous and include high patient compliance, ease and low cost of application (i.e., no need of trained personnel) and a decrease in the risk of the unwanted needle-borne infections (acquired immune deficiency syndrome (AIDS), hepatitis, etc.,).[39,40] Further, vaccination at mucosal surfaces may stimulate both systemic and mucosal immunity; not only at the site of vaccination, but also at distant mucosal epithelia. It could also prevent infection by neutralizing the pathogen at the site of entry. Because antigens alone are not sufficiently taken up after mucosal administration, these need to be coadministered with adjuvants or delivery systems. Since then, discovery of the adjuvant activity of aluminum compounds over eight decades ago, more than 100 empirically derived adjuvants and adjuvant variations have been tested both preclinically and clinically. Nearly all of these adjuvants failed to win approval for use in routine

vaccines due to toxicity concerns. An ideal adjuvant would elicit a persistent, high quality immune response to an antigen while being nontoxic, biodegradable and non immunogenic. A number of mucosal adjuvants such as aluminum hydroxides, Freund's adjuvant, cholera toxin, *E. coli* heat-labile enterotoxin have been tried.[41,42] Renewed interest in making *H. pylori* DNA vaccines has increased considerably in the past few years. These DNA vaccines have been effective in protecting against a wide array of pathogens. They provide heterologous cross-protection and can easily be prepared as polyvalent vaccines. They are construed relatively stable, generally safe, and induce both humoral and cell-mediated immunity. They could become feasible for treating H pylori infection.[38,39,42] *H. pylori* can occur very early in life; vaccines would be most beneficial if given during the first few months infection after birth.[41,42] An ideal vaccine not only has a well-established safety and efficacy record but also is inexpensive, confers long-term immunity with minimal dose repetitions, is effective in preventing as well as curing infection, and requires no special storage and transport.[37-42] Need of the hour is to gear up our research programs to find that ideal vaccine against *H. pylori* infection.

### Demand of the hour: Need based but comprehensive research

*Questions are more than answers*

The eradication of *H. pylori* from human body may not be without bad repercussions, however, decision to treat a patient should not be with-held once a clear indication is there. Anyway there are more questions than answers. As human race keeps evolving, so do the diseases that affect humans. Unfortunately, medical science is not evolving at the required pace, especially in India as well as in other developing nations. There is a huge disparity in the standard of treatment in different areas and regions within and outside the country due to inadequate infrastructure. This is partly because of the dull research scenario, which has not been able to tap the intellectual capability. Research is the base of development of any science but there is serious lack of need-based research. In fact we are dependent on the studies carried out in the developed countries. This makes it very important for India and other developing nations to carry out indigenous research, based on our own need and requirements. It is also important that all research be brought into public domain so that it can benefit maximum number of people.Since it continues to be a major problem in developing world the need of the hour is comprehensive but need-based research to address many burning issues of *H. pylori*:

- Agreed upon eradication of *H. pylori* is needed in symptomatic patients who test positive for screening with anti *H. pylori* antibodies, gastrin, and pepsin 1, pepsin 11 but what about normal asymptomatic individuals who test positive for *H. pylori*, while doing population surveys in developing countries?
- Among the level of antibodies (anti-pylori), gastrin or pepsin1or pepsin11,- which is/are more accurate scientifically for screening purposes in terms of sensitivity, specificity and predictive values?
- In early gastric atrophy and metaplasia what should be the management protocol? Whether antibiotics alone, surgery alone or both antipylori and surgery should be used?
- Guidelines for management of extragasric diseases with established role of *H. pylori* like ITP and IDA are lacking.

## CONCLUSION

The organism, which was discovered decades ago in Perth, Australia, leads to gastrodudenal and other extragastric diseases besides its beneficial role in body. It seems that the bacterium is changing its behavior and predilection for tissues and organs in humans, is possibly due to changes in structure of the organism or due to the change in immunity of the patient. There is a big list of diseases where the role of *H. pylori* is dubious, which needs further trials/ studies for clarification. *L. reuteri* under the trade name of Apylori is now freely available in Indian markets for usage. An upcoming vaccine can be ideal for both prevention of gastric diseases and inducing antiallergic and antiobesity effects. The need of the hour is to focus on research on these aspects.

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