

H Pylori in Humans : Where are We Now

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ABSTRACT

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H. pylori has been associated with humans for millions of years and its association with gastro duodenal diseases has well been established. Research explosion has added vastly to the current dimensions. The new and unusual pattern of involvement in the form of diffuse duodenal nodular lymphoid hyperplasia (DDNLH) due to specific strain of H. pylori has been reported from Kashmir recently, which heckles early recognition and treatment and on the other hand, we continue to face challenges so far as the prevention of ca- stomach, a worst sequelae of H. pylori is concerned, although population screening and prevention surveys are underway in many countries. Continued scientific work has now unfolded involvement of H.pylori in extra gastric diseases like Cerebrovascular, cardiovascular, idiopathic thrombocytopenia, sideroblastic anaemia, mental diseases, collagen vascular disease. Moreover the beneficial effects of H. pylori with respect to allergic diseases and obesity are clear. Problem of drug resistance for eradication of H. pylori has arisen for which novel treatments are tried. Lactobacillus reuteri having ant H.pylori action is one of the promising treatment as is now available in India for usage. The main challenges which 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.

Keywords: H. pylori, Novel clinical behaviour, Gastric-ca and its prevention, Extragastric diseases, Beneficial aspects, Treatment challenges, Tactobacillus reuteri, Vaccination, Research questions

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INTRODUCTION

H.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

1. Gastro duodenal involvement & clinical issues
2. Extra gastric diseases and H.pylori—Culprit or innocent bystander
3. Beneficial aspects of h. pylori /other face of the bug
4. Treatment issues / upcoming remedies
5. Comprehensive need based research.

1. 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 pan gastritis is linked to gastric ulceration and adenocarcinoma.^{2,3} It is also a risk factor for MALT(mucosa- associated lymphoid tissue) lymphoma.^{1,2,3}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 mucosa associated lymphoid tissue (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}

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Evolving/ Novel Clinical Behaviour: A Worrisome Matter

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 2nd, 3rd and 4th part of duodenum and in few cms. of jejunum. If not diagnosed and treated immediately (by anti *H. pylori* antibiotics) may prove detrimental.⁴ The disease is regarded to be due to immune deficiency. If left untreated it can lead to dreaded complications. These pts. are very sick clinically and have deficiency of many vitamins.⁴ All these patients were heavily infected with *Helicobacter pylori* (*H pylori*). 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 potentially treatable. Thirdly 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 some of these patients may transform to lymphoma (cancer of lymphoid disease). The patients with DDNLH presented with epigastric pain and vomiting, clinically suggesting gastric stasis and obstruction. Weight loss, diarrhea, gastric symptoms, iron lack anemia, and hypoalbuminemia were caused by selective and dominant involvement of the duodenal mucosa. Histology of these lesions demonstrates hyperplastic lymphoid follicles with mitotically active germinal centres, abnormalities in immunoglobulins. The new entity is being routinely missed so high emphasis has been put on early recognition and treatment.⁴

Can we prevent CA Stomach ? Answer is Yes:

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 pts. at risk for gastric cancer development much before the onset.^{1,2,3,4,5} 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 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 yrs. resulted in adequate reduction in the life time risk for gastric ca. (14.5% in males, 26.6% in females).^{3,5,6,7,8} Several studies have shown conflicting results whether preneoplastic changes might return to normal, remain invariant, or show progress.^{8,9,10,11} There is point of no return which is critical for prevention. However in Japan, for the prediction of gastric ca. and atrophic gastritis serological testing with a combination of pepsinogen1 and pepsinogen 11, gastrin and antibodies to *H pylori* are done, which yields accurate results with high specificity.^{10,11,12}

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 ca.^{12,13,14,15} However there are not proper guidelines.

2. H. Pylori and Extra gastric Diseases: Culprit or innocent bystander?

The establishment of casual link between *H.pylori* and extra gastric diseases has added new dimensions to this chapter. A possible association between *H.pylori* infection and extra gastric diseases like neurological diseases, IHD, CVS, skin diseases, cirrhosis, mental diseases including Parkinsonism can not be ruled out. However the strength of these associations is reduced if confounding factors are taken into consideration.^{1,2,3,5,16} Therefore further studies/trials are needed to find the real association.

In two extra gastric diseases namely ITP and IDA (iron deficiency anemia) 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 g.i. bleed and attempt anti *H.pylori* treatment along with iron administration, if *H. pylori* is present.^{16,17,18,19,20}

3. Beneficial effects/ other Face of H. Pylori Infection

A, In esophageal disorders like 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 depicts this effect. In most studies *cagA*+ strains is significantly lower among these pts. of esophageal disorders than among controls.^{1,21}

B, Allergic disorders, asthma and atopic diseases seem to have negative relationship with *H. pylori* i.e., *H. pylori* having a protective role.^{1,22,23} The acquisition of infection in childhood is associated with reduced risk of allergic diseases and obesity. Furthermore NAP (neutrophil activating protein) 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 no. 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.

4. Treatment issues / Upcoming Remedies

Due to problem of antibiotic resistance to clarithromycin, amoxicillin and metronidazole, other treatment combinations for *H. pylori* infection are needed. Also efficacy of PPI is under question.^{1,26,27} Now levofloxacin is tried, replacing clarithromycin. (PPI-A,L) Sequential double therapy initially by one antibiotics and PPI (5 days) and then other antibiotic and PPI(5 days) to effect different strains is tried in Japan, Korea. Quadruple therapy (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 pts. compared to 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} *Lactobacillus 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. Reuterin inhibits the growth of some harmful gram+ and gram negative bacteria along with yeast, fungi and protozoa. Naturally a gut organism capable of frightening other, harmful gut organisms was of great interest. Researchers found that reuterin has desired antimicrobial side effects. *Lactobacillus reuteri* is also found in breast milk. It has been tested for tolerance in children, healthy adults, and immunosuppressed pts like HIV. No adverse effects except flatulence in healthy adults and mild nausea in HIV pts has been observed. Research has shown that several different strains of *Lactobacillus 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 percent of the population. Today it is found only in 10-20 percent.³⁴ This drop has been ascribed to changes in lifestyle.^{33,34} We don't eat fermented foods, such as sauerkraut, to the same extent as before and 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.

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 treatments 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. 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 *Helicobacter pylori* (*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.^{36,37,38} 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.^{39,40,41} 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 neutrophil-activating protein (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 non-invasive 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 in availability of suitable adjuvant. For oral immunization cholera toxin and *E. coli* 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 micro grams LT given in 4 wky 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 (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 co-administered 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 pre-clinically 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 non-toxic, biodegradable and non-immunogenic. A number of mucosal adjuvants such as aluminum hydroxides, Freund's adjuvant, cholera toxin, *Escherichia coli* heat-labile enterotoxin.^{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} 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 *H. pylori* infection can occur very early in life; vaccines would be most beneficial if given during the first few months after birth.^{41,42}

5. 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 pt. should not be withheld once a clear indication is there. Any way 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 the maximum number of people. Almost 90% population in developing nations and 60% in developed nations is effected by *H.pylori*. 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 1,11 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 pepsin 1 or pepsin 11 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 extra gastric diseases with established role of *H. pylori* like ITP, IDA are lacking.

CONCLUSION

The organism which was discovered decades ago in Perth, Australia, leads to gastro duodenal and other extra gastric diseases besides its beneficial role in body. It seems as that the bacterium is changing its behaviour and predilection for tissues and organs in humans

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. *Lactobacillus 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 anti-allergic and anti-obesity effects. The need of the hour is to focus research on these aspects.

END NOTE

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