AN OVERVIEW OF HELICOBACTER PYLORI INFECTIONS WITH SPECIAL REFERENCE TO PATHOGENESIS AND MECHANISM OF COLONIZATION

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ABSTRACT

Helicobacter pylori is the major causative agent of gastrointestinal diseases. The bacterial pathogen, H. pylori has co-evolved with humans and colonize about 50% of the human population, which however is largely asymptomatic, nevertheless H. pylori plays a major role in the long term interaction in humans considerably increase the risk for peptic ulcer disease, non cardiac gastric adenocarcinoma, chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, Gastroesophageal reflux disease (GERD) and gastric cancer, H. pylori express a spectrum of virulence factors that deregulate host intracellular signaling pathways. In addition to bacterial determinants, numerous host and environmental factors increase the risk of gastric carcinogenesis. Due to their startle rate of drug resistance, eradication and control of H. pylori remains a global challenge. Triple therapy consisting of proton pump inhibitor, clarithromycin and either amoxicillin or metronidazole is commonly recommended standardization for treatment of H. pylori infection. This review discusses about the pathogenesis of H. pylori and the mechanisms it uses to promote persistent colonization of the gastric mucosa, with a focus on recent insights into the role of the virulence factors vaculating associated gene A (VacA), cytotoxin associated gene (CagA), BabA and also describe the H. pylori treatment.

KEYWORDS: Helicobacter pylori, gastric carcinogenesis, pathogenesis, colonization.

INTRODUCTION

The bacterial infections are more significant causes of cancer worldwide and nearly one in five malignancies resulting from infectious agents.[1][1] Until the discovery of H. pylori in 1982, the normal human stomach was generally considered to be sterile or transiently populated by oropharyngeal bacteria carried there by peristalsis. However, studies highlighted that from one-third to one-half of the human population carries H. pylori and that once infected, most persons remain infected for decades, if not for life.[2] The frequent observation of bacteria-like organisms in biopsy samples of almost all patients with active, chronic gastritis, duodenal ulcer, or gastric ulcer to obtain the culture of the organism in vitro. They succeeded in the process and isolated gram negative, microaerophilic, flagellated organism from human gastric biopsy samples.[3] The isolated organism was found to be a species related to Campylobacters. Initially it was given the name Campylobacter pyloridis and then renamed as Campylobacter pylori. But later studies revealed several properties unique to the organism and in October 1989 a new genus name Helicobacter was published.[4] The bacteria have been colonized in stomach and other gastrointestinal tract and co-evolved with infections for the last 10,000 years.[5]

H. pylori lives near the surface of human gastric mucosa and it causes gastro duodenal diseases such as chronic gastritis, duodenal ulcer, mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[6,7] It colonizes the gastric epithelial surface and withstands the stomach hostile ambience by microaerophilic growth capacity.[8] Bacterial pathogenesis cause is due to the host genetic predisposition and environment factors.[9] The major pathogenic factor of this organism includes the CagA, VacA and BabA, which may majorly involve in the pathogenesis of disease. In addition, it produces numerous virulence enzymes such as urease, oxidase, catalase and host factors may also play a pathogenic role, since auto antibodies appear during H. pylori infection in certain patients.[10] Although the lower incidence of gastric cancer in developed countries, it remains the second primary cause of cancer related death throughout the world; annually 700,000 deaths are attributed due to this disease.[11] The evidence of epidemiological factors indicates that gastric cancer is the long multi factorial process.[12] An improved understanding of the pathogenesis of infection will facilitate further medical
progress for better diagnostic treatments. In India, the infection of *H. pylori* is high and recent reports indicated 80-95% as the infection rate, particularly in specific regions of the country.[13,14]

The prevalence of *H. pylori* infections is about 40% in developed countries and 80-90% in the developing countries.[15] The prevalence of *H. pylori* in the people is related to three factors:

1. The rate of acquisition of infection, which is incidence;
2. The rate of loss of the infection;
3. The prolonged perseverance of the bacterium in the gastroduodenal mucosa between infection and eradication.

The difference in the prevalence is dominated in between communities’ incidence of infection during childhood.[16,19] Even though, the universal occurrence of *H. pylori* very extensive changes in the prevalence of infection within the middle of countries such as Brazil are high, with up to 80% of the population being infected.[17,18] Despite years of occurrence with *H. pylori* treatment, the ideal treatment for the infection remains subtle. The most effective eradication treatment is the combination of a proton pump inhibitor with two antibiotics, but nearly 10 to 20% of the patients are not get complete eradication of the infection.

Antibiotic resistance is a major factor affecting the outcome of treatment which is growing global concern that needs public health attention.[19] It is known that *H. pylori* could be eradicated by a combination of therapeutic agents such as antibiotics, bismuth subsalicylate, proton pump inhibitors and H₂ blockers, which have been shown to result in ulcer healing, prevention of peptic ulcer recurrence and may also reduce the prevalence of gastric cancer in high risk population.[18,20] Although there are several promising lead studies which are the most part preliminary, additional work is needed before any of these treatments can be considered viable alternatives to conventional therapy.[22] The present review deals about the pathogenesis, clinical manifestation and treatment of *H. pylori*.

Pathogenesis of *Helicobacter pylori*

*H. pylori* is a microaerophilic, short (0.2 to 0.5m long), spiral shaped bacillus which habitually causes chronic gastritis. It is a primary etiological factor link with the development of gastritis, peptic ulcer diseases and gastric carcinoma. It is found in the portions of the mucus layer (that coats the gastric mucosa) and in between the mucus gel layer and the apical surfaces of the gastric mucosal epithelial cells and sometimes adhere to the luminal surfaces of gastric epithelial cells.

*H. pylori* induce an inflammatory response in the gastric mucosa.[23] and it possesses several mechanisms to survive and persist in the gastric lumen. For example, it utilizes highly active urease enzyme to buffer the gastric environment of pH 1 to 2.[24] The survival is facilitated by its helical morphology and unipolar flagella enabling movement within the gastric mucous layer overlaying gastric epithelial cells.[25] It may also be colonized in the proximal duodenum when there is gastric metaplasia in those sites. In some studies, the colonization of the gastric metaplasia of a Meckel’s diverticulum or in the rectum has also described.[26]

The pathogenesis effect starts with the contact of bacteria with the gastric epithelial cells, induces chemokines, in particular interleukin 8 (IL-8), which attracts and activates the macrophages and polymorphs. It increases the permeability of the mucosa, allowing the passage of antigens such as urease which will also active the polymorphs and macrophages leads to proinflammatory cytokines, TNFα and IFNγ is released.[27]

The mechanism of urease

The enzyme urease play a major role in the conversion of urea into bicarbonate and ammonia, it leads to the neutralization of gastric hydrochloric acid (HCl) which helps to bacterium protect from the acidic environment of the stomach (Figure 1). Due to the equilibrium of water and ammonia, hydroxide ions are generated leads to gastric mucosal epithelium damage tend to more diffusion of HCl into the mucosa, causing damage of the gastro-duodenal lining leading to the formation of ulcers. This infection activates the vago-vagal reflexes (gut-brain axies) in the gastroduodenal mucosa that damage the mucosal cells directly and enhance the secretion of gastric HCl, which leads to ulcerogenesis.[28,29] The native urease of *H. pylori* has a molecular mass of approximately 540 kDa and is a nickel containing hexameric molecule consisting of two subunits (UreA 30kDa and UreB 62kDa) in a 1:1 molar ratio.[30] The *H. pylori* urease gene cluster contains nine genes, including the UreA and UreB structural genes, as well as regulatory genes involved in the synthesis and assembly of the holoenzyme.[31]
Figure 1: Role of urease in *Helicobacter pylori* infection.

[1 – Adhesion of *H. pylori* in the epithelial cells; 2 – *H. pylori* releases urease that neutralize gastric acid; 3 – Activation of the vago-vagal reflexes (gut-brain axies) and 4 - Gastroduodenal mucosa that damage]

**Role of Virulence Factors**

**Cytotoxin associated gene A (CagA)**

The cag pathogen island (Cag PAI) is a 40kB locus composed of 27-31 genes. Several genes within this island encode the CagA protein and the Cag type IV secretion system (T4SS). The T4SS forms a syringe like pilus structure by which CagA can be injected into the target cells and its binding to the ectodomain of α5β1 integrin, which helps for the translocation of CagA into the host cells. CagA binds to the inner surface of the cell membrane, leads to the phosphorylation of tyrosine at its glutamic acid-proline-isoleucine-tyrosine-alanine (EPIYA) motif by proto-oncogene tyrosine-protein kinase src family. The phosphorylated and unphosphorylated CagA interact with a number of host proteins to activate downstream signal pathways, such as the Ras/mitogen-activated protein kinase (MEK)/ extra cellular signal-regulated kinase (ERK) pathway and it enhance the proliferative ability of gastric epithelial cells. The src-homology protein tyrosine phosphatase (SHP-2) acting as a mediator for CagA induced downstream signaling as a result the interaction between CagA and SHP-2 dephosphorylates and inactivates focal adhesion kinase (FAK), resulting in cell elongation.

**VacA**

VacA is a highly immunogenic 95kD protein; it induces substantial vacuolization in epithelial cells *in vitro*. The VacA protein plays an important role in the pathogenesis of both peptic ulceration and gastric cancer. The protein forms pores in epithelial cell membrane and inducing the release of urea and anions from the host cells and also increases transepithelial permeability, leading to the release of nutrients and cations. The activities of VacA include membrane channel formation, disruption of endosomal and lysosomal activity; it also shows the effect on integration receptor induced cell signaling, induction of apoptosis and immune modulation. The secreted VacA does seem to penetrate into deeper tissues, where it can interact with lymphocyte cells. The interaction of VacA with these immune cells results in inhibition of antigen presentation and T-cell proliferations.

**BabA**

BabA is the 78kD protein, most likely represents as a best characterized *H. pylori* adhesion protein, encoded by BabA gene. BabA mediates the binding of fucosylated Lewis b blood group antigen (Leb) to the human host cells. Different studies have reported the action of BabA protein, the binding of BabA to Mucin 5AC gene.
in a healthy stomach provides a primary attaching site. The matrix of *H. pylori* helps in the survival and nutrient source also involved in proliferation process, which induces the noticeable change in the formation and function of gastric mucins, thereby causing an imbalance between offensive and defensive factors in the host stomach. Another study revealed the binding of BabA to mucin1 expressed on the apical surface of epithelial cells in the healthy stomach; it allows the microbe to rest on relatively neutral and favorable condition. The Mucin limit the *H. pylori* is directly attached to the gastric cells by steric inhibition binding to the other cell surface legends and it's acting as a releasable decoy, which restrains the over activation of pathogenic related signal transduction pathway.

The study reported that BabA adhesion to the host surface using genetically modified cell lines expressing Leb. The isogenic *H. pylori* mutants defective in BabA and virB7 transcription factor (TF). The binding between the BabA and Leb on the host cell surface plays a major role in potentiating TFs - mediated secretion; it leads to inflammation and intestinal metaplasia. The crystal structure of the extracellular domain of BabA from *H. pylori* strain J99, in the absence and presence of Leb in 2.0, 2.1Å resolutions. The molecular basis of Leb recognition by BabA, provides a development of therapeutic targeted at inhibiting *H. pylori* adherence to the gastric mucosa.

**Clinical manifestations**

*H. pylori* changes the gastric environment (Figure 3) and causes the diseases like gastritis, peptic ulcers, non ulcer dyspepsia, gastric cancer, gastric MALT lymphoma, gastroesophageal reflux disease (GERD).

**Gastritis**

*H. pylori* colonize the gastric epithelial cell it leads to the disease called as gastritis, in world half of the people effect with gastritis. The most common causes of infection include *H. pylori* the other factors like smoking, alcohol, cocaine, radiation therapy, autoimmune problems and Crohn’s disease. The symptoms mostly related to transient nonspecific dyspeptic disease, such as nausea, vomiting, proximal stomach mucosa inflammation, distal stomach mucosa inflammation and pangastritis. When colonization becomes stable, a close correlation exists between the level of acid secretion and distribution of gastritis (Chronic gastritis). When in the case of autoimmune diseases the percentages of neutrophil cells are low in the blood due to the lack of vitamin B12. The symptoms closely related to free radical activity the oxygen derived...
free radicals that initiate the membrane damage by lipid peroxidation.[53]

**Peptic ulcer disease**
The disease usually occurs in the stomach and proximal duodenum, thereby symptoms include epigastric discomfort (food intake or antacids and pain that causes awakening at night or that occurs between meals), weight loss, and loss of appetite are documented.[54] The dietary factors like caffeine and coffee, also commonly thought to cause or exacerbate ulcers, appear to have little effect.[55] Gastric ulcers mostly occur at the transition from corpus to antrum mucosa, which cause major complications of perforation, bleeding and stricture formation. Bleeding is the most common complication of ulcer disease and is estimated to occur in 15 to 20% of ulcers.[53,55]

**Non-ulcer dyspepsia**
Non-ulcer dyspepsia symptoms include upper abdominal fullness, nausea, heartburn, belching.[56] In this case, the individual feels full earlier then eating.[57] *H. pylori* plays a role in the etiology of dyspeptic symptoms of upper gastrointestinal distress which may have a reflex like character may appear dysmotility, with early satiety and nausea; with pain and vomiting. The 30% to 60% of patients with functional dyspepsia carry *H. pylori*, where dyspepsia is not a diagnosis but merely a cluster of symptoms believed to be referable to the upper gastrointestinal tract.[58]

**Gastric cancer**
Gastric cancer is one of the most common cancer in the worldwide and accounting for over 8.7 lakhs new cases and over 650,000 deaths annually.[59] The cancer may spread from the stomach to other parts of the body, particularly the liver, lungs, bones, the lining of the abdomen and lymph nodes.[60] Gastric cancer develops only in persons infected with *H. pylori* but not in uninfected persons.[61] Tumors of the stomach may be either malignant or benign and can be classified based on gross morphological and histopathological features. Several factors are alleged to play a role in gastric carcinogenesis, infectious agents and pathological conditions in the stomach.[62] Evidence those *H. pylori* increases the risk of gastric cancer development through atrophy and metaplasia originates from various studies and it has been estimated that this organism colonization increases the risk approximately ten fold therefore designated a class I carcinogen by the WHO.[63] These bacteria play a major role in 53% of gastric cancer cases in developing countries and in 60% in developed countries.[64]

**Gastric MALT lymphoma**
Gastric MALT lymphoma is a potentially involving chronic inflammation due to the action of *H. pylori* virulence factors such as CagA.[65] It is a typically a low-grade, β-cell neoplasia strongly associated with *H. pylori* infection.[66] The disease cause due to the proliferation of centrocytic like cells and epithelial destruction that causes lymph epithelial lesions detected on histological examination and the initial stage of tumors may also affect the results of treatment. This evidence supports the role of *H. pylori* infection in the development of these gastric lymphomas. Some studies revealed the MALT lymphoma diagnosis is based on histological appearance during microscopy and an expression of clonality by immunohistochemistry or molecular techniques, such as PCR; nearly all MALT lymphoma patients are *H. pylori* positive.[67,51]

**Gastroesophageal reflux disease (GERD)**
GERD is a chronic condition that requires long-term treatment.[68] *H. pylori* have been demonstrated as the causative factor of various gastrointestinal diseases; nevertheless, the relationship between its infection and gastroesophageal reflux disease is still debated.[69] However, further studies needed to explore the protective mechanisms against *H. pylori* and its diseases; as such also be of benefit to their hosts. This slowly emerging concept came from repeated observations of a low prevalence of *H. pylori* among GERD patients, particularly of more virulent strains.[51] The *H. pylori* could contribute to GERD through different mechanisms including delayed gastric emptying and cytotoxin production, causing esophageal epithelium injury, increased acid secretion due to antral gastritis.[67] Various challenges are associated with GERD treatment that includes lack of symptoms does not correlate with the absence of or the healing of esophageal lesions and proton pump inhibitors, the current standard of care for GERD, are ineffective for the majority of GERD patients who have non-erosive disease.[66] People may possess certain risk factors like obesity has been found to increase the risk of gastric adenocarcinoma by contributing to the development of gastroesophageal reflux disease.[69]
Treatment of H. pylori

The most effective therapies of H. pylori infection is triple therapy (levofloxacin/clarithromycin + amoxicillin + proton pump inhibitor) and bismuth quadruple therapy (bismuth + tetracycline + metronidazole + proton pump inhibitor). However, this treatment is not effective on H. pylori due to the resistance development. Thus the necessity to search for effective treatment is mandatory for the infection management. The fluoxamine is the antibiotic it shows effect against the H. pylori; which is a selective serotonin reuptake inhibitor (SSRI) drug, it inhibits the cytochrome P450 super family enzyme (CYP1A2). The fluoxamine shows antiulcer effects by activation of antioxidant mechanisms in stomach tissues. The biologically active compounds like selenocysteine (SeCys) and ebselen (Ebs) exhibit excellent ulcer healing and moderate antibacterial effect against H. pylori confirmed by in vitro and in vivo analysis. The omeprazole therapy increase in corpus gastritis associated with profound acid suppressive and it also prevents the development of atrophic gastritis.

CONCLUSION

The present literature analyzes the pathogenesis and major virulent factors (CagA, VacA, BabA) of H. pylori. It also explains the H. pylori causes the diseases like gastritis, peptic ulcer disease, non-ulcer dyspepsia, gastric cancer, gastric MALT lymphomas, gastroesophageal reflux disease. Based on the review done for this study, it was found that the “test-and-treat” (TAT) strategy is currently a rational way to deal with many patients with uncomplicated dyspepsia, provided that the following conditions are met.

1. The positive predictive value of the test should be adequate. Therefore, an accurate test should be used and the prevalence of the infection should be monitored.
2. An effective anti H. pylori treatment regimen should be used and time should be taken to instruct the patient in order to improve compliance.

If the prevalence of H. pylori gets low, as is the case in the younger age group in Western countries, the TAT strategy becomes less suitable. Thus “test-and-cope” (TAS) becomes more appropriate as the positive non-invasive H. pylori test can be confirmed by two or more biopsy based tests. Further it was identified, if the infection is confirmed, it should be treated even if no peptic ulcer disease is detected as such an approach may prevent future diagnostic dilemmas and possibly future disease. In both strategies all patients testing negative can safely be treated with acid suppression (or prokinetics if symptomology suggests a motility disorder). If this treatment is successful, the medication should gradually be stopped if possible. If this approach fails and the patient remains symptomatic endoscopy should be considered mainly to reassure the patient, as it is unlikely to reveal underlying disease or change treatment.

If the prevalence of H. pylori gets very low, as is likely to be the case in the future, non-invasive testing for the microorganism is probably not appropriate any more. Acid suppressive drugs, especially proton pump inhibitors are then the drugs of choice. Prokinetics may become a definite alternative but cisapride has recently
been withdrawn from the market and other comparably effective prokinetic drugs for the patients with functional dyspepsia. Any alarm symptom should urge for an immediate endoscopy. A strong family history for peptic ulcer disease may be a persuasive argument in favour of a TAT approach even if the prevalence of the infection is low. Therefore, taking of an adequate medical history remains the mainstay of the approach of every patient. Therefore, early appropriate diagnosis and immediate therapeutic interventions play vital role in the disease management.

REFERENCES


