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# Oncogenic Effect of Helicobacter Pylori, Prevention and Treatment Approach- A Review

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**Abstract**

Chronic gastritis has been long known to be related with gastric cancer. Most importantly, for most instances of gastric cancer, the fundamental reason for gastritis is ascribed to H. Pylori infection. Understanding the pathophysiologic mechanism that lead to gastric cancer is important for screening, prevention and treatment purposes. Gastritis can activate an oncogenic mechanism via the Correa cascade. However, studies reported that the risk of gastric malignancy increments fundamentally when gastritis is combined with H. Pylori contamination. Other than the upper gastrointestinal tract, H. Pylori is additionally engaged with the pathogenesis of colorectal cancer. Treatment aiming at eradicating H. Pylori through the appropriate regimens is important. The triple standard therapy or the quadruple therapies are the universally accepted regimens. All infected patients should be subjected to H. Pylori treatment. An essential issue is to recognize those individuals at a greater possibility of developing H. Pylori infection including those with peptic ulcer illness, previous history of peptic ulcer disease, low-grade gastric mucosa-related lymphoid tissue (MALT) lymphoma, or a past history of endoscopic resection of early gastric disease.

***Keywords:*** Helicobacter pylori; Gastric cancer; Colorectal carcinogenesis; GERD.

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## 1. Introduction

Perhaps the most important advancement to understand the mechanism behind the onset of gastric carcinogenesis has been the acknowledgement of the implication of H. Pylori infection. The latter is the furthermost prevalent paramount risk factor of developing gastric cancer accounting for 90% of cases through activation of the Correa cascade [1]. Having possessed the capacity to build up a connection between gastric tumour and H. Pylori infection has led to successful strategies towards prevention and treatment. It was only until 1994 that H. Pylori has been considered as a class I human carcinogen [2]. Presently, H. Pylori is the most widely recognized infection related cancer-causing agent accounting for 5.5% of overall cancer cases. Moreover, many studies have shown there exist a positive association between H. Pylori and onset of other type cancers such as lung cancers, hepatocellular and colorectal [3]. However, more studies with greater sample sizes are needed to get more reliable information.

H. Pylori infection is typically inherited in childhood [4]. Many risk factors are known together with low socioeconomic status [5], more siblings and having an infected parent, particularly an infected mother [6]. The incidence rate between male and female are similar in children. Warren and Barry Marshall first prosperously isolated and culture H. Pylori. Since then, data regarding the role of H. Pylori infection within the pathological process of diseases is rising. The treatment of H. Pylori is a most faced problem due to drug resistance, mainly to clarithromycin [7].

In this review, we will discuss about oncogenic result of H. Pylori and its pathological process in the gastrointestinal tract cancers and diseases.

### H. Pylori induces Inflammation involved in pathogenesis of gastric cancer

H. Pylori has the ability to survive in the stomach environment, causing damage to the gastric mucosa and inducing several pathways that can be involved in the oncogenic process one of which is inflammation [8]. Most infected people will remain asymptomatic throughout their lives but almost all will develop chronic inflammation. Several mechanisms have been proposed to be involved in the onset of gastric inflammation and ultimately to gastric cancer [9]. These mechanisms are related to the harmful substances produced by the bacteria H. Pylori, which interfere with the normal signaling pathways thus causing neoplastic onset. Among the most pathogenic substances include CagA (cytotoxin-associated gene A) and VacA (vacuolating cytotoxin A) [10].

Perhaps the most pathogenic factor of H. Pylori associated with the greatest risk of developing gastric cancer is the cag pathogenicity island (PAI). Observations made from the study conducted by Hanada and his colleagues revealed that the risk of developing gastric cancer is as much as two times greater in those suffering from cagPAI positive strains as opposed to those infected by cagPAI negative strains. cagPAI had also been linked to elicit an inflammatory response to H. Pylori through chemokine mediators such as CXCL1-3, CXCL5, CXCL8, CLL20, beta-defensin 2 and tumour necrosis factor-alpha [11].

CagA is inserted into the host cell via the T4SS where they bind to the cell membrane's inner surface and some get phosphorylated. Both phosphorylated and unphosphorylated CagA interfere with host proteins within the cell thereby activating various signaling pathways [12]. Ultimately, the consequences of these changes will enhance the gastric cells proliferative ability and activate various oncogenic pathways in host cells. Reports have shown that the oncogenicity of HP infection is associated with the p53 inhibition by CagA [13].

VacA, a pore-forming toxin secreted by almost all strains of HP, is one among the most virulent factor associated in the pathogenesis of HP infection. The exact mechanism by which the VacA toxins are secreted remains however unclear. After entering host cells, VacA secretion causes various cellular alterations and cell death [14, 11]. The mechanisms behind cellular death by VacA are still unclear. Studies have shown evidence that death of gastric cells occurs via the Cx43-dependent pathway. This apoptotic pathway induced by VacA was observed to be controlled by endoplasmic reticulum (ER) stress signaling. Another adverse effect of VacA toxins is inhibition of the T cells of the immune system thereby causing persistent prolongation of H. Pylori infection [11].

Besides the above-mentioned virulent factors, there are few other bacterial virulent elements that add to the pathogenesis of H. Pylori contamination. Among is the outer inflammatory protein A (OipA), an OMP, along with other virulence factors can induce inflammatory responses through IL-8 [15]. Sialic acid-binding adhesion is another OMP whose study has provided a better insight concerning its pathogenesis [16].

**2. Evidence linking H. Pylori infection to gastric cancer**

HP contamination assumes an imperative cancerogenic part in both gastric carcinoma and MALT lymphoma [5,17]. HP is thought to colonize the stomach in about a portion of the total world population, with a variable predominance in various nations. In a study, it has been figured that the risk of gastric adenocarcinoma and MALT lymphoma in HP-contaminated people is 3-to 6-fold higher than in the individuals who are uninfected [3,5]. Back in the 1980s and mid 1990s, numerous examinations were led to locate a positive link between HP and gastric cancer, however every one of them gave only weak evidence. 13 European nations together led an investigation and revealed a positive connection between HP seroprevalence and gastric cancer in a cross-sectional sampling. Significantly more persuading proof was acquired from three large cohort studies where serum had been banked from disease free subjects and the cohort had been followed up for around 10 years. In each of the cohort studies, proof of earlier HP disease (confirm by ELISA in the banked serum) was observed to be considerably more typical in those subjects who along developed gastric malignancy contrasted with those individuals who had not. In a meta-analysis, these 3 investigations gave a general odd ratio for gastric tumor advancement in H pylori– infected versus - uninfected people of 3.8. This prompted to the grouping of HP as a definite class 1 cancer-causing agent in 1994 by the World Health Organization's International Agency for Research on Cancer [1,18].

**HP and gastro-esophageal reflux disease**

Helicobacter pylori have been shown to be the causative factor of many gastrointestinal diseases, however, the

link between HP infection and GERD is still not clear [19]. Till now a wide range of studies has been done to look at the connection between atrophic gastritis because of HP disease with conflicting outcomes [20]. It was beforehand proposed that HP could add to GERD through a few distinct mechanisms: the inflammation of cardia causing diminish in LES pressure; advancement of antral gastritis that causes acidity; impedance of gastric filling and cytotoxins generation bringing about the damage of the esophageal epithelium [21,22]. However, on the other hand, HP disease has been accounted for to be conversely connected with the development of GERD. With the widespread utilization of eradication treatment, the falling pervasiveness of HP contamination has been paralleled by an expansion in the occurrence of GERD and its complexities [23]. Therefore, it seems, by all accounts, to be a defensive factor for GERD, in spite of the fact that this idea has not yet been affirmed by very much planned, population based data. Expanding proof supports a negative relationship between HP disease and GERD, including its complications (esophagitis, Barrett's oesophagus and esophageal adenocarcinoma) [24]. However, HP eradication does not exacerbate pre-existing GORD nor does it influence proton pump inhibitor treatment efficacy [25].

**HP and colorectal cancer**

Half of the world's population is contaminated by the global Helicobacter pylori [26]. Apart from gastric malignancy, there has been a growing concern in examining the potential role of H. pylori in evolving carcinogenesis of different organs in the gastrointestinal tract, for example the colon [27]. But, unlike the stomach H. pylori does not colonize in the colon, nevertheless, it travels past its lumen by indirect pathogenic mechanisms like increased production of the peptide hormone mediator gastrin [28]. Several studies, including two potential examinations, affirmed a measurable connection between the high level of serum/plasma gastrin levels and the risk of colorectal adenoma as well as colorectal cancer [29]. Another hypothesis is the decreased gastric acid secretion affiliated to H. pylori- related chronic atrophic gastritis leading to alterations of the colorectal micro flora, which in turns promotes carcinogenesis of the colon [30]. Other possible hypothesis includes induction and perpetuation of inflammatory responses and release of mutagenic toxins [31]. The connection of bacterial inflammation, toxin release, and cellular reactions creates a pro carcinogenic environment, increasing proliferation of cells, angiogenesis and constraining apoptosis [32]. In vitro, H. pylori are able to transform colorectal cells leading to hyper proliferation and carcinogenesis [33]. Infection with a harmful strain of H. pylori that express CagA gene may add to colorectal carcinogenesis by instigating greater inflammatory responses, including increased release of cytokines for example IL-8, which is a known growth factor for colorectal cancer growth [15, 34]. Until now, about four reports have determined a positive relationship between CagA seropositivity and colorectal neoplasia. Additionally, advanced studies are anticipated to substantiate H. pylori as an infectious contributor in the multifaceted procedure of colorectal carcinogenesis [35].

**3. Microbiota and H. pylori Infection**

The outcome of H. pylori infection is believed to be due to host hereditary factors, bacterial virulence determinants, and environmental mechanisms [36]. However, recently the significance of the gastrointestinal micro biota has included another possible determinant, the physiology and immunology of bacterial groups in

the stomach may influence the ability of H. pylori to alter the gastric micro biota. At the point when the stomach is infected with H. pylori, it involves the majority of the gastric micro biota. Consequently, microbial diversity is decreased under the H. pylori-infected stomach compared to healthy stomach [37]. However, in the condition of chronic infection of H. pylori, gastric microbial diversity rises again [38]. There are conceivable clarifications for this. The first, H. pylori-induced inflammation causes gastric atrophy and lessens the parietal cell mass, raising gastric pH, which inclines to colonization by environmental micro biota that cannot outlast in the normal gastric ph [39, 40]. There are other reasonable explanations for H. pylori-induced changes in the micro flora. H. Pylori produce ammonia and bicarbonate from urea that can be utilized as substrates by other microorganisms, and H. pylori contamination is linked with slower migrating motor complex (MMC) phase III activity, which adds to the clearing of adherent bacteria from the antral mucosal compartment [41]. Various studies in H. Pylori positive groups that have utilizes pyrosequencing indicated that the diversity of gastric microbiota augmented with development from chronic gastritis to gastric cancer [42]. Some examinations additionally analyzed the recognized changes in the microbiota of the gastrointestinal system as a result of H. pylori infection and eradication. The consequences of these examinations presented that H. pylori-induced gastric immunopathogenesis in the form of low stomach acid and abundance of gastrin in the blood can aggravate large intestinal microbiota changes, predominantly in the distal inflamed gastrointestinal tract [43].

## 4. Treatment approach of H. Pylori

H. Pylori is a major reason behind several diseases of the upper gastrointestinal tract [44]. If the H. Pylori test result is positive, then the patient should be treated for H. Pylori infection. Education should be provided to the patients about the significance of finishing the prescription with the correct dosage and about the related negative impacts of medicine used [45].

The pharmacotherapies are aiming to kill the microorganism, to avoid complications, and to lessen morbidity. The triple therapy regimen is now universally accepted and used with a positive cure rate of around 90% [46]. However, a major problem arising is antibiotic resistance resulting in increased failure rate of standard triple therapy [47]. Triple therapy treatment is meant for 10-14 days [48]. The treatment regimens are omeprazole, amoxicillin, and clarithromycin (OAC) for 10 days; bismuth subsalicylate, metronidazole, and tetracycline (BMT) for 14 days; and lansoprazole, amoxicillin, and clarithromycin (LAC), which has been endorsed for either 10 days or 14 days of treatment [49]. The LAC regimens have appeared to be more compelling for H. Pylori eradication. H. Pylori testing ought be done at least one month after the treatment. If the test shows that the treatment was unsuccessful, subsequently another round of treatment with a different combination of antibiotic medications is used [50]. With the increase rate of resistance towards antibiotics mainly clarithromycin, quadruple therapy is now often being used. The quadruple therapy consists of “TOMB”, mainly tetracycline (T), omeprazole (O), metronidazole (M), and bismuth citrate (B). Studies have demonstrated that quadruple therapy is better for H. Pylori eradication when contrasted with the standard triple therapy [51].

## 5. Conclusion

With the rising of recent understanding in respect of the pathogenesis of H. Pylori have expanded our

comprehension of gastric carcinogenesis [52]. Various virulence factors related with H. Pylori are associated with the carcinogenesis of the gastrointestinal tract. Understanding the pathological process of H. Pylori give us a superior knowledge about the mechanism involved [53]. Prevention and treatment is of extreme significance for the annihilation of H. Pylori contamination. Education about the subject assumes an essential part in the eradication as well [54].

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