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STOMACH AND DUODENUM (J PISEGNA, SECTION EDITOR)

Helicobacter pylori in Gastric Malignancies

Abhishek Bhandari · Sheila E. Crowe

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Abstract Helicobacter pylori infection remains common worldwide and is significantly associated with gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT)lymphoma. This article reviews recent developments in the field of H. pylori with an emphasis on mechanisms of carcinogenesis, and the bacterial, environmental and host factors that may alter risk of developing gastric cancer or gastric MALT lymphoma. The topic of eradication of H. pylori to prevent the development of malignancy and the possibility of a vaccine against H. pylori are also explored.

Keywords Helicobacter · Pylori · Gastric · Malignancy · Adenocarcinoma · MALT · Lymphoma · Cancer · Stomach · Mucosa-associated lymphoid tissue

Introduction

Helicobacter pylori haa been implicated in numerous gastrointestinal diseases after its association with chronic gastritis was established in 1983 by Warren and Marshall [1]. The spiral-shaped Gram-negative bacteria remains the most common chronic bacterial infection in humans worldwide. The prevalence of the infection varies greatly throughout different parts of the world, with an increased prevalence in developing countries and places with lower socioeconomic status compared to developed nations, where the frequency of infection has fallen substantially. There is as much as an 80 % or greater prevalence rate in developing countries as opposed to 20–50 % in developed countries [2] (Fig. 1). Gastric cancer is largely attributable to H. pylori infection, and it is the second most common cause of cancer death worldwide.

Of the various disorders that are associated with H. pylori, the relationship between H. pylori and gastrointestinal malignancy has become one of the best studied in the last three decades. Gastric malignancies that are most commonly associated with H. pylori are gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. As early as 1994, the International Agency for Research declared H. pylori a Group I human carcinogen for gastric adenocarcinoma [1].

Diagnosis and Classification of Gastric Adenocarcinoma and MALT Lymphoma

Gastric adenocarcinoma accounts for more than 90 % of cancers of the stomach and can be divided into two distinct types, intestinal and diffuse. The diagnosis of gastric adenocarcinoma continues to be made through endoscopy and tissue biopsy. A single biopsy of a suspicious lesion has 70 % sensitivity for diagnosing gastric cancer; however, increasing this number to 7 biopsies of the ulcer margin and base increase the sensitivity to 98 % [3].

There are two major classifications systems for gastric adenocarcinoma. The Japanese classification is based upon specific anatomic locations, focusing on the location of affected lymph nodes [4]. The more commonly used system in the United States was developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUAC). As outlined in Table 1, this system is based on 3 major components of carcinoma, tumor (T),

A. Bhandari
Department of Medicine, University of California, San Diego,
9500 Gilman Drive,
La Jolla, CA 92093-0063, USA
e-mail: abbhandari2@ad.ucsd.edu

S. E. Crowe (✉)
Division of Gastroenterology, Department of Medicine,
University of California, San Diego,
9500 Gilman Drive,
La Jolla, CA 92093-0063, USA
e-mail: secrowe@ucsd.edu

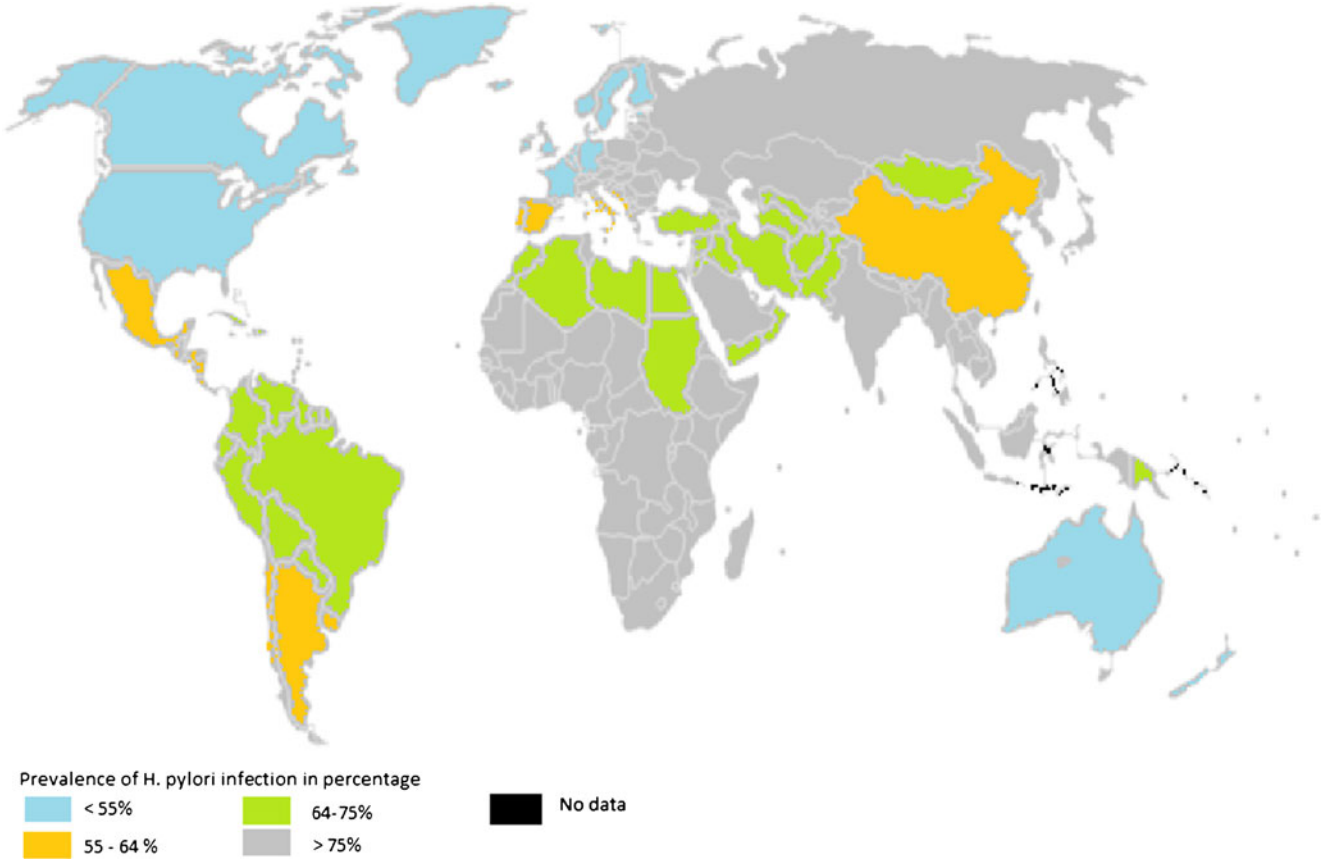

Fig. 1 Color-coded map depicting the worldwide prevalence of H. pylori infection. More than three-quarters of the population in certain areas of Africa and Asia are infected with H. pylori, whereas the infection is less prevalent in Europe and North America. (Modified from the figure in "The Human Gastric Pathogen Helicobacter pylori and Its Association with Gastric Cancer and Ulcer Disease", Ulcers, 2011) [69]

nodal involvement (N), and metastases (M) [5]. Tumor classification is based on layer of invasion of the primary tumor. Nodal classification reflects the number and location of the lymph nodes that are involved in the disease. Metastases classification is simply based on whether or not distant metastases are present.

Mucosa-associated lymphoid tissue lymphoma, or MALT lymphoma, accounts for up to 3 % of all gastric malignancies [6]. The diagnosis of MALT lymphoma is based on tissue histology from endoscopy, along with immunocytochemistry for B lymphocyte markers. Histological findings including lymphoepithelial changes, polymorphic cellular content, and centrocyte-like cells, impact the grade of the lymphoma and depends on the number of large blast cells present, with greater than 20 % leading to classification as high grade lymphoma [7].

Helicobacter pylori Infection and Gastric Adenocarcinoma

There is a substantial body of data that links H. pylori infection to gastric adenocarcinoma. A recent review indicates that 2 million cases of cancer each year are attributable to infection with H. pylori being a key infectious agent leading to gastric cancer worldwide [8•].

The EUROGAST study observed diverse populations and found a 6-fold increase in likelihood of developing gastric adenocarcinoma in patients with evidence of in H. pylori infection in comparison to those without infection [9]. Additionally, there is a much greater risk of developing adenocarcinoma in H. pylori infected individuals younger than 30 years of age[10].

Helicobacter pylori infection has been associated with an increase in both intestinal and diffuse types of gastric adenocarcinoma [10, 11]. However, there may be a difference in the location of gastric cancer found in H. pylori-infected patients. Distal gastric cancer is much more likely to occur in H. pylori-infected patients than gastroesophageal junction adenocarcinoma [12].

Despite the well-established and clear association between persistent H. pylori infection and gastric adenocarcinoma, only a small percentage of infected individuals will develop malignancy. This is likely due to a myriad of external or environmental factors that are believed to affect the disease course and progression. Factors that

Table 1 TMN staging for gastric adenocarcinoma

Anatomic stage/prognostic groups	Tumor	Nodal	Metastasis
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

TMN staging criteria for gastric cancer as recommended by the American Joint Committee on Cancer Staging. TMN staging uses combinations of depth of invasion, nodal involvement, and level of metastasis to stage and classify gastric carcinoma. (Based on American Joint Committee on Cancer Staging Manual, 2010) [5]

promote development of malignancy include certain dietary influences, such as high salt diet, red and processed meat, and nitrosamines, while other factors including diets high in fresh foods and vegetables may reduce the risk [13, 14]. Recently, an association between an elevated white blood cell count and an increased risk for development of gastric cancer has been reported in Japanese subjects [15]. The greatest risk was in patients with H. pylori infection and an elevated white blood cell count.

Obesity has been reported to be associated with gastric cardia adenocarcinoma [16]. This association may be related to H. pylori infection as there is an apparent increased prevalence of H. pylori infection in obese patients [17]. A mechanism explaining this phenomenon has not yet been proven, and the observation may not directly reflect obesity per se. This may relate to reports suggesting that hyperglycemia is a factor increasing the risk of developing gastric cancer [18]. Collectively, these studies lead to the possibility that eradication of H. pylori in conjunction with weight loss or better glycemic control might decrease risk of gastric cancer.

Mechanisms of Carcinogenesis and Helicobacter pylori Infection

Despite the extensive data linking H. pylori and gastric cancer, the exact mechanisms by which gastric cancer develops as a result of infection have not been established; however, data support the role of host factors modulating the immune and epithelial response, environmental factors such as diet, and, to a certain extent, bacterial factors. Emerging information about the human microbiome may reveal further insights into why only subsets of infected individuals develop gastric cancer.

Epithelial Response to Infection

A key aspect of the chronic infection involves establishing infection of the mucosal layer, which reflects bacterial properties including expression of flagella, adhesion molecules and other established virulence factors. A newly proposed mechanism of H. pylori infectivity involves the interaction between H. pylori and protein kinase C isozymes. H. pylori have been reported to induce phosphorylation of protein kinase C. This, in turn, activates matrix mettaloproteinase-1 (MMP-1) expression and secretion. MMP-1 is an interstitial collagenase, which, in increased quantities, facilitates H. pylori cellular invasion [19].

H. pylori infection causes hyperproliferation of epithelial cells and increased rates of apoptosis in antral cells in H. pylori-infected individuals, which return to normal once eradication of the infection occurs [20]. There are multiple proposed pathways for how H. pylori leads to dysregulation of apoptosis and, eventually, to gastric cancer. A proposed pathophysiology is that H. pylori infection induces increased expression of the FAS receptor on gastric epithelium cells. This causes increased activation of apoptosis through the FAS death receptor pathway [21]. Hyperproliferation of gastric epithelial cells may occur due to the fact that dysplastic gastric proliferating cells may produce increased levels of Bcl-2, an antiapoptotic protein, and thus are more resistant to apoptosis [22, 23]. A recent report indicates that c-Src and c-Abl kinases sequentially phosphorylate CagA [24]. The two phosphorylation events need not occur on the same CagA molecule but are both required for the biological effects of CagA. Another recent study demonstrated that vacuolating cytotoxin and variants in Atg16L1 disrupt autophagy and promote H. pylori infection in humans. As autophagy protects against infection with H pylori, this could contribute to inflammation and eventual carcinogenesis [25].

The bacterial virulence factor CagA is a possible culprit in the activation of the apoptosis pathway. A recent article about H. pylori found a relationship between CagA and the p53 tumor suppressor gene. CagA interacts with an apoptosis-stimulating protein of p53 and leads to degradation of p53. This can lead to unsuppressed cell growth and replication

[26]. Cellular inhibitor of apoptosis protein 2 (clAP2) may be a potential gene to target in H. pylori-induced carcinogenesis. In mice with H. pylori-induced gastric cancer, knocking out of clAP2 in cancer cells resulted in a 30 % decrease in cellular proliferation and 20 % increase in apoptosis [27]. The majority of human gastric cancer cells are thought to have higher amounts of clAP2 and it is hypothesized that targeting clAP2 in humans could actually be more effective than in the reported mice trials. A mechanism for the interaction with H. pylori and cIAP2 has not yet been explored.

Inflammatory Response to Infection and Oxidative Stress

Activation of neutrophils in response to H. pylori infection appears to be an important aspect of gastric carcinogenesis. Neutrophils produce nitric oxide synthase, which leads to the formation of nitric oxide and reactive oxygen metabolites, including superoxides and hydroxyl ions. These compounds lead to significant DNA damage, mutations, and eventually malignancy. This DNA damage can be in the form of DNA demethylation which is reported in multiple studies to be a key factor in H. pylori-induced carcinogenesis. Demethylation of the Sat α repetitive gene sequence has in particular been correlated with H. pylori-positive gastric cancer. This increase is observed predominantly in patients under the age of 45 [28].

Chronic H. pylori infection can lead to atrophic gastritis, intestinal metaplasia, and the loss of parietal cells, with an increase in stomach pH levels and decreased amounts of ascorbic acid in the stomach. This provides a receptive environment for nitrate-reducing bacteria to thrive and to produce nitrates and free radicals. Normally, ascorbic acid blocks this nitrosation reaction by scavenging nitrates and radicals. However, in cases of intestinal metaplasia, the decreased parietal cell mass leads to reduced levels of ascorbic acid and, thus, increased damaging products in the gastric lumen. A recent study suggests that, by inducing spermine oxidase which metabolizes the polyamine spermine into spermidine and generates H_2O_2, H pylori CagA generates cells with oxidative DNA damage, rendering a subpopulation of these cells resistant to apoptosis and, thus, at high risk for malignant transformation [29].

Regulation of Host Response to Infection

Apurinic-apyrimidinic endonuclease (APE)-1 is a rate-limiting DNA base excision DNA repair enzyme. The molecule is also known as redox factor 1 (ref-1) for its transcriptional regulatory activity. APE-1's function and expression can be altered in the setting of H. pylori infection. APE-1 expression is increased in gastric cancer and other malignancies and it is increased in gastric epithelial cells by H. pylori infection. These results suggest that it plays a role in carcinogenesis [30] and, interestingly, APE-1 is known to regulate oxidative stress, chemokine expression, and apoptosis [31].

Runt-related transcription factor (RUNX3) is a candidate tumor suppressor gene whose deficiency has been seen with gastric cancer. A recent study found that abnormal methylation of the gene along with H. pylori infection was associated with an increased risk of gastric cancer in patients with chronic atrophic gastritis [32], implicating RUNX3 as a potential biomarker in early gastric cancer.

One very intriguing genetic polymorphism that has been found to be protective against H. pylori carcinogenesis in mice is vitamin D3 upregulated protein 1 (VDUP1). This leads to the possibility of a link between vitamin D deficiency and propensity for H. pylori infection to progress into gastric cancer in patients [33].

Helicobacter pylori Virulence Factors

Cag A is the most studied of H. pylori virulence factors. There is now evidence that Cag A may be an oncogene, regardless of the presence of gastritis [34]. There have been studies that show transgenic expression of Cag A leads to cancer in mice, despite the absence of gastritis. However, to date, there have been no human studies like this. Additionally, there may be variations in propensity to develop gastric cancer in H. pylori-infected patients based on the presence of distinct virulence factors. In an Iranian study, the presence of the homB gene was found to be significantly higher in H. pylori patients with gastric cancer as opposed to peptic ulcers or gastritis [35].

The combination of specific bacterial virulence factors and specific genetic polymorphisms can significantly potentiate disease risks. For example, patients infected with the vacA s1 genotype (vacuole cytotoxin), who possessed a particular IL-1B polymorphism (IL-1B-511), were found to have a significantly increased risk of developing gastric cancer with an odds ratio of 87 [36]. However, despite the data for multiple virulence factors, the updated Maastricht guidelines still state that no particular bacterial virulence marker can be used for clinical practice at this time [37•].

Management of Gastric Adenocarcinoma and H. pylori Infection

There are multiple options for the treatment of gastric adenocarcinoma. They include endoscopic resection, surgical gastrectomy, adjuvant chemotherapy, and H. pylori eradication. There are specific criteria for eligibility for endoscopic resection which takes in to account tumor size, histology, nodal involvement, and level of invasion [38, 39]. The latest Maastricht guidelines have made a grade A recommendation that H. pylori infection is the most consistent risk factor

for gastric cancer and that its elimination is the most promising strategy to reduce the incidence of gastric cancer [37•].

Treatment of H. pylori has been proven to decrease the risk of developing gastric cancer and decreases recurrence following treatment of gastric cancer [40, 41]. A recent study once again demonstrated that, after H. pylori eradication, the risk of developing gastric atrophy and intestinal metaplasia are all significantly decreased. This can lead to a reduction in gastric cancer in previously H. pylori-infected people[40]. In contrast, a study of mass eradication of H. pylori infection starting in 2004 in Taiwan demonstrated a reduction of gastric atrophy, but not intestinal metaplasia, when compared to the 5-year period before the study started [42•]. There was an associated decrease in gastric cancer and peptic ulcer disease and an increase in esophagitis. Further studies, including longer-term follow-up, are needed to confirm these findings.

Once intestinal metaplasia and gastric cancer are established, there are mixed data as to what the eradication of H. pylori actually accomplishes. In some studies, H. pylori eradication has been observed to aid prevention of the reoccurrence of early gastric cancer (EGC) even after endoscopic resection [41, 43]. This was studied in a randomized control trial comparing standard endoscopic resection of EGC versus the addition of triple therapy for H. pylori eradication. The group receiving triple therapy was observed to have a lower risk of metachronous gastric cancer over a 3-year period from diagnosis [41, 43]. However, recently, a retrospective study showed that there was no significant difference in development of metachronous gastric cancer in patients who underwent endoscopic gastric cancer resection, whether or not they received H. pylori eradication treatment, when analyzed after 5 years post-eradication [44•].

There may be a difference in outcomes of eradication of the disease based upon which portions of the stomach are affected. A meta-analysis of 12 studies, including over 2,600 patients, found that eradication of H. pylori significantly improves corpus gastric atrophy, but not antral gastric atrophy. This same study reported no effect of eradication on gastric intestinal metaplasia [45]. Whether eradication of infection once premalignant changes are established is beneficial with regard to the development of cancer remains unclear and warrants further study.

It has been proposed that measurement of serum pepsinogen I may predict whether H. pylori eradication will be effective in preventing development of gastric cancer. In a pooled analysis of 6,695 patients, only patients with normal pepsinogen levels were seen to have a significant reduction in gastric cancer incidence [46]. This suggests that cancer which arises after H. pylori eradication is due to the presence of extensive atrophic gastritis prior to eradication and that eradication is most beneficial in patients with absent or mild atrophy. Serum pepsinogen has been proposed as a possible screening test for gastric cancer, due to the ability to detect severe atrophy [47].

Helicobacter Pylori and Gastric Lymphoma

Chronic H. pylori infection leads to chronic gastritis which involves both T cells and B cells arising from the mucosal-associated lymphoid tissue (MALT). The recognition of the H. pylori antigen by the immune system leads to T cell activation, lymphoid follicle formation, and B cell proliferation. The gastric follicle that forms has three layers: an inner center of centroblasts and centrocytes and two outer layers comprising of B cells, the middle mantle layer and the outer marginal layer. It is thought that the H. pylori antigen-presenting cells interact with CD4-expressing cells. This CD4 cell then binds to a B cell in the marginal zone causing hyperproliferation of B cells [48, 49]. In this milieu, it is believe that chronic stimulation leads to the development of B cell lymphoma, also known as a MALT lymphoma or maltoma.

When H. pylori is present in patients with gastric MALT lymphoma, eradication of H. pylori has been an effective initial method of treatment of localized early stage gastric MALT lymphoma with anywhere from 50 to 80 % rates of complete histological remission [50–56, 57•]. However, recent studies have further stratified this by looking at outcomes by stage. H. pylori eradication led to remission in greater than 75 % of patients in with stage I gastric MALT lymphoma and about 55 % in patients with stage II disease [58]. Additionally, the location of the lymphoma may make a difference in remission rates. There has been at least one study that has shown that patients with more superficial tumors located in the distal stomach were more likely to achieve complete remission [59]. Complete remission has been documented as early as 5 months and as long as 3 years from time of treatment [50–56, 57•]. The chromosomal translocation, t(11;18)(q21;q21), and gene expression, nuclear BCL, have been found to be resistant to H. pylori eradication [60].

H. pylori eradication is not thought to be effective in patients with metastases, lymphadenopathy, or diffuse large B cell lymphomas [61–63]. However, a recent study showed that, in early stage gastric diffuse large B-cell lymphomas both with and without features of mucosa-associated lymphoid tissue, H. pylori eradication resulted in complete pathologic remission in a significant percentage of cases [64].

Alternative therapies such as radiation therapy have been found to have just as effective, if not more effective, in achieving complete remission as eradication of infection, and have also been found to have lower recurrence rates than following H. pylori treatment. However, there are significantly more complications with radiation treatment as well as with gastrectomy than eradication of infection.

Future Developments: Vaccination?

Research on the development of a vaccine for the prevention or treatment of H. pylori dates back to the early 1990s, but unfortunately, successes have been few and far between. Immunity has rarely been achieved in animal models and no consensus opinion has been reached on adjuvants, antigens, or method of delivery. There have been a few clinical trials that for the most part have been unsuccessful, but there is some hope for the future. Much of the current research focuses on Th1, Th17, and regulatory T cell-based immunity including exploration of the role of Th17 cells and the role of IL-17 in H. pylori infection and vaccination [65, 66].

T cell epitopes have been studied as a target of H. pylori vaccination [67]. In a recent study, conserved DNA sequence encoding was used to develop HLA-2 epitopes and administered via an intranasal vaccine [67]. This vaccine led to about 25 % (5/19) sterile immunity at 32 weeks in mice [67]. Although many barriers still remain, this approach did provide some promising results and a possible method for further studies of vaccine development. H. pylori urease has been extensively studied as a target for vaccination, given its integral role in H. pylori colonization. However, developing epitopes that induce immunity has been challenging, and some researchers have proposed that combination with other antigens may provide more promising results, including genetic fusion of multiple proteins to develop a multivalent vaccine [68]. Other antigens have been explored, such as Omp18, TonB, superoxide dismutase, and protein-conjugated LPS, but the results are not conclusive. Human vaccination still faces numerous obstacles, both in development and in safety; however some progress has been made, and research on this topic is ongoing.

Conclusions

Helicobacter pylori infection remains the most common chronic bacterial infection of humans, but, due to improved socioeconomic status of the developed world, rates are declining in these nations. Given that gastric malignancies result from longstanding infection, the burden of gastric cancer is still high in areas of the world where H. pylori infection is common, such as the Far East, Central and South America, and eastern Europe. First generation immigrants from these at-risk areas of the world will also have an increased risk of gastric cancer. Early and effective eradication of infection continues to remain the mainstay of treatment or prevention of gastric malignancy at this time. When, in the sequence of progression to malignancy, it is best to eradicate infection requires additional study. Prevention of H. pylori has been studied, but socioeconomic advances are the major reason for decreasing rates of infection. Since complete elimination of H pylori infection worldwide is unlikely to happen for many generations, if ever, research is needed to identify which infected individuals will go on to develop gastrointestinal malignancy, and potentially target those populations for treatment to prevent gastric cancer. Strategies to modulate infection and the ensuing inflammatory response to reduce the likelihood of developing cancer are another area for further investigation.

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