HELICOBACTER PYLORI INFECTION IN PEPTIC ULCER DISEASE AND GASTRIC MALIGNANCY

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1. ABSTRACT

Helicobacter pylori infection is the world's most common chronic infection in humans and is the cause of most gastritis cases. This infection is accepted as the etiology of the majority of peptic ulcers. It has been implicated as a significant contributing factor in the development of gastric malignancy – both gastric MALT lymphoma and gastric adenocarcinoma. Both endoscopic and non-endoscopic tests are available for accurate diagnosis of the infection. Several multi-drug regimens are useful for effective eradication of the infection. Strategies have been developed for managing patients with gastric MALT lymphoma. Criteria to identify populations with increased risk for gastric malignancy are being developed. *H. pylori* induces gastritis; it is also involved in both apoptosis and cellular proliferation. The role of *H. pylori* infection in the pathogenesis of premalignant lesions, altered gastric acid secretion, and significant clinical presentations is the subject of numerous studies worldwide.

2. INTRODUCTION

H. pylori is one of the most common chronic human bacterial infections with an estimated world wide infection rate approaching 50%. An estimated 30-40% of the U.S. population is infected with *H. pylori*. *H. pylori* infection rates are higher in developing countries where low socioeconomic status, poor sanitation and crowded living conditions are believed to be the major mitigating factors in the prevalence of the infection. *H. pylori* clearly has a role in the pathogenesis of peptic ulcer disease.

However, the rate of infection associated with peptic ulcer disease in the U.S. may not be as high as previously thought. Studies in many regions indicated that *H. pylori* was associated with up to 95% of duodenal ulcers. However, a recent analysis of U.S. patients with non-NSAID duodenal ulcers showed that only 73% were confirmed to be infected with *H. pylori* at the beginning of the study (1). A lower infection rate was detected in a small, single center study in Rochester, N.Y. where *H. pylori* was associated with only 61% of gastric and duodenal ulcers (2).

3. PATHOPHYSIOLOGY OF *HELICOBACTER PYLORI* AND PEPTIC ULCER DISEASE

The role of *H. pylori* in peptic ulcer disease has not been fully elucidated, although several theories have been proposed. *H. pylori* can have varied effects on gastric acid secretion in the stomach. There is an increased gastric acid secretion in nonatrophic antral-predominant gastritis. This pattern is most commonly seen in patients with duodenal ulcers. In atrophic pangastritis involving the body and antrum there is either normal or decreased acid production. This pattern is frequently seen in patients with gastric ulcers and gastric cancer (3,4).

Dietary protein stimulates the G cells in the antral mucosa to release gastrin into the blood. Gastrin directly stimulates parietal cells to secrete acid and adjacent enterochromaffin-like cells to release histamine. To protect against excessive acid production, the D cells of the antrum release somatostatin to inhibit gastrin release. Compared to healthy, non-infected volunteers, infected patients with duodenal ulcer can have a six-fold increase in gastrin-stimulated acid secretion and non-ulcer infected patients may have a threefold increase. These *H. pylori*-induced alterations in acid response resolve gradually over the following year after eradication of the infection (5). In patients with duodenal ulcers, *H. pylori* colonizes the entire stomach but with a greater degree of inflammation and increased density of organisms in the antrum. This is described as antral-predominant gastritis and may lead to disruption of somatostatin inhibition of gastrin release with an excessive gastric acid load presented to the duodenum. The increased acid load may damage the duodenal mucosa and eventually lead to gastric metaplasia. This mucosal alteration may allow *H. pylori* to colonize the areas of gastric metaplasia and eventually lead to duodenal mucosal ulceration (3).

Conversely, patients with pan-gastritis often have decreased acid production. This can be secondary to several factors. G cells, which produce gastrin, are located primarily in the antrum. Atrophy of the antrum leads to loss of G cells and disruption of gastrin release. Atrophy in the body leads to loss of parietal cells with the chronic inflammation disrupting the function of the remaining parietal cells (3). The net result is decreased acid production.

Duodenal bicarbonate secretion is important in neutralizing acid as it is emptied from the stomach into the duodenum. *H. pylori*-infected patients have lower basal and acid-stimulated duodenal mucosal bicarbonate secretion. The decrease in bicarbonate response is independent of histopathologic abnormalities. Therefore, the decrease in bicarbonate secretion is likely secondary to cellular and physiological regulatory defects. Eradication of *H. pylori* in patients with duodenal ulcers will normalize basal and acid-stimulated proximal duodenal mucosal bicarbonate secretion, which may help prevent ulcer recurrence (6). Many bacterial factors probably play a role in the pathogenesis of *H. pylori* infection and associated host clinical presentations. Some of these factors are present in all strains, while other factors are strain-specific. One of the conserved factors is urease. Urease is present in the cytoplasm, on the surface of the gastric epithelium and may present extracellularly by bacterial autolysis (7,8). *H. pylori* organisms in stationary growth phase may undergo lysis releasing cytoplasmic urease into the surrounding milieu; some urease may adhere to other *H. pylori* organisms as extracellular presentation. *H. pylori* urease metabolizes gastric urea to produce ammonia. This increases the gastric pH surrounding the bacteria, allowing the organism to survive in the hostile acidic environment of the stomach. Without functional urease the microorganism is unable to infect the stomach, which has been demonstrated in animal models involving the gnotobiotic piglet (9).

H. pylori moves through the gastric mucus to reach the gastric epithelium by utilizing its 4-6 flagella, which consist of a flagellar filament and sheath. The flagellar filament has two separate flagellins, Fla A (major species) and Fla B (minor species). Both are necessary for complete colonization (10).

H. pylori also has significant effects on its microenvironment and has developed several strategies to ensure its survival. Attachment of *H. pylori* to the gastric epithelium results in effacement of the microvilli at the site of attachment, pedestal formation and actin filament rearrangement. It may avoid detection by the host immune system by producing Lewis blood group antigens that mimic surface glycomolecules located on the gastric epithelium (11). *H. pylori* also possess cecropins, which are antibacterial peptides with activity against gram-negative and gram-positive organisms. When *H. pylori* undergoes autolysis, surrounding organisms are destroyed, therefore protecting the microenvironment from competing bacteria (12).

Two heterogeneous virulence factors include the *cag*A gene and *vac*A gene alleles. The vacuolating cytotoxin (VacA) induces cytoplasmic vacuolation of many epithelial cells. The *vac*A gene contains a signal region existing as s1 (s1a, s1b, s1c) or s2, and a middle region with m1 and m2 allelic types. Although the gene coding for the VacA protein is present in most strains of *H. pylori*, vacuolating cytotoxin production may be regulated through its allelic diversity (13). The s1 allele has been associated with increased peptic ulceration, increased inflammation, and cytotoxin production when compared to strains with the s2 allele. Also the s1/m1 strain produces more cytotoxin activity in vitro than the s1/m2 strain (14,15).

Table 1. Diagnosis of *H. Pylori*

Test	Sensitivity	Specificity	Notes
Invasive			
Rapid Urease Test	>90%	>90%	? Can be inaccurate with active bleeding ? decreased sensitivity while on PPIs
Histology	>90%	>90%	? expensive ? provides permanent record ? decreased sensitivity while on PPIs
Culture	~50-85%	100%	? may be important as resistance to therapies increases to determine sensitivities ? time consuming and expensive ? decreased sensitivity while on PPIs
Non-Invasive			
^{13}C Breath Test	>90%	>90%	? not radioactive, therefore can be used in pregnant women and children ? sensitivity decreased by PPI use
^{14}C Breath Test	>90%	>90%	? does not require test meal and can be analyzed in 30 minutes ? radioactive, therefore relative contraindication in pregnant women and children ? sensitivity decreased by PPI use
ELISA	>85%	>75-90%	? laboratory-based, relatively expensive ? sensitivity not affected by PPI, bismuth containing compounds or antibiotics ? cannot distinguish between active or recent infection
Serum Antibody	~85%	75-90%	? Fast test results ? Can be used in primary care office setting ? sensitivity not affected by PPI, bismuth containing compounds or antibiotics ? cannot distinguish between current or past infection
Whole blood Antibody	76-84%	79-85%	? Does not require phlebotomy or centrifugation ? Less accurate than serum antibody tests
Stool Antigen	~90%	~78%	? Good sensitivity for initial diagnosis ? Unknown accuracy for post-eradication testing ? inexpensive and easy to perform

The CagA protein is coded by the *cag*A gene, which is a marker for a 40kb region of the *H. pylori* genome called the pathogenicity island (PAI). The PAI encodes about 30 genes, which are important in severe inflammation and virulence (16,17). There is a strong correlation between CagA-postive strains and increased risk of duodenal ulceration. In one study CagA was present in 88% of patients with duodenal ulcers versus 76% of patients with gastric ulcers and 56% of patients with non-ulcer dyspepsia (18). There was a statistically significant increase in patients with peptic ulcer disease compared to the other groups. However, the high frequency (>50%) of CagA in all groups precludes its use as a single marker to predict more severe clinical disease.

4. DIAGNOSTIC TESTS

The diagnosis of *H. pylori* can be divided into tests that require endoscopy to perform a biopsy and tests performed without endoscopy (Table 1). Biopsy-based tests include the rapid urease test (RUT), histology, and culture. Tests that can be performed without endoscopy include antibody-based tests and the urea breath test (UBT). Antibody tests include quantitative (ELISA), qualitative (serum or whole blood rapid tests) and the stool antigen. UBTs can be subdivided into the ^{13}C and ^{14}C-urea breath tests.

4. Endoscopic Tests
4.1.1. Rapid Urease Test (RUT)

The RUT is based on the ability of *H. pylori* to hydrolyze urea to bicarbonate and ammonia. The biopsy specimen is placed in the test medium with a pH-sensitive dye. When urea is metabolized to form ammonia, the pH rises and the color of the medium changes indicating the presence of *H. pylori*. The sensitivity and specificity of this test is about 90% (19). This test can be inaccurate in the face of active bleeding, in the early post-eradication treatment period, and in patients on proton pump inhibitors (20). In one study evaluating efficacy of RUT in patients with bleeding duodenal ulcers, the test had a sensitivity of 98% in patients with dyspeptic symptoms alone compared to 75% sensitivity in patients with bleeding ulcers. The negative predictive value was 83% in dyspeptic patients versus 60% in patients with bleeding peptic ulcer (21). Recent or current antibiotics can decrease the sensitivity of the RUT from 91-92% to 61% (22). The decreased sensitivity is likely secondary to the low number of organisms in the biopsy specimen (23). Despite these drawbacks, the RUT is an inexpensive and rapid method of detecting *H. pylori* infection.

4.1.2. Histology

H. pylori is a Gram-negative, spiral-shaped organism residing on the gastric epithelial surface, in

gastric pits or in mucous overlying the cell surface. The patchy distribution of *H. pylori* can lead to high false negative rates, particularly in biopsies of the corpus. Many stains can be used to detect the microorganisms. These include the Warthin-Starry silver stain, which was first utilized to visualize the organism, the Genta stain, and more commonly, the Giemsa stain (24). Histological identification can yield sensitivities and specificities >90% (25). One drawback to this method is that processing histological specimens is time-consuming and expensive. As with the RUT, the sensitivity of histological stains can be significantly lowered by PPIs and antibiotic therapy. Presence of *H. pylori* can be missed in as many as 19% of antral and body biopsies after antibiotic treatment compared to 2% in those not on antibiotics (20,26).

4.1.3. Culture

Culture is 100% specific for *H. pylori*. The problem is that the microorganism is fastidious and requires microaerophilic culture conditions. Therefore, the sensitivity of culture with optimal techniques is lower than 85% (20). In the clinical setting the sensitivity of culture may approach 50%. This method of testing is not routinely available and should not be considered a method of diagnosis outside of the research setting. As antibiotic resistance to current therapies becomes more common, culture may become important to determine antibiotic susceptibility.

4.2. Non-endoscopic tests
4.2.1. Urea Breath Test

The UBT relies on the ability of *H. pylori* to hydrolyze urea into ammonia and bicarbonate. Bicarbonate is rapidly absorbed into the bloodstream where it is converted to water and carbon dioxide. Labeling urea with ^{13}C or ^{14}C allows detection of labeled CO_2 in the patient's exhaled breath. The ^{13}C-urea breath test utilizes a non-radioactive isotope and breath samples are analyzed by mass spectrometry. The absence of radioactive material allows this test to be used in pregnant women and children. Until recently, a test meal was needed which lengthened test duration from 30 to 60 minutes. However, the use of a citric acid rapid-release tablet has shortened the duration of the test to 10 minutes while maintaining high accuracy (27). Using infrared spectrometry rather then mass spectrometry may make this less expensive for hospitals outside of research centers (28). Advantages of the ^{14}C-urea breath test are that it does not require a test meal and it can be easily analyzed in less than 30 minutes. Although the amount of radiation from the ^{14}C is equivalent to 1/60 of a chest radiograph, it is a radioactive compound and therefore is not recommended in pregnant women and children (29).

The sensitivity and specificity of both UBTs is above 90% (31). As with any test for active infection, the sensitivity of this test can be adversely affected by recent proton-pump inhibitor use. One study showed that 33% of patients with *H. pylori* developed false-negative results on UBT after a 28-day course of proton-pump inhibitor therapy. Most patients (97%) without eradication were positive after 1 week and all were positive after 2 weeks.

Currently it is recommended that patients wait at least 4 to 6 weeks after completion of proton pump-based eradication therapy before being retested (30).

4.2.2. Serology

Serum-based assays detect IgG antibodies against *H. pylori*. Only IgG-based serologic tests are reliable because results from IgM or IgA serological tests are not always reproducible (31-33). The enzyme-linked immunosorbent assay (ELISA) is commonly used in commercial and hospital laboratories and yields a titer. ELISA assays utilize enzyme labeled anti-immunoglobulins that are detected by the appearance of color upon addition of a proper substrate (25). The rapid office-based serologic tests also test for IgG antibodies. These qualitative tests have the advantage of rapid results (about 5-10 minutes). This test is most useful for clinicians who need immediate results and do not have the volume of samples to justify ELISA testing (34). In general, tests using a fingerstick whole blood sample are less accurate than those using spun serum samples (35).

A major advantage of the antibody-based test is that the sensitivity is not affected by use of proton pump inhibitors, bismuth containing compounds or antibiotics. The disadvantage is that these tests cannot distinguish between current or past exposure to infection. Antibodies can persist for months to years after successful *H. pylori* eradication. Antibody-based tests should not be used to verify eradication of *H. pylori* (35).

4.2.3. Stool Antigen

This test is appealing because it is relatively easy to perform, non-invasive and does not require special equipment. A stool sample is evaluated for *H. pylori* antigens and results can be available within 1.5 hours. The sensitivity and specificity of this test in the initial diagnosis of *H. pylori* are approximately 89% and 77% respectively. A European multi-center study determined that the *H. pylori* stool antigen test yielded a sensitivity (95.6%) and specificity (94.7%) similar to the UBT used as the gold standard, when tested 4 weeks after eradication therapy. However, a more recent study in Spanish patients found that at 6 weeks and 6 months after eradication therapy the sensitivity was 70.4% and 50%, respectively. The specificity was 81.6% and 79.3% at 6 weeks and 6 months, respectively (36,37). At this time the stool antigen test can be used for the initial diagnosis of current *H. pylori* infection, but its role for post-treatment testing is unclear.

Patients with a new or recurrent peptic ulcer can undergo *H. pylori* testing with serology, urea breath test or stool antigen. The rapid urease test and histological evaluation can be utilized in patients undergoing endoscopic evaluation. Testing for eradication of *H. pylori* infection should occur at least 4-6 weeks after completion of therapy. The best tests in this setting are the urea breath test, endoscopy with rapid urease testing or histological examination of biopsy specimens. The accuracy of the stool antigen test in the post-treatment setting is still unclear. Patients who have failed first line antibacterial therapy can be considered for culture and sensitivity testing

Table 2. Treatment of *H. Pylori*

Therapy
FDA Approved Triple Therapies

BMT triple therapy for 14 days

- Bismuth subsalicylate 2 tabs qid
  - Metronidazole 250 mg qid
  - Tetracycline 500 mg qid + H₂RA for additional 4wks
- LAC (approved for 10 days and 14 days)
  - Lansoprazole 30 mg bid
  - Amoxicillin 1g bid
  - Clarithromycin 500 mg bid
- OAC for 10 days
  - Omeprazole 20 mg bid
  - Amoxicillin 1g bid
  - Clarithromycin 500mg bid

  - EAC for 10 days
  Esomeprazole 40 mg qd
  Amoxicillin 1g bid
  Clarithromycin 500 mg bid

Emerging and Alternative Therapies
  RBC-AC: Ranitidine Bismuth Citrate,
   Amoxicillin, Clarithromycin
  M-PPI-C: Metronidazole, PPI, Clarithromycin
   (without Metronidazole resistance)
    BMT-PPI: BMT + PPI x 14 days

by endoscopy or retreated with another approved multiple-drug regimen.

5. THERAPIES (Table 2)

5.1 First Line Therapies

The most effective FDA-approved regimens for eradication of *H. pylori* are the proton pump-based triple therapies and the bismuth-metronidazole-tetracycline combination therapy: (1) bismuth subsalicylate, metronidazole, and tetracycline [BMT] (2) lansoprazole, amoxicillin, clarithromycin [LAC]; (3) omeprazole, amoxicillin, clarithromycin [OAC] and most recently esomeprazole, amoxicillin, clarithromycin [EAC]. These regimens have eradication rates from 85 to 90%. A recent meta-analysis showed intention-to-treat cure rates of 75-85% for these regimens (38). Length of treatment is 14 days for BMT, 10 or 14 days for LAC, 10 days for OAC and EAC. In Europe the following regimens are recommended: a standard dose proton pump inhibitor and (1) metronidazole or tinidazole plus clarithromycin; (2) amoxicillin plus clarithromycin; (3) amoxycillin plus metronidazole. The European Maastricht Consensus developed guidelines that indicate seven days of treatment was adequate for effective (>85-90%) *H. pylori* eradication in the European population. This is in contrast to the 10 or 14-day treatment regimens approved by the FDA, which are based on clinical trials in the U.S. The duration differences in the effectiveness of *H. pylori* eradication treatments in the U.S. and Europe are not understood; compliance and antimicrobial resistance have been excluded when detailed analyses of clinical trials have been conducted.

Many studies have examined efficacy of shorter treatment regimens. A meta-analysis of short (7 days) versus standard therapy (10-14 days) with a PPI, clarithromycin and either metronidazole or amoxicillin showed intention to treat eradication rates of 72% for seven days and 81% for 14 days of therapy (39).

Causes of treatment failure include medication non-compliance and antibiotic resistance. A recent study in the U.S. showed the resistance rate to clarithromycin was 12 % by Etest antibiotic strips and 10.6% by agar dilution. Metronidazole resistance was 39% by Etest antibiotic strips and 21.6% by agar dilution. This study showed no difference in antibiotic resistance in different geographic regions. The high frequency of antibiotic resistance may indicate a need for antimicrobial susceptibility testing prior to *H. pylori* therapy in the future (40).

5.2. Second Line Therapies

If a patient fails initial first-line therapy, then one can use another first-line therapy for retreatment. For example, if a PPI-based triple therapy was initially used, then BMT therapy can be used for retreatment. A recent pooled analysis of alternative or second-line treatment regimens showed that PPI-based triple therapy, ranitidine bismuth-based triple therapy and quadruple therapy had retreatment eradication rates of 69.8%, 80.2%, and 75.8% respectively. The ranitidine bismuth-based triple therapy and quadruple therapy eradication rates were similar and significantly higher than that of PPI-based triple therapy. This study also demonstrated that eradication rates were higher when two new antibiotics were used as opposed to one. This study was limited since it did not consider factors such as drug dose, treatment duration, intervals between first and second line therapies and anti-microbial resistance of different *H. pylori* strains, but it does suggest that ranitidine bismuth-based triple therapy and quadruple therapy are very effective second-line therapies. Also, adding new antibiotic agents may have some utility in improving eradication rates (41).

6. NSAIDS AND *HELICOBACTER PYLORI*

H. pylori and NSAIDs together account for nearly all gastroduodenal ulcers (42-45). There continues to be much debate on the role of *H. pylori* in NSAID-associated ulcers. Some studies have shown that patients with NSAID-associated gastric ulcers have lower rates of *H. pylori* infection and less gastritis than patients with non-NSAID gastric ulcers. The gastritis found in these patients is secondary to *H. pylori* and not NSAID ingestion. Therefore, ulcers associated with NSAID use arise by a different mechanism than *H. pylori*-associated ulcers (46). Even though the mechanisms may be different, the question remains as to whether *H. pylori*-infected individuals are at greater risk for development of gastroduodenal ulcers when taking NSAIDs. *H. pylori* infection is associated with the presence of an increased inflammatory response represented by neutrophils. Furthermore, the presence of neutrophils is associated with an increased incidence of ulceration in long-term NSAID users (47). This suggests that the eradication of *H. pylori* may protect long-term NSAID users from the risk of ulcers. One study showed that when *H. pylori* gastritis was present, there

was more mucosal damage in long-term aspirin users than in their non-infected counterparts (48). Chan and colleagues studied the effect of *H. pylori* eradication with BMT prior to NSAID therapy. After 8 weeks of Naproxen therapy, only 3% of patients with successful *H pylori* eradication developed ulcers compared to 26% of patients still infected with *H. pylori* (49). It has been speculated that bismuth contains additional mucosal healing properties independent of *H. pylori* eradication. Another study suggested that *H. pylori*-infected individuals have an almost two-fold increased risk of bleeding peptic ulcer compared with NSAID users without *H. pylori* (50). The HELP NSAIDs study in the U.K. suggested that eradication of *H. pylori* might actually impair healing of gastric ulcers in patients taking NSAIDs. Differences in this study compared to the Chan study were that these patients were chronically taking NSAIDs and different NSAIDs were included (51).

Another study done by Chan and colleagues evaluated whether *H. pylori* eradication therapy or omeprazole alone was more effective in preventing recurrent upper gastrointestinal bleeding in patients taking 80 mg of aspirin or naproxen 500 mg twice daily. In patients taking aspirin 80 mg per day the probability of recurrent bleeding during a six-month period was 1.9% in the eradication group versus 0.9% in patients who received omeprazole only. This was in contrast to the naproxen group in which 18.8% of patients receiving eradication therapy had recurrent bleeding versus 4.4% of patients in the omeprazole group. This suggests that omeprazole is as effective as eradication of *H. pylori* in preventing recurrent upper gastrointestinal bleeding in patients taking low-dose aspirin. However, omeprazole appeared to be superior to eradication of *H. pylori* in prevention of gastrointestinal bleeding in patients taking conventional NSAIDs (52). Further studies are needed to confirm these differences between aspirin and NSAIDs in patients infected with *H. pylori*, particularly related to gastrointestinal bleeding.

7. *HELICOBACTER PYLORI* AND NONULCER DYSPEPSIA

Nonulcer dyspepsia (NUD) is persistent pain or discomfort centered in the upper abdomen without evidence of organic disease after diagnostic evaluation (53). The link between *H. pylori* and NUD has been heavily debated. McColl et al. showed a statistically significant improvement in symptoms in 21% of patients who received *H. pylori* eradication therapy compared to 7% of patients given omeprazole alone (54). Other multi-center studies have shown some symptom resolution but these findings were not statistically significant at long-term follow-up. A recent meta-analysis of all randomized, controlled trials showed that eradication of *H. pylori* did little to improve long-term resolution of symptoms of NUD (55). The current data do not support empiric treatment of all *H. pylori*-positive patients with NUD but a smaller proportion may have sustained benefit from *H. pylori* eradication.

8. *H. PYLORI* AND GASTRIC MALT LYMPHOMA AND GASTRIC ADENOCARCINOMA

In addition to its well-documented association with peptic ulcer disease, *H. pylori* infection has also been associated with gastric MALT lymphoma and gastric adenocarcinoma. In 1994 the International Agency for Research on Cancer (IARC) acknowledged the role of *H. pylori* in gastric cancer and classified *H. pylori* as a Group 1, or definite human carcinogen with an estimated attributable risk of 50 to 60% (56). Three large scale cohort studies showed that people chronically infected with *H. pylori* have a 2-6 fold higher risk of developing gastric cancer (57-59). Other recent cohort and case control studies have revealed conflicting results with an odds ratio (OR) of developing gastric cancer ranging from 0.54 to 13.3. These studies have been summarized in a recent meta-analysis of 19 studies including 2,500 cases and 4,000 controls. The OR for developing gastric cancer in *H. pylori*-infected persons was 1.92 (95% Confidence Interval (CI) 1.32 – 2.78) (60). Another recent meta-analysis combining 42 observational epidemiologic studies confirmed the modest risk with a pooled OR of 2.04 (95% CI, 1.69-2.45) (61). *H. pylori* infection is an important risk factor, but it alone is not sufficient for gastric cancer development. Its exact role in the pathogenesis of gastric malignancy is the subject of numerous worldwide investigations.

Gastric lymphomas are the most common extranodal lymphoma, but they comprise less than 5% of gastric cancers. Gastric MALT (mucosa-associated lymphoid tissue) lymphomas are a heterogeneous group of B-cell proliferations and commonly found in the setting of *H. pylori* infection. These MALT lymphomas have been classified as extranodal marginal zone B-cell lymphomas of the MALT type (REAL classification) (62). MALT lymphomas are detected at a median age in the fifth decade. The male to female ratio is 1.5:1. As a general rule these are slow-growing, indolent tumors that tend to remain localized at their site of origin for years. *H. pylori* infection is found in almost all (>85%) gastric MALT lymphomas. A large, nested case control study with over 230,000 patients showed that patients with gastric MALT lymphomas were more likely to have evidence of *H. pylori* infection compared to their matched controls (OR, 6.3: 95% CI, 2 to 19.9) (63).

8.1. Malt Lymphoma
8.1.1.Clinical and Endoscopic Presentation of Gastric MALT lymphoma

The clinical presentation of MALT lymphoma depends upon the size, location, and systemic spread of the tumor. Patients with low-grade MALT lymphoma may be asymptomatic or have varying degrees of dyspepsia. However, patients with systemic spread may present with bleeding, anemia from lymphoma ulceration, obstruction, weight loss, fever and night sweats. The endoscopic presentation varies from normal-appearing gastric mucosa to gastric erythema, ulcerations, diffuse gastric nodules, and larger malignant appearing masses. If gastric MALT lymphoma is suspected, gastric mapping should be performed with ten gastric biopsies, 4 in the antrum and 6 in the corpus, to further define the histologic extent of the disease (64). The increasing use of gastric biopsies to evaluate dyspepsia has led to an increased number of gastric MALT lymphomas being diagnosed at a very early stage, prior to endoscopic mucosal abnormalities.

8.1.2. Pathogenesis of MALT Lymphoma

The normal adult gastric mucosa contains no organized lymphoid tissue. *H. pylori* stimulates antigen-sensitizing T – cells which increases the number of plasma cells and lymphocytes. These cells organize into lymphoid follicles with clearly-defined germinal centers and mantle zones. These lymphoid follicles become prominent with spilling of B cells into the gastric epithelium which is characteristic of gastric MALT lymphomas. The follicles are induced and sustained by *H. pylori* antigen-sensitized T cells. This suggests that gastric MALT lymphomas develop in response to chronic antigenic stimulation by *H. pylori*.

Initially, the survival of these monoclonal B cell populations is dependent upon the *H. pylori*-sensitized T cells. At this early stage, these gastric MALT lymphomas can be cured by eradication of *H. pylori*. Over time these monoclonal B cell populations lose their dependence on the *H. pylori*-sensitized T cells. When this occurs, these monoclonal B cell populations acquire the independent growth potential of malignant lymphomas.

8.1.3. Histologic Features of Gastric MALT Lymphoma

It was first recognized in 1983 that certain extranodal lymphomas had clinical and histologic features more consistent with MALT than nodal lymphoid tissue (65). The histologic features of low-grade gastric MALT lymphoma are similar to that of the Peyer's patch, with the MALT lymphoma cells surrounding active B-cell follicles in the marginal zone (66-67). These B-cell MALT lymphomas share the same immuno-phenotype (CD20+, CD21+, CD35+, IgM+, IgD-) as normal marginal zone B-cells (68).

The histologic criteria for diagnosis of gastric MALT lymphoma include: (1) formation of follicular centers; (2) diffuse inter-follicular infiltrates of light chain restricted monotypic centrocyte-like B cells; (3) infiltrates of plasma cells; and (4) the presence of lympho-epithelial lesions with centrocyte-like cells invading a gastric gland (69-71). Unfortunately, lesions that meet the above criteria range from low-grade clinically indolent tumors (formerly called pseudolymphomas) to more aggressive high grade tumors.

8.1.4. Evaluation of gastric MALT Lymphoma

After the initial histologic diagnosis of gastric MALT lymphoma is confirmed, the clinician must determine the local and distant tumor burden. The first step usually involves endoscopy with gastric mapping biopsies to determine the local extent of the tumor. Endoscopic ultrasound (EUS) should be used in conjunction with gastric mapping as it is the best method to stage the horizontal extension of the tumor, depth of tumor invasion, and involvement of paragastric lymph nodes. Barium radiographs of the upper gastrointestinal tract can show thickened gastric folds or mass lesions, but add little to EUS (72-75).

Distant spread of tumor is associated with a higher grade of tumor. Patients with high-grade tumors need more aggressive treatment than *H. pylori* eradication alone, including surgical resection and/or chemotherapy. A CT scan of the abdomen is recommended to rule out regional lymph node involvement. Most experts also recommend a bone marrow biopsy. If bone marrow biopsy results are positive for tumor, these patients should be referred to an oncologist for evaluation of therapeutic options.

The strongest evidence for the role of *H. pylori* infection in gastric MALT lymphoma is the regression of the tumor when *H. pylori* is eradicated. This has been demonstrated in multiple studies. Therefore all patients with MALT lymphoma should be evaluated for *H. pylori*.

Some laboratories perform immunohistochemical and molecular studies to document the monoclonality of tumors. However, there can be a delay between histologic improvement and loss of monoclonality. The meaning of the persistence of the monoclonal band despite absence of histologic evidence of lymphoma is unknown (76). Many molecular events thought to be important in the development of gastric MALT lymphoma are currently being studied, including the p53 mutation, bcl-2 gene rearrangement, immunoglobulin H gene rearrangement, replication error phenotype (RER+), trisomy 3, and other chromosomal translocations and deletions (77-81).

8.1.5. Treatment of gastric MALT Lymphoma

The patient with low-grade gastric MALT lymphoma and *H. pylori* infection should undergo *H. pylori* eradication therapy with confirmation of *H. pylori* eradication following treatment. In addition to *H. pylori* eradication the treatment options for gastric MALT lymphoma include chemotherapy, radiotherapy, and surgery. Several studies have indicated that in low grade gastric MALT lymphoma with disease confined to the stomach, *H. pylori* eradication alone can cause tumor regression in 60-100% of patients (71, 82-88). Response to eradication treatment is not predicted by age, gender, or endoscopic appearance at diagnosis. However, the stage of the tumor as determined by EUS can predict the response to treatment. When tumor was limited to the mucosa or submucosa, tumor regression was seen in 60% at 6 months, 79% at 12 months, and 100% at 14 months (88). The Ann Arbor staging system stages most lesions at a stage EI or EII at diagnosis. Although eradication of *H. pylori* was initially proposed only for those patients with low grade B-cell gastric MALT lymphoma stage E1, it is not yet known whether later stages of MALT lymphoma may also respond to eradication therapy (71).

Patients without evidence of extragastric disease should be offered treatment for *H. pylori* infection as first line therapy for gastric MALT lymphoma. After treatment patients should have frequent follow-up visits. Some centers recommend follow up at 3, 6, 9, and 12 months for endoscopic evaluation and gastric biopsy mapping to document tumor status. Patients with tumor regression at 1 year should have endoscopic follow-up every 6-12 months indefinitely to document continued resolution. If tumor regression is not seen within 12 months of eradication therapy, the patient should be referred to an oncologist for consideration of other therapeutic options.

Many long-term follow-up studies after *H. pylori* eradication are still in progress, so it is not clear if, or how often gastric MALT lymphoma recurs after complete remission. Neubauer et al. followed 50 patients for a median of 24 months. Forty patients (80%) had a complete remission, and only 4 relapsed within the 24-month follow-up period. Another study documented complete remission in all 17 patients with stage E1 MALT lymphoma, but 2 patients relapsed within 15 months, with one relapse occurring when the patient was reinfected with *H. pylori* (88). The presence of lymphoid aggregates and monoclonality may persist for 2 years after successful *H. pylori* eradication, even in the absence of macroscopic evidence of tumor or histologic evidence of lymphoma (89). Due to limited experience, the optimal length of follow-up must be determined by the clinician often in consultation with an oncologist and/ or pathologist.

8.2. Gastric Adenocarcinoma

8.2.1. Clinical and Endoscopic Presentation of Gastric Adenocarcinoma

Patients with gastric adenocarcinoma are often asymptomatic until the tumor is in an advanced stage. Symptoms are nonspecific, but include epigastric pain, nausea, vomiting, early satiety, bloating, and weight loss. Patients with locally advanced disease may present with gastrointestinal hemorrhage or obstruction. Patients with symptoms suggestive of gastric malignancy should be evaluated with upper gastrointestinal endoscopy or double contrast barium radiography.

Gastric cancer can be evaluated by either endoscopy with biopsy or double-contrast barium radiography. Upper gastrointestinal endoscopy with biopsy has a sensitivity of 95% and specificity of 99% in detecting gastric cancer. All gastric ulcers should be biopsied at the base and at 4 quadrants along the ulcer edge. Sensitivity may be improved with cytologic brushing in conjunction with forceps biopsy. However, since the sensitivity is not 100% all ulcers should be re-evaluated with upper endoscopy to confirm healing. Double contrast barium radiography of the upper gastrointestinal tract has a sensitivity of over 90% in the detection of gastric adenocarcinoma. Characteristic radiographic findings include an asymmetric ulcer crater, nodular folds radiating from an ulcer, loss of gastric distensibility, and mass lesions. Unfortunately, tissue samples cannot be obtained with radiography.

8.2.2. Pathogenesis of Gastric Adenocarcinoma

H. pylori has been implicated in both tissue types of gastric adenocarcinoma: intestinal and diffuse. Intestinal and diffuse types account for 80% and 20% respectively of gastric adenocarcinoma (93). The diffuse type of gastric cancer may be more frequently seen in low-risk populations, such as in the U.S., whereas the intestinal type is more common in countries where gastric cancer is endemic. The intestinal type of gastric cancer is more likely to be associated with atrophic gastritis and intestinal metaplasia, and has a better prognosis than the diffuse type. While the diffuse type of gastric cancer has no known precursor lesion, the intestinal type appears to develop in a background of chronic gastritis. *H. pylori* has been implicated as the initiator of this chronic gastritis.

Chronic gastritis appears to have two topographical distributions: (1) the non-atrophic pattern usually has inflammation dominant in the antrum which is more common in developed regions and is associated with a higher risk of duodenal ulcer and a lower risk of gastric cancer, and (2) the multi-focal atrophic pattern with a diffuse inflammatory process involving the entire stomach which is more common in low socioeconomic populations and is associated with a higher incidence of gastric cancer (94).

Infection with *H. pylori* alone is not sufficient to cause gastric cancer in man. Other contributing factors include dietary factors, host genetics, and environmental exposures. Gastric cancer has been linked to diets that are high in carbohydrates and salt-preserved foods, whereas fruits and vegetables seem to confer a protective effect (95-97). The hypothesis is that fruits and vegetables protect against gastric cancer through their natural antioxidants. Vitamin C levels have been shown to be negatively associated with progression of precancerous lesions to gastric cancer (98). Furthermore, *H. pylori* infection has been associated with decreased gastric ascorbic acid levels, which normalize with eradication of the infection.

Intestinal type gastric cancer probably occurs through a multi-step cacinogenesis pathway, which begins with chronic gastritis. The recognition that virtually all those infected with *H. pylori* developed chronic gastritis and association of the infection with premalignant gastric lesions helped implicate this infection as a potential initiator of chronic gastritis and subsequent premalignant lesions (99). Correa proposed that the gastric mucosa evolves through a temporal sequence starting with chronic gastritis and ending with gastric cancer (100). The actual sequence of events is thought to be chronic gastritis, multi-focal atrophic gastritis and intestinal metaplasia, dysplasia, and finally ending with gastric cancer. Several studies have shown that atrophic gastritis is associated with decreased gastric acid secretion and luminal levels of vitamin C (101-102). It is theorized that the decreased antioxidant level in the gastric lumen allows DNA to be damaged by reactive oxygen species, which leads to the development of intestinal metaplasia. Intestinal metaplasia is the precursor lesion to gastric cancer. The extent and distribution of intestinal metaplasia has been correlated to cancer risk (103).

8.2.3. Animal Model for Gastric Cancer

Mongolian gerbils were the first animal model to successfully show a link between *H. pylori* infection and gastric cancer. Recent studies showed that Mongolian gerbils infected with *H. pylori* develop severe chronic active gastritis, ulcers, and intestinal metaplasia about 26 weeks after onset of infection (104). At 62 weeks 37% of these *H. pylori*-infected gerbils had adenocarcinoma of the stomach. These animals are being studied to help determine whether premalignant gastric lesions can be

reversed and whether gastric cancer can be prevented by eradication of *H. pylori*. Significant differences exist between *H. pylori* infection in humans and rodents. The ulcers that occur in Mongolian gerbils are more proximal and multiple versus the more distal and usually solitary lesions seen in humans. However, this remains the best animal model for studying gastric carcinogenesis.

8.2.4. Management of Intestinal Metaplasia

The exact role of *H. pylori* infection in the evolution of gastric cancer is still unclear. Infection with *H. pylori* leads to chronic inflammation of the gastric mucosa and eradication of the infection leads to improvement in gastric inflammation. Whether *H. pylori* eradication will result in regression of premalignant features such as atrophy and intestinal metaplasia remains unclear.[105] Several small pilot studies have examined the histologic effects of *H. pylori* eradication. These studies have shown conflicting results on histologic regression after *H. pylori* eradication, (105-110) which are likely due to small sample size, lack of a control group, and short term follow-up. A recent prospective study randomized 587 *H. pylori*-infected patients to *H. pylori* eradication treatment versus placebo and followed them for one year to observe the effects on pre-malignant gastric lesions (115). Endoscopic evaluation with biopsies performed one year after eradication treatment showed a significant reduction in acute and chronic gastritis, but there were no differences in intestinal metaplasia between the two groups. Increased gastric atrophy was seen in the corpus of *H. pylori*-infected patients. These results suggest that *H. pylori* eradication treatment prevents progression of pre-malignant lesions, but does not cause regression of these lesions.

A non-randomized study showed that *H. pylori* eradication treatment after endoscopic mucosal resection for early gastric cancer prevents metachronous gastric cancers (112). This study suggests that *H. pylori* might also be a promoter of gastric cancer and not just an initiator.

Several long-term randomized, prospective chemoprevention trials are in progress to examine the effects of *H. pylori* eradication and vitamin supplementation. The first of these trials was recently reported by Correa et al. This study included 852 Columbian patients with chronic atrophic gastritis or intestinal metaplasia and randomized them to receive *H. pylori* eradication therapy and/or dietary supplementation with ascorbic acid, beta-carotene, or their corresponding placebo (113). Endoscopic surveillance with biopsy was performed at 3 and 6 years while taking the vitamin supplements or placebo. Gastric biopsy specimens taken at baseline were compared to the specimens taken at 3 and 6 years with respect to regression or progression of precancerous lesions. Patients receiving placebo had a histologic regression rate of 7% while the treatment groups had a regression rate ranging from 19-29%. This demonstrates that *H. pylori* eradication and vitamin supplementation can cause histologic regression, but there appears to be little benefit to combining these treatments. Progression of lesions to a more advanced stage occurred at a similar rate in all groups. There appears to be a point of

no return in the carcinogenesis cascade. Treatment of patients beyond this point does not cause regression or prevent progression of precancerous lesions. The exact point at which this occurs remains to be defined. The authors conclude that all three-treatment regimens were effective with no additional benefits of combining regimens. This is the first study to document pre-malignant lesion regression with anti-oxidant / vitamin supplementation.

8.2.5. Cost Effectiveness of Screening for Gastric Cancer

Gastric cancer is the second most common cause of cancer death in the world (114). In the U.S. most patients present with local or distant spread of tumor at diagnosis because routine screening is not performed. Many authorities therefore suggest that it is important to follow-up incidental biopsy findings of atrophic gastritis and intestinal metaplasia, as they are precursor lesions to gastric cancer. Unfortunately there are no clinical signs or symptoms indicating the presence of these lesions and they are not detectable with routine endoscopy. Intestinal metaplasia can be seen endoscopically if the gastric mucosa is stained with methylene blue (90-92). Therefore, it is possible to direct endoscopic biopsies to those areas that stain positive for intestinal metaplasia.

With 5 year survival rates in most countries below 20%, there is a considerable public impact to be made by early diagnosis and treatment of gastric cancer (115). In Japan where a mass screening program for detection of early gastric cancer is in place, early detection has allowed a resection rate approaching 90% with a five year survival of 37% (116). Further studies are needed to identify those populations at increased risk of gastric cancer so that screening programs may be targeted to those populations.

The question remains whether large scale screening for gastric cancer is cost-effective. Parsonnet et al. examined this question using a sensitivity analysis on three U.S. ethnic groups: Caucasians with a low incidence of gastric cancer (6.8/100,000), African – Americans with a moderate incidence (12.6/100,000), and Japanese – Americans with a high incidence (28.5/100,000) (117). In patients at high risk for gastric cancer, treatment of almost any efficacy is cost effective, but in patients with low risk such as Caucasians, the treatment efficacy must reach 20-30% before it is cost effective. The overall cost of gastric cancer screening was $25,000 per year of life saved, but ranged from $4,500 in Japanese-Americans to $34,900 in Caucasians. Therefore, a cost-effective approach to screening for gastric cancer depends upon the incidence in the population being studied and the cost of effective treatments. Further studies are needed to define those patients where screening for gastric cancer is cost effective.

Until further studies defining the efficacy of *H. pylori* eradication in the prevention of gastric cancer, the individual clinician must establish his/her own guidelines regarding whom to treat. Currently it seems reasonable to treat first degree relatives of patients with gastric cancer

and immigrants from areas with a high incidence of gastric cancer.

9. PERSPECTIVE

H. pylori is accepted as the single most important cause of peptic ulcer disease; eradication of the infection markedly reduces recurrence of both gastric and duodenal ulcers. It is implicated as a significant factor in the pathogenesis of gastric malignancy. Several international multi-center studies indicate that eradication of *H. pylori* infection will probably not result in sustained resolution of symptoms in the majority of patients with non-ulcer dyspepsia. Whether *H. pylori* infection is important in esophageal disease remains uncertain. Recent studies suggest that the infection is important in aspirin-related gastric injury and less important in disorders associated with non-steroidal anti-inflammatory gastroduodenal disease. Accurate tests are readily available for diagnosis of the infection. Effective antibiotic regimens have been developed for eradication of *H. pylori* infection. The focus of many studies is now on how *H. pylori* infection results in the wide spectrum of gastroduodenal disorders that are linked to it.

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