Association between Helicobacter pylori infection and gastrointestinal malignancy

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INTRODUCTION

Since the discovery of *Helicobacter pylori* in the 1980s, much has been learned about this gram-negative spiral bacteria and its associated disease states. In 1994, the National Institutes of Health Consensus Conference recognized *H. pylori* as a cause of gastric and duodenal ulcers. Later that year, the International Agency for Research on Cancer declared *H. pylori* to be a group I human carcinogen for gastric adenocarcinoma [1]. There is also evidence that *H. pylori* infection is a risk factor for gastric mucosa-associated lymphomas (MALT lymphomas). (See "Clinical presentation and diagnosis of primary gastrointestinal lymphomas".)

Despite these clear associations, there is marked individual variability in the outcomes of *H. pylori* infection, with most patients having a non-neoplastic rather than neoplastic process. *H. pylori* infection is associated with a complex interaction between genetic, environmental, and bacterial factors, which potentially explains the different outcomes possible following infection. Until these factors are better defined and their interactions better understood, practitioners should limit testing for and treating *H. pylori* to those situations where there is evidence to support a clinical benefit.

GASTRIC CANCER

Gastric cancer is one of the most common causes of cancer-related death in the world [2] (see "Epidemiology of gastric cancer"). Gastric cancers can be categorized by site of occurrence: gastroesophageal junction, proximal stomach, and distal stomach (body and antrum). In the 1930s in the United States, distal cancers were the most common. Over the subsequent 70 years, the incidence of gastric cancer has fallen primarily due to a reduction in distal cancers. In comparison, an increase in the incidence of gastroesophageal junction and proximal cancers has been noted during the past several decades [3,4]. These observations suggest that gastroesophageal and proximal gastric cancers share a common pathogenesis, which is distinct from that of distal cancers [5].

Adenocarcinomas, which accounts for more than 90 percent of tumors arising in the stomach, are of two distinct morphologic types: intestinal-type and diffuse. A sequence of steps with phenotypic changes in the gastric mucosa has been hypothesized as a model for carcinogenesis of intestinal type adenocarcinomas: superficial gastritis; chronic atrophic gastritis; intestinal metaplasia (picture 1); dysplasia; and finally carcinoma (algorithm 1) [6]. No similar sequence has been described for the diffuse type. (See "Gastric cancer: Pathology and molecular pathogenesis".)

H. pylori can cause chronic active gastritis and atrophic gastritis, early steps in the carcinogenesis sequence [7,8]. In animal models, *H. pylori* infection has induced gastric adenocarcinoma [9]. Furthermore, a number of studies in humans have demonstrated a clear association between *H. pylori* infection and gastric adenocarcinoma [10-12]. The link has been demonstrated in both the intestinal and diffuse subtypes of gastric cancer [10,13].

The relationship between *H. pylori* infection and gastric carcinogenesis in humans can be illustrated by the following observations:

- *H. pylori* has been identified histologically in the uninvolved mucosa from stomachs harboring cancers or precancerous changes (eg, atrophic gastritis with or without accompanying intestinal metaplasia) [14,15].

- Epidemiologic studies demonstrate a strong correlation between *H. pylori* seropositivity and gastric cancer. As an example, the EUROGAST study of 17 populations from 13 different countries (11 European countries, the United States, and Japan) found a sixfold increased risk of gastric cancer in *H. pylori*-infected populations compared with uninfected populations [16]. Similar findings have been noted in nested-case control studies in which the stored serum of patients with known gastric adenocarcinoma and that of matched controls were tested for *H. pylori* IgG antibody. *H. pylori* infection was associated with odds ratios ranging from 2.8 to 49 and attributable risks of 46 to 63 percent [12,17-20]. In a

nested case control study of Japanese Americans living in Hawaii, for example, *H. pylori* seropositivity was present in 94 percent of patients with gastric cancer compared with 76 percent of matched controls; the odds ratio was 6.0 [18].

- Two meta-analyses of cohort and case control studies examining the relationship between *H. pylori* seropositivity and gastric cancer found that *H. pylori* infection was associated with a twofold increased risk for developing gastric adenocarcinoma [10,11]. The relative risk for gastric cancer was greatest for younger patients (9.29 at age less than 29) in whom the absolute risk is still quite low [10].

One of the largest prospective studies addressing *H. pylori* and cancer risk included 1526 Japanese patients of whom 1246 had *H. pylori* infection [21]. Patients underwent endoscopy with biopsy at enrollment and then between one and three years after enrollment. During a mean follow-up of 7.8 years, 36 patients developed gastric cancer (2.9 percent), all of whom were *H. pylori* infected. No uninfected patient developed cancer.

The International Agency for Research on Cancer estimates that 36 and 47 percent of all gastric cancers in developed and developing countries, respectively, are solely attributable to *H. pylori* infection. This accounts for almost 350,000 gastric cancers annually worldwide. One report indicated that of the 12.7 million new cancers occurring in 2008, the population attributable fraction due to infections was over 16 percent for *H. pylori* [22].

Despite the clear association between *H. pylori* and gastric adenocarcinomas, only a minority of infected individuals will develop gastric cancer. It is thought that modulation of the effects of infection by external, mostly environmental factors (and possibly strain differences in *H. pylori*, see below) influence whether infection results in a neoplastic or non-neoplastic process.

Role of H. pylori in carcinogenesis — Several hypotheses have been proposed to explain the role of *H. pylori* in carcinogenesis, although the exact mechanism is incompletely understood [23]. At present, it is believed that bacterial properties, host response, and environmental factors all play a role.

H. pylori strain differences — The strain of *H. pylori* also may be a determinant of its potential to cause cancer or ulcer disease. (See "Pathophysiology of and immune response to Helicobacter pylori infection", section on 'Bacterial strain differences'.)

Host immune responses — Host genetics that regulate the immune response and mucosal events that result from infection play important roles in gastric cancer development in chronically infected individuals.

Cytokine polymorphisms — Certain polymorphisms in IL-1 beta and other cytokines may confer an increased susceptibility to non-cardia gastric adenocarcinoma caused by *H. pylori* by inducing a hypochlorhydric and atrophic response to *H. pylori* infection [24-29]. An illustrative study compared IL-1 beta polymorphisms in 393 patients with gastric cancer with 430 controls [24]. Two specific polymorphisms (IL-1B-31T and IL-1RN*2) were associated with low acid secretion and gastric atrophy. The authors concluded that 38 percent of *H. pylori*-related gastric cancer could be attributed to the presence of these alleles. IL-1 beta, a potent inhibitor of gastric acid secretion, is upregulated by the presence of H. pylori.

A similar report compared polymorphisms in genes for several cytokines in patients with a variety of gastric and esophageal malignancies with a control population [25]. Proinflammatory genotypes of tumor necrosis factor alpha and IL-10 were associated with more than a doubling of the risk of non-cardia gastric cancer. Carriage of multiple proinflammatory polymorphisms of IL-1 beta, IL-1 receptor antagonist, tumor necrosis factor A, and IL-10 conferred even greater risk (OR 2.8 for one, 5.4 for two, and 27.3 for more than three). By contrast, these polymorphisms were not associated with an increased risk of esophageal or gastric cardia cancers.

These data suggest that gene polymorphisms influence cytokine expression, gastric inflammation, and risk for development of precancerous lesions in those infected with *H. pylori*. Infection with certain virulent bacterial strain types augments inflammation and cancer risk, supporting a complex interaction between host and bacterial in the development of GI pathology [30]. (See "Risk factors for gastric cancer", section on 'Genetic polymorphisms'.)

Neutrophil activation — One hypothesis has been demonstrated in vitro. CD11a/CD18- and CD11b/CD18-neutrophils, induced by *H. pylori* infection, interact with intercellular adhesion molecule-1 (ICAM-1), resulting in the migration of neutrophils to the site of infection and adhesion to the surface epithelium. The recruited neutrophils then produce inducible nitric oxide synthase and release nitric oxide and reactive oxygen metabolites, such as superoxide and hydroxyl ions, which in turn damage DNA. This is followed by mutation and malignant transformation. (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'Helicobacter pylori'.) *H. pylori* induces oxidative stress in epithelial cells [31].

Epithelial responses — *H. pylori* and the immune response induce altered rates of gastric epithelial cell growth and death, which involve various signaling pathways leading to apoptosis, proliferation, differentiation, and autophagy.

Apoptotic pathways — Two important processes in carcinogenesis are apoptosis (programmed cell death) and hyperproliferation [32]. Following severe DNA damage, apoptosis

occurs as a protective mechanism to prevent replication of mutated DNA. Atrophic gastritis with destruction and loss of the glands could be the result of apoptosis. This hypothesis is supported by the finding of an increased rate of antral apoptosis in *H. pylori*-infected subjects [33,34], which returns to normal following eradication therapy [33]. The mechanism by which *H. pylori* induces apoptosis is unclear. One study suggested that the organism causes apoptosis by both direct and indirect mechanisms [35]. In the latter circumstance, *H. pylori* appears to sensitize epithelial cells for apoptosis which is induced by proinflammatory stimuli (eg, tumor necrosis factor alpha). *H. pylori* enhances expression of the Fas receptor on gastric epithelial cells and may mediate apoptosis through signaling mechanisms related to the Fas death receptor [36]. Proliferating cells may be resistant to apoptosis. This would upset the balance between cell growth and death, leading to hyperproliferation and the promotion of neoplasia [37]. There is evidence of an increased amount of the anti-apoptosis protein, Bcl-2, in the setting of gastric dysplasia [38]. Other reports have found that apoptosis may be due to plasminogen activator inhibitor (PAI)-2, the expression of which is increased by *H. pylori*. PAI-2 is increased in gastric cancer [39]. An uncoupling of epithelial proliferation and apoptosis may be a strain-dependent phenomenon. Hyperproliferation has been seen in CagA-infected patients in whom apoptosis is not increased [40].

Cell signaling events — One report indicated that c-Src and c-Abl kinases sequentially phosphorylate CagA [41]. The two phosphorylation events need not occur on the same CagA molecule but are both required for the biological effects of CagA. Another 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 [42]. A potentially important observation is that the source of gastric cancer may not be from gastric epithelial cells themselves but rather from bone marrow-derived cells that differentiate into gastric epithelial cells in the presence of *H. pylori* [43]. If this observation is confirmed, it would have significant implications for the treatment of *H. pylori*-associated gastric cancer as well as other epithelial cancers associated with chronic inflammation. (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'The preneoplastic cascade'.)

Environmental factors

Interaction between H. pylori and diet — The consumption of salted food appears to increase the possibility of persistent infection with *H. pylori* infection [44,45]. In addition, a synergistic interaction between *H. pylori* infection and salted food intake to increase the risk of gastric cancer has also been reported in case control studies [46,47] (see "Bacteriology and epidemiology of Helicobacter pylori infection"). Animal studies also suggest that *H. pylori*

infection and high-salt intake act synergistically to promote the development of gastric cancer [48]. In one study in Mongolian gerbils, expression of the proinflammatory mediators, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), were significantly upregulated. Both iNOS and COX-2 overexpression have been demonstrated in gastric cancer [49-52]. On the other hand, there was no significant effect on these mediators in noninfected animals [53].

Studies suggest that *H. pylori* might affect other dietary associations with gastric cancer [54,55]. The potential protective effect of dietary antioxidants such as vitamins C and E and beta-carotene seems to be stronger in those infected by *H. pylori*, even though results are inconsistent. The risk of gastric cancer associated with red meat, processed meat, or endogenous formation of nitrosamines appears to be observed only in patients infected with *H. pylori*. A reported genetic polymorphism found to be protective against *H. pylori* carcinogenesis in mice, vitamin D3 upregulated protein 1, suggests a possible link between vitamin D deficiency and propensity for *H. pylori* infection to progress into gastric cancer in humans [56].

Hypochlorhydria and ascorbic acid — Another hypothesis involves a role for hypochlorhydria and ascorbic acid (algorithm 1) [6]. In the sequence of carcinogenesis from atrophic gastritis to metaplasia, loss of the acid-secreting parietal cells results in an elevated gastric pH. Nitrate-reducing bacteria proliferate in the stomach and, at the high pH, nitrite is formed, which can interact with other nitrogen-containing compounds and with carcinogens. Ascorbic acid may block this nitrosation reaction by scavenging nitrates and free radicals [6].

The following observations suggest a role for the relative lack of ascorbic acid in the pathogenesis of gastric cancer:

- The level of ascorbic acid in gastric juice is markedly reduced in the setting of chronic gastritis, elevated gastric pH, and *H. pylori* infection; this may be due to impaired secretion of ascorbic acid due to the chronic gastritis [57].
- Patients with intestinal metaplasia have lower serum levels of ascorbic acid compared with controls [58].
- Low levels of dietary ascorbic acid can lead to progression of precancerous lesions to dysplasia and cancer in high-risk individuals [59]. Ascorbic acid ingestion was associated with a decreased risk of gastric cancer in case-control studies [60,61].

Hemoglobin A1c — Other host factors may contribute to the development of gastric cancer in *H. pylori*-infected individuals. A study of 2603 Japanese subjects aged ≥40 years were stratified into four groups according to baseline hemoglobin A1c (HbA1c) levels (≤4.9 percent, 5.0 to 5.9 percent, 6.0 to 6.9 percent, and ≥7.0 percent) and followed up prospectively for 14 years [62].

During the follow-up, 97 subjects developed gastric cancer. The age- and sex-adjusted incidence of gastric cancer significantly increased in the two higher HbA1c level groups. This association remained substantially unchanged even after adjusting for the confounding factors including *H. pylori* seropositivity. Among subjects who had both high HbA1c levels (≥6.0 percent) and *H. pylori* infection, the risk of gastric cancer was dramatically elevated. The mechanism whereby elevated blood sugar enhances the risk of gastric cancer is unclear but the risk of other cancers has been shown to be increased in those with diabetes mellitus.

Obesity — Obesity has been reported to be associated with gastric cardia adenocarcinoma [63,64]. A mechanism explaining this association has not been established but it may be related to *H. pylori* infection as there is an apparent increased prevalence of *H. pylori* infection in patients with obesity. Another possibility is that hyperglycemia increases the risk of developing gastric cancer [62]. 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.

Importance of other factors — Gastric carcinogenesis cannot be explained by *H. pylori* infection alone as illustrated by the following observations:

- Only a small fraction of *H. pylori*-infected individuals develop cancer.
- The incidence of gastric cancer varies regionally despite similar prevalence of *H. pylori* worldwide [5,65].
- The gastric cancer risk is not increased in patients with *H. pylori*-related duodenal ulcer disease. To the contrary, in a study from Sweden evaluating the incidence of gastric cancer in patients previously hospitalized for gastric or duodenal ulcer, the incidence was significantly **decreased** in the group with duodenal ulcer (standardized incidence ratio 0.6 versus 1.8 in those with gastric ulcer) [66].

The explanation for this protective feature of *H. pylori*-induced duodenal ulcer is unclear. One theory is that atrophic gastritis, which is an early step in gastric carcinogenesis [67], occurs with *H. pylori*-related gastric ulcers but not duodenal ulcers. Host factors may influence the susceptibility to *H. pylori*-induced gastric atrophy. Support for the relationship between atrophic gastritis and *H. pylori* infection was derived from a study which found that an HLA-DQA1 allele appeared to contribute to resistance against *H. pylori*-associated gastric atrophy and gastric adenocarcinoma [68].

Strain differences may also provide some explanation. As noted above, infection with *H. pylori* that contain a duodenal ulcer promoting gene, DupA, appears to lower the risk for gastric cancer [69]. Another hypothesis is that duodenal ulcer may be associated with an increased

level of ascorbic acid [70], which may protect against subsequent development of gastric cancer.

Finally, as noted above, cytokine polymorphisms associated with cancer result in more diffuse gastritis and low acid secretion, gastric histology, and physiology unusual in duodenal ulcer patients.

Role of family history — A family history has been associated with a 1.5- to 3-fold increased risk of gastric cancer [71,72]. Whether this reflects clustering of *H. pylori* within families with gastric cancer is uncertain. A case control study suggested that the two risks were independent [73]. Relatives of patients with gastric cancer are more likely to be infected by *H. pylori* than unrelated controls. Infected relatives are also more likely to have low gastric acid secretion, a known marker/risk factor for gastric cancer [74]. As noted above, this observation may be explained by hereditary differences in inflammatory cytokine polymorphisms that determine a host's acid secretory profile and the degree and distribution of gastric inflammation that results from *H. pylori* infection. (See "Risk factors for gastric cancer", section on 'Importance of Helicobacter pylori infection'.)

Does treatment reduce risk of gastric cancer? — Eradication of *H. pylori* appears to reduce the risk of gastric cancer [75]. The magnitude of reduction varies by the baseline incidence of gastric cancer, but is seen even in populations with low gastric cancer incidence. A meta-analysis of 27 studies included 48606 *H. pylori* infected individuals with 715 incident gastric cancers [76]. Individuals with eradication of *H. pylori* had a lower incidence of gastric cancer as compared with those who did not receive eradication therapy (pooled incidence rate ratio 0.53; 95% CI 0.44-0.64). As compared with individuals in the lowest tertile of baseline cancer incidence, those in the intermediate and highest tertile of cancer incidence had a greater reduction in gastric cancer incidence rate with *H. pylori* eradication (incidence rate ratio 44 and 38 percent, respectively). The magnitude of benefit was not significantly different between asymptomatic individuals and those who had undergone endoscopic resection of gastric cancer. (See "Early gastric cancer: Treatment, natural history, and prognosis", section on 'Helicobacter pylori infection'.)

Even if treatment does reduce the gastric cancer risk, difficulties with screening for *H. pylori* and treatment arise. The cost of screening and treating would be large given the worldwide prevalence of *H. pylori* infection. Nevertheless, one study that economically modeled the cost of screening per year of life saved estimated that, in selected populations such as Japanese American, serologic screening for *H. pylori* beginning at age 50 was more beneficial than breast cancer screening [77]. Another cost-effectiveness analysis concluded that screening and

treatment could be cost-effective if the cancer risk following eradication could be restored to that of a population that had never been infected with *H. pylori* [78].

A number of major medical organizations have issued guidelines related to *H. pylori* screening and eradication in high-risk populations. As examples, Asian-Pacific guidelines and European guidelines support population-based screening in high-risk settings [79,80]. Screening for gastric cancer is discussed in detail separately. (See "Gastric cancer screening".)

GASTRIC LYMPHOMA

Primary gastric lymphoma accounts for 3 percent of gastric neoplasms and 10 percent of lymphomas [81]. The stomach is the most common extranodal site of lymphoma. Lymphoma can arise from lymph nodes or mucosal areas; the latter is referred to as a mucosa (gut)-associated lymphoid tissue tumor (MALToma, MALT-type lymphoma, or MALT lymphoma, now called extranodal marginal zone B-cell lymphoma of MALT type in the REAL classification), of which the stomach is the most common site (picture 2A-B). (See "Splenic marginal zone lymphoma".)

Presenting symptoms of gastric lymphoma include epigastric pain (which is the most common), weight loss, anorexia, vomiting, melena, hematemesis, back pain, and nausea. The diagnosis is based upon histologic criteria and the presence of B-cell markers by immunocytochemistry. Histology shows lymphoepithelial changes, polymorphic cellular content, centrocyte like cells, and reactive germinal centers. High-grade lymphoma (eg, diffuse large B-cell lymphoma) is distinguished from low-grade disease when the number of large blast cells exceeds 20 percent [82].

The normal stomach does not contain significant lymphoid tissue [83]. However, *H. pylori*-induced gastritis leads to an aggregation of CD4+ lymphocytes and B cells in the gastric lamina propria. Antigen presentation occurs followed by T cell activation, B cell proliferation, and lymphoid follicle formation. The gastric follicle resembles those seen in the ileum in Peyer's patches [84]. A follicle is characterized by a center consisting of centroblasts and centrocytes. The center is surrounded by a B cell zone referred to as a mantle. The mantle is enclosed by a marginal zone, which is also comprised of B cells.

A hypothesis has been proposed to describe the development of gastric B-cell lymphoma of marginal zone type (previously called low-grade MALToma). The antigen-presenting cell interacts with a CD4+ T-cell. The activated T-cell then binds to a B-cell with an aberrant ability for unsuppressed proliferation. A population of centrocyte-like B-cells arise to form the marginal

zone, thereby representing low-grade lymphoma [84,85]. This hypothesis was supported in a report of two patients with gastric MALToma who had a previous gastric biopsy several years before the onset of lymphoma [86]. The lymphomas were shown to arise from a B cell clone at the site of chronic gastritis.

H. pylori infection and MALToma — Multiple studies have demonstrated an association between *H. pylori* infection and MALToma, and have begun to elucidate the mechanisms underlying this association [87-93]. As with gastric cancer, the development of MALToma may be related to specific *H. pylori* strains expressing the CagA protein. In one report, for example, serum IgG antibody to CagA was much more common in patients with MALToma than an *H. pylori*-infected control group (95 versus 67 percent) [89]. It is also possible that other species of Helicobacter are involved in the development of gastric MALT lymphomas. As an example, an association with *H. heilmannii* has been described [92,94].

Efficacy of anti-H. pylori therapy — The most dramatic evidence supporting a pathogenetic role for *H. pylori* in MALToma is remission of the tumor following eradication of *H. pylori* with antibiotic therapy [95-102]. The role of *H. pylori* treatment in the management of gastric lymphoma is discussed in detail elsewhere. (See "Treatment of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)", section on 'Stage I or II H. pylori positive'.)

COLON CANCER

An association between *H. pylori* infection and colorectal polyps and colorectal cancer has been described but remains controversial [103-114].

The biologic basis for such an association is uncertain. One possibility is elevated serum gastrin levels in patients with *H. pylori* infection [104]. Gastrin receptors have been identified on a variety of colon cancer cell lines, and endogenous serum gastrin levels have been correlated with the risk of colonic neoplasms. However, studies have not found an association of serum gastrin levels with an increased risk for colonic neoplasia [110,113]. (See "Physiology of gastrin".)

PANCREATIC CANCER

An association between *H. pylori* infection and pancreatic cancer has been reported [115-119]. In a meta-analysis that included 1083 patents with pancreatic cancer and 1950 controls, infection with *H. pylori* was associated with an increased risk of pancreatic cancer (OR 1.47, 95%

CI 1.2-1.8) [120]. On subgroup analysis, CagA positive *H. pylori* strains were not associated with an increased risk of pancreatic cancer. Another report found an association between colonization with non-CagA *H. pylori* strains and pancreatic cancer in patients with non-O blood types; no association was found in patients with non-O blood types infected with CagA positive *H. pylori* [117]. (See 'H. pylori strain differences' above.)

A possible mechanism proposed for the association of pancreatic cancer and *H. pylori* is the link between pancreatic cancer and chronic hyperacidity [121] (see 'H. pylori strain differences' above and "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer"). Additional studies are needed to confirm the association of pancreatic cancer and *H. pylori* infection and also to better support the putative role of hyperacidity.

HEPATOBILIARY CANCER

Several studies report an association between biliary tract carcinoma and infection with *H. pylori* [122-126]. Although a cause and effect relationship has not been proven, some have suggested that *H. pylori* may be involved in the pathogenesis of biliary neoplasms through enhanced biliary cell inflammation and proliferation [125,127].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: H. pylori infection (The Basics)")
- Beyond the Basics topics (see "Patient education: Helicobacter pylori infection and treatment (Beyond the Basics)")

SUMMARY

- Approximately 36 and 47 percent of all gastric cancers in resource-abundant and resource-limited countries, respectively, are solely attributable to *H. pylori* infection. This accounts for almost 350,000 gastric cancers annually worldwide.
- Several hypotheses have been proposed to explain the role of *H. pylori* in carcinogenesis, although the exact mechanism is incompletely understood. (See 'Role of H. pylori in carcinogenesis' above.)
- Multiple studies have demonstrated an association between *H. pylori* infection and mucosa-associated lymphoid tissue lymphoma (MALToma). The most dramatic evidence supporting a pathogenetic role for *H. pylori* in MALToma is remission of the tumor following eradication of *H. pylori* with antibiotic therapy. (See 'Gastric lymphoma' above.)

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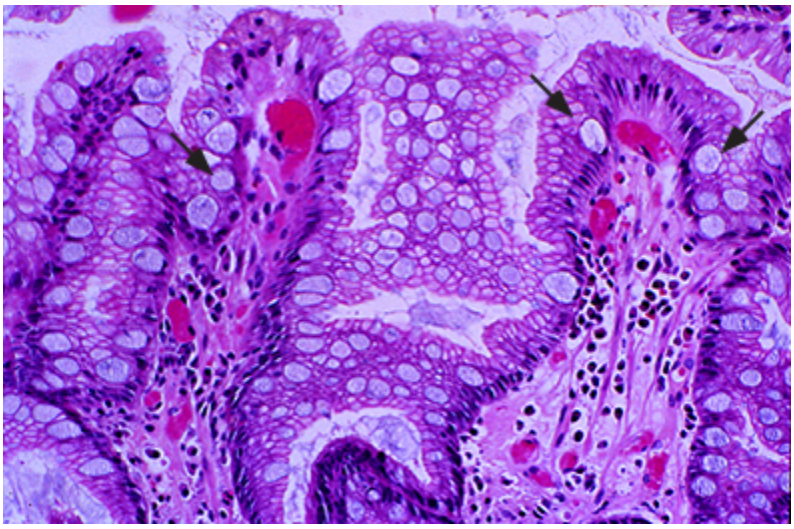
Topic 2514 Version 34.0

GRAPHICS

Incomplete intestinal metaplasia

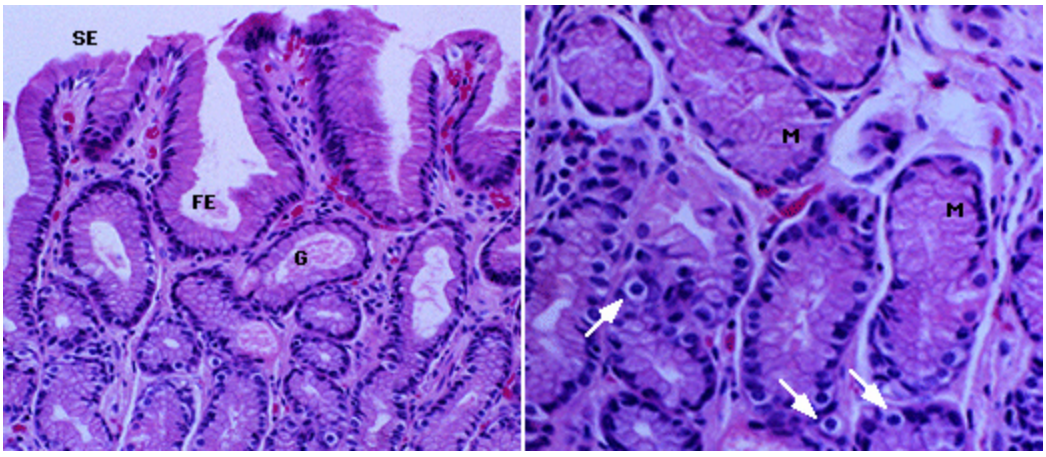


High power view (H&E stain) of chronic atrophic gastritis with incomplete intestinal metaplasia showing metaplastic goblet cells in the surface and foveolar epithelium (arrows).

Courtesy of Robert Odze, MD.

Graphic 64199 Version 3.0

Normal gastric antrum

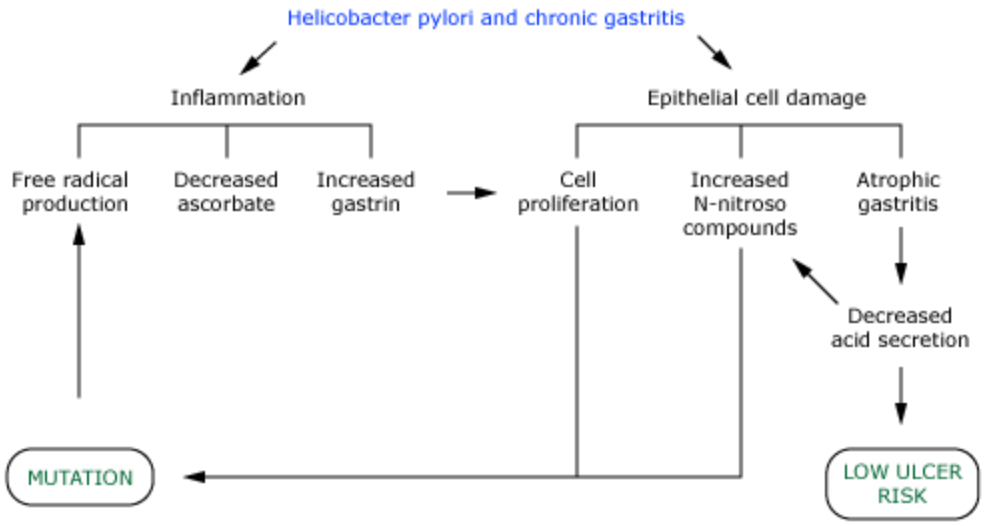


Left panel: Normal surface (SE) and foveolar epithelium (FE) and glands (G). Right panel: Higher power view of the glands shows mucous cells (M) and gastrin-secreting endocrine cells (arrows).

Courtesy of Robert Odze, MD

Graphic 79895 Version 1.0

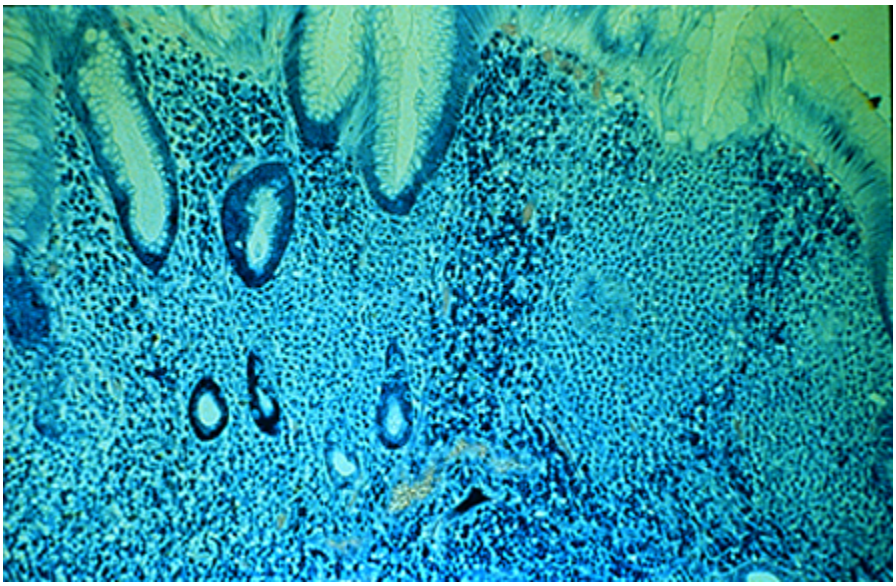
Possible mechanisms of Helicobacter pylori-induced gastric carcinogenesis



Adapted from: Blaser, MJ, Parsonnet, J, J Clin Invest 1994; 94:4.

Graphic 73741 Version 2.0

Extranodal marginal zone lymphoma of the stomach

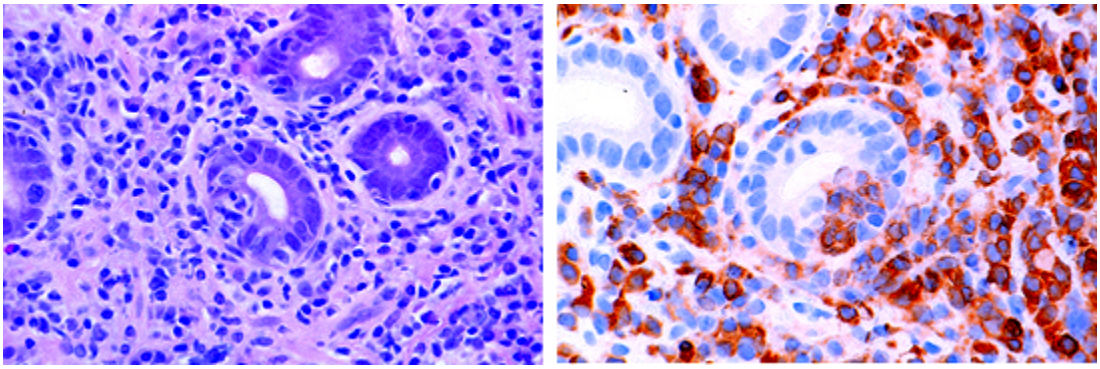


Medium power view of a gastric marginal zone lymphoma shows dense, monotonous, lymphoid infiltrate in the lamina propria, and pale- staining cells consistent with marginal zone B-cells surrounding and infiltrating the epithelium (lymphoepithelial lesion).

Courtesy of Nancy Lee Harris, MD.

Graphic 68386 Version 3.0

Extranodal marginal zone lymphoma of the stomach



Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT). Left panel: Infiltrating lymphoma cells with loss of glands and a lymphoepithelial lesion. Right panel: Staining with the monoclonal B cell antibody CD-20 shows that most of the infiltrating cells show B cell reactivity.

Courtesy of Paul C Schroy III, MD.

Graphic 59651 Version 4.0

Contributor Disclosures

J Thomas Lamont, MD Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Mark Feldman, MD, MACP, AGAF, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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