Helicobacter pylori Strikes Again

Gastric Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

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Infection with *Helicobacter pylori* is common. Over 50% of the world's population is estimated to be colonized with the bacteria. The association between *Helicobacter pylori* and gastric mucosa-associated lymphoid tissue (MALT) lymphoma is well documented. Anti-*Helicobacter pylori* treatment and the successful eradication of the bacteria can potentially cure patients who test positive for the bacteria and who are diagnosed with low-grade gastric MALT lymphoma. The purpose of this article is to review the evidence implicating *Helicobacter pylori* as a causal pathogen for the development of gastric MALT lymphoma and to determine that anti-*Helicobacter pylori* therapy is an effective first-line treatment. The clinical presentation, endoscopic findings, diagnosis, staging, treatment, and follow-up of patients with gastric MALT lymphoma who are treated with anti-*Helicobacter pylori* therapy are also discussed.

Since its discovery in 1983 by Warren and Marshall, much has been learned about *Helicobacter pylori* (*H. pylori*) (Knigge, 2001). *H. pylori* is a Gram-negative spiral flagellated bacterium that colonizes gastric-type mucosa and resides between the gastric epithelium and the protective mucous barrier lining the stomach (Atherton & Blaser, 2005; Knigge, 2001). Through adaptive mechanisms, *H. pylori* is able to buffer the acidic gastric environment and maintain the pH within a range which assures its survival. As a result, it is estimated that over 50% of the world's population is colonized with *H. pylori*. Those persons infected with *H. pylori* are now widely accepted to be at increased risk for developing gastric or duodenal ulcers. In 1994, the National Institutes of Health (NIH) Consensus Development Conference concluded that all patients with ulcers, initial or recurrent, who are concurrently infected with *H. pylori* require treatment with antibiotics and antisecretory drugs (NIH, 1994). More recently, gastric mucosa-associated lymphoid tissue (MALT) lymphoma has been associated with *H. pylori*.

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Background

During the same year that *H. pylori* was discovered, Isaacson and Wright identified a distinct entity of extranodal, low-grade, lymphoma known as gastric MALT lymphoma (Farinha & Gascoyne, 2005). Overall, primary gastric MALT lymphoma is uncommon and accounts for 5% or less of all primary gastric neoplasms (Ahmad, Govil, & Frank, 2003; Al-Akwaa, Siddiqui, & Al-Mofleh, 2004). Although rare, gastric MALT lymphoma is the most common extranodal lymphoma, accounting for up to 20% to 50% of cases. There have been reports of primary gastric MALT lymphoma in patients as early as the second decade of life; however, the reported median age of occurrence is 60–65 years of age, with men being affected 2 to 3 times more than women (Al-Akwaa et al., 2004).

Subsequently, much research has implicated *H. pylori* as a causal pathogen for the development of gastric MALT lymphoma. In the 1990s, a large nested case-control study determined that primary gastric non-Hodgkin's lymphoma was associated with previous infection by *H. pylori* (Parsonnet et al., 1994). More specifically, it was found that gastric MALT lymphoma was associated with *H. pylori* infection as well (Wotherspoon, Ortiz-Hidlago, Falzon, & Isaacson,

1991). Since that time, research has attempted to prove the hypothesis that *H. pylori* plays a causative role in the pathogenesis of gastric MALT lymphoma.

This hypothesis has been strengthened by the plethora of research showing that anti-*H. pylori* therapy is an effective first-line treatment for patients who tested positive for the bacteria with low-grade gastric MALT lymphoma. Long-term follow-up of these patients for 6 years or more revealed that successful *H. pylori* eradication resulted in a MALT lymphoma complete regression (CR) rate of 80% (Wundisch et al., 2005).

In a prospective study, 65% of patients with low-grade gastric MALT lymphoma who received anti-*H. pylori* therapy achieved CR (Nakamura et al., 2005). These data are congruent with a prospective study published in 2004 (Fischbach, Goebeler-Kolve, Dragosics, Greiner, & Stolte, 2004). This study, which followed patients for approximately 4 years, found that 62% of patients achieved CR of low-grade gastric MALT lymphoma following successful eradication of *H. pylori*.

Unfortunately, patients with gastric MALT lymphoma who are successfully treated against *H. pylori* do not always maintain their state of regression. Relapse can occur at any time. Research shows relapse occurring in less than 6 months after documented CR of gastric MALT lymphoma; however, for some, relapse does not occur until as long as 15 months or more after documented CR (Nakamura et al., 2005). For some patients, relapse might be attributed to reinfection with *H. pylori*. The literature suggests that in those patients who relapse, a second course of treatment for *H. pylori* results in long-term regression of gastric MALT lymphoma (Fischbach et al., 2004). In a prospective study of 20 patients with a median follow-up of 24 months, one patient relapsed with the recurrence of *H. pylori* infection; however, with reeradication of the bacteria, this patient's low-grade gastric MALT lymphoma regressed (Yeh et al., 2003).

One may speculate whether relapse of gastric MALT lymphoma after successful eradication of *H. pylori* is a matter of an occult and undiagnosed high-grade component of the initial lymphoma (Fischbach et al., 2004). In a study of 120 patients who were initially diagnosed with low-grade gastric MALT lymphoma, components of more aggressive types of lymphoma were revealed during long-term follow-up after *H. pylori* eradication (Wundisch et al., 2005). Similarly, a prospective study confirmed initial diagnosis and low-grade staging with at least three endoscopic biopsies; however, 6 months later, gastrectomy revealed high-grade large-cell lymphoma in a patient (Yeh et al., 2003).

Pathogenesis of MALT

The normal stomach is devoid of lymphoid tissue. It follows to reason that in order for lymphoma to develop in the stomach, the gastric wall must first experience an acquisition of lymphoid tissue. Normally, the immune system is triggered by bacterial colonization and responds by promoting lymphoid infiltration of the host (Du & Isaccson, 2002). The stomach, however, is protected from this reaction by its innate ability to produce gastric acid as well as a cytoprotective membrane. In general, these protective mechanisms limit the ability of bacterial colonization. *H. pylori* is the exception. This bacterium produces an enzyme known as *urease*, which neutralizes the acidic pH of the stomach, thus enabling its survival within the hostile gastric environment (Knigge, 2001). In addition, *H. pylori* has the benefit of flagella, which enhance its ease of motility and penetration of the gastric wall. Because of the combination of its ability to promote alkalinity as well as its effortless motility, *H. pylori* can easily flourish within the stomach.

The cellular progression of gastric MALT lymphoma can be explained by the natural history of *H. pylori* infection. As illustrated in Figure 1, once *H. pylori* establishes itself as an antigen, the stomach sustains chronic antigenic stimulation (Lenze et al., 2006; McQuaid, 2006). The result of this persistent bacterial exposure is an increased lymphocytic inflammatory response that presents as gastritis (Ahmad et al., 2003). Furthermore, the ongoing exposure of the lymphoid cells to *H. pylori* causes uninterrupted proliferation in an attempt to eliminate the antigen. Neutrophils are also activated, which release genotoxic reactive oxygen species (Du & Isaccson, 2002).

During this process, known as *monoclonal lymphoproliferation*, the risk of genetic alteration of the cells increases. This process is histologically known as intestinal metaplasia and dysplasia. Ultimately, apoptosis (programmed cell death designed specifically to eliminate rapidly proliferating cells) becomes deregulated, and lymphoid follicles develop, resulting in the culmination of MALT lymphoma (McCance & Roberts, 2002).

Genetics

Several genetic alterations have been linked to the development of gastric MALT lymphoma. The cytotoxin associated gene A (cagA) is a particular strain of *H. pylori* thought by some researchers to be particularly virulent and proinflammatory. For example, it has been shown that infection of the gastric mucosa with *H. pylori* leads to increased apoptosis

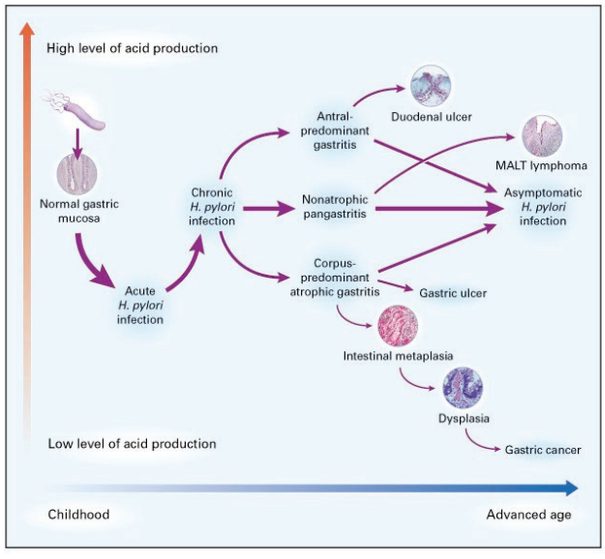

FIGURE 1. Natural history of *H. pylori* infection. Reprinted with permission from Suerbaum, S., & Michetti, P. (2002). *Helicobacter pylori* infection. *New England Journal of Medicine, 347,* 1175–1186.

of the gastric epithelial cells, which enhances antigen survival (Neu et al., 2005). Infection with a cagA (+) strain of *H. pylori* induces downregulation of apoptosis while simultaneously upregulating antiapoptosis. With limited apoptosis of the gastric tissue, *H. pylori* is able to maintain its survival with less effort.

In a meta-analysis, infection with a cagA (+) strain of *H. pylori* was associated with an increased risk of gastric cancer when compared with cagA (–) strains (Huang, Zheng, Sumanac, Irvine, & Hunt, 2003). Conflicting evidence concluded that the pathogenesis of low-grade gastric MALT lymphoma is not linked with more proinflammatory *H. pylori* strains such as cagA (Lehours et al., 2004).

In addition to cagA, chromosomal translocations have been identified in association with MALT lymphoma. The most common translocation found in MALT lymphoma is the t(11;18)(q21;q21) (Farinha & Gascoyne, 2005). As illustrated in Figure 2, this means that the two chromosomes involved in the translocation are chromosomes 11 and 18. These chromosomes then exchange the genetic material located at a physical landmark in position q21. Thus, on chromosome 11, there is a break at position q21 on the long arm and this portion of genetic material is now attached to chromosome 18 at location q21. Similarly, the genetic material located at position q21 on the long arm of chromosome 18 is now attached to chromosome 11 at location q21. Once this translocation occurs, the apoptosis inhibitor 2 (API2) gene, which is highly expressed in lymphoid cells, fuses with the MALT1 gene. The product formed by the fusion of the API2 and MALT1 genes ultimately leads to oncogenesis.

Research has linked cagA (+), t(11;18)(q21;q21) and gastric MALT lymphoma. A retrospective study showed that t(11;18)(q21;q21) was significantly associated with cagA (+) strains of *H. pylori* (Ye et al., 2003). This association suggests that cagA (+) strains of *H. pylori* promotes t(11;18)(q21;q21), thereby promoting oncogenesis and the development of gastric MALT lymphoma. In a subset of patients who tested positive for *H. pylori* and who achieved successful eradication, it was found that those with the t(11;18)(q21;q21) experienced a worse clinical outcome, including only partial remission, no change, relapse of gastric MALT lymphoma, or histologic residual disease (Wundisch et al., 2005). Those patients without the translocation were more likely to remain in CR.

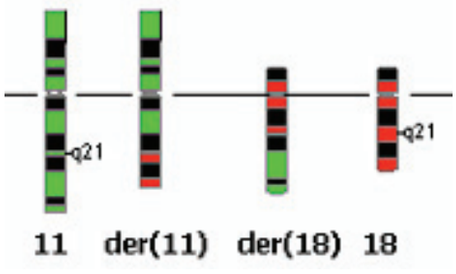

FIGURE 2. MALT lymphoma-associated t(11;18)(q21;q21). Reprinted with permission from Mathijs, B., & Marynen, P. (2002). t(11;18)(q21;q21) (Courtesy of Charles Bangs). *Atlas of Genetics & Cytogenetics in Oncology & Haematology 2002, 6,* 88–90. Retrieved online July 16, 2007, from http://AtlasGeneticsOncology.org/Anomalies/t1118ID2022.html

Clinical Presentation

The clinical presentation of gastric MALT lymphoma is similar to that of adenocarcinoma (McQuaid, 2006). In a study evaluating patients with primary gastric non-Hodgkins lymphoma, pain (78%), anorexia (47.3%), weight loss (24.5%), bleeding (18.8%), and vomiting (18.1%) were the most common presenting signs and symptoms (Koch et al., 2001). Night sweats (11.2%) have been reported, but they are not as frequent.

Diarrhea, constipation, fever, perforation, and ileus are rare when lymphoma is isolated to the stomach. In a retrospective study of patients with low-grade gastric MALT lymphoma, 56.4% experienced abdominal pain, 23.6% experienced indigestion, 12.7% experienced epigastric pain, and only 1% experienced vomiting (Lee et al., 2004). In a review of the literature published in 2004, it was reported that up to 55% to 60% of patients with gastric MALT lymphoma can have a completely normal physical exam (Al-Akwaa et al., 2004).

Endoscopic Findings

Endoscopic findings are very similar to those of adenocarcinoma (McQuaid, 2006). It has been reported that three main endoscopic patterns can be recognized: (a) a tumor-like appearance with a polypoid mass; (b) ulceration or multiple small ulcerations; and (c) large, nodular (sometimes giant) folds (see Figure 3) (Ahmad et al., 2003). Other studies have revealed similar data (Lee et al., 2004; Yeh et al., 2003).

Diagnosis

Primary diagnosis of gastric MALT lymphoma is established with endoscopic tissue forcep biopsy during esophagogastroduodenoscopy (EGD) (Al-Akwaa et al., 2004). Early gastric MALT lymphoma can be difficult to diagnose with forcep biopsy, however. To optimize diagnostic yield, aggressive tissue sampling with multiple biopsy specimens of the grossly abnormal gastric tissue as well as normal mucosa should be taken from various sites within the gastric lumen.

The gastric body and antrum have been reported to be the most common sites of low-grade gastric MALT lymphoma occurrence; however, the fundus and cardia have been implicated as well (Lee et al., 2004). With the potential of noninvasive cure, accurate diagnosis is imperative. As mentioned earlier, the possibility of a component of high-grade gastric MALT lymphoma existing, while an initial diagnosis of low-grade lymphoma is erroneously made, can affect treatment response.

To enhance tissue diagnosis, special endoscopic biopsy techniques have been recommended for the gastroenterologist. In a consensus statement endorsed by the Patient Care Committee of the American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG), by other physicians and surgeons with expertise in gastroenterology, and by the governing boards of the American Society for Gastrointestinal Endoscopy (ASGE), the AGA, the ACG, and the Society of American Gastrointestinal and

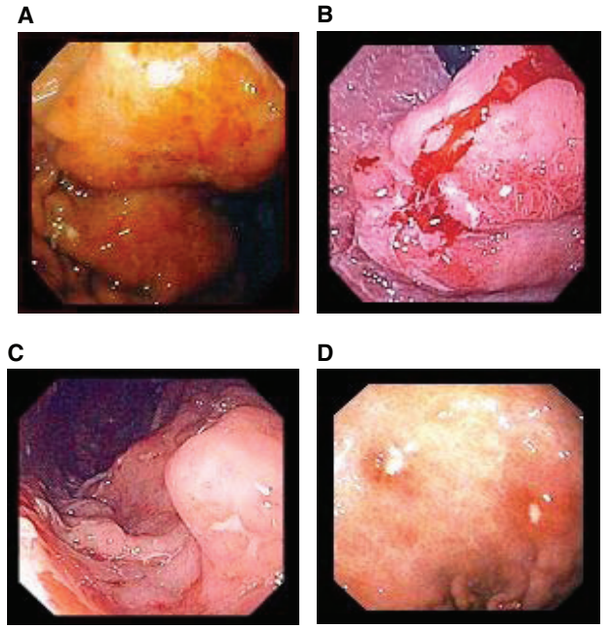

FIGURE 3. Endoscopic findings of gastric MALT lymphoma. A: Bilobed mucosal swelling in the proximal gastric body. B: Gastric fundic tumor, focally ulcerated and bleeding. C: Lobulated, polypoid, proximal gastric mass, with several focal ulcerations. D: Several small antral gastric ulcers with raised surrounding mucosa. Reprinted with permission from Martin, D. (2006). *Atlas of gastrointestinal endoscopy.* Retrieved July 16, 2007, from www.EndoAtlas.com.

Endoscopic Surgeons (SAGES), adequate tissue sampling sometimes requires a combination of techniques (www.sages.org/sg_asgepub1025.html).

Ulcerative or polypoid masses are best sampled by pinch biopsy with a standard biopsy forcep. A minimum of six total biopsies should be obtained from the edge of each quadrant of an ulcer. Polypoid lesions should be biopsied, and ideally, polyps greater than 2 cm should be both biopsied and removed. Deep biopsies can be obtained by taking multiple biopsies from the same site (burrowing). Burrowing can increase diagnostic yield of suspicious submucosal lesions. Finally, endoscopic ultrasound (EUS) with the addition of a fine needle aspirate may yield a diagnosis without the necessity of a full thickness biopsy (www.sages.org/sg_asgepub1025.html). In addition, a snare biopsy can be utilized in the presence of thickened or giant folds or a polypoid mass. If the lesion is unable to be safely removed by snare biopsy, then a saline-assisted mucosal resection can be performed by the gastroenterologist. Finally, jumbo biopsy forceps and multibite biopsy forceps can be utilized to enhance sampling of deeper gastric mucosal layers (Ahmad et al., 2003).

Once the diagnosis of gastric MALT lymphoma is suspected or confirmed, tissue biopsy of the antrum should be performed to establish the presence or absence of *H. pylori*. Histologic confirmation is considered the "gold standard" by many gastroenterologists (Knigge, 2001). The most common and least expensive invasive test used to detect infection with *H. pylori*, however, is the rapid biopsy urease test. This test is commonly referred to as a *CLO test*. The sensitivity of the CLO test is 90%, and the specificity is 100%. Both histologic testing and rapid biopsy urease testing for *H. pylori* can result in a false negative result in patients receiving a proton pump inhibitor (PPI). To ensure accurate results, it has been recommended that PPIs should be discontinued 2 weeks prior to biopsy when possible.

Staging

Accurate staging of gastric MALT lymphoma is an essential component of the diagnostic process. Planning the optimal approach to treatment depends on the stage of disease. All of the aforementioned studies used similar modalities to assess the stage of disease. Staging workup included some combination of the following: a thorough physical exam; complete blood count and serum chemistry analysis; EUS; abdominal ultrasound; computed tomography of the chest, abdomen, and pelvis; positron emission tomography scan; small bowel series; evaluation of the colon with either barium enema or colonoscopy; and bone marrow aspiration and biopsy. Evaluating the presence of gross lesions outside the stomach can be determined with the various radiologic exams.

Also, it is important to assess nodal involvement above and below the diaphragm. Tumor spread is further evaluated with bone marrow biopsy. Endoscopic ultrasound is particularly useful in evaluating the depth of an infiltrating tumor as well as the presence or absence of perigastric lymphadenopathy (Caletti et al., 2002). Furthermore, EUS has been shown to have predictive value for long-term survival in patients with gastric MALT lymphoma after successful anti-*H. pylori* therapy (Nakamura et al., 2001).

A variety of staging systems are available. Table 1 compares three common systems for staging gastric MALT lymphoma: Lugano Staging System for gastrointestinal lymphomas, TNM Staging System adapted for gastric lymphoma, and the Ann Arbor Staging System. A system similar to the Lugano Staging System was used in a prospective study that found patients with Stage I gastric MALT lymphoma reached a higher rate of disease regression after *H. pylori* eradication treatment than did patients diagnosed with Stage II or Stage IV disease (Nakamura et al., 2005). Although these results did not reach statistical significance, it is reasonable to speculate about the prognostic implications of staging systems.

Treatment

Various pharmacologic regimens against *H. pylori* have been investigated. Most of these anti-*H. pylori* therapies include a combination of either two or three antibiotics along with either a PPI or an H2-receptor antagonist. The most efficacious treatment regimens are depicted in Figure 4. A meeting of worldwide experts and specialists, representatives from the National Gastroenterology Societies, and European general practitioners was organized by the European *Helicobacter pylori* Study Group in 2005 (Malfertheiner et al., 2007). The purpose of this meeting was to update the guidelines set forth in 2000 on the management of *H. pylori*. These updated guidelines are known as the Maastricht 3-2005 Consensus Report.

As recommended in the report, first-line treatment includes a PPI b.i.d., plus clarithromycin 500 mg b.i.d., plus amoxicillin 1,000 mg b.i.d. or metronidazole 500 mg b.i.d. for

TABLE 1

Staging of Gastric MALT Lymphoma Comparing Different Systems

Lugano Staging System for Gastrointestinal Lymphomas		TNM Staging System Adapted for Gastric Lymphoma	Ann Arbor Stage	Tumor Extension
Stage I	Confined to GI tract (single, primary or multiple, noncontiguous)	T1 N0 M0 T2 N0 M0 T3 N0 M0	I_E I_E I_E	Mucosa, submucosa Muscularis propria Serosa
Stage II	Extending into abdomen II_1 = local nodal involvement II_2 = distant nodal involvement	 T1-3 N1 M0 T1-3 N2 M0	 II_E II_E	 Perigastric lymph nodes More distant regional lymph nodes
Stage II_E	Penetration of serosa to involve adjacent organs or tissues	T4 N0 M0	I_E	Invasion of adjacent structures
Stage IV	Disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement	T1-4 N3 M0 T1-4 N0-3 M1	III_E IV_E	Lymph nodes on both sides of the diaphragm/distant metastases (e.g., bone marrow or additional extranodal sites)

Note. Reprinted with permission from Zucca, E., Bertoni, F., Roggero, E., & Cavalli, F. (2000). The gastric marginal zone B-cell lymphoma of MALT type. *Blood, 96,* 410–419.

14 days. First-line triple therapy with PPI, clarithromycin, and amoxicillin or metronidazole given for 14 days rather than 7 days has been shown to be more efficacious in eradicating *H. pylori* (Malaty, Stigleman, & Hansen, 2003). Triple therapy with PPI plus clarithromycin and amoxicillin is preferred (Fischbach, Goodman, Feldman, & Aragaki, 2002). This treatment regimen has been commercially packaged (PrevPac) for ease of administration and to increase treatment compliance. Metronidazole is most often used in patients who are allergic to penicillin.

The Maastricht 3-2005 Consensus Report recommends that second-line therapy should include PPI b.i.d., plus bismuth q.i.d. if available, plus metronidazole 500 mg b.i.d., plus tetracycline 500 mg q.i.d. for a minimum of 7 days. A randomized controlled trial found that PPI b.i.d., amoxicillin 1,000 mg b.i.d., and levofloxacin 500 mg b.i.d. was a comparable alternative for second-line treatment (Wong et al., 2006). Although the use of PPI, amoxicillin, and levofloxacin as second-line treatment against *H. pylori* shows promise, the research is limited and this regimen should be used with caution; however, in patients with resistance to both metronidazole and clarithromycin, this latter combination may be the only option. *H. pylori* eradication therapy consisting of dual therapy regimens are not recommended (Peterson et al., 2000).

Follow-Up

Indefinite and vigilant follow-up is essential, though there are no specific guidelines pertaining to follow-up after successful *H. pylori* eradication in a patient with low-grade gastric MALT lymphoma. Routine EGD with EUS and biopsy are invaluable to follow-up care. Follow-up is at the discretion of a prudent healthcare provider.

As mentioned earlier, patients with gastric MALT lymphoma who are successfully treated against *H. pylori* do not always maintain their state of regression. Relapse can occur over an undefined amount of time. It is necessary to determine the *H. pylori* status at the time of relapse. If the patient is *H. pylori* positive, administer a second-line quadruple therapy for eradication. It is also necessary to restage the gastric MALT lymphoma at the time of relapse to ensure the appropriate treatment options are explored. There have been case reports of patients developing gastric adenocarcinoma as long as 4–5 years after CR of low-grade gastric MALT lymphoma treated with successful *H. pylori* eradication therapy (Morgner et al., 2001). For this reason alone, indefinite follow-up is warranted.

Follow-up is also necessary to determine *H. pylori* eradication failure. A delayed response of *H. pylori* to treatment is possible. The authors of a retrospective study believe that because relapse is relatively rare after a year, it is necessary to wait 12 months before defining a *H. pylori* treatment failure (Lee et al., 2004). Once anti-*H. pylori* treatment fails a patient, other treatment modalities must be considered.

Future Implications

Although the evidence is not abundant, several interesting relationships between *H. pylori* eradication treatment and MALT lymphoma warrant mention. In a retrospective analysis of two prospective studies, researchers tried to compare the long-term results of anti-*H. pylori* therapy in a group of patients with low-grade gastric MALT lymphoma with a group of patients with the high-grade counterpart (Chen et al., 2005). Sixty percent of patients with high-grade gastric MALT lymphoma experienced CR following success-

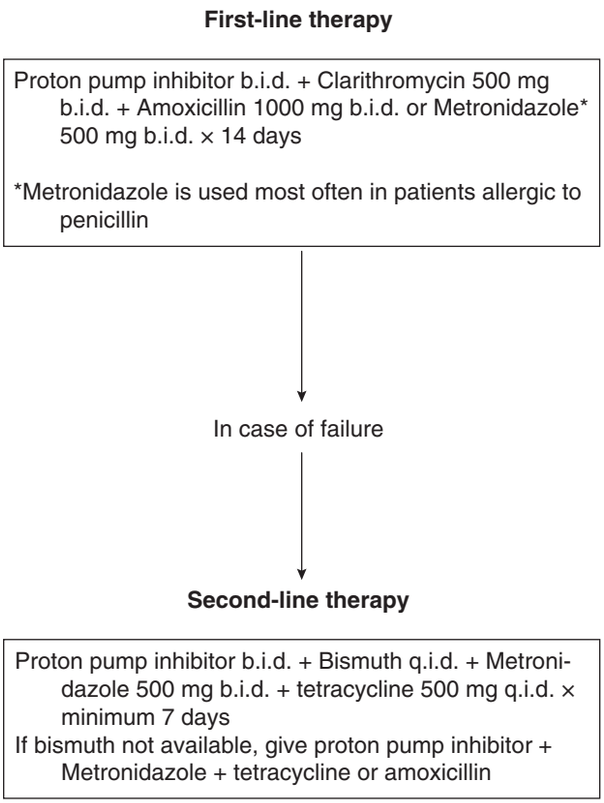

FIGURE 4. The most efficacious treatment regimens against *H. pylori.*

ful *H. pylori* eradication treatment. Furthermore, these patients remained relapse-free for a median of greater than 5 years.

Another interesting finding in the literature involved a study of patients with gastric MALT lymphoma who were *H. pylori* negative. Following anti-*H. pylori* antibiotic treatment, patients responded with lymphoma regression (Raderer, Streubel, Wohrer, Hafner, & Chott, 2006). Although this study was small, one can speculate that *H. pylori* negative gastric MALT lymphoma can potentially benefit from *H. pylori* eradication treatment.

Finally, there are case reports of low-grade colonic MALT lymphoma that regressed after being treated with amoxicillin 1,500 mg a day, and clarithromycin 800 mg a day. These patients were *H. pylori* negative prior to treatment (Kikuchi et al., 2005). Although the above findings do not have sufficient data to support a change in practice, such findings do promote thought provoking presumptions about the future of MALT lymphoma research.

Conclusion

Given the rarity of gastric MALT lymphoma, the best treatment is often controversial. The goal of therapy is always to provide the appropriate treatment that delivers the greatest benefit to the patient while simultaneously placing that patient at the least risk. Recent evidence supports anti-*H. pylori* therapy as an effective first-line treatment for patients who test positive for the bacteria with low-grade gastric MALT lymphoma. Most studies support this conservative approach in patients with both low-grade and early stage disease. Most studies define early stage as either Stage I via the Lugano Staging System or one similar, or Stage IE or IIE according to the Ann Arbor Staging System or one similar.

Every attempt should be made to accurately diagnose and stage low-grade gastric MALT lymphoma. Patient outcome depends on the treatment received in response to the diagnostic and staging results. Once it is determined to proceed with conservative management, long-term and indefinite follow-up is mandatory. Regular monitoring with EGD and EUS and biopsy allows for determining *H. pylori* status, relapse, and progression of disease. Because there are no specific guidelines pertaining to follow-up after successful *H. pylori* eradication in a patient with low-grade gastric MALT lymphoma, adequate follow-up is at the discretion of a prudent healthcare provider.

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