ABSTRACT

- **Objective:** To review the evidence and current recommendations regarding screening indications and testing methodology for *Helicobacter pylori* infection.
- **Methods:** Review of the literature.
- **Results:** Absolute indications for *H. pylori* screening include active peptic ulcer disease, confirmed history of peptic ulcer disease, gastric mucosal associated lymphoid tissue (MALT) lymphoma, and following endoscopic resection of early gastric cancer. Other clinical conditions warranting screening include uninvestigated dyspepsia, iron deficiency anemia, and primary immune thrombocytopenia. Clinical conditions in which *H. pylori* testing should be considered on a case-by-case basis include functional dyspepsia, chronic nonsteroidal anti-inflammatory drug/aspirin use, chronic proton pump inhibitor use, and those with a strong family history of gastric cancer. *H. pylori* screening is not indicated in the evaluation of gastroesophageal reflux disease. Endoscopic-based testing methods include rapid urea test, histology, culture, and polymerase chain reaction. Noninvasive test modalities include the urea breath test, fecal antigen test, and *H. pylori* antibody tests. Accuracy of testing can be impaired by the use of antibiotics, antisecretory drug therapy, bismuth-based compounds, or with active gastrointestinal bleeding. The positive predictive value of *H. pylori* antibody testing is highly dependent upon the prevalence of *H. pylori* and should not be the sole method of testing in populations with a low prevalence.
- **Conclusions:** *H. pylori* remains a common chronic infection with a worldwide prevalence. Although *H. pylori* can remain clinically silent, it has been linked with peptic ulcer disease and gastric malignancy and associated with dyspepsia, iron deficiency anemia, and primary immune thrombocytopenia. Given these potential complications of *H. pylori* infection, it is important to understand the appropriate clinical conditions to screen for *H. pylori* and the most accurate testing methodology to identify infection.

*Helicobacter pylori* remains a common bacterial pathogen in humans, infecting more than half the world’s population. Although its prevalence varies widely, occurring more commonly in developing countries and in lower socioeconomic classes of developed countries, *H. pylori* infection has been reported in virtually every country, spanning all socioeconomic classes, with associated clinical syndromes affecting children as well as adults [1,2]. It is believed that most individuals acquire *H. pylori* infection in childhood, with 80% reported to be infected by age 20 in developing countries [3]. As untreated *H. pylori* infection can remain lifelong without appropriate eradication, so can the potential complications associated with the infection. Despite decreasing infection rates in developed countries, *H. pylori* remains clinically relevant with prevalence estimates of 30% to 40% in the United States [4]. *H. pylori* remains a major cause of chronic gastritis [5] as well as peptic ulcer disease [6], and is closely linked with gastric malignancy including gastric MALT (mucosal associated lymphoid tissue) lymphoma [7] and gastric adenocarcinoma [8]. *H. pylori* has recently been deemed a human carcinogen by the World Health Organization. For these reasons, the identification of *H. pylori* infection in any individual mandates treatment with the goal of successful eradication. Furthermore, infection eradication rates with established treatment regimens continue to fall, leaving as many as 25% persistently infected following an initial course of therapy [9]. It is for these reasons that it is not only logistically difficult but also economically impractical to pursue mass screening and treatment of *H. pylori* infection. Moreover, it is well known that most individuals chronically infected with *H. pylori* fail to manifest any clinical syndromes associated with the infection, with global estimates of only 15% to 20% developing peptic

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ulcer disease and less than 1% developing gastric cancer [10]. Therefore, the most important decision for a clinician is not who to treat but instead who to test. Furthermore, the testing modalities available can present the clinician with additional challenges. There are tests that directly identify active infection or simply suggest infection via the presence of antibodies to H. pylori. Through an evidenced-based review of the literature, the appropriate clinical setting for testing and appropriate testing methodology for H. pylori infection will be presented.

DIAGNOSTIC TESTING FOR H. PYLORI

Diagnostic tests for H. pylori infection can be divided into invasive test modalities, that is, those requiring endoscopy, and noninvasive test modalities, those independent of endoscopy. Noninvasive studies can be further divided into those directly identifying active infection and those identifying an antibody response to the infection which may or may not be indicative of active infection.

Invasive Tests

Endoscopic-based testing modalities include the rapid urea test (RUT), histology, culture, and polymerase chain reaction (PCR) (Table 1). RUT and histology are the most widely used and readily available test modalities for tissue obtained during endoscopy. RUT utilizes the urease activity of H. pylori to identify the organism’s presence on mucosal biopsies, providing results within 1 to 24 hours depending on test kit used. Although this represents a quick, simple and inexpensive testing modality, it relies on the presence of widespread colonization and intact urease activity of H. pylori. Proton pump inhibitors (PPIs), bismuth-based drugs, and antibiotics can affect H. pylori's distribution in the stomach and/or its urease activity and consequently, adversely affect the accuracy of the RUT [11]. Therefore, it is recommend that these medications be held for 1 to 2 weeks prior to testing, and biopsies be obtained from both the antrum and body of the stomach [12].

Histology, considered the gold standard by some, represents a highly sensitive and specific method of diagnosing H. pylori with the added advantage of providing accompanying pathologic changes in the gastric mucosa [13]. Histology relies on the quality and number of mucosal biopsies obtained and ultimately on the distribution of H. pylori, which can be affected by a number of factors, including PPIs, bismuth, and antibiotics [14]. It is important to obtain a minimum of 3 biopsies from 2 different areas of the stomach, including the antrum and body, to maximize diagnostic accuracy [13].

Culturing mucosal biopsies is a highly specific methodology that also provides invaluable information on antibiotic resistance of the organism; however, it is not commonly used in clinical practice due to its expense, limited availability of specialized laboratories to perform culture, and technical challenges regarding tissue processing [15]. From a practical standpoint, culture is typically reserved for cases of persistent H. pylori infection failing multiple courses of eradication therapy.

PCR represents a DNA amplification technique providing a highly specific method to identify H. pylori as well as bacterial resistance patterns of the organism; however, cost and availability are limiting. It has remained largely in the research arena [16].

Noninvasive Tests

Noninvasive testing modalities include the urea breath test (UBT), fecal antigen test (FAT) and the H. pylori antibody tests (Table 1). The clear practical advantage of these tests is that they can be performed without the need for endoscopy. The UBT and FAT have the advantage over antibody testing in that they assess for active H. pylori infection. The UBT is considered the gold standard noninvasive test and, like the RUT, relies on the urease activity of H. pylori to identify active infection. Two versions of the UBT are available: one using a small dose of the radioactive C14 and the other using the nonradioactive C13, with both representing an accurate means to diagnose H. pylori infection [17,18] and confirm eradication following treatment [19,20]. Similar to the RUT, the UBT’s diagnostic accuracy can be adversely affected by the use of PPIs, bismuth, and antibiotics, which may reduce the H. pylori population and/or urease activity. Therefore, it is imperative that these medications are held prior to testing. Current recommendations include holding antibiotics and bismuth for 28 days, PPIs for 7 to 14 days, and histamine receptor antagonists (H2RAs) for 1 to 2 days [11]. UBT is more expensive than the FAT and antibody testing, and is limited by personnel and equipment needs.

FAT, available either as a polyclonal or monoclonal antibody kit, utilizes an enzyme immunoassay technique to identify the H. pylori antigen in the stool [21]. The polyclonal and monoclonal tests are accurate in screening for H. pylori, with the monoclonal test performing slightly better [22], although only the monoclonal test should be used to confirm H. pylori eradication [23].
FAT is considered an alternative to UBT in screening for *H. pylori*, although, similar to the UBT, its accuracy is affected by PPIs, bismuth, and antibiotics [24]. Antibody tests confirm exposure to *H. pylori* through the identification of IgG antibodies to the organism, in serum, saliva, or urine [16,25]. The advantages of antibody testing are ease of administration, rapidity of results, and low cost. However, its greatest weakness is the inability to distinguish between past and present *H. pylori* infection. Given its low sensitivity (85%) and specificity (79%) [26], antibody testing should not be used as a screening strategy where a low background prevalence of *H. pylori* exists (< 20%), as is the case in many regions of the United States and other developed countries [11]. It also is not appropriate for confirming *H. pylori* eradication, as the antibodies can

<table>
<thead>
<tr>
<th>Table 1. Test Modalities for <em>H. pylori</em> Infection</th>
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<td><strong>Endoscopic-based (invasive)</strong></td>
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| Rapid urea test | • Rapid results (1–24 hours)  
• Inexpensive  
• Sensitivity > 90%, specificity > 95% [12]  
• Increase in false-negative results with antibiotic, antisecretory† and bismuth use  
• Increase in false-negative results in setting of acute upper GI bleeding |
| Histology | • Considered gold standard invasive test  
• Sensitivity and specificity > 95% [11]  
• Minimum of 3 biopsies from 2 different sites in stomach (antrum and stomach)  
• Increase in false-negative results with antibiotic, antisecretory† and bismuth use  
• Increase in false-negative results in setting of acute upper GI bleeding |
| Culture | • Provides antibiotic sensitivity profile  
• Limited availability due to need for specialized personnel and laboratory facilities |
| Polymerase chain reaction | • Limited availability  
• Largely limited to research arena |
| **Independent of endoscopy (noninvasive)** | |
| Urea breath test | • Gold standard noninvasive test  
• Sensitivity and specificity > 95% [17,18]  
• Useful in the setting of low *H. pylori* prevalence  
• Increase in false-negative results with antibiotic, antisecretory† and bismuth use  
• Limited by need for specialized equipment and personnel |
| Fecal antigen test | • Useful in the setting of low *H. pylori* prevalence  
• Increase in false-negative results with antibiotic, antisecretory† and bismuth use  
• Monoclonal test preferred to polyclonal test  
• Sensitivity of 94%, specificity of 97% [23] |
| Antibody test | • Inexpensive and easy to perform  
• Very useful in the setting of high pretest probability of infection  
• Does not necessarily identify active infection  
• Sensitivity of 85%, specificity of 79% [26]  
• Poor positive predictive value in setting of low *H. pylori* prevalence |

*Testing should only be performed if endoscopy is done for another reason.*  
†Proton pump inhibitors, histamine receptor antagonists.
remain in the serum long after disappearance of the organism [16].

INDICATIONS FOR H. PYLORI SCREENING

Peptic Ulcer Disease

The role of *H. pylori* in the pathogenesis of peptic ulcer disease (PUD) has been well characterized [27]. Indeed, at one time more than 90% of duodenal ulcers and nearly 70% of gastric ulcers had been associated with *H. pylori* infection [28]. Although these percentages have been steadily decreasing, particularly in developed countries, with the fall in the background prevalence of *H. pylori* infection, *H. pylori* remains a significant causative agent in PUD. More importantly, eradication of *H. pylori* infection improves ulcer healing and is preventive in ulcer recurrence. A meta-analysis of 57 randomized controlled trials (RCTs) found *H. pylori* eradication to be superior to use of PPIs or H$_2$RAs alone in promoting duodenal ulcer healing [29]. Another meta-analysis of 24 RCTs (> 2000 total patients) found the 1-year remission rate for duodenal and gastric ulcer to be superior in those successfully treated versus those with persistent *H. pylori* infection, 98% vs. 65% and 97% vs. 61%, respectively [30]. For these reasons, PUD and an established history of PUD remain absolute indications for *H. pylori* screening (Table 2) [11,31,32]. Given the high pretest probability of having *H. pylori* infection with PUD, any of the diagnostic modalities are appropriate, including antibody testing. If endoscopy is pursued for other reasons, the test performed should be endoscopy-based. In the setting of bleeding peptic ulcer, endoscopy-based test modalities and FAT have demonstrated higher rates of false-negative results [33]. A meta-regression analysis of 71 clinical trials involving 8496 patients found the performance of delayed diagnostic test 4 weeks following the peptic ulcer bleed more likely to identify *H. pylori* infection with an odds ratio (OR) of 2.08 (95% confidence interval [CI], 1.10–3.93; *P* = 0.024) [34]. An expert panel from the American College of Gastroenterology (ACG) recommends the serologic antibody test with negative RUT and/or histology in the setting of an active upper gastrointestinal (GI) bleed [11]. An international expert panel has also recommended that negative *H. pylori* diagnostic tests done during an acute peptic ulcer bleed be repeated [35].

Gastric MALT Lymphoma

*H. pylori’s* causal role in the development of gastric MALT lymphoma is well established [36] and the pathogenesis well described [37]. More importantly, in localized disease effective *H. pylori* eradication results in tumor regression in 60% to 90%, with only 10% to 15% relapsing [38]. For these reasons, screening for *H. pylori* infection in the setting of gastric MALT lymphoma is universally recommended in all expert panel guidelines [11,31,32]. Equally important is testing following therapy to confirm effective infection eradication. If the diagnosis is not made at endoscopy, the noninvasive test methodology of choice is serologic antibody testing given the high pretest probability and the possibility of low *H. pylori* density in mucosal atrophy or MALT lymphoma [39,40].

Gastric Cancer

Although epidemiologic studies are largely limited to China and Japan, where both gastric cancer and *H. pylori* infection are common, a link between *H. pylori* infection and early gastric cancer has been established [41]. A recent meta-analysis of 19 case-control studies demonstrated a significantly higher prevalence of *H. pylori* infection in patients with early gastric cancer versus noncancer controls (OR, 3.38 [95% CI, 2.15–5.33]) and those with advanced gastric cancer (OR, 2.13 [95% CI, 

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<tr>
<th>Table 2. Indications for Screening for <em>H. pylori</em> Infection</th>
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<tr>
<td><strong>Absolute indications:</strong></td>
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<tr>
<td>• Active peptic ulcer disease (gastric and/or duodenal ulcer)</td>
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<tr>
<td>• Confirmed history of peptic ulcer disease (gastric and/or duodenal ulcer)</td>
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<tr>
<td>• Gastric mucosal associated lymphoid tissue (MALT) lymphoma</td>
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<tr>
<td>• Following endoscopic resection of early gastric cancer</td>
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<td><strong>Strong indications:</strong></td>
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<tr>
<td>• Uninvestigated dyspepsia</td>
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<tr>
<td>• Unexplained iron deficiency anemia</td>
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<tr>
<td>• Primary immune thrombocytopenia (previously termed idiopathic thrombocytopenic purpura)</td>
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<tr>
<td><strong>Indications to be considered on a case-by-case basis:</strong></td>
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<tr>
<td>• Functional dyspepsia (previously termed non-ulcer dyspepsia)</td>
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<tr>
<td>• Chronic nonsteroidal anti-inflammatory drug (NSAID) and/or aspirin use</td>
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<tr>
<td>• Chronic proton pump inhibitor</td>
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<td>• First-degree family member with gastric cancer</td>
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Screening is not recommended for the evaluation of gastro-esophageal reflux disease (GERD)
SCREENING FOR \textit{H. pylori}

1.75–2.59]) \cite{42}. \textit{H. pylori} eradication has also been shown to significantly reduce the incidence of cancer recurrence following the endoscopic resection of early gastric cancer \cite{43}. Furthermore, emerging evidence suggests a preventative role for \textit{H. pylori} eradication in the development of gastric cancer. A meta-analysis of 7 trials (6 from Asia and 1 from Central America) found patients with successfully treated \textit{H. pylori} infection to have a reduced risk of developing gastric cancer compared with controls, (relative risk, 0.65 [95% CI, 0.43–0.98]) \cite{44}. Presently, \textit{H. pylori} is believed to promote gastric cancer development through virulence factors expressed by the organism and the chronic mucosal inflammation caused by infection promoting mucosal atrophy and intestinal metaplasia \cite{8}. Expert panel guidelines universally recommend screening for \textit{H. pylori} in individuals undergoing endoscopic resection of early gastric cancer \cite{11,31,32}. However the value of screening of individuals at increased risk for gastric cancer remains unclear. A recent meta-analysis was performed on 11 studies (none from the United States) involving 1500 individuals with first-degree relatives developing gastric cancer and 2638 controls. The first-degree relatives had a higher prevalence of \textit{H. pylori} (OR, 1.9 [95% CI, 1.4–2.6]), gastric atrophy (OR, 2.2 [95% CI, 1.3–3.8]) and intestinal metaplasia (OR, 2.0 [95% CI, 1.4–2.9]) \cite{45}. Presently, screening those with first-degree relatives developing gastric cancer has been endorsed by several international working groups \cite{31,32}, although this remains controversial in the United States, where gastric cancer remains rare \cite{11}.

\section*{Uninvestigated Dyspepsia}

Dyspepsia, a chronic, recurrent pain or discomfort centered in the upper abdomen, may represent uncomplicated PUD \cite{46}. It stands to reason that identifying and treating \textit{H. pylori} in a subset of those presenting with dyspepsia most likely to have PUD offers clinicians an effective and straightforward treatment strategy. An evidence-based strategy that has been developed and universally endorsed in clinical guidelines is the pursuit of noninvasive testing for \textit{H. pylori} infection followed by treatment for positive results, known as the test-and-treat strategy \cite{11,31,32,47}. This strategy is reserved for a select population consisting of persons under age 45 to 55 with no alarm features (GI bleeding, weight loss > 10% of body weight, anorexia, early satiety, vomiting, dysphagia, odynophagia, anemia, presence of an abdominal mass, lymphadenopathy, family history of upper GI cancer, personal history of PUD, prior gastric surgery or malignancy) \cite{46}. This is considered a cost-effective approach to avoiding invasive testing for dyspepsia \cite{48,49}. In this clinical scenario, the noninvasive \textit{H. pylori} test chosen should be based on the background prevalence of \textit{H. pylori}. In regions where the prevalence of \textit{H. pylori} is low (< 20%), the accuracy of the antibody test in confirming infection is no better than a coin toss \cite{50}; it is therefore strongly recommended that either the UBT or FAT be used. If the antibody test is chosen, a negative result is reassuring but a positive result should be confirmed with testing identifying active infection such as the UBT or FAT.

\section*{Iron Deficiency Anemia}

There is growing evidence to suggest an association between \textit{H. pylori} infection and iron deficiency anemia (IDA). This association has been well established in the pediatric population \cite{51}. The association in adults remains less clear. A recent meta-analysis of 20 studies (15 observational, 5 RCTs, total of 15,183 patients) reported a positive association between \textit{H. pylori} infection and IDA with an OR of 2.22 (95% CI, 1.52–3.24; P < 0.001) \cite{52}. However, only 4 of these studies included adults and the association was weaker with an OR of 1.55 (95% CI, 0.67–3.62). Although the exact manner in which \textit{H. pylori} leads to iron deficiency is debated, a number of pathophysiologic mechanisms have been suggested. Purported pathophysiologic mechanisms include occult blood loss due to chronic erosive gastritis, decreased iron absorption from either hypochlorhydria or achlorhydria, or an increased sequestration and utilization of iron by \textit{H. pylori} \cite{53}. More important than the evidence suggesting such an association is the evidence demonstrating a benefit of \textit{H. pylori} eradication therapy plus oral iron replacement versus oral iron replacement alone on hemoglobin level, serum iron, and serum ferritin in those with IDA testing positive for \textit{H. pylori} \cite{51}. This study found \textit{H. pylori} eradication therapy plus iron replacement superior to iron therapy alone with regard to the rise in hemoglobin (mean difference of 1.48 g/dL [95% CI, 0.96–2.00; P < 0.001]), serum iron (mean difference of 1.15 µmol/L [95% CI, 0.87–1.43; P < 0.001]), and serum ferritin (mean difference of 1.84 µg/L [95% CI, 1.20–2.48; P < 0.001]). These results should still be
interpreted with caution as the majority of these studies were conducted in China, most studies were of marginal methodological quality, and only 4 of the studies included adults. It is for this reason that the ACG expert panel categorized IDA as a controversial indication for H. pylori testing, citing an absence of adequately powered randomized trials confirming a benefit of H. pylori eradication to those with unexplained IDA [11]. On the other hand, the European Helicobacter Study Group and the expert panel for the Asia-Pacific Consensus Conference have both recommended screening for H. pylori infection in those with unexplained IDA [31,32]. Most recently, the British Society of Gastroenterology provided guidelines for the management of IDA in 2011 recommending H. pylori testing for unexplained IDA at the time of diagnostic upper endoscopy or testing by noninvasive means for persistent, unexplained IDA following a nondiagnostic endoscopic evaluation [54]. Based on the above stated evidence, it is reasonable to test adults with unexplained IDA for H. pylori infection. However, a test for active infection such as the UBT, FAT, or endoscopy-based testing should be performed.

**Primary Immune Thrombocytopenia**

There is also growing evidence to suggest an association between H. pylori and primary immune thrombocytopenia (previously idiopathic thrombocytopenic purpura [ITP]). ITP represents an immune-mediated hematologic disorder defined as a platelet count of less than 100 x 10^9/L in the absence of any other cause for the thrombocytopenia [55]. The association between H. pylori and ITP was first reported in 1998 [56]. Although the prevalence of H. pylori infection in ITP is similar to that in the general population, a number of observational and clinical studies have suggested positive effects of H. pylori eradication on platelet counts in ITP. An initial review and meta-analysis of 17 studies (788 ITP patients) revealed a significant correlation between H. pylori eradication and an increase in platelet count [57]. However, it is important to note that these findings were limited by the fact that 16 of 17 studies in the analysis were observational studies. A subsequent systematic review of 25 trials (669 evaluable patients) revealed an complete response (platelet count > 100 x 10^9/L) of 42.7% (95% CI, 31.8%-53.9%) and overall response (platelet count > 30 x 10^9/L and doubling of basal count) of 50.3% (95% CI, 41.6%-59.0%) on those ITP patients with successful H. pylori eradication [58]. This response appeared to be better in countries with higher background prevalence of H. pylori infection, and in milder cases of ITP. Once again, this review was limited in that 24 of the 25 clinical trials were observational. Similar to IDA, the exact manner in which H. pylori relates to ITP remains obscure. A leading purported pathophysiologic mechanism is the production of antibodies to H. pylori cross-reacting with platelet glycoprotein antigens. One such group of antibodies is those against the cytotoxin-associated gene A (CagA) protein expressed on some strains of H. pylori. An Italian study of 62 patients with ITP has demonstrated a platelet response in 82% who had CagA (+) H. pylori versus 12.5% of those who had CagA (-) H. pylori (P = 0.026) [59]. It has also been suggested that the platelet response to eradication therapy is independent of H. pylori and related to the effects of the antibiotics used for treatment [60]. However, a recent meta-analysis refutes this claim [61]. This analysis of 11 clinical trials (282 total patients) reported a platelet response of 51.2% in those who were H. pylori positive compared with a response of only 8.8% in those H. pylori negative following antibiotic therapy. Collectively, the clinical studies to date provide reasonable evidence for a causal relationship between H. pylori infection and ITP. However, more adequately powered RCTs are still needed to establish a clear benefit of H. pylori eradication with improvement in ITP. Questions also remain regarding predictors for treatment response and applicability across more diverse geographical locations than Japan and Italy, where most trials have occurred. It is for these reasons that expert panels still differ on ITP as a clinical indication for H. pylori testing. The ACG has not recognized ITP as an indication for the diagnosis and treatment of H. pylori [11], whereas the European Helicobacter Study Group and the expert panel at the Asia-Pacific Consensus Conference have recommended that clinicians “should seek and treat H. pylori in those with ITP” [31,32]. Although not yet formally recognized as a treatment strategy by either the American Society of Hematology or the British Committee for Standards in Haematology, screening for H. pylori in ITP is considered by some experts in hematology to be a reasonable approach. If a decision is made to screen for H. pylori in ITP, a noninvasive test assessing for active infection such as the UBT or FAT should be utilized.

**Other Indications for Screening**

Clinical conditions in which screening for H. pylori infection remains controversial include functional dyspepsia,
gastroesophageal reflux disease (GERD), individuals taking nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin (ASA), and individuals taking long term PPIs. A Cochrane meta-analysis of 17 RCTs (3566 patients) revealed a small but significant benefit for dyspeptic symptoms in functional dyspepsia patients following H. pylori eradication when compared with placebo or a short course of PPI therapy (10% relative risk reduction) suggesting a number needed to treat (NNT) of 14 (95% CI, 10–25) to cure 1 case of dyspepsia with H. pylori eradication [62]. The relationship between H. pylori and GERD remains unclear. A recent meta-analysis of 11 RCTs (4038 patients) found no significant differences in the response of GERD symptoms (heartburn, acid regurgitation) or endoscopically proven erosive esophagitis between those with successful H. pylori eradication and those with persistent infection [63]. Presently, no clinical guidelines recommend the routine screening for H. pylori infection in the evaluation of GERD [11,31,32]. The primary reason for considering H. pylori screening in individuals taking chronic NSAIDs/ASA is the prevention of PUD. Both H. pylori infection and NSAID/ASA demonstrate independent as well as a synergistic effect on the development of PUD [64]. However, the interaction between H. pylori and NSAID/ASA use in the pathogenesis of PUD remains complex. H. pylori eradication is likely to reduce but not eliminate the risk of PUD in chronic NSAID/ASA users. It should be understood that the eradication of H. pylori in individuals at increased risk for NSAID/ASA-related PUD should not replace co-therapy with an antisecretory agent (PPI or H2RA). Although screening those on long-term NSAIDs/ASA is recommended in the international community, this is not yet the case in the United States [11,31,32]. Ideally, the risk profile for PUD should be considered on a case-by-case basis and screening for H. pylori may be considered based on each individual’s risk profile (risk factors would include age > 75 years, comorbidities, co-administration of other drugs promoting ulceration and bleeding, smoking, past history of PUD or GI bleeding) [65]. A less understood interaction is that of H. pylori infection and the long-term use of PPIs. The rationale for concern is the theoretical acceleration in the development of atrophic gastritis and/or intestinal metaplasia leading to an increased risk in gastric cancer. Limited evidence has suggested a decrease in mucosal inflammation and atrophy with H. pylori eradication [66,67], but the link to metaplasia and subsequent gastric cancer has not been demonstrated. Presently, the screening of those on chronic PPI therapy is not universally endorsed and should be considered by the clinician on a case-by-case basis.

**INDICATIONS FOR H. PYLORI SURVEILLANCE**

Ideally, testing to confirm H. pylori eradication should be pursued in all cases, as treatment failure to an initial course of therapy can occur in as many as 25% of patients in certain populations. Furthermore, persistent infection can lead to future H. pylori-related complications. However, in practice such universal confirmatory testing is oftentimes not possible. There are, however, clinical conditions in which confirmatory testing is imperative. ACG guidelines recommend that any individual with an H. pylori-associated peptic ulcer, an H. pylori-associated MALT lymphoma, recent resection of early gastric cancer, or persistent dyspepsia following the test-and-treat strategy undergo confirmatory testing [11]. Guidelines from other international expert panels recommend confirmatory testing in all cases [31,32]. Confirmatory testing should be done no less than 4 weeks after the completion of a course of eradication therapy and PPI therapy should ideally be held for a minimum of 2 weeks prior to testing.

**CONCLUSION**

In conclusion, with the widespread prevalence of H. pylori and the minority of those infected with H. pylori developing clinical syndromes, the most important decision is deciding when and how to test for H. pylori. Given the established risks associated with H. pylori infection, it is imperative that every effort be made to successfully eradicate the infection once identified. The challenges associated with treatment can be significant with the growing prevalence of multiple drug resistant strains of H. pylori. Therefore, the most important question is not who to treat, but instead who to test for H. pylori infection.

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