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COMMUNIQUÉ

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Helicobacter pylori and Dyspepsia: Where to start?

Over the last 10 years, various recommendations for the identification and treatment of dyspepsia and concomitant *Helicobacter pylori* infection have been offered. Dyspepsia is defined as "impaired gastric function or 'upset stomach' characterized by epigastric pain, sometimes burning, nausea, and gaseous eructation."[1] Biopsy of infected gastric or duodenal tissue and evaluation of that tissue by stains, rapid urease testing, and/or culture has long been considered the gold standard for diagnosis of *H pylori* infection. Newer noninvasive methods such as urea breath testing or stool antigen testing do not require tissue biopsy and because of high sensitivity may be acceptable alternative testing methods depending on the severity of disease, age of patient, and local medical resources. The following discussion provides a brief review of dyspepsia and recommendations for the laboratory diagnosis of *H pylori* infection.

Dyspepsia

Dyspepsia frequently presents as chronic or recurrent pain or discomfort in the upper abdomen.[2] When evaluating the patient presenting with such symptoms, the differential diagnosis includes *H pylori*-related disease (gastritis and peptic ulcer disease), gastroesophageal reflux disease, acute abdominal conditions (eg, cholecystitis, appendicitis), chronic pancreatitis, pancreatic cancer, celiac disease, lactose intolerance, and medication-induced (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]) symptoms.[2] In the American Gastroenterological Association's (AGA) technical review, 4 major causes were identified for patients' dyspeptic complaints: chronic peptic ulcer disease (15% to 25%), gastroesophageal reflux (5% to 15%), malignancy (<2%), and functional (or nonulcer) dyspepsia.[2]

According to the Centers for Disease Control and Prevention (CDC), 10% of the US population has peptic ulcer disease, accounting for $6 billion in direct and indirect costs.[3] Because a link has been established between peptic ulcers and infection with *H pylori*, patients with this condition should be evaluated for the presence of the organism.[2,4-7] Also, when an ulcer is found, it is important to differentiate between *H pylori*-associated ulcers and medication-associated ulcers, as the treatment will differ.

Helicobacter pylori

Infection with *H pylori* is widespread and the organism is involved in most cases of peptic ulcer disease of the stomach and duodenum. According to the CDC, *H pylori* is probably the most common chronic infection, with infection rates of up to 90% in some populations.[3] In Caucasian populations in industrialized countries, *H pylori* infection is infrequent in childhood, but

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prevalence increases 0.5% to 2% with each year of age, reaching about 50% in those 60 or older. Prevalence rates appear to be higher in blacks and Hispanics than in whites. In a recent Mayo study of a random population of 200 apparently healthy blood donors, the positive rate for *H pylori* IgG antibody level was 27.5%.[8]

Research has shown that up to 95% of patients with chronic duodenal ulcers and 70% of patients with chronic gastric ulcers are infected.[1] This flagellated Gram-negative bacillus is successful at colonizing the gastrointestinal mucosa because it alters the alkalinity of the mucus by producing urease. The organism also plays an etiologic role in dysplasia and metaplasia of the gastric mucosa, gastric adenocarcinoma, and non-Hodgkin lymphoma of the stomach. Infection increases the risk of developing gastric cancer and mucosa-associated-lymphoid-type (MALT) lymphoma 2-fold to 6-fold.[5]

While the distribution of the organism is widespread in humans, many people infected with *H pylori* will never develop ulcers. What causes some people to develop ulcers, and not other people, is unknown, but additional risk factors that make individuals more susceptible include abnormal intestinal immune response, genetic predisposition, and lifestyle factors such as coffee consumption, smoking, and stress.

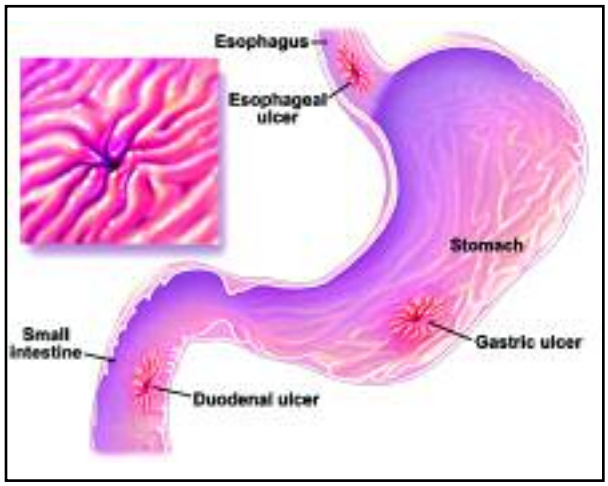

Figure 1. **Ulcers**

While there is widespread recognition of the association of *H pylori* with gastritis or peptic ulcer disease, the approach to diagnosis and treatment varies. For this reason, evidence-based medicine ratings (both recommendations and strength of the evidence supporting the ranking) from the Maastricht 2-2000 Consensus Report are provided where applicable.[9]

The recommendations are ranked by strength:

- Strongly recommended
- Advisable
- Uncertain

The evidence supporting the ranking is described as follows:

Level 1	Well-designed and appropriately controlled studies.
Level 2	Well-designed cohort or case-controlled studies, somewhat flawed studies of persuasive indirect evidence.
Level 3	Case reports, seriously flawed studies or suggestive indirect evidence.
Level 4	Clinical experience.
Level 5	Insufficient evidence to form an opinion.

In addition, Graded Recommendations for Clinical Practice are also provided from newly released practice guidelines developed by the American College of Gastroenterology and the American Gastroenterological Association.[10] These recommendations are based on the strength of evidence and are graded as follows:

Grade	Strength of Evidence to Guide Clinical Practice
A	Supported by 2 or more level I studies without conflicting evidence from other level I studies.
B	Supported by 2 or more level I studies with conflicting evidence from other level I studies or supported by only 1 level I or 2 or more level II studies.
C	Supported by level III-V evidence.

Levels of Evidence[10]:

Level I	Evidence from RCTs with low false positive rates (ie, significant p values), adequate sample sizes (low likelihood of type II errors) and appropriate methodology (low likelihood of type I errors)
Level II	Evidence from RCTs with high false positive rates, inadequate sample sizes, or inappropriate methodology
Level III	Evidence from nonrandomized trials using a contemporaneous cohort of controls
Level IV	Evidence from nonrandomized trials using a historical cohort of controls
Level V	Evidence from case series without controls

Reference citation

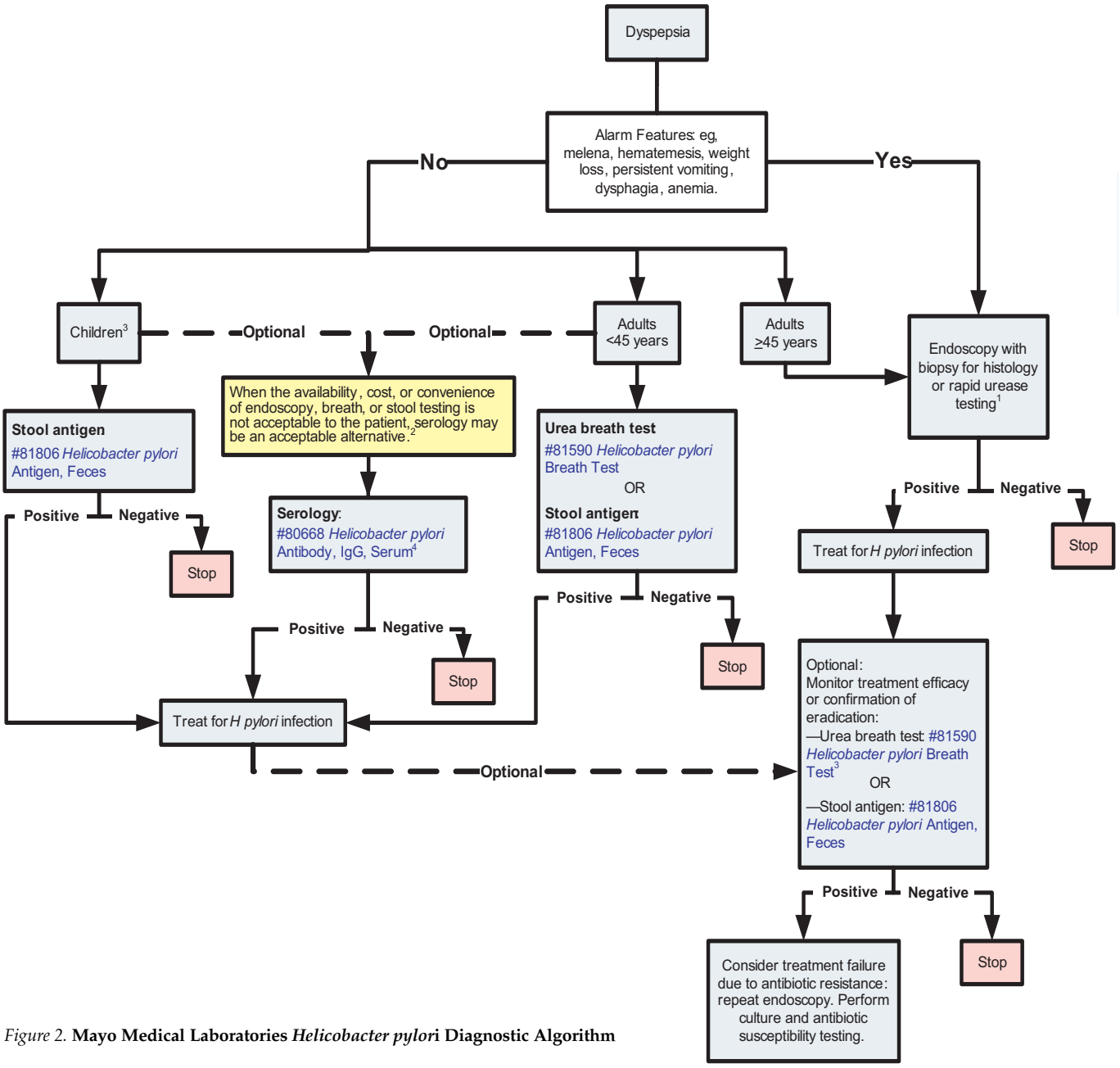

Figure 2. **Mayo Medical Laboratories *Helicobacter pylor*i Diagnostic Algorithm**

Footnotes: 1. While culture is an option, it is not routinely utilized for initial diagnosis of *H pylori* infection in the Mayo Clinic practice. Culture is required for antibiotic susceptibility testing if physicians suspect antibiotic resistance in patients who have previously failed therapy.
2. Histology with special staining for *H pylori* organisms, breath test, stool antigen, and/or culture are the gold standard tests for diagnosis with associated high sensitivity, specificity, and cost.
3. The urea breath test is not FDA approved for use in patients under the age of 18. (as of 7/2005)
4. Due to a low specificity confirmation of positive serologies (especially IgG) by either stool antigen testing or urea breath testing may be useful

Diagnostic Options—*H pylori* Infection

When selecting the appropriate tests and procedures to perform, the first concerns are optimizing detection of gastric cancer, preferably at an early, curable stage, while minimizing unnecessary procedures. Secondly, because dyspepsia may be associated with *H pylori* infection without the presence of ulcers, identification and eradication of infection are recommended.[9]

Maastricht 2-2000 Consensus Report
A "test and treat" (for H *pylori*) is recommended for dyspeptic patients less than 45 years of age.[4] (Recommendation: advisable; based on level 2 evidence.

Endoscopy is useful for gross inspection of tissue to identify inflamed mucosa (gastritis, duodenitis), ulcers, potentially cancerous tissue, strictures, bleeding, or other abnormalities. Endoscopy is also required for obtaining biopsied tissue for delineation of the specific pathogenic process by histopathologic inspection and to confirm the presence of *H pylori* infection. While the specific age cutoff may vary, it has been demonstrated that as patients age, the benefit of endoscopy for diagnosis increases.[2,4] However, for younger patients without alarm symptoms (eg, melena, hematemesis, weight loss, persistent vomiting, dysphagia, anemia), testing for *H pylori* infection by noninvasive (nonendo-scopic) means may be the most economical first step.

Maastricht 2-2000 Consensus Report
For patients with peptic ulcer disease taking long-term and intermittent antisecretory therapy, a "search and treat" approach should be utilized. (Recommendation: strongly recommended; based on level 3 evidence.)

The "search and treat" and "test and treat strategies" represent the same concept, a noninvasive *H pylori* test followed by treatment for positive cases.[18]

Several alternatives to endoscopic biopsy are available for identification of *H pylori* infection. These include the urea breath test, stool antigen test, and serology testing.[9,10] Deciding which of these noninvasive tests to utilize depends upon multiple factors including patient demographics, local access to endoscopy, economic considerations, patient preference, and convenience. Figure 2 provides a diagnostic algorithm that may be useful for selecting the appropriate tests for diagnosing *H pylori* disease in various clinical settings.

Maastricht 2-2000 Consensus Report
In primary care, diagnosis of *H pylori* infection should be by urea breath test or stool antigen test (in the <45 age category). (Recommendation: strongly recommended; based on level 1 evidence.)

ACG/AGA Graded Recommendations (October 2005)
For patients ≤55 years without alarm features, the clinician may use either "test and treat" for *H pylori* or acid suppression therapy, which are both graded A.

Endoscopy

While an invasive procedure, upper gastrointestinal endoscopy carries a low risk of complications.[2] Major complications include perforation, bleeding, cardiopulmonary problems, and infection.[2,11] It has been shown that aggressive evaluation of high-risk patients ≥40 years of age improved the proportion of detectable and curable early gastric cancer from 1% to 26%.[2] Endoscopy allows collection of biopsies, cultures, cytology brushings or washing specimens, as well as visualization of the mucosal tissue.

Some debate continues about whether it is more cost-effective to always perform endoscopy as the first step in diagnosing any suspected *H pylori* infection or to reserve this invasive procedure for patients with alarm features. Depending on antibiotic costs, facility costs, and other charges, it is possible to find supporting data for both approaches. Various studies support proceeding directly to endoscopy based on the patient's age, but agreement on the minimum age has not been reached. The new AGA guidelines support proceeding directly to endoscopy with patients who are more than 55 years of age, or any age patient with alarm features.[10] In Mayo's algorithm (Figure 2), endoscopy is recommended for all patients age 45 or older, or in any patient with alarm features. Endoscopy is also used for obtaining cultures for antibiotic susceptibility determination in patients who fail antibiotic therapy.

Tests on Biopsied Tissue

Biopsied tissue specimens obtained during endoscopy can be evaluated by histology (including special stains for bacteria), a direct rapid urease test, and/or culture.

- Histological evaluation involves direct visualization by a pathologist of hemotoxylin and eosin-stained tissues for mucosal structural changes. Additionally, special stains (eg, Gram, silver, Giemsa, acridine orange, immunofluorescence, or immunoperoxidase stains) are used to visualize *H pylori* bacteria. Sensitivity and specificity ranges for histological evaluation summarized in a recent review were 93% to 98% and 95% to 98%, respectively.[12] As with the rapid urease test, multiple biopsies increase the sensitivity.

- The rapid urease test (CLO-Test is the most commonly recognized, but other brands are available) is a test that detects the urease enzyme produced by *H pylori*. Combined results from 2 recent reviews report a sensitivity of 80% to 98% and a specificity of 93% to 100%.[2,12] Importantly, the more biopsies tested for urease activity, the greater the sensitivity.
- Culture of the organism from the tissue specimen is the slowest method for identifying *H pylori* infection and is no longer a preferred method for diagnosis. While originally considered the gold standard test for *H pylori*, it offers the lowest sensitivity of any of the diagnostic options. Combined results from 2 recent reviews report a sensitivity of 70% to 95%.[7,12] More rapid tests are now preferred for diagnosis. Culture (#9388 Culture, *H pylori*) is required for antimicrobial susceptibility testing.

Urea Breath Test

Patients being tested using a urea breath test consume a drink containing either ^{13}C- or ^{14}C-labeled urea. The *H pylori* organisms rapidly metabolize the urea, absorbing the labeled carbon, and releasing it into the bloodstream as $^{14}CO_2$ or $^{15}CO_2$, which is then exhaled in the breath. The patient breathes into tubes before (baseline) and after (postdose) consuming the drink. The urea breath tests have a sensitivity and specificity ranging from 90% to 95% and 90% to 98%, respectively.[9,12] Based on the 2005 AGA recommendations, the urea breath test is one of the most accurate noninvasive tests currently available (stool antigen testing offers a similar degree of confidence).[10] This test is available from Mayo Medical Laboratories (MML) as #81590 *Helicobacter pylori* Breath Test.

Maastricht 2-2000 Consensus Report
Confirmation of eradication of *H pylori* infection should be by the urea breath test. (Recommendation: advisable; based on level 2 evidence.)

The advantage of the breath test is that it is a relatively simple, noninvasive test, with good acceptance by patients and can be performed as a point-of-care test. Disadvantages to the urea breath test include a 1-hour fasting requirement, and because some medications (antimicrobials, proton pump inhibitors, and bismuth preparations) are known to suppress *H pylori*, patients must abstain from use prior to testing. Ingestion of these medications within 2 weeks prior to performing the test may give false-negative results. Performance of the breath test also requires that staff be properly trained in its use, as adherence to timing and administration guidelines must be closely followed. Also, the kits for collecting the breath are relatively expensive when compared to other testing options. The urea breath test is not only useful as a primary test for diagnosing *H pylori* infection, but also can be used to assess eradication following treatment.

Maastricht 2-2000 Consensus Report
For the diagnosis of the (*H pylori*) infection in primary care, it is strongly recommended that a urea breath test or stool antigen test be used. (Recommendation: strongly recommended; based on level 1 evidence, although such strong evidence is not specifically available in the primary care setting.)

Stool Antigen Test

In the past few years, stool antigen testing has become available as an alternative noninvasive test for the detection of *H pylori* infection. Unlike the urea breath test, stool collection can be performed off-site and without the assistance of trained personnel. While collecting stool specimens is noninvasive and relatively simple, some patients are averse to this procedure, which may impact the physician's decision of which testing method to perform. Based on the 2005 AGA recommendations, the stool antigen test, like the urea breath test, is one of the most accurate noninvasive tests currently available.[10]

In 3 independent studies, the sensitivity and specificity of one of the first available polyclonal commercial antigen tests, the Premier Platinum HpSA (Meridian Diagnostic, Inc., Cincinnati, OH) ranged from 92% to 97% and 90% to 95%, respectively.[13-15] A recent report compared another commercially available test, the FemtoLab *H pylori* test (Connex, Martinsried, Germany). This monoclonal antigen assay appeared to be more sensitive than the Premier Platinum HpSA test (sensitivity 93% vs 84%).[16] Further studies are necessary to confirm these findings.

Mayo's #81806 *Helicobacter Pylori* Antigen, Feces requires collection of 5 grams of stool (without preservatives or other additives), shipped frozen. Negative results do not eliminate the possibility of infection due to *H pylori*. Watery, diarrheal specimens are not appropriate for testing. Also, the test is impacted by treatment with antimicrobials, bismuth, and proton pump inhibitors. Patients should not use these therapeutics for at least 2 weeks prior to stool collection, as they may cause false-negative results. A negative result in

conjunction with the use of the therapeutics should be followed up with a repeat test at least 2 weeks after discontinuing therapy.

Serology

Serologic testing for *H pylori* provides a surrogate assessment for the presence of the organism by detecting IgG, IgM, or IgA antibodies formed in response to *H pylori* antigens. Serologic methods, compared with other methods, are convenient for the patient, easy to perform, do not rely on the accuracy of specimen sampling, and are sufficiently sensitive to detect new cases of *H pylori* infection. However, serologic tests lack specificity when compared to gold standard tests for *H pylori* infection.

Patients with *H pylori* infection nearly always develop antibodies of the IgG class and less frequently develop antibodies of the IgA class. *H pylori*-specific IgM antibodies may be produced shortly after the onset of infection. In some cases, IgA and IgM may be positive in the absence of IgG, especially in early disease. The value of IgA and IgM determinations for indicating active disease is less defined than IgG. Due to the chronicity of this disease, detection of *H pylori*-specific IgG antibodies is the most useful of these serologic markers.

At the time of the Maastricht Consensus Report, it was recognized that "… whole blood tests and office-based serology tests have not reached acceptable accuracy for the diagnosis of *H pylori* infection in primary care (level of evidence, 1)."[9] Since then, serology tests have improved and provide greater accuracy. A recent evaluation at Mayo compared the results for the IgG test to the results for culture biopsies for 204 specimens. For this analysis, the VIDAS HPY assay showed a sensitivity of 98% and specificity of 91%.[17]

Serology tests for *H pylori* available from MML include:
Preferred:
#80668 Helicobacter pylori Antibody, IgG, Serum
Optional:
#84409 Helicobacter pylori Antibody, IgA, Serum
#84408 Helicobacter pylori Antibody, IgM, Serum

Because serology may lack specificity, additional noninvasive tests should be used to confirm *H pylori* infection including the urease breath or stool antigen test.

Verification of Eradication of *H pylori* Infection

Selection of specific therapy depends on the individual patient, the medications available and affordable in the patient's health care system, and physician preference.

Eradication of the infection removes the risk of complications and, when verified, reassures the patient. Eradication of infection may be confirmed by urea breath testing or by stool antigen testing 4 weeks after completion of treatment. Retesting earlier may not detect treatment relapses reliably.

Serology is not an acceptable option to verify eradication, as IgG and IgA levels may remain elevated for more than a year following eradication.

Maastricht 2-2000 Consensus Report
H pylori eradication should be confirmed by urea breath test, which is the recommended first-line posttreatment diagnostic test. (Recommendation: advisable; based on level 2 evidence.)

The widely accepted *H pylori* guidelines from the Maastricht Report strongly recommend *H pylori* eradication therapy in the following populations when patients are found to be positive for the organism:[9]

Population	Strength of supporting evidence
Peptic ulcer disease (active or not, including complicated ulcer)	1
MALT lymphoma	2
Atrophic gastritis	2
Postgastric cancer resection	3
Patients who are first-degree relatives of gastric cancer patients	
Patients' wishes (after full consultation with their physician)	4

Economics of Peptic Ulcer Disease and H pylori Infection

Peptic ulcer disease affects 1 in 10 Americans, with 500,000 to 850,000 new cases diagnosed each year and more than 1 million ulcer-related hospitalizations.[5,9] The associated health care costs, estimated at $6 billion, include hospitalization and physician office visits, as well as decreased productivity and lost work time.[5] *H pylori* infection causes 90% of all peptic ulcers, and eradication of the infection shortens healing time and reduces ulcer recurrence rates.[5] For more than 80% of patients, the ulcer does not recur, reducing the cost of

follow-up care.[5] Curing ulcers costs 90% less than treating ulcer symptoms over a lifetime.[5] Testing for *H pylori* infection should be performed only on patients with gastrointestinal symptoms because of the large percentage of *H pylori*-colonized individuals, especially in older age groups (estimated to be 40% to 60% of asymptomatic Caucasians older than 60 years). One exception is those patients who have gastric cancer or patients with first-degree relatives with gastric cancer.

Maastricht 2-2000 Consensus Report

Patients who are first-degree relatives of gastric cancer patients and infected patients who have early gastric cancer resection should receive treatment to eradicate *H pylori* infection. (Recommendation: strongly recommended; based on level 3 evidence.

Evidence-Based Medicine

The Maastricht Report on *H pylori* and the 2005 AGA guidelines on dyspepsia support a test and treat approach to patients >18 years and <45 years (Maastricht) or ≤55 years (2005 AGA).[9,10] For patients >55 years of age, as well as in patients with alarm symptoms, the AGA guidelines support proceeding directly to endoscopy. In the case of children, Maastricht supported investigation for *H pylori* infection in children only when the child presents with signs or symptoms of organic disease severe enough to outweigh the risks of therapy.[9] When justified, the urea breath test* and the stool antigen test are preferred for children without alarm features, while endoscopy is the preferred method for evaluation of children with alarm features.

Summary

Dyspepsia and *H pylori* infection are widespread problems that represent a significant cost in our health care environment. Detection and eradication of *H pylori* infection has been identified as the first step in the management of dyspepsia. For this reason, guidelines have been developed to help the primary care physician determine the appropriate approach to the patient with *H pylori* infection. Endoscopy with evaluation of biopsied tissue serves as the gold standard test for *H pylori* infection, yet in many locations, endoscopy facilities and trained endoscopists are not readily accessible. The costs and risks associated with endoscopy may also make it unacceptable to the patient. When endoscopy is not performed, stool antigen, urea breath testing, and serology offer noninvasive/minimally invasive options for *H pylori* detection. Stool antigen and urea breath testing are the preferred noninvasive tests for identification of *H pylori* infection. However, costs, patient inconvenience, and patient attitudes also may make these options unacceptable to patients or physicians. Serology is an alternative that is minimally invasive and the process is familiar to most patients.

*The urea breath test is not FDA approved for use in patients under the age of 18 (as of 7/2005).

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Abstracts of Interest

B-Type Natriuretic Peptide as a Biomarker Beyond Heart Failure: Speculations and Opportunities

Paul M McKie BS and John C Burnett Jr MD

Cardiac secretion of B-type natriuretic peptide (BNP) increases with the progression of heart failure (HF), and plasma measurement of BNP has emerged recently as a useful, cost-effective biomarker for the diagnosis and prognosis of HF. The diagnostic utility of BNP is complemented by its therapeutic use in decompensated HF. Although clinical use of BNP as a biomarker in HF is increasing, the specificity of BNP for HF is not robust, suggesting that other mechanisms beyond simple ventricular stretch stimulate BNP release. Several studies have shown that BNP levels increase in other cardiovascular disease states including ischemia, arrhythmias, fibrosis, cardiac hypertrophy, and coronary endothelial dysfunction. Furthermore, 2 important studies revealed recently that moderate elevations in BNP level, well below the HF range, have prognostic value for future cardiovascular events. Specifically, BNP levels greater than 20 pg/mL were associated with significantly increased risk of HF and atrial fibrillation. These observations increase speculation that elevated BNP levels represent a final common pathway for many cardiovascular pathologic states and that BNP can be used as a biomarker for non-HF mechanisms, preclinical disease, and other pathologic states of myocardial disease.

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