



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Helicobacter Pylori (H. Pylori) Testing

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Hyperlink to Related Coverage Policies

Proton Pump Inhibitor Therapy

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers any of the following methods as medically necessary for diagnosing Helicobacter pylori (H. pylori) infection:

- endoscopic biopsy with urease testing, histology and/or culture
- H. pylori stool antigen (HpSA)
- serology in individuals not previously treated for H. pylori infection
- urea breath testing (as outlined below)

CIGNA covers the urea breath test (UBT) as medically necessary for diagnosing H. pylori infection in adults when ALL of the following criteria are met:

- The individual presents without alarm symptoms of cancer or ulcer complications (e.g., melena, hematemesis, persistent vomiting, anemia, acute onset of total dysphagia or involuntary weight loss greater than 5%).
- The individual has not been treated with proton pump inhibitors (PPIs) for at least two weeks prior to testing.
- The individual requires H. pylori testing for **ANY** of the following indications:
 - active peptic ulcer disease (PUD) or symptoms consistent with PUD
 - documented history of PUD
 - low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma

- recurrent symptoms at least four weeks after completion of treatment for H. pylori infection
- post-treatment testing following resection of early gastric cancer or to confirm eradication of H. pylori infection for those with recurrent or refractory PUD prior to cessation of treatment

CIGNA does not cover screening for H. pylori infection in the absence of upper gastrointestinal tract symptoms and/or pathology because it is considered not medically necessary.

General Background

Helicobacter pylori (H. pylori) is a key causal factor in most peptic ulcer disease and a primary risk factor for gastric cancer. The pathogenic role of H. pylori in peptic ulcer disease, both duodenal and gastric, is well-recognized. Nearly 95% of patients with duodenal ulcers and 80 % of patients with gastric ulcers are found to be infected with H. pylori. Treatment for H. pylori infection includes varied combinations of antibiotics, proton pump inhibitors (PPIs), histamine H2 receptor antagonists and bismuth compounds. Eradication of H. pylori significantly lowers the recurrence rate of H. pylori-associated peptic ulcers.

Associations have been made between H. pylori and both dyspepsia and gastroesophageal reflux disease (GERD). Dyspepsia is clinically defined as nausea, epigastric pain or discomfort experienced on more than seven days of a four-week period. Factors that affect the management of dyspepsia include the patient's age, routine use of NSAIDs, and presence of any alarm symptoms. Alarm symptoms are identified as melena, hematemesis, persistent vomiting, anemia, acute onset of total dysphagia or involuntary weight loss greater than 5%. The procedure of choice for evaluation of dyspepsia is endoscopy, especially when alarm symptoms are present. For patients with a documented history of PUD who present with dyspepsia in the absence of reflux or alarm symptoms, management should begin with testing for H. pylori, followed by eradication therapy if results are positive. It has not been proven that eradication of H. pylori improves symptoms in patients with non-ulcer dyspepsia.

The relationship between H. pylori infection and GERD remains unclear. The majority of patients with typical reflux symptoms respond to lifestyle changes and acid suppression therapy. If these interventions are not effective, additional testing, such as upper gastrointestinal series, endoscopy or 24-hour pH monitoring, may be needed. There is no recommendation for H. pylori testing in patients with GERD (The Institute for Clinical Systems Improvement [ICS], 2006).

H. pylori infection also significantly increases the risk of gastric lymphoma of mucosa-associated lymphoid tissue (MALT) (Suerbaum, 2002). Eradication of H. pylori alone has been found to induce regression of gastric MALT lymphoma in 70–80% of cases. Most of the patients whose lymphomas respond to eradication therapy stay in remission for several years

H. Pylori Testing Methods

H. pylori infection can be confirmed by invasive or noninvasive methods. Invasive tests require upper esophagogastroduodenal (EGD) endoscopy, which is considered the reference method of diagnosis. Noninvasive methods include H. pylori stool antigen (HpSA), serology, and urea breath testing. The clinical utility of these testing methods lies in their ability to accurately identify H. pylori infection, which allows for subsequent treatment and eradication.

Endoscopy: During endoscopy, biopsy specimens of the stomach and duodenum are obtained, and the diagnosis of H. pylori can be made by urease testing, histology and/or culture. If possible, noninvasive testing is done before tissue testing.

H. pylori stool antigen (HpSA): HpSA testing is based on monoclonal antibody immunochromatography of stool samples. This testing method identifies active infection and can be used to detect eradication after treatment. A sensitivity and specificity range of 92–98% is reported in the literature for stool antigen testing.

Serology: Serological assays measure specific H. pylori immunoglobulin G (IgG) antibodies that can determine if an individual has been infected. The sensitivity and specificity of these assays range from 80–95%, depending on the assay used. Serological testing has been the mainstay of H. pylori diagnosis, particularly in primary care,

due to the accessibility, rapid results and low cost of this testing method. However, some serological tests have not been locally validated and therefore have suboptimal sensitivity and specificity in practice. The value of noninvasive *H. pylori* testing is also related to the background prevalence of *H. pylori* infection. False-positives are more likely to occur in areas where *H. pylori* infections are less prevalent (Talley, et al., 2005a). Serological tests are also unreliable indicators of *H. pylori* status in patients who have received treatment for the infection. Because it cannot distinguish between current and past infection, serological testing has poor accuracy in settings of low and intermediate *H. pylori* prevalence, limiting its value in the United States (Vakil and Fendrick, 2006).

Urea Breath Test: In a UBT, the patient is given an oral preparation of either nonradioisotope carbon-13- (¹³C-) labeled urea, or radioactive isotope carbon-14- (¹⁴C-) labeled urea. In the presence of *H. pylori* infection, bacterial urease metabolizes the urea to produce labeled carbon dioxide (CO₂) and ammonia. The labeled carbon diffuses into the bloodstream and is excreted by the lungs. This labeled carbon can then be measured as CO₂ in the patient's expired breath to determine the presence of *H. pylori*. UBT is indicated for the initial diagnosis of *H. pylori* infection and for follow-up of eradication therapy. The sensitivity and specificity of UBT ranges from 94–98%. False-negatives can result from acid suppression with PPIs; therefore, acid suppression treatment should be withheld for two weeks prior to testing. In addition, retesting for confirmation of eradication should be done at least four weeks after completion of therapy.

U.S. Food and Drug Administration (FDA)

The Meretek UBT[®] Breath Collection Kit (Meretek Diagnostics Inc., Nashville, TN) was cleared for marketing on November 1, 1996, by the FDA. Subsequently, the UBT Lite[™] and the BreathTek[™] - UBiT[™] were granted 510(k) approval by the FDA on February 24, 2000, and January 17, 2002, respectively. The FDA considers them both substantially equivalent to the Meretek UBT Breath Collection Kit. Meretek UBT systems are intended for use in the qualitative detection of *H. pylori* and as an aid in the initial diagnosis and post-treatment monitoring of *H. pylori* infection in adult patients (i.e., age 18 and older). The test may be used to monitor treatment if used at least four weeks following completion of therapy. The BreathID[™] system (Oridion, Jerusalem, Israel), was granted marketing approval by the FDA via the 510(k) process on July 9, 2001. The UBT component of the BreathID system is a ¹³C-urea test.

Literature Review

There is sufficient evidence in the form of randomized controlled trials (RCTs), comparative, and evaluation studies (Gatta, et al., 2005; Islam, et al., 2005; Perri, et al., 2005; Israeli, et al., 2003; McColl, et al., 2002; Shirin, et al., 2001) to support the accuracy of UBT, HpSA, and serology as testing methods for *H. pylori*, using histology and urease testing as the reference standard. The UBT has been proven to be a safe and effective test for identifying the presence of *H. pylori* with established sensitivity and specificity ranges of 94–98%. The accuracy of the UBT is comparable to endoscopic biopsy and to HpSA testing which has a sensitivity and specificity of 92–98% (Islam, et al., 2005; Perri, et al., 2005). Serology testing for *H. pylori* pre-dates the UBT and the HpSA test, and has been reported to have decreased accuracy based on local validation with a wider sensitivity and specificity range of 80–95%.

The effectiveness of urea breath testing in children has been controversial. Guarner et al. (2010) conducted a systematic review of the evidence on *H. pylori* diagnostic tests in children and found UBTs to have a >75% sensitivity for the detection of *H. pylori* before and after treatment. A study (n=108) by Frenck et al. (2007) evaluated UBT results and reported sensitivity and specificity values of 98% and 89%, respectively. It was found that the sensitivity of the UBT was not affected by age, but the specificity was lower in children < six years of age (86%) compared to children ≥ six years of age (95%).

In another evaluation study (n=274) by Yang and Seo (2005), the cut-off value of the ¹³C-UBT was adjusted to determine the optimal level for children. High false-positive results and low specificity were noted in children ≤ six years of age compared to children older than six years at a cut-off value of 4.0 per thousand (false- positives; 8.3% vs. 0.85%, specificity; 89.8% vs. 98.8% respectively). In the context of this study, the optimal cut-off values were found to be 4.0 per thousand in children older than six years and 7.0 per thousand in children ≤ six years.

Inconsistent results from the available studies make it difficult to draw conclusions as to the accuracy of this testing method for children, especially those under the age of six.

Professional Societies/Organizations

According to the ACG practice guidelines for the management of *H. pylori* infection, there is no single test that can be considered the gold standard for the diagnosis of *H. pylori*. The most appropriate test for any particular situation will be influenced by the clinical factors, the pretest probability of infection and the availability of a given diagnostic test. The *H. pylori* test of choice also depends on whether or not endoscopy is needed and understanding the strengths and weaknesses of each test. If endoscopy is required and there is active bleeding at time of the procedure, then a negative histology or rapid urease test result should be confirmed by another testing method such as serology. The guidelines state that antibody testing (e.g., serum, whole blood, urine) is widely available but has poor positive predictive value in populations with a low prevalence of *H. pylori* infection, limiting its usefulness in clinical practice. Antibody testing is of limited benefit in documenting eradication of *H. pylori*, as results can remain positive years after successful cure of the infection. The UBT and fecal antigen test are reliable methods of identifying active *H. pylori* infection before and proving *H. pylori* eradication after antibiotic therapy. Established indications for the diagnosis and treatment of *H. pylori* include the following:

- active PUD (gastric or duodenal ulcer)
- confirmed history of PUD (not previously treated for *H. pylori*)
- gastric MALT lymphoma (low grade)
- after endoscopic resection of early gastric cancer
- uninvestigated dyspepsia (depending upon *H. pylori* prevalence)

Controversial conditions associated with *H. pylori* testing include nonulcer dyspepsia, GERD, unexplained iron deficiency anemia, the use of NSAIDs and populations at higher risk for gastric cancer (Chey, et al., 2007).

The Institute for Clinical Systems Improvement (ICSI) guideline for dyspepsia and GERD states that testing and treatment of *H. pylori* is the cornerstone of the management of PUD. According to ICSI, there are serological testing products that permit the accurate diagnosis of *H. pylori*; however, stool antigen is now the noninvasive office-based test of choice due to the high positive likelihood ratio of serological testing. Post-treatment testing is not typically recommended but may be indicated in selected patients with complicated ulcer disease, low-grade MALT lymphoma and following resection of early gastric cancer. The UBT is the test of choice in those cases where post-treatment testing is needed (ICSI, 2006).

The American Gastroenterological Association (AGA) guidelines state that patients age 55 or younger without alarm features should receive *H. pylori* testing and treatment, followed by acid suppression if symptoms continue. According to the AGA, noninvasive *H. pylori* testing is optimally performed by a ¹³C-urea breath test or stool antigen test. The AGA also recommends endoscopic evaluation for patients older than 55 years of age and for younger patients with alarm features (e. g., weight loss, progressive dysphagia, recurrent vomiting, evidence of gastrointestinal bleeding, or family history of cancer) who present with new-onset dyspepsia. Biopsy specimens for *H. pylori* should be obtained at the time of endoscopy, and eradication therapy offered to those who are infected, as this may reduce the risk of subsequent PUD and gastric malignancy (Talley, 2005).

In 2004, the Canadian Helicobacter Study Group (CHSG) updated their guidelines, defining appropriate management strategies for the identification and eradication of *H. pylori* in children and adolescents. The CHSG states that the current gold standard for the detection of *H. pylori* in children remains upper endoscopy with mucosal biopsies. The ¹³C-UBT is the best noninvasive diagnostic test for *H. pylori* infection in children. To date, studies indicate that the ¹³C-UBT is a reliable testing method in children older than six years of age. The consensus group found insufficient evidence to recommend stool antigen tests as an acceptable noninvasive diagnostic tool for *H. pylori* in children (Bourke, et al., 2005).

According to the National Institute for Clinical Excellence (NICE) guidelines for the management of dyspepsia in adults, *H. pylori* can be initially detected using either a carbon-13 urea breath test (UBT), stool antigen test or laboratory-based serology where its performance has been locally validated. (NICE, 2004).

Summary

Esophagogastroduodenal (EGD) endoscopy with biopsy is considered the reference method for the diagnosis of *Helicobacter pylori* (*H. pylori*). The overall body of literature suggests that noninvasive testing with the urea breath test (UBT) is as effective as endoscopy in managing select patients with uncomplicated upper gastrointestinal symptoms. *H. pylori* stool antigen (HpSA) testing provides an acceptable alternative to UBT. Serological testing cannot distinguish between active and resolved infection and is therefore not recommended

for monitoring infection or confirming the eradication of H. pylori. Serology-based tests are also not recommended as the first choice for diagnosis.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
43239	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; with biopsy, single or multiple
78267	Urea breath test, C-14 (isotopic); acquisition for analysis
78268	Urea breath test, C-14 (isotopic); analysis
83009	Helicobacter pylori, blood test analysis for urease activity, non-radioactive isotope (eg, C-13)
83013	Helicobacter pylori; breath test analysis for urease activity, non-radioactive isotope (eg, C-13)
83014	Helicobacter pylori; drug administration
86677	Antibody; Helicobacter pylori
87338	Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple step method; Helicobacter pylori, stool
87339	Infectious agent antigen detection by enzyme immunoassay technique, qualitative or semiquantitative, multiple-step method; Helicobacter pylori

ICD-9-CM Diagnosis Codes	Description
041.86	Helicobacter pylori (H. pylori) infection
200.30	Marginal zone lymphoma, unspecified site, extranodal and solid organ sites
533.00 – 533.91	Peptic ulcer, site unspecified
535.20	Gastric mucosal hypertrophy without mention of hemorrhage
V12.71	Personal history of peptic ulcer disease
V45.75	Acquired absence of organ, stomach
	Multiple/Varied

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	04/15/2008	0308	Helicobacter Pylori (H. Pylori) Testing

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