Helicobacter Pylori Testing AHS – G2044 “Notification”

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Policy Effective August 13, 2019

Description
Helicobacter pylori (H. pylori) is a gram negative bacteria which causes chronic inflammation (infection) in the stomach and is associated with conditions, such as peptic ulcer disease, chronic gastritis, gastric adenocarcinoma, and gastric mucosa associated lymphoid tissue (MALT) lymphoma (Crowe, 2018).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
BCBSNC will provide coverage for helicobacter pylori testing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member’s Benefit Booklet for availability of benefits. Member’s benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Helicobacter Pylori Testing is covered

1. Urea Breath testing OR stool antigen testing for H. Pylori infection is considered medically necessary for adult patients (>18y) in the following situations:
   a. In the evaluation of a patient with suspected H.Pylori infection and the following symptoms:
      i. dyspeptic symptoms, or
      ii. active peptic ulcer disease (PUD), or
      iii. past PUD without H.Pylori history, or
      iv. low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or
      v. a history of endoscopic resection of early gastric cancer (EGC), or
      vi. patients with uninvestigated dyspepsia who are under the age of 60 years and without alarm features, or
      vii. Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID), or
      viii. Patients with unexplained iron deficiency anemia
ix. In the evaluation of a patient with chronic immune thrombocytopenic purpura (ITP) and suspected *H. Pylori* infection.

b. Re-evaluation to measure success of eradication of *H. Pylori* infection, at least 4 weeks post-treatment.
   1. Any patient with an *H. pylori*-associated ulcer.
   2. As part of the follow-up of patients with persistent symptoms of dyspepsia following appropriate antibiotic treatment for *H. Pylori*.
   3. In patients with Gastric MALT Lymphoma.
   4. In individuals who have undergone resection of early gastric cancer

2. Urea Breath testing OR stool antigen testing for *H. Pylori* infection is considered medically necessary for pediatric patients (<18y) in the re-evaluation to measure success of eradication of *H. Pylori* infection, at least 4 weeks post-treatment

3. Biopsy-based endoscopic histology test and either Rapid Urease Test or culture is considered medically necessary in pediatric patients (<18y) for the diagnosis of *H. Pylori* infection in the following situations:
   a. Children with gastric or duodenal ulcers
   b. Children with refractory iron deficiency anemia (IDA) in which other causes have been ruled out

4. Biopsy-based endoscopic histology test and Rapid Urease Test or culture is considered medically necessary in adult patients (>18 y) undergoing endoscopic examination or in those with alarm symptoms for the diagnosis of *H. Pylori* infection

**When Helicobacter Pylori Testing is not covered**

1. Urea Breath testing OR stool antigen testing for *H. Pylori* infection is considered not medically necessary for asymptomatic pediatric (<18y) and asymptomatic adult (>18y) patients in all other situations and adult patients with typical symptoms of gastroesophageal reflux disease (GERD) who do not have a history of peptic ulcer disease (PUD)

2. Serologic testing for *H. Pylori* infection is considered not medically necessary in adult and pediatric patients as it does not distinguish between currently active infection with past exposure and an infection that has been cured.

3. Biopsy-based endoscopic histology test and Rapid Urease Test or culture is considered not medically necessary in pediatric patients (<18y) for the diagnosis of *H. Pylori* infection in the following situations:
   a. Children with functional abdominal pain
   b. As part of initial investigation in children with iron deficiency anemia
   c. When investigating causes of short stature

4. Testing with the Urea Breath test and/or stool antigen and/or biopsy-based testing is considered not medically necessary in patients with recent use of antibiotics, proton pump inhibitors (PPIs) or bismuth.

5. Concurrent testing with the Urea Breath test and/or stool antigen testing and/or biopsy-based testing is not considered not medically necessary as simultaneous use of both methods does not improve clinical understanding.
6. The use of nucleic acid testing for H. pylori, including polymerase chain reaction (PCR), 16S rRNA, 23S rRNA, and next-generation sequencing (NGS) of H. Pylori, is considered not medically necessary as it is not practical for routine diagnosis.

Policy Guidelines

Background

Infection with H. pylori is common, with conservative estimates at 50% of the world’s population affected. Prevalence in the United States is significant, estimated to be 30 – 40% in the general population (Siao & Somsouk, 2014). H. pylori is associated with many conditions, such as peptic ulcer disease, chronic gastritis, and gastric mucosa associated lymphoid tissue (MALT) lymphoma. Other conditions such as dyspepsia have been attributed to H. pylori as well (Crowe, 2018). Common symptoms of these conditions include gastritis, dyspepsia, heartburn, and stomach pain (Jensen, 2019; Longstreth, 2017).

Identification of H. pylori infection is accomplished with one or more of the several tests available. The choice of test is guided by the reason for the test, cost and availability of the test, the patient’s age and clinical presentation, prevalence in a population, and the patient’s use of certain medications. Testing for H. pylori infection is done for two main reasons: to detect active infection that will be treated and to confirm eradication of the infection post-treatment. Invasive and non-invasive approaches have been used. Endoscopy and collection of biopsy specimens for evaluation of H. pylori infection typically is done in older individuals and those with “alarm” symptoms, including bleeding, unexplained anemia, unexplained weight loss, progressing dysphagia, recurrent vomiting, a family history of gastrointestinal cancer, or a personal history of esophagogastric malignancy. Tissue samples can be tested for H. pylori via methods, such as a rapid urease test, culture, or staining. Testing for eradication of infection may be performed with the same tests used for diagnosis (Crowe, 2018).

Analytical Validity

Non-invasive options for detection of active H. pylori infection include urea breath tests and stool antigen testing. The stool antigen test is an immunoassay that detects the presence of H. pylori in a stool sample. The test is reported to have greater than 90% sensitivity and specificity for detection of active H. pylori infection, and its use has been FDA cleared for all ages. This test may be used for initial diagnostic purposes and for post-treatment testing. Urea breath tests, which take advantage of the bacteria’s urease activity, may also be used to detect active H. pylori infection. The patient ingests a solution containing either 13C or 14C labeled urea, after a set amount of time, the patient’s breath is collected and analyzed for the presence of 13C or 14C labeled CO2. If H. pylori is present it will have metabolized the labeled urea and labeled CO2 will be detected, thus indicating infection with H. pylori. This test takes approximately 15-20 minutes (Crowe, 2018).

ELISA-based serological tests are also available for detection of H. pylori. However, serological tests often need validation at the local level, which may not be practical in routine practice. Furthermore, serological tests do not distinguish between past and present infections. Serological tests also have a very low positive predictive value in populations with low or average prevalence, as the antibodies will be detected even after an infection has been treated or naturally resolved. In these low-prevalence areas, a positive serological test is more likely to be a false positive (Crowe, 2018).

Other tests such as PCR-based tests are infrequently used. The PCR test, despite its high accuracy, is often too expensive for routine use. In fact, nested PCR tests have approached 100% sensitivity and 100% specificity for detection of H. pylori (Singh et al., 2008), but the test may not be widely available and may be of limited use due to high cost (Crowe, 2018; Patel, Pratap, Jain, Gulati, & Nath, 2014). PCR tests have been used for diagnostic purposes as well as identifying genetic variants of the bacteria and pathogenic genes present in a patient. A variety of body fluids, such as stool and saliva, have been used in PCR tests for this bacterial species (Patel et al., 2014).
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Some medications are known to inhibit the growth or urease activity of *H. pylori* and can cause a false negative *H. pylori* test result. Proton pump inhibitors, antibiotics, and bismuth-containing medications may decrease sensitivity of tests, thereby increasing rates of a false negative. Eradication testing is often done weeks after treatment is completed (Crowe, 2018).

**Clinical Validity and Utility**

The stool antigen test has been shown to have strong accuracy. A meta-analysis by Gisbert et al focusing on 2499 patients of 22 studies found the diagnostic test to have a sensitivity of 0.94 and a specificity of 0.97. The monoclonal version of the test was shown to be more sensitive than the polyclonal one (0.95 vs 0.83). The authors also evaluated the diagnostic test after eradication of the bacteria in 957 patients of 12 studies. The authors evaluated the antigen test at 0.93 sensitivity and 0.96 specificity post-eradication (Gisbert, de la Morena, & Abraira, 2006).

The rapid in-office, monoclonal test is widely used and provides significant benefit in terms of availability and speed. However, a study using the test as a reference to compare against a new test found the in-office test to only have a 0.50 sensitivity and 0.96 specificity out of 162 patients (Korkmaz, Findik, Ugurluoglu, & Terzi, 2015).

The UBT has also been well-validated. A meta-analysis by Ferwana et al including 3999 patients of 23 studies found the diagnostic test to have a pooled sensitivity of 0.96 and a pooled specificity of 0.93. The authors noted that their populations had significant heterogeneity, but concluded that the UBT had high diagnostic accuracy for detecting an *H. pylori* infection (Ferwana et al., 2015). This test is often considered the gold standard for diagnosing an *H. pylori* infection (Patel et al., 2014).

Serological tests to assess infection have also been used. A meta-analysis by Loy et al focused on commercial serological kits assessing *H. pylori*. Loy et al found these kits to have a pooled sensitivity of 0.85 and specificity of 0.79. The authors concluded that there was no major difference in accuracy between any of the kits tested (Loy, Irwig, Katelaris, & Talley, 1996).

**Guidelines and Recommendations**

**American Gastroenterological Association (AGA)**

The AGA recommends that “patients 55 years or younger without alarm features should receive *H. pylori* test and treat followed by acid suppression if symptoms remain” and note that “*H. pylori* testing is optimally performed by a 13C-urea breath test or stool antigen test.” Alarm features include symptoms such as recurrent vomiting and weight loss. Additionally, the AGA indicates that “although the yield of endoscopy is low, it is recommended for patients older than 55 years of age and for younger patients…presenting with new-onset dyspepsia.” They reason that endoscopy with biopsy is the preferred test for this age group because upper gastrointestinal malignancy becomes more common after age 55 years (Talley, 2005).

Joint guidelines from the AGA and Canadian Association of Gastroenterology (CAG) noted that dyspepsia patients under 60 should be tested for *H. pylori* (ACG, 2017).

In 2015 the AGA published a Technical review on Upper Gastrointestinal biopsy to evaluate dyspepsia in the absence of visible mucosal lesions and found that:

- In the defined population, biopsy of normal-appearing gastric mucosa can detect HP [*H. pylori*] infection that would be missed on the exam without biopsies. The quality of evidence is very low, and there are noninvasive methods to detect HP infection.
- “Detection of HP infection with tissue biopsy and its eradication in patients with dyspepsia is associated with symptom improvement and reduction of risk for HP-related comorbidities, including gastric cancer compared with no biopsy (or
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no eradication). The quality of evidence is moderate. The effect on symptom resolution is not universal and it does not appear to improve well-being. Quality of evidence for this statement is low” (Allen, Katzka, Robert, & Leontiadis, 2015).

American College of Gastroenterology (ACG, 2017)

The ACG has released guidelines on testing for H. pylori:

- All patients with active peptic ulcer disease (PUD), a past history of PUD (unless previous cure of H. pylori infection has been documented), low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or a history of endoscopic resection of early gastric cancer (EGC) should be tested for H. pylori infection. Those who test positive should be offered treatment for the infection.
- In patients with uninvestigated dyspepsia who are under the age of 60 years and without alarm features, non-endoscopic testing for H. pylori infection is a consideration. Those who test positive should be offered eradication therapy.
- When upper endoscopy is undertaken in patients with dyspepsia, gastric biopsies should be taken to evaluate for H. pylori infection. Infected patients should be offered eradication therapy.
- Patients with typical symptoms of gastroesophageal reflux disease (GERD) without history of PUD need not be tested for H. pylori infection. For those who are found to be infected, treatment should be offered, acknowledging that effects on GERD symptoms are unpredictable.
- In patients taking long-term low-dose aspirin, testing for H. pylori infection could be considered.
- Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID) should be tested for H. pylori infection. Those who test positive should be offered eradication therapy.
- Patients with unexplained iron deficiency (ID) anemia despite an appropriate evaluation or idiopathic thrombocytopenic purpura should be tested for H. pylori infection.
- There is insufficient evidence to support routine testing and treating of H. pylori in asymptomatic individuals with a family history of “gastric cancer or patients with lymphocytic gastritis, hyperplastic gastric polyps and hyperemesis gravidarum”.
- The ACG recommends the breath test and fecal stool antigen test as eradication tests, supported by moderate evidence (Chey, Leontiadis, Howden, & Moss, 2017).

National Institute for Health and Care Excellence (NICE)

NICE recommends testing for H. pylori with a carbon-13 urea breath test or a stool antigen test. A re-test should be with a breath test. Office-based serological tests are not recommended. NICE recommends a “2-week washout period after proton pump inhibitor (PPI) use before testing for Helicobacter pylori.” NICE recommends that individuals with positive H. pylori tests be offered therapy to eradicate the bacteria; however, they note that re-testing to confirm eradication should not be routinely offered. NICE limits the recommendation for post-treatment testing to “people with peptic ulcer (gastric or duodenal)...6 to 8 weeks after beginning treatment, depending on the size of the lesion (NICE, 2014).

NICE released further guidelines in 2015 reaffirming the carbon-13 urea breath test and the stool antigen test to test for H. pylori. A locally validated lab-based serology test may also be used to
assess *H. pylori*. NICE reaffirms the 2 week washout period before testing for *H. pylori* if the patient is on PPIs as well as the 4 week washout period if the patient is on antibiotics (NICE, 2015).

**American College of Cardiology**

The American College of Cardiology recommends testing for and eradicating *H. pylori* in patients with a history of ulcer disease before starting chronic antiplatelet therapy (Bhatt et al., 2008).

**The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN, 2016)**

The ESPGHAN and NASPGHAN have issued updated guidelines for management of *H. pylori* in children and adolescents. They have proposed recommendations for diagnosis and management of *H. pylori* infection in pediatric patients. They have defined pediatric patients as children and adolescents below 18 years of age. The following recommendations were stated:

The guidelines recommend biopsies for rapid urease test and other cultures should only be taken if treatment is likely to be offered in the case of a confirmed infection. Treatment may be considered if *H. Pylori* is an incidental finding at endoscopy.

The guidelines recommend against a “test and treat” strategy for *H. pylori* infection in children. The panelists explained that performing a noninvasive test to detect infection and treat is not needed because *H. pylori* infection usually does not cause any symptoms in the absence of peptic ulcer disease (PUD).

The guidelines recommend that “testing for *H. pylori* be performed in children with gastric or duodenal PUD.”

The guidelines recommend against diagnostic testing for *H. pylori* infection in children with functional abdominal pain, iron deficiency anemia, and when investigating causes of short stature. Serology-based testing was also not recommended.

PPIs should be stopped 2 weeks before *H. pylori* testing, and antibiotics should be stopped 4 weeks before *H. pylori* testing. Diagnosis should be based on either: “positive culture or *H. pylori* gastritis on histopathology with at least 1 other positive biopsy-based test”.

The non-invasive diagnostic testing was indicated in children when investigating causes of chronic immune thrombocytopenic purpura or for the assessment of anti-*H. pylori* therapy at least after 4 weeks of therapy (L. Jones et al., 2017).

**Maastricht V/Florence Consensus Report (2017)**

This report was published on behalf of the European Helicobacter and Microbiota Study Group and Consensus panel. The panel reports that UBT is “the most investigated and best recommended non-invasive test in the context of a ‘test-and-treat strategy’”. The panel also notes that monoclonal tests can be used and that serological tests can be used only after validation. However, rapid “office” serology tests are not recommended and “should be avoided”. The guidelines recommend the rapid urease test (RUT) as a first line diagnostic test if there is an indication for endoscopy and no contraindication for biopsy. The guideline state that *H. pylori* is linked to “unexplained iron deficiency anemia (IDA), idiopathic thrombocytopenic purpura (ITP), and vitamin B12 deficiency”, and in these disorders, an *H. pylori* infection should be “sought and eradicated”. The guidelines state that PPIs should be stopped 2 weeks and antibiotics and other bismuth compounds should be stopped 4 weeks before testing for *H. pylori*. In cases of chronic (active) gastritis in which *H. pylori* is not detected by histochemistry, immunohistochemical testing of *H. pylori* can be used as an ancillary test. If histology is normal, no immunohistochemical staining should be performed. It is recommended to
perform clarithromycin susceptibility testing when a standard clarithromycin-based treatment is considered as the first-line therapy, except in populations or regions with well documented low clarithromycin resistance (<15%). Pepsinogen (Pg) serology is considered the most useful non-invasive test to explore gastric mucosa status (non-atrophic vs atrophic). The PgI/PgII ratio can never be assumed as a biomarker of gastric neoplasia. UBT is the best option for confirmation of \textit{H. pylori} eradication and monoclonal SAT is an alternative. It should be performed at least 4 weeks after completion of therapy (Malfertheiner et al., 2017).

The Maastricht IV from 2012 also addressed testing for the cagA and vacA variants, stating that no specific genetic or virulence markers can be recommended at this time (Malfertheiner et al., 2012).

\textbf{American Society for Clinical Pathology (ASCP, 2016)}

The ASCP recommends against using the serological tests for \textit{H. pylori} and recommends the stool antigen and breath tests instead. The ASCP states that serological evaluation is no longer clinically useful and the stool and breath tests have superior statistical power (ASCP, 2016).

\textbf{American Society of Hematology (ASH, 2011)}

Due to the association of \textit{H. pylori} with immune thrombocytopenic purpura (ITP), the ASH has released recommendations on \textit{H. pylori}. ASH recommends against routine testing for \textit{H. pylori} in children with chronic ITP, as well as eradication therapy for patients with \textit{H. pylori} infection (“based on urea breath tests, stool antigen tests, or endoscopic biopsies”) (Neunert et al., 2011)

\textbf{Applicable Federal Regulations}

A search for “\textit{pylori}” yielded 55 results on January 14, 2019, which encompasses various immunoassays and breath tests (FDA, 2019).

On Feb 22, 2012, the FDA approved the BreathTek UBT for \textit{H. pylori} Kit created by Otsuka America Pharmaceutical, Inc. The BreathTek UBT for \textit{H. pylori} Kit (BreathTek UBT Kit) is intended for use in the qualitative detection of urease associated with \textit{H. pylori} in the human stomach and is indicated as an aid in the initial diagnosis and post-treatment monitoring of \textit{H. pylori} infection in adults, and pediatric patients 3 to 17 years old. The test may be used for monitoring treatment if used at 4 weeks following completion of therapy. The FDA notes its sensitivity and specificity to be 0.958 and 0.992 respectively (FDA, 2012).

On Jan 17, 2002, the FDA approved the BreathTek UBiT for \textit{H. pylori} created by Meretek Diagnostics Inc. The scientific basis underlying the BreathTek UBT and the BreathTek UBiT UBT kit is identical. The urea breath test is FDA cleared for use in individuals 18 years of age and older (FDA, 2002).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

\textbf{Billing/Coding/Physician Documentation Information}

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.
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Applicable service codes: 83009, 83013, 83014, 86677, 87081, 87077, 87181, 87186, 87205, 87338, 87339, 88305, 87149, 87150, 87153, 0008U

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BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


FDA. (2002). 510k summary.


FDA. (2019). Devices@FDA. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?start_search=1&q=chlsb3Jp&approval_date_from=&approval_date_to=&sort=approvaldatedesc&pagemenu=10
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Policy Implementation/Update Information
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1/1/2019  New policy developed. BCBSNC will provide coverage for helicobacter pylori testing when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

6/11/2019  Reviewed by Avalon 1st Quarter 2019 CAB. Under the When Covered section, added “either” to item #3. Under the When Not Covered section, added the following statement to item #6: “The use of nucleic acid testing for H. pylori, including polymerase chain reaction (PCR), 16S rRNA, 23S rRNA, and next-generation sequencing (NGS) of” H. Pylori, is considered not medically necessary as it is not practical for routine diagnosis. Policy guidelines and references extensively revised. Under the Coding/Billing section, the following changes were made: 86677 – changed to Not Covered, and added code 87149, 87150, 87153, 0008U to the policy as Not Covered. References updated. Policy noticed 6/11/19 for effective date of 8/13/19. Medical Director reviewed 5/2019. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.