Healthy Blue

Medical Policy

Subject:	Serological Antibody Testing For Helicobacter Pylori		
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Description/Scope

This document addresses the use of serological antibody testing for *Helicobacter pylori* (also known as *H. pylori)*, a causative agent for peptic ulcers, gastritis, dyspepsia and stomach cancer.

Position Statement

Investigational and Not Medically Necessary:

The use of serological antibody testing for *Helicobacter pylori* is considered **investigational and not medically necessary** for all indications.

Rationale

H. pylori is a causative agent for peptic ulcers, gastritis, dyspepsia and stomach cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma. Innovations in the detection of this bacteria have been instrumental in the identification and treatment of pathological *H. pylori* infections.

Many types of tests have been developed to identify the presence of *H. pylori*, including urea breath testing (UBT), stool antigen testing, tissue biopsy, and serological testing.

At this time, the available evidence addressing the use of serological antibody testing is limited to a small number of studies. However, several major authoritative organizations have published recommendations on the use of such tests as well as identified issues which limit its clinical utility.

Serological antibody testing is based on the quantitation of immunoglobulin G antibodies against *H. pylori.* This type of testing may be useful for detecting newly infected individuals, but has been shown to be inappropriate for follow-up of treated individuals due to the persistent presence of antibodies in the bloodstream following *H. pylori* eradication. Additionally, because there is significant geographical variation in *H. pylori* strains, testing must be sensitive to the locally prevalent strains. This requires local validation studies of the specific test being used, which may not have been conducted. Finally, because the predictive value of a test is reliant on the prevalence of a disease, in low prevalence areas such as the U.S., the predictive value of serological antibody testing is low.

In a meta-analysis, Loy and colleagues (1996) compared the results of 21 different studies, and the overall observation of the authors was that the quality of the study methodology was often poor. Only three of the studies

were properly blinded, reference standards varied significantly, and in several studies consecutive subjects were not enrolled. The authors noted that their results found that the testing kits being evaluated had a sensitivity of 85% and specificity was estimated to be 79%. Test accuracy measured was significantly higher in studies with smaller proportions of infected individuals. The study concluded that the overall accuracy of these kits may not be adequate for clinical decision making in all groups. The findings by Loy regarding accuracy were contradicted in a more recent study by Burucoa et al. (2013) evaluating 29 different serological tests on 108 French subjects. Their findings reported that sensitivity ranged from 55.6% to 100%, specificity from 57.4% to 97.9%, and median accuracy from 73.9% to 97.8%. The positive predictive value ranged from 84.9% to 100% and negative predictive value ranged from 78% to 100%.

Pourakbari and others (2013) reported the results of the only available prospective comparative study addressing the use of *H. pylori testing.* This study compared the suitability of rapid urease test (RUT), serology, histopathology, and stool antigen tests with polymerase chain reaction (PCR) for detection of *H. pylori*, and correlated the diagnostic methods with PCR in 89 subjects. Histopathology showed high overall performance in adults and children with sensitivity and specificity 100% and 90%, respectively. Sensitivity, specificity, and accuracy for stool antigen test were 87.8%, 75% and 82%, respectively. For serology using IgG, results were 50%, 83.3%, and 65%. Correlation to PCR of RUT, serology, histopathology, and stool antigen testing was 1.0, 0.17, 0.92, and 0.46, respectively.

In the American College of Gastroenterology's clinical guideline for the treatment of *H. pylori*, the authors only briefly mention antibody testing (Chey, 2017). They note that individuals with peptic ulcer disease have a higher pre-test probability of infection and that testing with an IgG *H. pylori* antibody test is reasonable. However, in populations with low pre-test probability, tests which identify active infection are preferred.

The Maastricht V/Florence Consensus Report (Malfertheiner, 2016) stated serological tests may have high accuracy when locally validated. However, the Consensus stated: "Serological tests can only be used after validation." This recommendation was made on the basis of the significant geographical variation in circulating *H. pylori* strains. At this time, the availability of locally validated serological testing for *H. pylori* is limited and unreliable. This document also reiterates the limitations of serological tests in the presence of past infections due to persistence of antigens in the blood stream, and does not recommend the use of this type of test to monitor the efficacy of eradication.

Raj and colleagues (2017) performed a retrospective study on the *H. pylori* serum antibody test as a diagnostic screening tool in symptomatic inner city children. This study design was a chart review of 474 pediatric subjects aged 1 to 18 years who had a first-time esophagogastroduodenoscopy (EGD) between January 2009 and December 2013. Inclusion criteria consisted of subjects who had *H. pylori* serum antibodies or a fecal antigen test and who had a second EGD with biopsy. The authors found 395 (83%) subjects met the inclusion criteria. There were 79 subjects who were excluded due to prior known history of *H. pylori* infection, administration of antibiotics between testing, time between testing, or age. Compared to histology, the serum *H. pylori* antibody test had a sensitivity of 88.4% and a specificity of 93.4%. The tissue rapid urease test and fecal antigen test had sensitivities of 89.3% and 55.6% and specificities of 89.9% and 98.9%, respectively. The authors suggest that *H. pylori* antibody testing may be useful as a screening tool in diagnosing symptomatic subjects, but acknowledge there are limitations to the

study. These limitations include retrospective design and multiple pathologists who were not blinded, which can cause observer or misclassification bias.

In a Cochrane review, Best and colleagues (2018) evaluated the accuracy of non-invasive tests used alone or in combination in the diagnosis of *H.pylori*. The results of the literature search yielded 101 studies with 11,003 individuals, of which 5839 individuals (53.1%) were diagnosed with *H.pylori*. Of the 101 studies, 34 studies (4242 individuals) assessed serological testing. For serological testing, the diagnostic odds ratio was 47.4 (95% confidence interval [CI], 25.5 to 88.1), and the sensitivity (95% CI) estimated at a fixed specificity of 0.90 was 0.84 (95% CI, 0.74 to 0.91). Direct comparison of urea breath test versus serological testing showed a diagnostic odds ratio of 0.68 (95% CI, 0.12 to 3.70; p=0.56). There was limited data for direct comparison of stool antigen test versus serological test. In regards to serological testing, the authors concluded that the results showed low diagnostic accuracy and higher quality studies are needed to demonstrate clinical utility.

Overall, the evidence regarding the use of serological antibody testing for *H. pylori* is weak, and raises significant concerns regarding accuracy and the ability to identify post-treatment infection. Until additional high-quality data is made available, the use of this type of testing should be considered investigational.

Background/Overview

H. pylori is a gram-negative, microaerophilic bacterium found usually in the stomach. It was identified in 1982 by Australian scientists Barry Marshall and Robin Warren, who found that it was present in a person with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial cause. It is also linked to the development of duodenal ulcers and stomach cancer. However, over 80% of individuals infected with the bacterium are asymptomatic, and it may play an important role in the natural stomach ecology.

More than 50% of the world's population harbor *H. pylori* in their upper gastrointestinal tract. Infection is more prevalent in developing countries, although incidence is decreasing in Western countries.

The current methods for *H. pylori* testing include biopsy, stool antigen testing, urea breath test, and *H. pylori* antibody testing.

Biopsy is an invasive test that requires the use of a tissue sample from the stomach or other digestive tract organ to confirm the presence of *H. pylori.* Serum antigen testing uses a blood sample to identify the presence of antibodies to *H. pylori.* Stool antigen testing is a non-invasive method and identifies antibodies to *H. pylori* in fecal matter samples. The urea breath test involves the swallowing of a slightly radioactive urea tablet which is digested in the stomach by *H. pylori* into ammonia and carbon dioxide. The amount of radioactive carbon dioxide is measured before and after, and is used to determine the presence or absence of the bacteria.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider

reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

86677	Antibody; Helicobacter pylori

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. Burucoa C, Delchier JC, Courillon-Mallet A, et al. Comparative evaluation of 29 commercial Helicobacter pylori serological kits. Helicobacter. 2013; 18(3):169-179.
2. Loy CT, Irwig LM, Katelaris PH, Talley NJ. Do commercial serological kits for Helicobacter pylori infection differ in accuracy? A meta-analysis. Am J Gastroenterol. 1996; 91(6):1138-1144.
3. Pourakbari B, Ghazi M, Mahmoudi S, et al. Diagnosis of Helicobacter pylori infection by invasive and noninvasive tests. Braz J Microbiol. 2013; 44(3):795-798.
4. Raj P, Thompson JF, Pan DH. Helicobacter pylori serology testing is a useful diagnostic screening tool for symptomatic inner city children. Acta Paediatr. 2017; 106(3):470-477.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Best LM, Takwoingi Y, Siddique S, et al. Non-invasive diagnostic tests for Helicobacter pylori infection. Cochrane Database Syst Rev. 2018;(3):CD012080.
2. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017; 112(2):212-239.
3. Malfertheiner P, Megraud F, O'Morain CA, et al.; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut. 2017; 66(1):6-30.

Websites for Additional Information

1. Medline Plus. Tests for *H. pylori*. Reviewed August 1, 2017. Available at: https://medlineplus.gov/ency/article/007501.htm. Accessed on September 16, 2020.

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Document History

Status	Date	Action
Review	11/05/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Websites section.
Reviewed	11/07/2019	MPTAC review. Updated Rationale, Websites, and Index sections.
Reviewed	01/24/2019	MPTAC review. Updated Description, Rationale, References, and Websites sections.
Reviewed	01/25/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale, References, and Websites sections.
New	02/02/2017	MPTAC review. Initial document development.