In Patients with Peptic Ulcer Disease, What Is the Most Accurate Diagnostic Test to Determine the Presence of Helicobacter pylori Prior to Treatment?

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Pacific University
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Abstract
INTRODUCTION: Helicobacter Pylori is a common bacteria found in the stomach that can cause ulcers and more rarely gastric cancer. There are multiple diagnostic tests that are currently available to detect this microorganism possibly making it difficult for providers to choose the most accurate or inexpensive test. It is important to diagnosis H. pylori in symptomatic patients due to the potential of eliciting a series of pathologic consequences in the extra-gastric regions. These consequences have been studied at length and can include cardiovascular and autoimmune disorders as well as certain digestive disorders such as liver disease.

METHODS: There are five diagnostic tests reviewed in this study including urea breath test, stool antigen assay, rapid urease test, serology and histology. An exhaustive literature search was performed using multiple search databases including Medline, CINAHL, PubMed and Evidence Based Medicine Review Multifile. Literature from the past 15 years was reviewed and evaluated to determine the most accurate and cost effective testing for the diagnosis of H. pylori. Complete analysis of each article was performed to determine the most relevant information regarding this topic. Article inclusion criteria included all relevant articles discussing the adult population in the English language, published after 1995, that assisted the author in the determination of the most appropriate test for a dyspeptic patient. Exclusion criteria were articles published before 1995 and ones that discussed patients under the age of 18.

RESULTS: Four studies were found to meet the inclusion and exclusion criteria as well as stating clear and precise data concerning the diagnostic tests needing to be examined.

CONCLUSION: For accurate results when a patient does not need an endoscopy or refuses such an invasive procedure, urea breath testing is the best choice for the diagnosis of H. pylori. Other diagnostic tests such as serology and stool antigen testing has been shown to either have a low accuracy rate or too many variables that can affect the outcome of the test.

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peptic ulcer, Helicobacter pylori, urea breath test, stool antigen, rapid urease

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 15, 2009

Faculty Advisor: Mary Von MS PA-C
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

Jason Kwiatkowski was born in Rochester, NY where he became a military dependent at an early age. He went to grade school in southern Georgia and junior high and high school in northern Texas. He received his Bachelors of Science in Exercise Science from the University of Utah in Salt Lake City, Utah. While in Utah, he worked as a Pediatric Technician at a local children’s hospital. With a passion to further his education in the medical field, he decided to move to the Pacific Northwest to pursue a career as a physician assistant. It was in Portland, Oregon where he worked as a hemodialysis technician and then became accepted to the Pacific University School of Physician Assistant Studies.
Abstract

INTRODUCTION: Helicobacter Pylori is a common bacteria found in the stomach that can cause ulcers and more rarely gastric cancer. There are multiple diagnostic tests that are currently available to detect this microorganism possibly making it difficult for providers to choose the most accurate or inexpensive test. It is important to diagnosis H. pylori in symptomatic patients due to the potential of eliciting a series of pathologic consequences in the extra-gastric regions. These consequences have been studied at length and can include cardiovascular and autoimmune disorders as well as certain digestive disorders such as liver disease. METHODS: There are five diagnostic tests reviewed in this study including urea breath test, stool antigen assay, rapid urease test, serology and histology. An exhaustive literature search was performed using multiple search databases including Medline, CINAHL, PubMed and Evidence Based Medicine Review Multifile. Literature from the past 15 years was reviewed and evaluated to determine the most accurate and cost effective testing for the diagnosis of H. pylori. Complete analysis of each article was performed to determine the most relevant information regarding this topic. Article inclusion criteria included all relevant articles discussing the adult population in the English language, published after 1995, that assisted the author in the determination of the most appropriate test for a dyspeptic patient. Exclusion criteria were articles published before 1995 and ones that discussed patients under the age of 18. RESULTS: Four studies were found to meet the inclusion and exclusion criteria as well as stating clear and precise data concerning the diagnostic tests needing to be examined. CONCLUSION: For accurate results when a patient does not need an endoscopy or refuses such an invasive procedure, urea breath testing is the best choice for the diagnosis of H. pylori. Other diagnostic tests such as serology and stool antigen testing has been shown to either have a low accuracy rate or too many variables that can affect the outcome of the test. KEYWORDS: peptic ulcer, Helicobacter pylori, eradication, test, diagnosis, serology, histology, urea breath test, stool antigen, rapid urease.
Acknowledgements

To My Parents and Kaitlin: Thank you for pushing me always to be the best I can be. I appreciate all your love and support through this life changing process.

To Jered: Thank you for putting up with me through this life transition. I appreciate all the love and support you have given me through this time which I know will make us a stronger team and our future together brighter.
# Table of Contents

- Biography .................................................................................................................. 2  
- Abstract ..................................................................................................................... 3 
- Acknowledgements ................................................................................................... 4 
- Table of Contents ...................................................................................................... 5 
- List of Tables ............................................................................................................. 6 
- List of Abbreviations ................................................................................................. 6 
- Introduction ............................................................................................................... 7 
- Methods ...................................................................................................................... 10 
- Results ....................................................................................................................... 11 
- Discussion .................................................................................................................. 14 
- Conclusion ................................................................................................................. 16 
- References ............................................................................................................... 17 
- Tables ........................................................................................................................ 18
### List of Tables

Table I: Summary of Articles Reviewed

### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACG</td>
<td>American College of Gastroenterology</td>
</tr>
<tr>
<td>EGD</td>
<td>esophagastroduodenoscopy</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>H. pylori</td>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>MALT</td>
<td>mucosa-associated lymphoid tissue</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>RUT</td>
<td>Rapid Urease Test</td>
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<tr>
<td>UBT</td>
<td>Urea Breath Test</td>
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In Patients with Peptic Ulcer Disease, What Is the Most Accurate Diagnostic Test to Determine the Presence of Helicobacter pylori prior to Treatment?

Introduction

Abdominal pain is one of the most common chief complaints a patient will give his/her provider. This complaint can be caused by a multitude of etiologies, however the most common is infection. Helicobacter pylori is a bacteria that resides in the stomach and duodenum which affects more than 50% of the human population making it one of the more widespread pathogens.\(^1\) This bacterium has been associated with the development of peptic ulcer disease, adenocarcinoma of the gastric lining and mucosa associated lymphoid tissue (MALT) lymphoma.\(^1\) It is important to diagnosis H. pylori in symptomatic patients due to the potential of eliciting a series of pathologic consequences in the extra-gastric regions. These consequences have been studied at length and can include cardiovascular and autoimmune disorders as well as certain digestive disorders such as liver disease.\(^1\)

Helicobacter pylori is a spiral shaped, slow growing gram negative bacterium. Biochemically characterized as catalase, oxidase and urease positive, this organism appears to require urease for its survival and colonization. Urease is produced in abundance which makes up more than 5% of the organism’s total protein weight. Urease produced by this bacteria is clinically important because it forms the basis for several invasive and noninvasive tests to diagnose infection.\(^2\)

The most common chronic bacterial infection in humans derives from the Helicobacter pylori bacterium. Humans have been infected with H. pylori since they first
migrated from Africa around 58,000 years ago according to studies that have performed genetic testing. Demonstrated worldwide and in individuals of all ages, H. pylori infection is more frequent at early ages in developing countries compared to industrialized nations. Gastroduodenal disease may or may not occur once a host acquires this bacterium and is subsequently infected. ³ It remains unknown exactly how and why a gastrointestinal disturbance is initiated or by which route infection occurs. Either fecal/oral or oral/oral exposure seems the most likely cause of person-to-person transmission. In developing countries, contaminated water supplies possibly serve as a source of these bacteria. Children who regularly swim in rivers, pools, drink stream water or eat uncooked vegetables are more likely to be infected. Person-to-person transmission is supported by the fact that infected individuals are more likely to have same household family members that are already infected. ⁴

Multiple combinations of medications have been evaluated for the treatment of Helicobacter pylori, however the optimal therapy has not yet been defined. The treatment that is selected must be effective, however it is important to consider cost, side effects and ease of administration. ⁵ In as many as 20 percent of patients fail eradication therapy for H. pylori after the first attempt. ⁶ A provider must have accurate and easily accessible diagnostic testing in order to successfully test for this organism and retest after treatment is complete to confirm the eradication.

Both invasive and noninvasive forms of testing exist for the diagnosis of H. pylori depending on the need for esophagogastroduodenoscopy (EGD). Diagnostics can also be either direct and indirect testing. Direct diagnosis can be from a culture or biopsy. Indirect diagnoses is from an antibody or antigen response or by the verification of the
presence of urease. Cost, availability, clinical situation, population, pretest probability of infection and factors such as the use of proton pump inhibitors and antibiotics will affect the choice of test and may influence certain test results. The American College of Gastroenterology (ACG) proposed the most recent guidelines for diagnosing H. pylori in 2007. The guidelines are as follows: only if the clinician plans to offer treatment for positive results should testing be performed; patients with active peptic ulcer disease, a past history of documented peptic ulcer or gastric MALT lymphoma should be tested; the test and treat if positive approach is a proven management for patients with uninvestigated dyspepsia who are under the age of 55 years and have no bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia, odynophagia, recurrent vomiting, family history of GI cancer or previous esophagogastric malignancy. The provider must decide which test to use in which circumstance based upon whether a patient requires evaluation with EGD and their understanding of the strengths, weaknesses and costs of the tests being performed. 

There are five diagnostic tests that will be reviewed in this study. The urea breath test (UBT) is based upon the hydrolysis of urea by H. pylori to produce CO2 and ammonia. A labeled carbon isotope is given by mouth which makes H. pylori release CO2 which can be detected in breath samples. Two UBTs have been approved by the Federal Drug Administration (FDA). Both the non-radioactive 13C test and the radioactive 14C test can be performed in about 20 minutes. Most providers prefer the 13C test because it does not use a radioactive isotope. The stool antigen assay was developed with the discovery of the presence of H. pylori in the stool of infected patients. The primary diagnosis of H. pylori can be made by a commercially available enzyme
immunoassay which is considered a reasonable method. The rapid urease test (RUT) uses specialized urea membrane kits that have been designed specifically to give a result within one hour. Antisecretory medications and antibiotics often affect these results. With these rapid urease tests, biopsy specimens are squeezed between a reagent strip with a pH indicator and a pad containing urea. Enzyme-linked immunosorbent assay (ELISA) technology is used for laboratory based serologic testing to detect Immunoglobulin G (IgG) antibodies. This technique is inexpensive, noninvasive and well suited to primary care practice. Histology testing is performed using gastric biopsy which can be helpful in making the primary diagnosis of an H. pylori infection. This type of testing provides additional information regarding the detection of gastritis and the presence of intestinal metaplasia and mucosa-associated lymphoid tissue (MALT). Laboratory based serologic testing from blood using ELISA to detect IgG antibodies is another test performed, however has had some low accuracy rates.

Methods

An exhaustive literature search was performed using multiple search databases including Medline, CINAHL, PubMed and Evidence Based Medicine Review Multifile. Specific keywords were used in performing this search such as *peptic ulcer, Helicobacter pylori, eradication, test, diagnosis, serology, histology, urea breath test, stool antigen, rapid urease*. Literature from the past 15 years was reviewed and evaluated to determine the most accurate and cost effective testing for the diagnosis of H. pylori. Complete analysis of each article was performed to determine the most relevant information regarding this topic. Article inclusion criteria included all relevant articles discussing the adult population in the English language, published after 1995, that assisted the author in
the determination of the most appropriate test for a dyspeptic patient. Exclusion criteria were articles published before 1995 and ones that discussed patients under the age of 18.

**Results**

A total of four articles were published between 1995 and 2009 that pertained to the diagnostic tests that are being compared and that fit my inclusion and exclusion criteria. (See Table 1)

Calvet et al. performed a prospective study which evaluated two noninvasive tests, the commercial infrared based UBT and the commercially available stool antigen test. They also evaluated biopsy based tests which included a histological exam and a rapid urease test. In the Calvet study, they considered a patient to be infected when at least two diagnostic test results were positive. A total of 199 patients with dyspepsia were enrolled after confirmation that they had never been treated for Helicobacter pylori infection at a previous visit. Rates for positive tests were similar (54%) for the rapid urease test, histopathological examination and the stool antigen test. However the rate for positive results for the UBT was 75% which was associated with a very low specificity (60%). After reconfiguring this data with a new delta cutoff value, the sensitivities and specificities for the UBT were 95% and 100% respectively. For the rapid urease test the sensitivity and specificity were 94% and 99% respectively, the histological exam 90% and 93% respectively, for the stool test were 90% and 93% respectively, and for the UBT 90% and 90% respectively. Calvet concluded that the histological examination and RUT remain the “uncontested gold standard” for the diagnoses of H. pylori infection. They also concluded that the UBT could produce a high
rate of false positive result and lead to unnecessary treatment and associated costs with the current cutoff value. 8

Pacheco et al. assessed the diagnostic value of the most common clinical tests to detect H. pylori infection with the polymerase chain reaction (PCR). They extracted serum and gastric biopsies from 106 dyspeptic patients. The biopsies were examined histologically for rapid urease activity and PCR amplification of a urea gene segment of H. pylori. Positive results were found for the serology, histology, rapid urease and PCR which were 56%, 86%, 64%, and 85% respectively. Most of the dyspeptic patients were found to have gastritis. Compared to the PCR, the sensitivity and specificity for the serology was 55% and 38% respectively, 86% and 13% for the histology respectively and 70% and 69% for urease respectively. They concluded that combining histology and urease for the diagnosis of infection showed no advantage over using the rapid urease test alone. Due to this fact according to Pacheco, histology should no longer be considered a gold standard for the diagnosis of H. pylori infection. The first option for a noninvasive diagnostic should be the urea breath test. Highly specific and sensitive molecular diagnostic methods should be used to examine specimens if an invasive procedure is justified for diagnosis. 9

Thijs et al. assessed the accuracy of six diagnostic tests commonly used to identify H. pylori infection. They prospectively studied 105 outpatients without using any specific test as a gold standard. The patients underwent an EGD study which showed that 62 of them had no significant abnormalities, 28 had gastroesophageal reflux disease, 19 had peptic ulcers, on with erosive gastritis and one with atrophic gastritis. Some patients had more than one diagnosis. Biopsies were taken from the antrum and were
used for culture, PCR, histological examination, and rapid urease test. Also performed were serology using ELISA and C urea breath test. The patients were considered infected when two or more tests were positive, no matter the symptoms. Sensitivity and specificity were as follows; culture, 98% and 100%; PCR, 97% and 100%; histological exam of the antrum, 96% and 98.8%; histological exam of the antrum plus the corpus; 98.4% and 98.8%; rapid urease test 90% and 100%; C urea breath test, 100% and 100%; and serological examination, 98.4% and 88.4% (95% in patients who had not been previously infected treated for H. pylori. They concluded that all antral biopsy based tests and the C urea breath test were accurate for the diagnosis of H. pylori infection.

Sampling error occurs, but is a minor importance. They state that the lower specificity of serological test may be due to previous treatment of H. pylori. 10

Nishikawa et al. performed a prospective study evaluating two branded rapid urease tests before and after eradication treatment for Helicobacter pylori. The aim of the study was to examine the accuracy of these specific tests and compare it to the accuracy with histology, culture and 13C-urea breath test as a gold standard. They studied two specific RUT, the Helicocheck and the PyloriTek. A total of 278 patients were examined, however they split the group into before treatment and after treatment groups. This study will focus on the accuracy of the tests that were performed on the 115 patients examined prior to eradication. Eight biopsy specimens were taken from both the antrum and the body of the subject for histology, culture and two rapid urease tests. The Helicobacter pylori infection was assessed by the combination of histology, culture and 13 C urea breath tests. These subjects were defined in their endoscopic diagnoses. There were 46 with gastric ulcers, 23 with duodenal ulcers, 7 with gastroduodenal ulcers, 24 with
gastritis and 15 with other diagnoses. It was found that the patients with these diagnoses can have a predominate presence of intestinal metaplasia in the antrum where biopsies were taken. This would make it difficult for H. pylori to colonize due to the loss of H. pylori specific receptor structures on the epithelium and active secretion of IgA from metaplastic mucosa. Due to this fact, additional biopsies were performed from the gastric body which would significantly improve the sensitivity. The overall sensitivity, specificity and positive and negative predictive values of the Helicocheck before eradication were 91%, 100%, 100% and 62.5% respectively; the PyloriTek had values of 92%, 100%, 100%, and 65.2% respectively. Both of these tests have “equally satisfactory overall sensitivity before eradication treatment.” It was determined that biopsies from the gastric body had a significantly higher sensitivity than the antral biopsies. There was no mention of sensitivities or specificities for the “gold standard” tests such as histology, culture or UBT, except for a sensitivity of 92.1% for the UBT. ¹¹

Discussion

The primary goal of this study was to identify accurate evidence from recent medical literature discussing diagnostic tests for the identification of Helicobacter pylori infection. The variability of the tests included in each article may have a skewing effect to determine the best diagnostic test available. More studies are needed comparing all of the main tests to determine a more accurate gold standard. The articles available either do not state a gold standard to compare against or the “gold standard” that they state is not consistent with other studies. The American College of Gastroenterology does not recommend a gold standard diagnostic test. A gold standard across the board for medical providers would make diagnosis such a common infection easier and in the long run more
cost effective for patients. Currently many factors account for the choosing of a specific diagnostic test for H. pylori. Cost, accuracy, availability, bleeding risk, former treatment, severity of symptoms and need for endoscopy.

Calvet’s study evaluated four commonly used diagnostic tests to determine the presence of H. pylori, the urea breath test, stool antigen test, histological exam, and the rapid urease test. The determination of a positive H. pylori patient was made when two of the tests became positive. Thijs chose a similar method in determining if the study participant was indeed positive for the bacteria. The UBT resulted in a very low specificity of 60% which led them to changing the cutoff value. After this change the specificity and sensitivity improved dramatically. Not including the UBT, the highest specificity and sensitivity values were concluded were with the rapid urease test of 94% and 99%. Calvet’s study made it clear that if the patient was going to go in for an endoscopy that a rapid urease test should be the test chosen based on its accuracy and speed.

Pacheco’s study assessed gastric biopsies and serum and then compared them to PCR. PCR is the best diagnostic test, but is expensive and time consuming so it is not a common diagnostic test used. The study used the biopsies to determine rapid urease activity and PCR amplification. After comparing the results, it was determined that histology should no longer be considered the gold standard and may consider the rapid urease test to replace it. However a RUT must be completed only after an endoscopy and biopsy which are both invasive. The study determined that the most accurate noninvasive test is the urea breath test, however they did not perform or calculate any urea breath tests on its subjects.
Thijs’s study examined six diagnostic tests commonly used to diagnose H. pylori, the largest amount of test found in the literature search. This article chose no gold standard to compare with its results. The tests that were included are PCR, histology, rapid urease, serology and urea breath test. Surprisingly this study calculated the sensitivity and specificity of the UBT to be 100% and 100%, both higher than culture and PCR. Serology was an poor choice for diagnosis due to its potential for false negatives.

The Nishikawa study compared two rapid urease tests with the combination of histology, culture and a urea breath test as a gold standard. Both the RUTs that were performed resulted in similar sensitivities and specificities. When compared with these values from the other studies, it was close in value except when compared with the Pacheco study which gave much lower values.

**Conclusion**

Based on literature review, rapid urease testing is the best choice for the diagnosis of H. pylori when an endoscopy is needed. For accurate results when a patient does not need an endoscopy or refuses such an invasive procedure, urea breath testing is the best choice for the diagnosis of H. pylori. Other diagnostic tests such as serology and stool antigen testing has been shown to either have a low accuracy rate or too many variables that can affect the outcome of the test. More prospective studies need to be performed examining all of the commonly used tests using better guidelines for a “positive” patient with H. pylori.
Table 1. Summary of Articles Reviewed

<table>
<thead>
<tr>
<th>Author/ Title/ Journal</th>
<th>Yr.</th>
<th>Patients/ Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study type</th>
<th>Validity (Jadad score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xavier Calvet, Accuracy of Diagnostic Tests for Helicobacter pylori: A Reappraisal</td>
<td>2009</td>
<td>199 dyspeptic patients</td>
<td>UBT, stool test, biopsy based tests, RUT</td>
<td>NONE</td>
<td>Histological and RUT showed excellent diagnostic reliability, with stool&gt;accuracy than UBT</td>
<td>Prospective</td>
<td>1/5</td>
</tr>
<tr>
<td>N. Pacheco, Comparison of PCT and common clinical test for the diagnosis of H. Pylori in dyspeptic patients</td>
<td>2001</td>
<td>106 dyspeptic patients. Serum and gastric biopsy specimens were examined</td>
<td>Tested dyspeptic patients with PCR, RUT, UBT</td>
<td>Compared with PCR</td>
<td>Indicates no advantage of using combination methods over RUT alone</td>
<td>Prospective</td>
<td>1/5</td>
</tr>
<tr>
<td>Nishikawa, A prospective evaluation of new rapid urease tests before and after eradication treatment of Helicobacter pylori, in comparison with histology, culture, and 13 C Urea breath test</td>
<td>2000</td>
<td>278 total patients, 115 before eradication and 163 after.</td>
<td>Eight biopsies taken from antrum and body of stomach for histology, culture and rapid urease tests. Also performed was 13C urea breath test.</td>
<td>Histology, culture and Urea breath test</td>
<td>Both RUT test have equal sensitivity before treatment however, after treatment is was lower.</td>
<td>Prospective</td>
<td>1/5</td>
</tr>
<tr>
<td>Thijs, Diagnostic Tests for Helicobacter pylori: A Prospective Evaluation of their Accuracy, without Selection a Single Test as the gold standard.</td>
<td>1996</td>
<td>105 outpatients undergoing upper GI endoscopy</td>
<td>Culture, PCR, histology, serology, rapid urease test and urea breath test</td>
<td>NONE</td>
<td></td>
<td>Prospective</td>
<td>1/5</td>
</tr>
</tbody>
</table>

NOTE: Jadad scores not valid due to the bases on RCT info such as randomization and double blind, difficult to find RCT when investigating a diagnostic clinical question.


