Diagnostic accuracy of tests for Helicobacter pylori in an Alaska Native population

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Abstract

AIM: To evaluate the accuracy of two non-invasive tests in a population of Alaska Native persons. High rates of Helicobacter pylori (H. pylori) infection, H. pylori treatment failure, and gastric cancer in this population necessitate documentation of infection status at multiple time points over a patient’s life.

METHODS: In 280 patients undergoing endoscopy, H. pylori was diagnosed by culture, histology, rapid urease test, 13C urea breath test (UBT), and immunoglobulin G antibodies to H. pylori in serum. The performances of 13C-UBT and antibody test were compared to a gold standard defined by a positive H. pylori test by culture or, in case of a negative culture result, by positive histology and a positive rapid urease test.

RESULTS: The sensitivity and specificity of the 13C-UBT were 93% and 88%, respectively, relative to the gold standard. The antibody test had an equivalent sensitivity of 93% with a reduced specificity of 68%. The false positive results for the antibody test were associated with previous treatment for an H. pylori infection [relative risk (RR) = 2.8]. High levels of antibodies to H. pylori were associated with chronic gastritis and male gender, while high scores in the 13C-UBT test were associated with older age and with the H. pylori bacteria load on histological examination (RR = 4.4).

CONCLUSION: The 13C-UBT outperformed the antibody test for H. pylori and could be used when a non-invasive test is clinically necessary to document treatment outcome or when monitoring for reinfection.

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Key words: Urea breath test; Antibody test; Sensitivity; Specificity

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INTRODUCTION

*Helicobacter pylori* (H. pylori) infection has been associated with peptic ulcer disease, gastric cancer, and acute gastritis[5]. Alaska Native persons have a high seroprevalence of *H. pylori* (75% all ages)[3], along with high rates of gastric cancer[3]. In rural Alaska, *H. pylori* seroprevalence is as high as 69% by the ages of 5-9 years and 87% among 7-11 year olds, as measured by the urea breath test (UBT)[6]. These findings have led to research investigations on *H. pylori* treatment outcome, reinfection rates after treatment, and the association of *H. pylori* infection with anemia in this population[4,8]. In Alaska, antimicrobial resistance rates in *H. pylori* are as high as 63% for metronidazole, 31% for clarithromycin, and 9% for levofloxacin[5,38]. Along with high levels of antimicrobial resistance, treatment failure rates approaching 30% in urban Alaska and 45% in rural Alaska have been demonstrated. The rate of *H. pylori* reinfection in Alaskan adults after two years was 14.5%[6]. In rural Alaskan children, aged 7 to 11 years, the reinfection rate exceeded 50% 32 mo after documented successful treatment[11]. Tests are needed after esophagogastroduodenoscopy (EGD) to document cure and continued infection-free status because of high rates of treatment failure and reinfection for *H. pylori*. Tests dependent on an EGD are not feasible for sequential follow-up or for longitudinal research studies. In rural and remote study populations, EGD testing is not available. Additionally, the cost and invasiveness of an EGD make *H. pylori* tests that are dependent upon them impractical in some settings.

This investigation was conducted as part of an Alaskan *H. pylori* reinfection study in which we enrolled persons scheduled for EGD over a three year period, treated them for *H. pylori*, and then followed them for two years with the 13C-UBT test. As part of a secondary objective, we enrolled persons both positive and negative for *H. pylori* infection who were undergoing EGD for clinical indications at the Alaska Native Medical Center (ANMC) in Anchorage, Alaska gave their consent to participate in an *H. pylori* reinfection study between September 1998 and December 2000. A description of this study cohort has been previously published[8]. From this cohort, we conducted a cross-sectional analysis to determine the sensitivity and specificity of five tests for *H. pylori* serology, culture, CLO test®, Ballard Medical Products, Draper, UT, United States), histology and 13C urea breath test (BreathTek™ UBT; Meretek Diagnostics Inc., Lafayette, CO, United States). The result of the breath test is measured as the delta over baseline (DOB), which is the difference between the ratio 13CO2/12CO2: after and before consumption of a Pranactin-Citric solution containing 13C-urea. The participants were recruited prior to EGD; therefore, the cohort consisted of persons both positive and negative for *H. pylori*. Upon enrollment, a medical chart review was performed at ANMC to determine the participants’ history of: peptic ulcer disease, previous EGD procedures, and previous treatment for an *H. pylori* infection. Endoscopic findings documented during EGD included location and type of ulcer and presence of antral and fundal gastritis.

This study was approved by the Centers for Disease Control and Prevention Institution Review Board (IRB), the Alaska Area IRB of the Indian Health Service, the Southcentral Foundation Board, as well as the Alaska Native Tribal Health Consortium Board of Directors. Written informed consent was obtained from all participants.

Laboratory methods

At the time of EGD (initial enrollment), blood was drawn and a 13C-UBT test was administered. Sera were tested for *H. pylori*-specific IgG by an in-house enzyme-linked immunosorbent assay (ELISA), as described previously[3]. Sera were negative if the optical density (OD) was ≤ 0.3, positive if ≥ 0.5, and indeterminate if in between. In-house ELISA cut-offs were determined using 254 sera collected from a previous study[3].

All participants had up to three gastric biopsy specimens taken for testing for *H. pylori* from the antrum and the fundus of the stomach. One biopsy was taken, as per the manufacturer’s instructions for the CLO test®, for the detection of urease. Biopsies were stained with Diff-Quik® (Mercedes Medical, Sarasota, FL, United States) stain, for identification of *H. pylori*, and with hematoxylin and eosin stain for histological examination. A research pathologist examined both histological slides for the presence of intestinal metaplasia, acute and chronic gastritis, and the amount of *H. pylori* present, according to the Updated Sydney System[5]. The final one or two biopsies were used to culture *H. pylori*. Cultures were incubated at 37 °C, 12% CO2, and 98% humidity for up to 10 d. Isolates were identified as *H. pylori* on the basis of positive catalase, oxidase, and urease reactions, typical colony morphology, and curved gram-negative bacilli on gram-stained smears.

MATERIALS AND METHODS

Patients

Persons ≥ 18 years of age undergoing EGD for clinical indications at the Alaska Native Medical Center (ANMC) in Anchorage, Alaska gave their consent to participate in an *H. pylori* reinfection study between September 1998 and December 2000. A description of this study cohort has been previously published[8]. From this cohort, we conducted a cross-sectional analysis to determine the sensitivity and specificity of five tests for *H. pylori* serology, culture, CLO test®, Ballard Medical Products, Draper, UT, United States), histology and 13C urea breath test (BreathTek™ UBT; Meretek Diagnostics Inc., Lafayette, CO, United States). The result of the breath test is measured as the delta over baseline (DOB), which is the difference between the ratio 13CO2/12CO2: after and before consumption of a Pranactin-Citric solution containing 13C-urea. The participants were recruited prior to EGD; therefore, the cohort consisted of persons both positive and negative for *H. pylori*. Upon enrollment, a medical chart review was performed at ANMC to determine the participants’ history of: peptic ulcer disease, previous EGD procedures, and previous treatment for an *H. pylori* infection. Endoscopic findings documented during EGD included location and type of ulcer and presence of antral and fundal gastritis.

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Statistical analysis
The gold standard used to compare test accuracies was a positive result by culture or in the case of a negative culture, a positive result by both histology and CLO test. Test accuracy was the number of true positives plus true negatives divided by the total sample size. The manufacturer's recommended cut-off (DOB $\geq 2.4$) for the $^{13}$C-UBT test was used for definition of a positive $H. pylori$ result for analysis.

RESULTS
The characteristics of the 280 patients who underwent EGD are shown in Table 1. The mean age of participants was 48 years and 66% were female. Of the 280 participants, 155 (55%) were positive by the $^{13}$C-UBT test (Table 2). Ninety-two persons tested positive for anti-HP IgG (OD value $\geq 0.5$), 168 persons tested negative (OD value $\leq 0.3$), and 20 were indeterminate. If persons with indeterminate results by the antibody test are considered negative for $H. pylori$ infection, then 60% of the entire 280 persons were positive by serology (Table 2). However, if those with indeterminate results were removed, then 65% were positive for $H. pylori$ antibodies (Table 2). Of the 280 participants, 50%, 51% and 49% of persons were positive for $H. pylori$ by histology, culture and CLO test, respectively. Using the gold standard of either a positive culture, or a positive result of both histology and CLO test, 53% (149/280) of persons were positive for $H. pylori$.

The performance of the non-invasive tests in comparison to the invasive tests and the gold standard are shown in Table 3. The sensitivity of the $^{13}$C-UBT test in relationship to invasive tests and the gold standard ranged from 93% to 97%. The specificity was somewhat lower, and ranged from 78% to 88% when compared against invasive tests and the gold standard. The accuracy of the $^{13}$C-UBT test ranged from 86% to 90%. The sensitivity of the serological assay (detection of anti-HP) in relation to the invasive tests and the gold standard was between 92% and 93%, and the specificity ranged from 58% to 68%. The concordance of anti-HP and $^{13}$C-UBT was 81%. For the two invasive tests of histology and culture, there was concordance on 89% of persons. Finally, the CLO test had a concordance of 90% and 92% with respect to histology and culture, respectively.

The sensitivity and specificity of the anti-HP assay presented in Table 3 were calculated with the indeterminate (0.3 $\leq$ anti-HP OD $< 0.5$) results removed. The overall accuracy of the anti-HP assay against the gold standard was 81.5%. Of 118 persons negative for $H. pylori$ by the gold standard, 32% ($n = 38$) were positive by anti-HP (representing the false positives) and 68% ($n = 80$) were negative by anti-HP. In these 118 persons, 55% (21/38) of persons positive by anti-HP had a previous treatment for $H. pylori$ documented in their medical record compared to 20% (16/80) of persons negative for anti-HP [relative risk (RR) = 2.8, 95% CI: 1.6-4.7]. In these 118 persons, the magnitude of the anti-HP OD was positively associated with previous treatment for $H. pylori$ ($P < 0.0001$, Figure 1). Persons with an anti-HP OD $\geq 0.8$ were 4.9 times (95% CI: 2.1-11.7) more likely to have had a previous treatment for $H. pylori$ than persons with an anti-HP OD $< 0.15$.

The receiver operating curves for the quantitative anti-HP OD measurements against the gold standard are shown in Figure 2, with indeterminate results included ($n = 280$). The accuracy of the serological assay was between 78%-80% for cut-off points between anti-HP OD values of 0.3 and 0.7. The accuracy of the serological test diminishes using cut-off points above an anti-HP OD value of 0.7. The sensitivity and specificity of the anti-HP assay at a cut-off point of 0.3 are 94% and 61%, respectively. At a higher cut-off point of 0.7, the specificity of the test improves to 82%, but the sensitivity decreases from 94% to 76%. At no cut-off point does the accuracy of the anti-HP assay exceed 80% when the indeterminate results are included. The optimal cut-off point when including the indeterminate results was an

Table 1 Characteristics of 280 patients enrolled in Anchorage, Alaska undergoing esophagogastroduodenoscopy during 1999 and 2000

| Characteristic                      | % (n)     |
|------------------------------------|-----------|
| Mean age (min, max)                | 48 yr (19, 88) |
| Sex (female)                       | 66% (184) |
| Medical chart review               |           |
| History of peptic ulcer disease    | 19% (35)  |
| Previous EGD                       | 32% (90)  |
| Previously treated for $H. pylori$ | 23% (63)  |
| Endoscopist evaluation during EGD  |           |
| Moderate-severe gastritis          | 41% (115) |
| Mild-no gastritis                  | 59% (165) |
| Ulcer                              | 9% (25)   |

EGD: Esophagogastroduodenoscopy; $H. pylori$: Helicobacter pylori.

Table 2 Percent positive for Helicobacter pylori by test type among 280 persons enrolled in Anchorage, Alaska for a Helicobacter pylori reinfection study, 1999-2000

| Test type     | % H. pylori positive (n/N) |
|---------------|----------------------------|
| Histology     |                           |
| Antrum        | 49% (135/278)             |
| Fundus        | 46% (124/271)             |
| Combined      | 50% (140/280)             |
| Culture       |                           |
| Antrum        | 48% (135/275)             |
| Fundus        | 50% (136/275)             |
| Combined      | 51% (144/280)             |
| CLO test<sub>TM</sub> |            |
| Antrum        | 53% (149/280)             |
| Fundus        | 55% (155/280)             |
| Combined      |                           |
| Indeterminates considered negative | 60% (168/280) |
| Indeterminates considered positive  | 67% (188/280) |
| Indeterminates removed               | 65% (168/260) |

<sup>1</sup>Rapid urease test, Ballard Medical Products. <sup>2</sup>A positive culture or in the case of a negative culture, a positive histology result and a positive campylobacter-like organism (CLO) test<sup>TM</sup>. <sup>3</sup>13C urea breath test (UBT)<sup>®</sup>. Breath-Tek<sup>®</sup>. Memetek Diagnostics Inc. H. pylori: Helicobacter pylori; Anti-HP IgG: Antibodies to $H. pylori$ immunoglobulin G.
anti-HP OD value of 0.5, which resulted in a test accuracy of 79.6%. A high anti-HP OD among persons positive for *H. pylori* by the gold standard was associated with male gender and chronic gastritis on histological examination (Table 4). The association with chronic gastritis was stronger in the antral specimen (*P* = 0.02) than the fundal specimen (*P* = 0.25).

The overall accuracy of the ¹³C-UBT test against the gold standard was 91%, with an area under the curve value of 0.97 (Figure 2). The accuracy of the ¹³C-UBT test was above 90% for all values in between a DOB of 2.0 and 4.0 and was highest, at 93%, between 2.8 and 3.0. Using a lower value of 2.0 as the cut-off point (91% accuracy) resulted in false negative and positive rates of 5% and 12%, whereas use of a higher value of 4.0 (90% accuracy) resulted in false negative and positive rates of 15% and 5%, respectively. The ¹³C-UBT had a specificity and positive predictive value of 100% for cut-offs ≥ 7.0 DOB. Additionally, among persons positive for *H. pylori* by the gold standard, a high ¹³C-UBT DOB was associated with the number of *H. pylori* organisms seen on histological slides and age ≥ 50 years (Table 4). Persons with a ¹³C-UBT ≥ 9 DOB were 4.4 (95% CI: 1.7-11.3) times more likely to have a large number of *H. pylori* bacteria on histological examination than persons with a ¹³C-UBT < 9 DOB (Figure 3).

**DISCUSSION**

Our study provides important information about the accuracy of five tests commonly used in clinical practice for the diagnosis of *H. pylori* infection. Clinicians have a
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![Graph](image1)

**Figure 1** Among persons negative for *Helicobacter pylori* by the gold standard, the percentage of persons with a documented previous treatment for *Helicobacter pylori* according to the antibodies to *Helicobacter pylori* immunoglobulin G optical density (n = 118). HP: Helicobacter pylori; OD: Optical density.

![Graph](image2)

**Figure 2** The receiver operating characteristic curves for anti-*Helicobacter pylori* level (serological test) and 13C urea breath test delta over baseline vs the gold standard for *Helicobacter pylori* infection in a group of 280 Alaskans undergoing esophagastroduodenoscopy. Gold standard was a positive *Helicobacter pylori* test by culture or, in the case of a negative culture result, a positive histology result and a positive campylobacter-like organism test. ROC: Receiver operating characteristic; UBT: Urea breath test; DOB: Delta over baseline; HP: Helicobacter pylori; IgG: Immunoglobulin G.

![Graph](image3)

**Figure 3** The amount of *Helicobacter pylori* (numerous, moderate, focal) on histological examination according to the delta over baseline value for the 13C urea breath test among *Helicobacter pylori* positive persons (n = 149).

variety of tests to choose from to diagnose *H. pylori* infection in patients with abdominal symptoms. The data comparing the sensitivity, specificity, and accuracy of each test are incomplete and can be confusing to clinicians. We evaluated the performance of the *H. pylori* tests in a population of Alaskan native adults with a high prevalence of *H. pylori* infection (53% using the gold standard). The 13C-UBT test accurately diagnosed 91% of persons relative to our gold standard, whereas the serological assay had a reduced accuracy of 81%. Our study suggests that in populations with high rates of sequelae from *H. pylori* (gastric cancer, duodenal ulcer disease), as well as high *H. pylori* treatment failure rates, and high reinfection rates after treatment, the 13C-UBT test may be the best non-invasive test option available for longitudinal evaluation of *H. pylori* infection.

The antibody assay had low specificity and positive predictive value because this test can be positive in persons with a previous successfully treated *H. pylori* infection and in those with a current active infection. In this study population of urban Alaska Native adults evaluated by EGD, over 1 in 5 persons were found to have had a treatment for *H. pylori* documented in their medical records prior to entering the study. We found some persons who were negative by the gold standard tests for active infection, among whom we were able to document that the presence of anti-HP IgG was associated with previous treatment for *H. pylori*. Indeed in this group, persons with a high level anti-HP IgG were close to five times more likely to have been previously treated for *H. pylori* compared to those with low levels of anti-HP. Previously published data from this study found that the mean anti-HP IgG level was 0.64 OD units (above the assay’s positive breakpoint) two years after documented successful treatment for *H. pylori*\(^1\), demonstrating that anti-HP antibodies persist long after eradication. The antibody assay may still be suitable in treatment naive populations in epidemiological investigations aimed at establishing baseline estimates of *H. pylori* prevalence. However, for the clinical purpose of identifying persons with active *H. pylori* infection, the antibody test has limited utility, because persons recovered from *H. pylori* infection might be mistakenly identified as harboring an active infection. In populations with a high prevalence of, and treatment for *H. pylori* infection, this assay is not optimal for use in a “test and treat” strategy in patients with dyspeptic symptoms. Patients identified by elevated antibody levels who are not actively infected may unnecessarily receive additional treatment for *H. pylori*.

We found that the anti-HP OD ≥ 1.1 was associated with male gender and chronic gastritis as determined by histological evaluation. The finding of an association with gastritis has been documented in other studies\(^13-16\). Sheu et al\(^16\) found the titer level of *H. pylori* to be associated with antral gastritis but not presence of ulcer,
similar to our study. In contrast, Chen et al.\textsuperscript{17} did not find an association with antral gastritis when restricting the analysis to H. pylori positive persons, an analysis similar to ours. Although the serological assay is less accurate in predicting active H. pylori infection in this Alaska Native population, high levels of anti-HP IgG increased the odds by 4-fold that chronic gastritis will be diagnosed by histology. The lower anti-HP level found in women could be attributable to inadvertent treatment of the H. pylori infection in the use of metronidazole for treating vaginal infections in women. Indeed, in this study group, women had higher levels of metronidazole use\textsuperscript{26}, and higher levels of metronidazole use were associated with lower anti-HP levels (CDC unpublished data).

With a sensitivity and specificity of 93\% and 97\%, respectively, using the manufacturer’s recommended cut-off point, the \textsuperscript{13}C-UBT provided the best non-invasive test for documentation of infection-free status. The accuracy of the test in our population compares well with performance of the UBT (both \textsuperscript{13}C-UBT and \textsuperscript{14}C-UBT) in other studies\textsuperscript{18-20}, and is in contrast to a recent study that found much lower specificity in Spain\textsuperscript{21}. In our study, we found that the accuracy of the \textsuperscript{13}C-UBT was > 90\% with cut-off points between 2.0 and 4.0 DOB, similar to findings in other reports\textsuperscript{22}. Additionally, we found that the DOB value was positively associated with the amount of H. pylori present on histological examination. Persons with very high DOB values were over four times more likely to have a high concentration of H. pylori bacteria than persons with low DOB values, an association documented elsewhere\textsuperscript{23-25}. The association between the concentration of H. pylori organisms on histology and other pathological outcomes (gastritis, intestinal metaplasia), as well as treatment outcome, is being investigated further.

In summary, in a population in the United States with a high background prevalence of H. pylori, we found that the \textsuperscript{13}C-UBT test outperforms the serological assay in the detection of active H. pylori infection. The \textsuperscript{13}C-UBT avoids the problem associated with the serological test of incorrectly identifying persons who have recovered from H. pylori as having active infection. For clinical purposes, in persons with gastrointestinal symptoms in whom an EGD procedure is not planned, the \textsuperscript{13}C-UBT appears to be useful to rule out or confirm H. pylori infection, and to test for a cure in persons who have been treated for H. pylori infection.

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