

Case Report

Reducing Inappropriate *H. pylori* Antibody Testing: A Quality Improvement Initiative

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ABSTRACT

It has been well-established that inappropriate and excessive laboratory testing presents a credible threat to patient safety and imposes unnecessary added costs to the healthcare system. This case report details our experience at the Providence VA Medical Center with a seemingly benign test with significant potential for misuse—the serology-based antibody screen for *H. pylori* infection. Although GI professional society guidelines—as early as 1998—have advocated use of urea breath testing or stool antigen testing as the standard of care for diagnosing active *H. pylori* infection, the antibody test remains in widespread use despite poor performance characteristics in lower prevalence populations, such as in much of the United States. In the past few years, in an attempt to minimize morbidity associated with treating false-positive patients, the antibody test has been discontinued from testing 'menus' of the major diagnostic labs and is increasingly no longer reimbursed by insurers. In light of this and since our facility still continued to offer the antibody test, a quality improvement initiative was undertaken to

characterize our current *H. pylori* testing practices and use that data to effect change—ideally in eliminating the test from our roster. In our study of 551 patients who presented for *H. pylori* testing over a 5 year period, we found that nearly 70% were initially diagnosed with the incorrect (antibody) test, and of those seropositive patients ultimately treated with antibiotics, approximately 80% were essentially mismanaged in that they received no other confirmatory testing before therapy was initiated. We furthermore noted that inappropriate ordering of antibody testing was concentrated in the primary care setting, likely by providers not familiar with current guidelines or the unfavorable performance characteristics of the antibody test in our low-prevalence, Veteran population. Sharing these data with our Laboratory Utilization Committee directly led to discontinuation of the antibody test at our facility.

Keywords: *H. pylori*; Quality improvement; Antibody; Serology; Testing; Lab

Case

A 44 year old gentleman presents to the Emergency Department with a complaint of severe, persistent weakness for the past several days. His medical history is remarkable for: Depression, gastroesophageal reflux disease, fibromyalgia, chronic low back pain, and prior history of pulmonary embolism for which he is currently on anticoagulation with rivaroxaban. He is on chronic opioid therapy with oxycodone and fentanyl patch for his back pain. Of note, the patient had recently presented to his primary care provider with symptoms of dyspepsia and was diagnosed with *H. pylori* infection following a positive antibody serology test. He is on Day 11 of a 14 day course of 'triple therapy' with clarithromycin, amoxicillin, and omeprazole.

The patient conveys that he was in his usual state of health until approximately 10 days ago when he began feeling extraordinary fatigue with his usual activities. His symptoms progressed to include dyspnea on exertion, nausea, and somnolence, for which he remained bedridden for the entirety of the last 3 days with minimal oral intake. He specifically denies:

fevers, decreased mood or recent changes in his medication regimen, other than the current antibiotics he is taking for *H. pylori*. On encounter in the Emergency Department, his physical exam is most notable for somnolence with no focal neurologic deficits, dry mucous membranes, poor skin turgor, and significant orthostasis suggesting hypovolemia. Labs revealed: grossly normal hematology profile, a metabolic panel notable for serum creatinine of 1.5 mg/dL (baseline 1.0) and potassium level of 3.4 mMol/L, normal liver function tests, negative troponin, negative influenza screen. EKG showed no changes from his baseline. Urine toxicology was positive for oxycodone and opioids, consistent with the current medication regimen.

The patient is fluid resuscitated and admitted to the medical ward for overnight observation. On further review of home medications, the admitting team astutely notes that clarithromycin is a potent P450 3A inhibitor and may decrease clearance of both oxycodone and fentanyl, potentially accounting for the patient's presentation. They further question the validity of his diagnosis of active *H. pylori* infection

given the patient's low-risk demographics and relatively poor positive predictive value of the serology based antibody test in this context. However, closer review of the chart revealed previous endoscopy with evidence of infection on histology, not previously treated. Opioids are withheld with nearly complete resolution of symptoms by the following day and the patient is advised to complete his course of antibiotics upon discharge, further avoiding narcotics in the interim. The patient was discharged to follow up with his primary provider.

Our patient suffered an adverse event attributable to a medication interaction following initiation of standard 'triple therapy' for his newly diagnosed *H. pylori* infection. Exploration of the root causes contributing to this outcome implicated a lack of awareness—at the prescriber level—of clarithromycin metabolism, and a failure of the relevant pharmacy mechanism to prevent dispensing a medication incompatible with the patient's current regimen. Although not the case for this particular patient given his previous positive endoscopy, there is a high potential for misdiagnosis and inappropriate antibiotic treatment when *H. pylori* infection is diagnosed only upon a positive antibody test. Given the potential morbidity related to test misuse in this context, we undertook further investigation of *H. pylori* diagnostic testing practices at our facility, the Providence Veterans Affairs Medical Center (Providence, RI).

Background

The problem of *H. pylori* testing

H. pylori is the most prevalent chronic bacterial infection worldwide, estimated to affect roughly half of the adult population, with the majority of cases concentrated in the developing world.¹ Infection is associated with significant gastroduodenal pathology, most notably: peptic ulcer disease, chronic gastritis, and gastric malignancy.² While carriers are usually asymptomatic, there is a recognized need for detection and treatment in certain populations given the potential morbidity associated with infection and the effectiveness of

eradication therapy. The most recent (2007) American College of Gastroenterology guidelines on the management of *H. pylori* infection cite the following as "clear indications" for testing for and treating *H. pylori*: active peptic ulcer disease, a past history of documented peptic ulcer, gastric MALT lymphoma, and uninvestigated dyspepsia in patients <55 without 'alarm' features that would first warrant endoscopy (i.e., bleeding, weight loss, early satiety, dysphagia, vomiting, family or personal history of GI cancer).³

Selection of an initial test for *H. pylori* should ideally be tailored to the specific clinical scenario—taking into account the need for endoscopy, pre-test probability and local prevalence of disease, cost, and availability. In the patient not undergoing endoscopy, the three available noninvasive options are: serology-based antibody testing, urea breath testing (UBT), and fecal antigen testing (FAT). UBT and FAT are endorsed as first-line tests for initial *H. pylori* diagnosis and for confirmation of eradication by current GI society guidelines, owing to their superior sensitivity and specificity in identifying active infection, low cost, and widespread availability (Table 1).³⁻⁵

While once the sole means of noninvasive testing for *H. pylori* prior to FDA approval of the UBT in 1996, continued use of the antibody test in lower prevalence populations has been discouraged by all major GI society practice guidelines for the last decade.³⁻⁶ Despite the current recommendations, antibody testing continues to be over-utilized as the screening modality of choice for *H. pylori*. A recent analysis of insurance claims data between 2010-2012, including >100 million patients, demonstrated that serology testing remained the preferred screening test among providers and was ordered 4.5 times and 6.2 times more often than UBT and FAT respectively, resulting in over 15,000 diagnoses not substantiated by other testing.⁷ Given insufficient evidence to support routine use in clinical practice, a number of major insurers including Cigna, Aetna and Geisinger no longer provide reimbursement for antibody testing; leading providers of laboratory testing services such

Table 1: Features of non-invasive diagnostic tests for *H. pylori*.

		Non-invasive tests for <i>H. pylori</i>			
	Advantages	Disadvantages	Sensitivity ^{13,14}	Specificity ^{13,14}	
Serology-based antibody detection	Inexpensive	Poor specificity, PPV	85%	79%	
	Good NPV	Cannot distinguish between active vs. previous infection—cannot monitor response to therapy			
Urea breath test	Not affected by use of PPIs/bismuth/antibiotics	No longer being reimbursed by several insurers	95%	90%	
	Test of active infection	Use not supported by current guidelines			
	Endorsed by current guidelines	Sensitivity decreased with use of PPI/bismuth/antibiotics with last 14d			
Stool antigen test	Excellent PPV/NPV	Specialized specimen collecting and processing requirements	93%	93%	
	Test of active infection	Availability remains inconsistent			
	Endorsed by current guidelines	Unpleasantness associated with collecting stool			
	Excellent PPV/NPV	Sensitivity decreased with use of PPI/bismuth/antibiotics with last 14d			

as Quest and Mayo Medical Laboratories have likewise discontinued availability.^{7,8}

Use of serologic antibody testing for *H. pylori* is problematic for a number of reasons. Its inferior performance characteristics in terms of sensitivity and specificity—when compared to UBT and FAT—is especially problematic in lower-prevalence populations, such as found in much of the United States.⁹ While considerably more prevalent in the developing world, previous analyses of NHANES data suggest an overall prevalence of *H. pylori* of 27.1-32.7% in US adults.¹⁰ Therefore, if a clinician were to employ antibody screening in a community with comparable baseline prevalence, a positive result would yield a positive predictive value of approximately 50%—essentially similar to chance.³ Repeat testing by UBT or FAT would then be required to confirm diagnosis, at additional cost. Initiating pharmacotherapy solely based on a positive serology could potentially expose half of all serology-positive patients to unwarranted antibiotic therapy and promote increased antimicrobial resistance. Additionally, reliance on detection of IgG antibodies against *H. pylori* renders the serology test unsuitable for distinguishing active from past infection and a poor choice for confirming post-treatment eradication.^{3,4}

Recognizing the potential for misdiagnosis, unnecessary treatment, and increased costs associated with continued, widespread use of an inappropriate screening test, this case report details the first phase of a quality improvement initiative underway at the Providence Veteran Affairs Medical Center seeking to better characterize local screening practices for *H. pylori* and retrospectively identify instances of mismanagement stemming from use of serology-based testing in a low-prevalence population.

Methods

Baseline data collection was obtained by searching the

local facility ‘VISTA’ (Veteran’s Integrated System Technology Architecture) database. Over a five-year time period between 11/1/2010–11/30/2015 the database was queried for all instances of resulted orders for either *H. pylori* stool antigen or antibody serology tests (the urea breath test is not available at our facility). For each qualifying order: test result, date and time collected, as well as ordering provider were recorded. Utilizing local personnel records, ordering providers were sub-categorized into one of three categories based on their role at the time of test order: 1) ‘Gastroenterology provider’ which includes attending gastroenterologists, fellows, and nurse-practitioners affiliated with the gastroenterology service, 2) ‘Residents’ which almost exclusively included medical and surgical interns and residents, and 3) ‘Outpatient providers’ which included those attending and nurse practitioner providers working in non-GI outpatient settings (inclusive of the emergency department). Subjects with a positive antibody serology result had the medical record reviewed to determine whether antibiotics were started, and also to further ascertain—if started—whether the decision to treat was based solely upon serology results alone or was informed by additional data (i.e. stool antigen test, pathology) to support the diagnosis of active *H. pylori* infection. Descriptive statistics as well as Pareto analysis delineating test ordering frequency by individual provider were performed by use of Excel.

Results

Over the five-year study period, 551 patients were identified in the VISTA database who received noninvasive testing for *H. pylori* with either antibody serology, stool antigen testing, or both. As is detailed in Figure 1, antibody testing was selected as the initial diagnostic test in 69.5% of patients. Of the 39 patients who had a positive serology test, confirmatory testing by stool testing was only performed in a third of the cases. In the serology-positive cohort, a stool-confirmed positive result

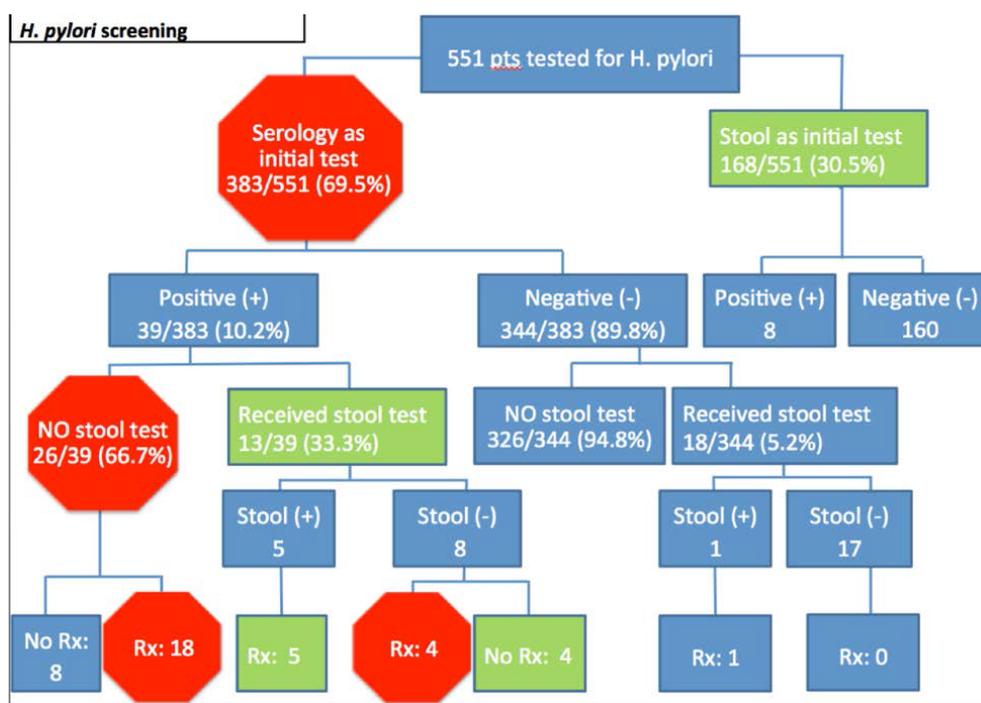


Figure 1: Testing ordered for *H. pylori* screening.

was seen in 5 patients, suggesting a positive predictive value of 38.5% of the antibody test.

Antibiotic therapy was started in 27/39 patients (69.2%) in the serology-positive group. These treatments reflected management not consistent with current guidelines in 22/27 cases (81.5%) – 18 patients having received treatment without further stool testing for confirmation of diagnosis, and 4 receiving therapy in spite of a negative stool test.

Analysis of ordering patterns associated with serology testing revealed: 317 (81.1%) of tests were initiated by primary care providers, 49 (12.5%) by resident physicians and 25 (6.4%) by GI providers, who exclusively comprised of either fellows or nurse practitioners (Table 2). Pareto analysis examining ordering frequency by provider revealed that 17/20 of the top ordering providers were based in a primary care setting; 6 of these primary care providers accounted for 51.2% of all serology tests ordered (Figure 2).

Stool antigen testing showed highest utilization by GI providers who ordered 80/215 tests (37.2%), compared with house staff (67 tests, 31.2%) and primary care providers (68 tests, 31.6%). Pareto analysis indicated 14 of the top 20 ordering providers were affiliated with GI (Figure 3).

Discussion

Table 2: All tests ordered by provider type.

Test	#ordered	Ordering provider		
		GI	Resident	PCP
Antibody	391	25 (6.4%)	49 (12.5%)	317 (81.1%)
FAT	215	80 (37.2%)	67 (31.2%)	68 (31.6%)

Ultimately, the optimal management protocol for *H. pylori* testing was executed in only 32.1% of cases when we consider those patients who were either initially referred for FAT screening, or subsequently referred for the test following a positive serology. A significant proportion of initially seropositive patients (69.2%) were directly referred for treatment without additional confirmatory testing. Assuming baseline disease prevalence similar to the rest of the US within our community, it is likely at least half of these patients were unnecessarily exposed to the risks of antibiotic therapy.

Performance characteristics of the serology-based antibody test reflected what has been previously reported in the literature when utilized in a low-prevalence population and taking the stool test to be the gold standard for diagnosis—notably, we observed a positive predictive value of 38.5%, negative predictive value of 94.4% in our predominantly Caucasian, native-born, Veteran cohort.³ Likewise, the serology-based test remained the preferred modality amongst our providers as an initial screen for *H. pylori*. This effect appeared to be concentrated in the primary care setting, as these providers generated 81.1% of all antibody test orders and ordered serology testing at least 4 times more often than stool-based testing.

These findings were observed over a study interval (2010-2015) well beyond the first published guidelines in 1998 discouraging use of antibody screening in low prevalence populations.⁶ Given the preponderance of testing for *H. pylori* in the outpatient, primary care setting and our findings that most of the erroneous antibody testing was generated in this context, our data suggests a lack of familiarity with ‘best-practices’ amongst non-specialists using this test. While a targeted

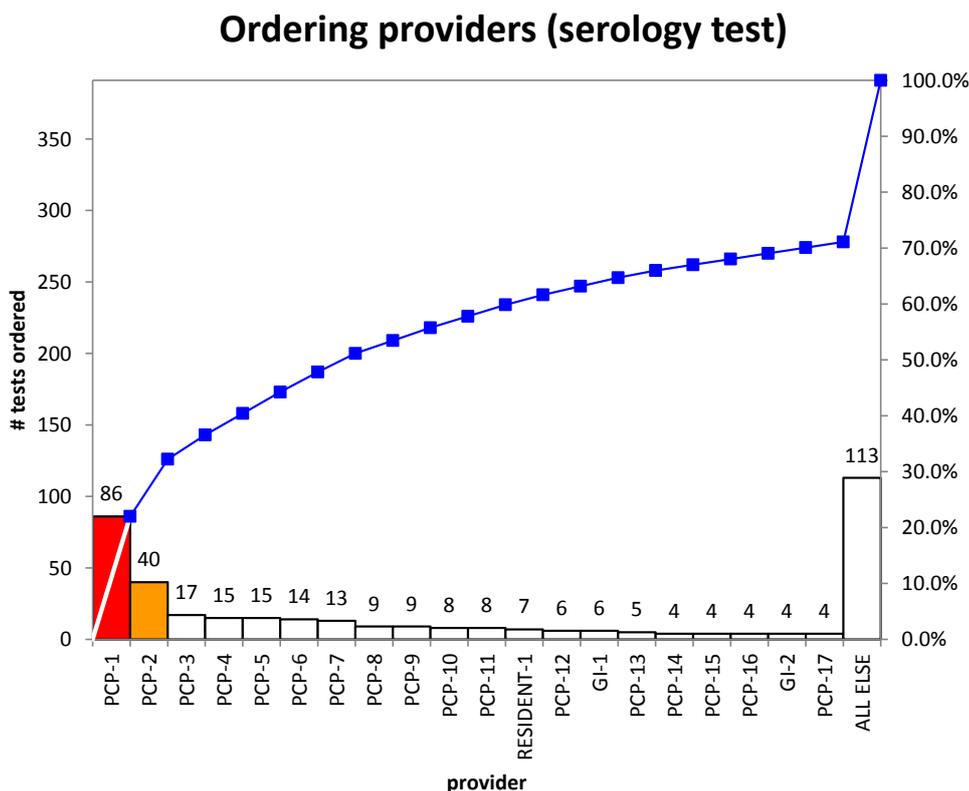


Figure 2: Pareto chart - Antibody serology orders by provider type.

Ordering providers (stool test)

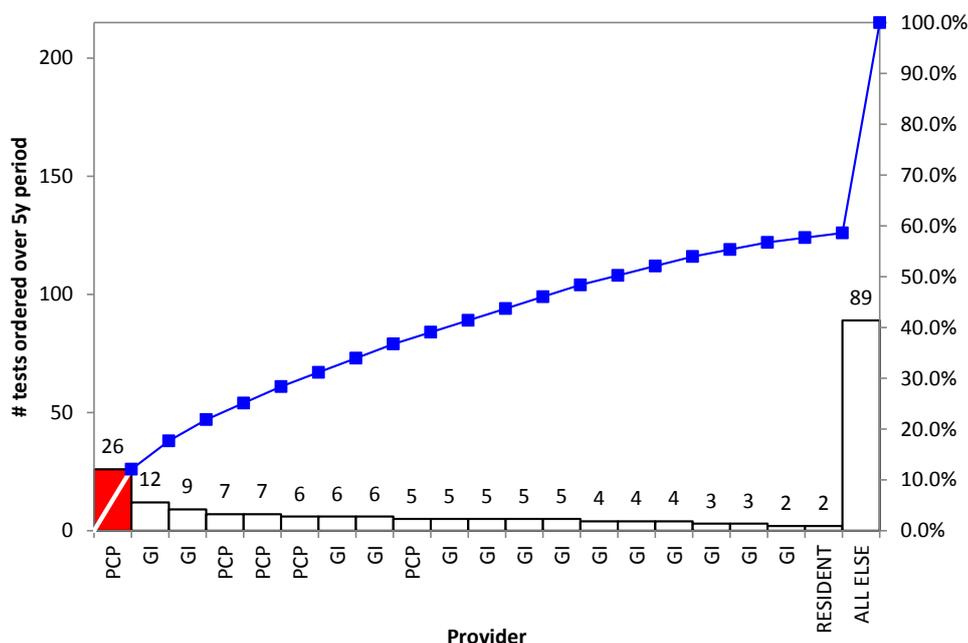


Figure 3: Pareto chart - Stool antigen orders by provider type.

educational intervention or enhanced use of clinical decision support tools may be of some benefit, continuing to offer a test with generally poor testing characteristics relative to our patient population represents a latent error within our current diagnostic infrastructure that predisposes to test misuse and the associated, resultant harms.

Laboratory testing is an essential aspect of the diagnostic process, however with over 3000 tests readily available, the sheer volume of options introduce considerable complexity in proper selection and interpretation to even the most seasoned clinician.¹¹ It is estimated that primary care providers order the greatest variety of lab-based tests and do so at approximately 30% of all patient encounters, however they report experiencing uncertainty regarding test selection in 15% of cases. In one CDC survey of test-ordering behavior in over 1700 generalist physicians, 22% reported reviewing relevant practice guidelines when confronted with uncertainty, and approximately three-quarters felt that a rigid intervention aimed at reducing cognitive burden, such as automated reflex testing, would improve the effectiveness of their diagnostic testing practices.¹²

As a result of this quality improvement initiative, serology-based *H. pylori* antibody testing has been discontinued at our institution, which is consistent with the current practices of several major insurers and diagnostic labs. Dissemination of recent guidelines and review of Pareto-based analysis localizing improper test utilization to a clinician cohort less likely to be familiar with current guidelines served to be an effective means of communicating with our Laboratory Utilization Committee to institute change. Given the breadth of diagnostic testing currently available to the generalist practitioner, as well as the inherent challenges of keeping abreast of evolving or unfamiliar guidelines, evidence-guided test restriction at the laboratory level may represent an effective means of reducing the harms

and financial cost associated with unnecessary or inappropriate testing.

CONFLICTS OF INTEREST

Dr. Brown, Dr. Anjelly and Dr. Lally report no potential conflict of interest in connection with this work. Dr. Moss is on the speaker's bureau of Otsuka America who manufactures a currently available *H. pylori* breath test.

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