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# How to test for *Helicobacter pylori* in 2005

Infection with *Helicobacter pylori* can be diagnosed either by invasive techniques requiring endoscopy and biopsy (histologic examination, rapid urease test, culture, polymerase chain reaction) or by one of several noninvasive testing methods—serologic tests, the urea breath test, and the stool antigen test. Guidelines for managing dyspeptic patients in primary care settings recommend the use of noninvasive tests for *H pylori* detection at the outset,<sup>1-3</sup> as this approach has been demonstrated to be clinically effective and less costly than invasive testing,<sup>4,5</sup> along with being more convenient.

This article briefly reviews the available noninvasive tests for *H pylori* detection and discusses factors that should inform the choice of an individual test.

## ■ ACTIVE VS PASSIVE TESTING

A fundamental distinction among tests for *H pylori* is whether they provide direct evidence that *H pylori* infection is currently present (ie, active tests) or indirect evidence, by detecting the presence of antibodies to *H pylori* (ie, passive tests). Because they only detect antibodies to *H pylori*, passive tests do not distinguish between currently active infection and infection that has resolved or been cured.

All serologic tests for *H pylori* are passive tests, whereas the urea breath test and the stool antigen test are both active tests. Recently introduced *H pylori* tests that evaluate saliva or urine also work by detecting antibodies to *H pylori* and thus share with serologic tests the limitations of passive testing. Because antibody concentrations are lower in saliva and urine than in blood, antibody detection is even more difficult with these tests than with serologic tests, so they will not be discussed further here.

**DISCLOSURES:** Dr. Vakil has received grant/research support from AstraZeneca Pharmaceuticals, Medtronic, Novartis, and Pfizer; has served as a consultant to AstraZeneca, Medtronic, Meridian Bioscience, and Novartis; and is on the speakers' bureaus of AstraZeneca, Novartis, and TAP Pharmaceutical Products. Dr. Fendrick has served as a consultant to Meridian Bioscience.

## ■ THE NONINVASIVE TESTS AT A GLANCE

### Serologic tests

Serologic testing detects the presence of specific IgG antibodies to *H pylori* in a patient's serum. These antibodies are present in serum about 21 days after infection and can remain present long after the organism is eradicated. They can be assessed quantitatively using enzyme-linked immunosorbent assay (ELISA) and latex agglutination techniques or qualitatively using office-based kits. Dozens of different serologic tests are commercially available.

Advantages of the serologic tests are their wide availability, their rapid results, the fact that they require no specialized equipment or techniques, and their low cost relative to active tests. For these reasons, serologic tests were the mainstay of *H pylori* diagnosis for a number of years.

The major disadvantage of serologic tests is that they cannot distinguish between active infection and previous exposure to *H pylori*. Because serologic testing detects only antibodies, a positive serology result can occur in three very different patient groups<sup>6</sup>:

1. Those with detectable antibody and active *H pylori* infection (true-positive for antibody, infected).
2. Those with detectable antibody but not actively infected (true-positive for antibody, not infected).
3. Those never infected and with no antibody detectable (false-positive result).

This distinction is critical because eradication therapy is of no clinical value in the second and third groups. As more and more people are successfully treated for *H pylori* in a population, the ranks of the "true-positive for antibody, not infected" group (group 2) will grow. Of course, the inability to distinguish between active and past infection also renders serologic testing useless for confirmatory testing to ensure *H pylori* eradication following treatment to cure the infection.

This inability to distinguish between current and past infection contributes to the other major

The major disadvantage of serologic tests is that they cannot distinguish between active and past infection with *H pylori*



shortcoming of serologic testing—that it is less sensitive and specific than the active noninvasive tests for *H pylori* (Table 1).<sup>7</sup> A meta-analysis of 21 clinical trials using commercially available ELISA serology kits found an overall sensitivity and specificity of 85% and 79%, respectively, for active infection with these serologic tests and revealed no significant differences among the various kits.<sup>8</sup> The authors concluded that the overall accuracy of serologic tests may not be adequate for clinical decision-making. A similar analysis by the London Department of Health of 16 serologic tests arrived at similar sensitivity and specificity rates,<sup>9</sup> as did studies from 2001 and 2002 of the more advanced “third-generation” ELISA tests.<sup>10-14</sup>

### Urea breath test

The urea breath test identifies active *H pylori* infection through the organism’s urease production. The patient ingests urea labeled with either the nonradioactive isotope carbon 13 (<sup>13</sup>C) (BreathTek UBT for *H pylori*, Meretek Diagnostics, Inc, Lafayette, CO) or the radioactive isotope carbon 14 (<sup>14</sup>C) (PYtest, Kimberly-Clark Corp, Draper, UT). If *H pylori* is present in the stomach, hydrolysis occurs and produces labeled carbon dioxide, which is detectable within a few minutes in the patient’s breath. The labeled urea is typically given to the patient with a test meal to delay gastric emptying and increase contact time with the mucosa. After urea ingestion, breath samples are collected for up to 20 minutes by exhaling into a carbon dioxide-trapping agent. Though the amount of radiation in the <sup>14</sup>C urea breath test is less than daily background radiation exposure,<sup>15</sup> the <sup>13</sup>C test is preferred in children and pregnant women.<sup>16</sup>

Recently, a new card test for <sup>14</sup>C urea has been described that uses a flat breath card that is read by a small analyzer, providing a near-patient testing option in primary care settings.

The urea breath test detects active *H pylori* infection and is highly accurate, with a weighted mean sensitivity and specificity from published trials of 94.7% and 95.7%, respectively (Table 1).<sup>7</sup>

### Stool antigen test

The stool antigen test is an enzymatic immunoassay (ELISA) that identifies *H pylori* antigen in stool specimens through a polyclonal anti-*H pylori* antibody (Premier Platinum HpSA, Meridian Bioscience, Inc, Cincinnati, OH). In addition, a rapid stool antigen test

TABLE 1

### Accuracy of noninvasive tests for *H pylori* infection

	SENSITIVITY FOR ACTIVE INFECTION	SPECIFICITY FOR ACTIVE INFECTION
Urea breath test	94.7%	95.7%
Stool antigen test	93.1%	92.8%
Serum IgG antibody (serology)	85.0%	79.0%

Data are weighted mean values compiled from multiple published clinical trials as detailed in reference 7.

(ImmunoCard STAT! HpSA, Meridian Bioscience, Inc, Cincinnati, OH) is available. Using the rapid assay, a diluted stool sample from the patient is dispensed into the sample port of the test device; after 5 minutes of incubation at room temperature, the device indicates a positive or negative result, providing a near-patient testing option in primary care settings.

The ELISA stool antigen test detects active *H pylori* infection and is highly accurate, with a weighted mean sensitivity and specificity from published trials of 93.1% and 92.8%, respectively,<sup>7</sup> rates that are virtually the same as those for the urea breath test (Table 1). Similar performance has been demonstrated in the rapid format.

### ■ CHANGING PREVALENCE PROFOUNDLY AFFECTS TEST PERFORMANCE

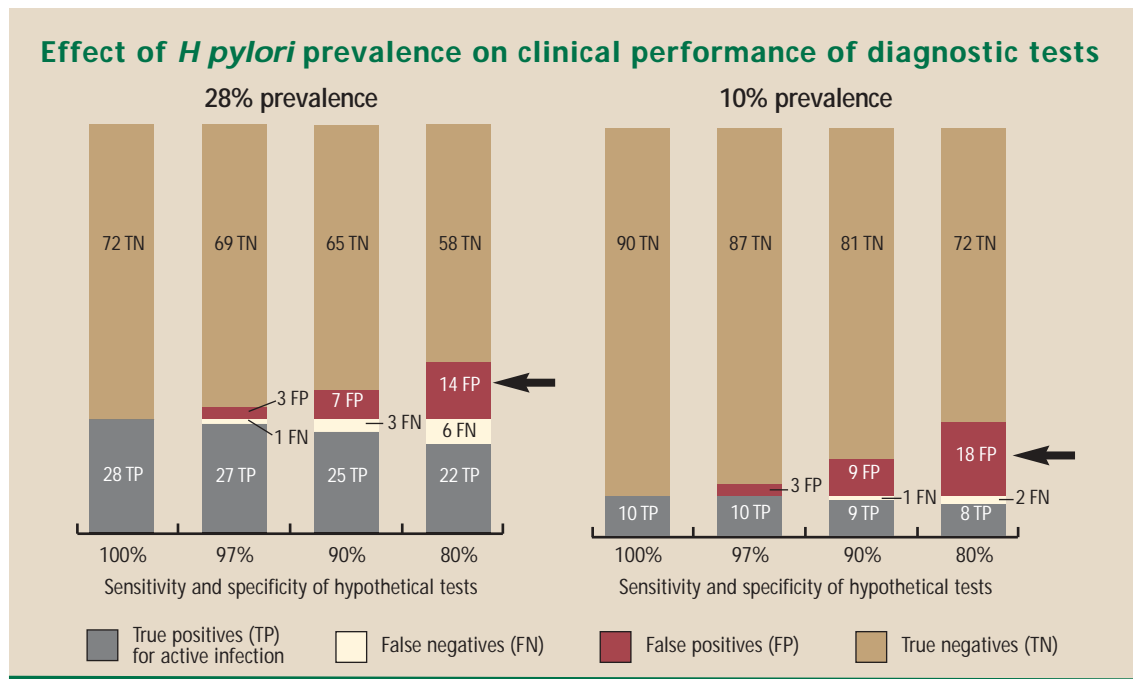
As Table 1 illustrates, the two tests for active infection, the urea breath test and the stool antigen test, are about 8 to 10 percentage points more sensitive and about 14 to 16 percentage points more specific than antibody testing with serology. How important are these differences in clinical practice? The changing prevalence of *H pylori* infection makes them far more significant than they first appear to be.

As the prevalence of *H pylori* infection declines in the United States,<sup>17</sup> the pretest probability that *H pylori* is present in a given patient with dyspepsia also declines. This has implications for the clinical performance of a diagnostic test even though the test’s sensitivity and specificity for active infection remain constant.

Figure 1 shows how four hypothetical tests with sensitivities and specificities for active infection of 100%, 97%, 90%, and 80%, respectively, perform in two different populations—one with a 28% prevalence of *H pylori* and one with a 10%

There is little point in sequential testing with serology followed by an active test for confirmation

## Effect of *H pylori* prevalence on clinical performance of diagnostic tests



**FIGURE 1.** Performance of four hypothetical diagnostic tests for *H pylori* with sensitivities and specificities for active infection of (a) 100%, (b) 97%, (c) 90%, and (d) 80% in two different populations—one with a 28% prevalence of *H pylori* infection and one with a 10% prevalence. The tests' clinical performance varies substantially even though their differences in sensitivity and specificity seem modest. In the 28% prevalence setting (left), the test with 80% sensitivity and specificity produces a high number of false positives (14 out of 100 patients; arrow)—twice as many as the test with 90% sensitivity and specificity. As the prevalence of *H pylori* falls to 10% (right), the number of additional false positives (arrow) climbs much more quickly with the test with 80% sensitivity and specificity than with the other tests. Adapted from reference 18.

### A test-and-treat strategy is advantageous for patients with a high likelihood of peptic ulcer disease

prevalence. As the figure illustrates, the clinical performance of the tests varies substantially even though their differences in sensitivity and specificity seem modest. In the population with 28% prevalence, the test with 80% sensitivity and specificity produces twice as many false positives as the test with 90% sensitivity and specificity and nearly five times as many as the test with 97% sensitivity and specificity.<sup>18</sup> As the prevalence of *H pylori* falls (in this case, down to 10% in the right-hand panel of **Figure 1**), the number of additional false positives climbs much more quickly with the test with 80% sensitivity and specificity than with the other tests.

Of course, an *H pylori* prevalence of 28% or lower is present in many primary care settings in the United States today, which means that a test method with a sensitivity and specificity for active infection of approximately 80%, such as serologic testing, will yield many false positives. This will lead to inappropriate treatment in numerous patients and a host of unwanted outcomes—lack of treatment response, encouragement of antibiotic resistance, patient inconvenience and disappointment, a need for further testing, and additional costs and resource use. This effect will only grow as the prevalence of *H pylori* continues to fall in the United States.

For this reason, the 2000 Maastricht 2 Consensus Report<sup>1</sup> concluded that serologic testing is not accurate enough for use in routine clinical practice.

### ■ WHAT ABOUT COST?

Even in light of data showing the clinical inferiority of serologic testing, the question sometimes arises of whether it is justified to first test with a low-cost serologic test and then follow up with a more accurate active test if deemed necessary.

This type of sequential testing strategy was assessed in an economic model evaluating non-invasive testing strategies in primary care settings.<sup>19</sup> The analysis compared the costs per number of correct diagnoses achieved with various sequential testing strategies and with single tests across three *H pylori* prevalence scenarios: low (30%), intermediate (60%), and high (90%). Estimates of prevalence and test characteristics were derived from a systematic literature review, and cost estimates were derived from the 2000 Medicare fee schedule.

Although serologic testing had the lowest cost per correct diagnosis (\$90 to \$95) at all three prevalence levels, its diagnostic accuracy was low (80% to 84%). At low and intermediate prevalence, use of an active test alone was substantial-

ly more accurate at a modest additional cost; the stool antigen test had a diagnostic accuracy of 93% at an average cost of \$126 to \$127 per correct diagnosis and an incremental cost of \$336 to \$381 per additional correct diagnosis (specific data were not reported for the urea breath test used alone). Only at high prevalence (90%) did a sequential strategy using serologic testing begin to justify itself; in this scenario, serologic testing with ELISA followed by confirmatory urea breath testing for negative ELISA results produced diagnostic accuracy of 96% at a cost of only \$112 per correct diagnosis.<sup>19</sup>

The authors concluded that active testing with the stool antigen test or urea breath test is clearly preferable at low and intermediate *H pylori* prevalence (60% or lower), given these tests' high level of accuracy at modest incremental cost over serologic testing. In high-prevalence settings, which are highly unusual in the developed world, serologic testing becomes competitive, but its relative accuracy is still poor. The authors recommended that, given the modest cost of the stool antigen and urea breath tests, there is little point in sequential testing with a low-cost test followed by an active test for confirmation. Because of the highly comparable accuracy of the stool antigen and urea breath tests, any differences between them in cost per correct diagnosis were due almost wholly to differences in the costs of the tests used in this analysis (\$50 for the stool antigen test and \$104 for the urea breath test, based on their Medicare reimbursement levels at the time).<sup>19</sup>

#### ■ IS 'TEST AND TREAT' STILL RECOMMENDED?

The "test-and-treat" strategy for *H pylori* in patients with uninvestigated dyspepsia was developed a number of years ago, when serologic testing was a still a recommended method of noninvasive testing and when the prevalences of both *H pylori* and peptic ulcer disease in the United States were higher than they are today. Recent decision analyses have reappraised the utility of the test-and-treat strategy in the context of (1) the changing epidemiology of *H pylori* and peptic ulcer disease<sup>20,21</sup> and (2) the newer options in noninvasive testing.<sup>6</sup>

'Test and treat' remains useful, but empiric PPI therapy may also have a role

Spiegel et al<sup>20</sup> performed a decision analysis that incorporated 6 weeks of empiric proton pump inhibitor (PPI) therapy into several management strategies for patients with uninvestigated dyspepsia. Of four strategies, initial PPI therapy

**TABLE 2**

### US populations with increased probability of *H pylori* infection

African Americans	Persons with poor socioeconomic status
Hispanics/Latinos	Native Americans from Alaska
Immigrants from developing nations	Persons older than 50 years of age

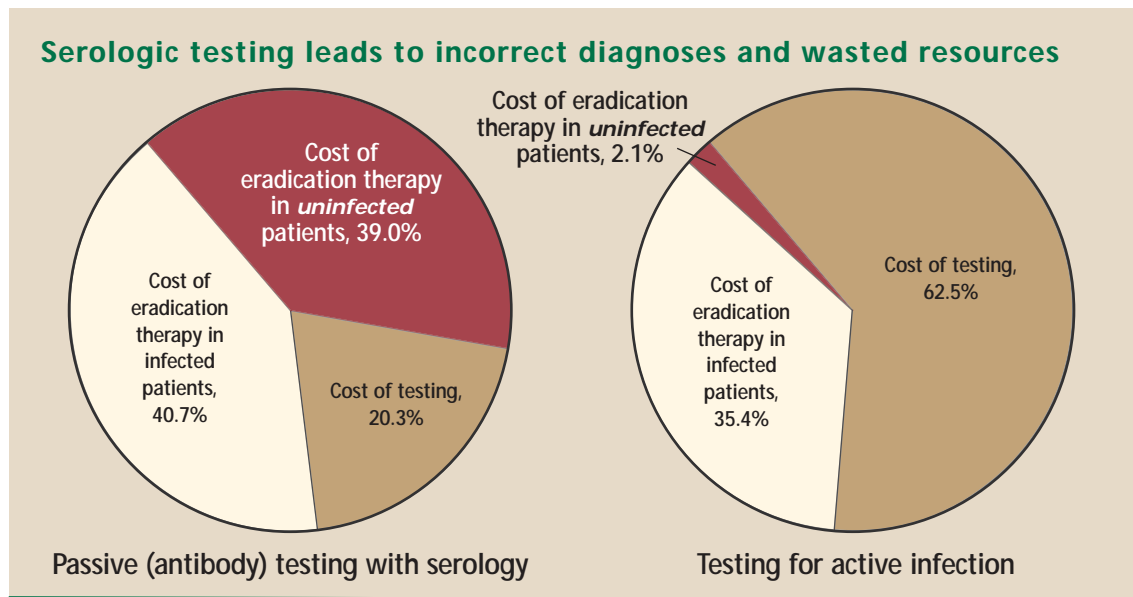
followed by endoscopy for nonresponders was found to be the least costly strategy per patient treated, but it left fewer patients symptom-free at 1 year than did two hybrid strategies that combined a test-and-treat approach for *H pylori* with empiric PPI therapy; these hybrid strategies were slightly more costly. The most costly and least effective strategy was a test-and-treat approach followed by endoscopy for nonresponders. (The strategies that included testing and treating assumed use of an ELISA serologic test, not a test for active *H pylori* infection.) The authors concluded that sequential use of a test-and-treat approach with PPI therapy may be more cost-effective than PPI therapy alone, especially when peptic ulcer disease is highly likely or symptoms are severe, but that PPI therapy alone may be more cost-effective when underlying erosive esophagitis is likely, *H pylori* infection is unlikely, or dyspeptic symptoms are not severe.<sup>20,22</sup>

Ladabaum et al<sup>21</sup> reached similar conclusions from a symptom-driven decision analysis that compared a test-and-treat strategy and empiric PPI therapy for patients with uninvestigated dyspepsia. (Again, the test-and-treat strategy assumed testing with an ELISA serologic test.) Under most epidemiologic conditions, costs per patient treated and clinical outcomes differed little between the two strategies. At the individual patient level, the prevalence of *H pylori* infection, the likelihood that a given patient had peptic ulcer disease, and the proportion of ulcers attributable to *H pylori* strongly influenced which strategy carried the lowest cost per patient treated. At the population level, empiric PPI therapy was consistently less costly if the *H pylori* prevalence was less than 20%.

Both of these decision analyses suggest that a test-and-treat strategy offers an advantage for patients who have a high likelihood of peptic ulcer disease. In light of this, as the prevalence of *H pylori* infection and peptic ulcer disease declines, clinicians should increasingly be attuned to their individual patients' likelihood of *H pylori* infection, based on demographic factors (Table

Because of its lower specificity, serologic testing leads to more treatment of patients without active infection, more antibiotic resistance, and wasting of resources

## Serologic testing leads to incorrect diagnoses and wasted resources



**FIGURE 2.** Breakdown of overall management costs per 100 patients tested with either serologic testing or testing for active infection (with urea breath test) in a test-and-treat strategy for *H pylori* in uninvestigated dyspepsia, assuming 30% prevalence of active *H pylori* infection (see text for details). Because it cannot distinguish between past and current infection, serologic testing leads to many more false-positive results and, in turn, to many incorrect diagnoses of *H pylori* infection and a high level of inappropriate treatment. As a result, 39% of overall spending with the serologic testing strategy is wasted on inappropriate therapy in uninfected patients, vs only 2% of overall spending with active testing. Data are from a decision analysis by Chey and Fendrick.<sup>6</sup>

2), and their likelihood of having peptic ulcer disease, based on symptoms (ie, epigastric pain).

**At least 1 in 4 patients remains infected after treatment to cure *H pylori*, so all patients should be retested following therapy**

'Test and treat' now requires an active test. When the suspicion of both *H pylori* and ulcer is reasonable and testing is indicated, physicians clearly should use a test for active infection. That is the conclusion of a decision analysis by Chey and Fendrick<sup>6</sup> that estimated the clinical and economic outcomes associated with either serologic testing for *H pylori* antibody (assumed sensitivity and specificity for active infection of 85% and 79%, respectively, and assumed cost of \$25 per test) or active testing with the urea breath test (assumed sensitivity and specificity for active infection of 95% and 98%, respectively, and assumed cost of \$100 per test). The model assumed an *H pylori* prevalence of 30%; of the 70% of individuals without active infection, 20% were assumed to have been infected at some time in the past, meaning that 14% of the overall population would have true-positive results for *H pylori* antibody but not have active infection. Patients who tested positive were to be treated with a 14-day regimen of lansoprazole, clarithromycin, and amoxicillin at a cost of \$200.<sup>6</sup>

The analysis showed that active testing dramatically reduced the number of patients inappropriately treated (ie, treated despite not having active *H pylori* infection), from 23.7 per 100 patients with serologic testing to only 1.4 per

100 patients with active testing. Moreover, when compared with serologic testing, active testing identified 3 additional patients with current infection per 100 patients tested.

To achieve these clinical advantages, active testing cost an additional \$37 per patient tested compared with serologic testing. However, on a population basis, a full 39% of the overall cost of a serology-based management strategy represents wasted resources in the form of inappropriate eradication therapy in incorrectly diagnosed patients (without current infection). With active testing, the corresponding proportion is just 2% (**Figure 2**). The authors concluded that the modest incremental cost of active testing is well worth it for the additional accuracy achieved and for the avoidance of inappropriate treatment, misuse of antibiotics, patient inconvenience, and wasted resources.

### ■ RETEST TREATED PATIENTS TO CONFIRM CURE

As recommended in the Maastricht 2 Consensus Report,<sup>1</sup> repeat testing after *H pylori* eradication therapy should be offered to all patients to confirm that the infection has been cured.

There are several reasons for this recommendation. First, intention-to-treat analyses of US randomized trials show that successful eradication was achieved in only about three quarters of patients receiving optimal treatment regimens for *H pylori* eradication. Thus, at least one in

four patients will remain infected after therapy and need to be identified for further management. Second, because treatment for *H pylori* involves taking multiple pills over 1 to 2 weeks, patients often fail to adhere to their full regimen. Third, antibiotic resistance is rising among *H pylori* organisms. Finally, confirmatory retesting is good medicine, and most patients who have the organism want to know that it has been eradicated. A study among US patients with peptic ulcer disease in the late 1990s found that most desired retesting to confirm *H pylori* cure at their own expense, and more than half said they were willing to pay more than \$50 for it.<sup>23</sup>

Because they detect only antibody to *H pylori*, serologic tests and other passive tests should *not* be used for retesting to confirm eradication. Both the urea breath test and the stool antigen test are appropriate for confirmatory retesting, and a recent trial found that they are equally accurate in confirming *H pylori* eradication after therapy.<sup>24</sup>

Current or recent PPI use can lead to false-negative results with either the urea breath test or the stool antigen test.<sup>18</sup> For this reason, PPIs should be withheld for 2 weeks prior to administration of either test, and post-treatment testing should not be done until 4 weeks after the patient has completed eradication therapy with a PPI and antibiotics.

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TABLE 3

## Why do confirmatory post-treatment testing?

- Eradication therapy fails in at least one quarter of patients
- Patients often do not adhere to full treatment regimens
- Antibiotic resistance is rising
- Patients want to know if their infection is cured, and most are willing to pay for this knowledge
- It's good medicine

## CONCLUSIONS AND RECOMMENDATIONS

Testing for *H pylori* infection in primary care settings should be limited to noninvasive testing methods. Active testing with the urea breath test or the stool antigen test is recommended for patients with suspected infection, both for initial detection of the organism and for retesting after therapy to confirm eradication. These two tests for active infection are virtually identical in accuracy, so the choice between them should take into account other factors, such as cost, availability, and patient and physician preference.

Because it cannot distinguish between current and past infection, serologic testing has poor accuracy in settings of low and intermediate *H pylori* prevalence and should no longer be used in the United States.

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