RAPID UREASE TEST IN THE DIAGNOSIS OF *HELICOBACTER PYLORI* INFECTION

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ABSTRACT: Many tests are available for the diagnosis of *H. pylori* infection. Broadly they can be divided into invasive- endoscopy biopsy based tests and non-invasive tests. Of the endoscopy biopsy based tests the rapid urease tests (RUT) have been found to be the most convenient, accurate and inexpensive tests and they have therefore been recommended by several consensus panels and working parties as the test of choice during endoscopy.

Several RUTs are available; some are commercial: CLO test, Pyloritek, Helicobacter urease test, *H. pylori* test and others- "homemade". We strongly recommend the "homemade" 1 min rapid urease test using an unbuffered solution as originally described by Arvind *et al.* This test has been shown to be easy to prepare, inexpensive and accurate on field-testing.

Several factors affect the accuracy of the RUT. The larger the size of biopsy samples, the quicker is the postive reaction time. With the CLO test, warming the tests to 37°C has also been shown to hasten the reaction time. The effect of blood on the RUT poses an important problem in testing. It is vitally important to determine the *H. pylori* status in patients with bleeding peptic ulcers as the recurrence of bleeding has been shown to be markedly reduced or virtually abolished with *H. pylori* eradication. While the results of studies have not been entirely consistent, it is likely that presence of blood does reduce the sensitivity of the RUT. It is therefore sensible that in patients with bleeding ulcers, the RUT should not be the sole endoscopy biopsy test used and that samples should also be taken for histological examination. *(JUMMEC 2000; 1: 11-16)*

KEYWORDS: Urease test, *Helicobacter pylori.*

Introduction

Since the isolation of *Helicobacter pylori* by Warren and Marshall(1) in 1983, this bacterium is now recognised as the main aetiologic factor in peptic ulcer disease, with 90% or more of duodenal ulcers and 70% or more of gastric ulcers(2) harbouring this bacterium. It also has been shown to play an important role in the pathogenesis of cancer of stomach and gastric maltomas(3,4). *H.pylori* infection is a ubiquitous infection and is believed to be the most common bacterial infection in the world.

H. pylori infection can be detected by invasive and non-invasive tests. The established invasive endoscopy biopsy based tests include culture, histology Gram stain of a fresh tissue smear and detection of urease activity in the biopsy samples. Serology and the radiolabelled carbon urea breath tests are the non-invasive tests. These tests have become increasingly popular(4,6). The detection of antigen in the saliva(7,8) and gastric juice(9) has been used in diagnosis but these tests have not been shown to be practical nor accurate. A stool antigen test has been introduced and shown to be accurate(10,11). Of the endoscopy biopsy based tests however, the rapid urease test (RUT) is perhaps the most useful and widely used test(3,4,6).

Materials and methods

Basis of the urease test

H. pylori is the only bacterium in the upper gastrointestinal tract that produces the enzyme urease(12). This characteristic is made use of in the urease test whereby the urea substrate is hydrolyzed by the urease enzyme to produce ammonia and carbamate(13). The ammonia will equilibrates with water to form ammonium hydroxide and the presence of this compound will result in a rapid increase in pH. This change in pH will be shown up by a colorimetric

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change in the pH indicator used such as phenolphthalein(13,14).

Development of the urease test for clinical use

The first description of this phenomenon by Langenberg *et al* (14) was soon followed by its clinical application to the diagnosis of *H. pylori* in biopsy specimens by McNulty and colleagues (15). The biopsy specimen is placed in Christensen's 2% urea broth which acts as the enzyme substrate and ammonia production by hydrolysis of the urea by bacterial urease results in a change in the pH of the medium, which is detected by a color change in the pH indicator. Although there was an excellent correlation between a positive *H. pylori* culture and a positive urease reaction, this method still took several hours to produce a positive result. In the first study only 50% of biopsy specimens containing *H. pylori* were positive by six hours. Some tests required up to 24 hours to yield a positive result. Following further modifications, a commercial test – the CLO test (Delta West, Perth, Australia) became available. Using this test, Marshall(16) and Morris(17) and colleagues reported a good correlation with culture. But even then, at least 20 minutes was required for a definite positive result to be demonstrated.

Different types of urease test

Both commercial and locally produced biopsy urease tests (BUT) are in use in different countries (4,18). The CLO test is the most widely used and studied commercially RUT. Sensitivities at 24 hours are reported to be in the range of 75-99%, with specifities in most studies of approximately 95-100% [Table 1] (6,18,19,20).

Some investigators have reported excellent sensitivities after shorter periods of test observation - approximately 75% within 1 hour and about 90% at 3 hours(21). The other commercially RUT available are PyloriTek urease test which is limited by its lack of specificity compared to the CLO test(22). When the *Helicobacter* Urease Test (HUT), Polish test were compared with the CLO test, there was no difference in the reaction time, although the Polish test was more accurate and had a quicker time interval to positivity than the HUT(23).

Rapid urease test

In 1988(24), Arvin *et al* described a rapid one minute urease test was described for the diagnosis of *H. pylori* infection. This test has now been found to be so useful in the endoscopy suite and is now is the initial test of choice among patients having diagnostic upper endoscopy (4,21). As the name denotes, the one minute test gives rapid results and has practical advantages for clinical gastroenterologists as the presence of *H. pylori* can be detected in the endoscopy room sometimes even before the instrument is withdrawn. This allows the endoscopist to prescribe treatment whilst the patient is still in the endoscopy suite (6,18). Furthermore, the rapid diagnosis in the endoscopy suite has the added benefit allowing the physician to make decision to discard samples by the end of the workday rather than banking the specimens until the next day (25). The test solutions are easy to prepare even for a gastroenterologist, and in fact large batches can be prepared at one time but should be stored in a freezer and only thawed before use (18). Field-testing has shown the test to be a reliable and robust test (1,26,27,28) with high sensitivity and specificity. However, the primary reason that the RUT is perhaps preferred as the initial diagnostic test is the low cost of this test (5,15).

Factors that may affect the outcome of urease test

Several factors are though to affect the accuracy of the urease tests. These include the size of the biopsy specimens, fresh preparation of the medium, incubation temperature after the biopsy and the effect of blood on the biopsy specimens. It has been well accepted now the fact that by increasing the number or size of biopsy specimens in the Closet, it will hasten the time to a positive test but does not alter the final sensitivity or specificity (18,21). The effect of storage temperature, warming and the effect of blood on the accuracy of the RUT however remain uncertain (29,30,31,32,33).

For the homemade 1 min RUT, it is generally

Table 1. Accuracy of urease tests-published results

Test (%)	Thillainayagam *et al.* (1991)(18)	Goh *et al.* (1994)(6)	Chu *et al.* (1997)(19)	Misra *et al.* (1999)(20)
Sensitivity	89.0	96.6	92.8	92.0
Specificity	100.0	92.2	97.6	100.0
Positive predictive value	100.0	99.3	97.5	66.0
Negative predictive value	94.0	96.2	93.0	93.0

recommended that the reagent be prepared daily although this can be quite troublesome and time consuming for a gastroenterologist. The reason for this is that prolonged storage can cause spontaneous orange discoloration, due to contamination by other urease-producing bacteria. Although it has been said that the test solutions can be prepared in large batches at one time and stored in a freezer, at what temperature it should be stored and how long can be stored is unclear. Katelaris *et al.* (34) suggested that unbuffered RUT be stored at -20°C, but the accuracy of the RUT was not evaluated explicitly. Ng *et al.* (29,30) demonstrated that the unbuffered RUT is highly sensitive and specific when the reagent is stored at 4°C for fewer than 6 days, and remained accurate if stored at -20° C even at a longer storage time. However, the urea denatured with prolonged storage at 4° C and the sensitivity decreases dramatically with longer storage time. The slower reaction time of both groups stored 4° C and -20° C compared to previous study (18) may be related to the lower initial temperature of the RUT because urease activity increases dramatically with temperature and optimizes at 4° C. Therefore, the unbuffered RUT remains highly sensitive and specific when stored at 4° C for up to 5 days. When it is expected to be stored for a longer period, the bottles should be frozen at -20° C.

Incubating the CLO test at 30° to 40° C for 3 hours after the biopsy is recommended, suggesting that warming will speed the urease chemical reaction. However, this decreases simplicity and requires the purchase of additional equipment. Laine *et al.* (31) demonstrated that incubating the CLO test at 37° C hastens the time to a positive test, although the time saved is less than 1 hour in most patients. The sensitivity is improved when the test is read at 1 to 2 hours, but no improvement is seen beyond this time. Specificity is not influenced by warming. The development of occasional false-positives at the 24-hour reading may occur because of other urease-producing bacteria or may represent cases in which *H. pylori* are present in relatively small numbers and are not identified histologically (i.e."false-negative" histology). Therefore, if a final reading of the CLO test is desired within 1 to 2 hours of biopsy, CLO test incubation at 37° C should be performed. If a final reading at 3 hours or more after biopsy is acceptable, then warming of the CLO test is not necessary.

Eradication of *H. pylori* is important as it cures peptic ulcer disease and is more cost-effective to than to maintain the patient on traditional maintenance therapy (3,5,,35,36,37,38). It has also been shown that *H. pylori* eradication reduces recurrent ulcer bleeding. *Laine et al.* (39) reported that patients with bleeding caused by *H. pylori* - associated ulcer disease rarely have recurrent bleeding after *H. pylori* eradication. Perhaps the most confounding factor is the effect of blood on the accuracy of the RUT. The observation that blood may affect the RUT comes about from observation of the low prevalence of *H. pylori* in upper gastrointestinal bleeders. Indeed, several workers have shown a lower sensitivity of the RUT in the presence of blood (3,26). However, some others have reported false-positive result (40) while some have found that the test will be unaffected (33) .

Perry *et al.* (40) found that heparinized blood and alcohol will enhanced the detection of urease, and therefore improve the sensitivity. However he also reported that it will reduced the specificity results on the CLO test and *H.pylori*fast. The unexpected positive results could be due to the alkalinity of blood on the urease test alone.

On contrary, several other studies have found reduced sensitivity of the BUT in bleeding peptic ulcers. Colin *et al.* (41) demonstrated the sensitivity of the BUT (31%) was low, but at the same time histology and culture results were also low, raising concerns about the accuracy of their serology test which was used as the gold standard. Lee *et al.* (42) clearly showed a significant drop in sensitivity of the BUT, from 93% in non-bleeding ulcers to 73% in bleeding ulcers, which was consistent with earlier studies (43,44). Although high dose of omeprazole (80 mg) has been shown to interfere with the accuracy of the BUT (45), this could not explain the low sensitivity of the test as, at least in the later study (44), patients with recent use of omeprazole and antibiotics were excluded. Lee *et al.* (46) attributed that the reduced sensitivity of the BUT is merely as a result of clotted blood obscuring the color change, but it would be difficult to comprehend why all three CLO test, *H. pylori*fast and Pyloritek tests failed to detect *H. pylori* even at the high concentration of 10^9 CFU.

Although blood in the stomach is thought to interfere with the BUT, the underlying mechanism remains unknown. Leung *et al.* (1998) (32) have postulated three possible mechanisms. Firstly, the presence of anti-*H. pylori* antibody in the blood may inhibit the production of urease by *H. pylori*. Secondly, serum inhibitors such as enzymes or electrolytes may suppress the urease activity of *H. pylori*. Thirdly, various buffering systems (e.g. albumin, bicarbonate and phosphate) may interfere with the pH changes of the reagent. In Leung's *et al* study, they showed that blood adversely affects the performance of the BUT and this is mediated by the buffering effect of serum albumin on the pH indicator, rather than by a direct inhibition of the urease activity. Owing to the lack of reliability of the BUT in the presence of the blood, it is generally recommended that BUT should not be used as the only diagnostic test for *H. pylori* infection in patients with bleeding ulcers.

In a study (33) evaluating the two different types of BUT in bleeders, they found that the number of positive Pyloritek and CLO tests at three different time intervals

- 1, 4 and 24 hours were nearly identical. The small number of discordant results presumably occurred as a result of the patchy distribution of organisms in the stomach and/or the variation in individual test performance characteristics. The authors concluded that since there is no evidence of alteration in the BUT, physicians may use RUT as the initial biopsy test for the diagnosis of *H. pylori,* just as they would in patients without bleeding.

A recent study (3) using the CLO test, culture, histology, urea breath test and serology test showed that only the CLO test had better sensitivity ($p < 0.05$) in group with no blood in the tested specimens compared to the one tested with fresh blood or blood-containing material in the gastric antrum. Although this might mean that blood in the gastric antrum can interfere with the diagnosis of *H. pylori* and decrease the sensitivity of the test, but the presence of blood in the antrum had no effect on the other 4 tests. The authors suspected that blood might affect the pH value of the CLO test medium and do not favor the hypothesis that *H. pylori* migrates from the antrum to the body of the stomach when blood is present. This study also demonstrated that the non-invasive tests seemed to be more sensitive than invasive tests in detecting *H. pylori* infection in patients with bleeding peptic ulcers. As a delayed positive CLO tests were recorded, the CLO test should be observed for more than 24 hours because of the possibility of a delayed positive result in some patients with bleeding peptic ulcers.

Proton-pump inhibitors are potent antisecretory medications widely used to treat gastrointestinal disorders. When given alone, proton-pump inhibitors rarely eradicate *H. pylori*, although they do suppress the organism and this may lead to false-negative results on diagnostic testing (endoscopic biopsy or urea breath tests) for *H. pylori*. The development of false-negative breath test results in these patients may be due to decreased viability of the organisms at high intragastric pH with potent antisecretory therapy and direct inhibition of urease activity by proton-pump inhibitors. Laine et al. demonstrated that 33% of H. pylori-positive patients develop false-positive urea breath test results while taking a standard course of proton-pump inhibitor therapy. Most patients with *H. pylori* infection revert to positive urea breath test results by 1 week after the discontinuation of proton-pump inhibitor therapy, however, to ensure that a false-negative result does not occur, patients should not receive proton-pump inhibitors for 2 weeks before a urea breath test for *H. pylori* is done (47).

Discussion

With the increasing recognition of the role of *H. pylori* in gastrointestinal diseases, there is a need for a reliable, efficient and yet inexpensive diagnostic test. The ideal test for the diagnosis of *H. pylori* at endoscopy should have excellent sensitivity and specificity, be inexpensive, and provide results rapidly so patients can be informed of their *H. pylori* status and started on proper therapy at the time they leave the endoscopy unit. At present, rapid urease testing of gastric biopsy specimen can be considered the ideal test for *H.pylori* at endoscopy (18).

Compared to the other invasive and non-invasive methods, RUTs are convenient and useful tests; both the "homemade" test as well as the commercially available CLO test. This is because RUT has practical advantages for clinical gastroenterologists who require a rapid, accurate, sensitive and specific method of diagnosing *H.pylori* infection. Furthermore, preparation of the RUT does not require special laboratory skills or equipment, can be prepared in large batches at one time, to be stored in a freezer and only thawed before use. As more than 90% of the infected patients can be detected in the endoscopy room even before the instrument is withdrawn, it may help in planning therapeutic strategies, lead where appropriate to prompt introduction of treatment, and possibly reduce recall outpatients appointment. All the other invasive and non-invasive methods except for the finger-prick office-based serological tests have a major disadvantage in common which is the time required to get a definitive result for detecting *H. pylori* and thus may not be available to the clinician during the endoscopy consultation. In our local context, most importantly is the usefulness of the test in the majority of the endoscopy units in this country where laboratory facilities are not always available (3,4, 6,18,21,36).

These finger-prick tests however suffer from a lower level of accuracy. Locally validated tests show a high specificity but relatively lower sensitivity. As with all other serological tests, these tests cannot be used to assess treatment response because of the variable decline in antibody titres (48,49).

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