Colonization of *Helicobacter pylori* in the gastric cardia: A comparison between the UFT300 and CLO tests

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**Key words**
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**Abstract**

**Background and aim:** To assess the detection rates of *Helicobacter pylori* colonization in the gastric cardia with two commercial kits of rapid urease test: 5 min UFT300 and 24 h CLO test in *H. pylori*-infected patients.

**Methods:** Eighty consecutive dyspeptic patients with confirmed *H. pylori* infection (serology and $^{13}$C-urea breath test) were prospectively studied. During endoscopy, tissue samples using separate biopsy forceps from the cardia were taken for the UFT300 and CLO tests. The results of the UFT300 were read at 5 and 30 min, and those of the CLO test were read at 24 h.

**Results:** Of 80 enrolled patients, 17 (21.3%) and 44 (55%) had positive findings with the UFT300 at 5 and 30 min, respectively, while 72 (90%) had positive findings with the CLO test at 24 h. The CLO test is significantly more sensitive than the UFT300 in evaluating *H. pylori* status in the cardia. On comparing patients with and without carditis, the detection rates of the CLO test were similar (91.1% vs 86.6%; *P* = 0.724), and the rates of the UFT300 were also similar at 5 and 30 min.

**Conclusions:** The rate of *H. pylori* colonization in the gastric cardia was 90% in *H. pylori*-infected patients detected with the CLO test. Although the UFT300 provides a more rapid reading of *H. pylori* status, the diagnostic yield of the CLO test is much higher than that of the UFT300. However, a positive result of the UFT300 may indicate a higher bacterial load in the cardia, which warrants a more effective therapeutic strategy.

**Introduction**

*Helicobacter pylori* (*H. pylori*) is a microaerophilic, Gram-negative, slow-growing, spiral shaped, and flagellated organism, which infects more than half of the world’s human population. The majority of *H. pylori*-infected individuals are asymptomatic. However, long-term infection increases the risk of developing site-specific disease, such as peptic ulcer disease in 10–15%, distal gastric cancer (non-cardia) in 1–3%, and mucosa-associated lymphoid tissue lymphoma (MALToma) in <0.1% of infected individuals. Antrum is the preferred biopsy site to detect *H. pylori* colonization, but corpus biopsy from the greater curve is suggested for patients with atrophic gastritis or intestinal metaplasia to avoid false negative results. Uneven distribution of *H. pylori* in the stomach in different clinical settings such as use of acid-suppressive agent or antibiotics inevitably leads to sampling bias in biopsy-based diagnostic tests. *H. pylori* colonization with high bacterial load in the cardia could be considered a risk factor for treatment failure. Persistent *H. pylori* colonization with chronic inflammation may contribute to the high incidence of gastric cardia cancer, and detection of cardiac colonization during endoscopy is important. Two previous studies found a high rate of *H. pylori* colonization in the cardia, but the bacterial density and inflammatory responses are lower than in the antrum. Rapid urease test (RUT) is the most useful invasive test to detect *H. pylori* during endoscopy. Previous studies used histology or the 24-h CLO test for the diagnosis of *H. pylori* colonization in the cardia, while no study used the commercial kit of the 5-min Ultrafast Urease Test. We aimed to assess the detection rates of *H. pylori* colonization in the gastric cardia with two RUT commercial kits: 5-min UFT300 (ABS, Cernusco sul Naviglio, Italy) and 24-h CLO test (HALYARD, Alpharetta, USA) in *H. pylori*-infected patients.
Biopsies adjacent to the prior sites were obtained with separate biopsies from the cardia (within 2 cm below the squamocolumnar change, such as ulceration or hyperemia, only high-bolus) and local anesthetic spray (lidocaine 10%). To judge tocol using a short-acting sedative (5 mg midazolam intravenous). Esophagogastroduodenoscopy (EGD) was conducted on each age, sex, laboratory data and endoscopic features (such as advanced CKD or decompensated cirrhosis) or inflammatory drugs, proton pump inhibitors (PPIs), H2-receptor antagonists (H2RAs), or bismuth salts during the previous 4 weeks; pregnant or lactating women; severe concurrent diseases (such as advanced CKD or decompensated cirrhosis) or malignancy; any contraindication to biopsy on endoscopy; or those unable or unwilling to give written informed consent. We excluded 20 patients and enrolled 80 patients with gastritis (antrum/corpus/cardia) or duodenal ulcer/douodenitis (25 (8/17)).

### Methods

#### Patients
This prospective study was conducted at a medical center (outpatient department) from April 2017 to August 2017. A total of 100 patients aged 20–75 years, with persistent dyspeptic symptoms for at least 1 month but no abnormality detected on abdominal sonography, were invited to undergo endoscopy. All patients were confirmed to have *H. pylori* infection based on initial noninvasive diagnostic tests, with positive findings on both serology (*H. pylori* IgG) and the urea breath test (*13C-UBT*).

Subjects with any one of the following criteria were excluded from the study: previous gastric surgery; previous eradication therapy for *H. pylori*; use of antibiotics, nonsteroidal anti-inflammatory drugs, proton pump inhibitors (PPIs), H2-receptor antagonists (H2RAs), or bismuth salts during the previous 4 weeks; pregnant or lactating women; severe concurrent diseases (such as advanced CKD or decompensated cirrhosis) or malignancy; any contraindication to biopsy on endoscopy; or those unable or unwilling to give written informed consent. We excluded 20 patients and enrolled 80 patients with *H. pylori* infection (39 males, 41 females). Table 1 demonstrates that the result of the CLO test was negative in 72 (90%) patients when read within 24 h, and an additional 6 patients had a positive finding after 24 h (2 on day 2, 1 on day 3, 1 on day 4, and 2 on day 5). There is no significant difference between the CLO test read within 24 h or extended to 5 days (90% vs 97.5%; *P* = 0.098). Only 17 (21.3%) patients had positive UFT300 at 5 min, and the detection rate increased to 55% (44/80) when we extended the reading time to 30 min (21.3% vs 55%; *P* = 0.000). The detection rate of the

#### Ethnics
Study research staff recruited potential participants and explained the purpose and eligibility requirements of the study. Written informed consent was obtained from each subject prior to endoscopic examination. The study complied with current ethical considerations and was approved by the Institutional Review Board of our hospital (IRB Number: 17MMHS020).

#### Statistical analysis
Unless otherwise indicated, values were expressed as mean ± standard deviation (SD). Student’s *t* test was used to compare the mean values of continuous variables. Categorical data were compared using the χ² test or Fisher’s exact test, as appropriate. All *P* values were two-tailed, with the level of statistical significance set at 0.05. The data were summarized by the primary measures of central tendency and dispersion, as well as by frequencies and percentages with 95% CI. The statistical analyses were performed using the SPSS V.21.0 statistical software for Windows 7 (IBM, Armonk, New York, USA). All authors had access to the study data and reviewed and approved the final manuscript.

### Results

Table 1 shows the demographic and endoscopic characteristics of the patient population. The patients’ age ranged from 24 to 74 years, with an average age of 52.6 ± 10.3. Among 80 patients, 39 patients were male, and 41 patients were female. EGD revealed features of gastroduodenitis in 72 patients, including gastric ulcer or erosion in 26 and duodenal ulcer or duodenitis in 25. Regarding the anatomical location of gastritis, involvement of antrum, corpus, and cardia was found in 30, 53, and 45 patients, respectively. On the other hand, eight patients had normal appearance under endoscopic evaluation.

Table 2 demonstrates that the result of the CLO test was positive in 72 (90%) patients when read within 24 h, and an additional 6 patients had a positive finding after 24 h (2 on day 2, 1 on day 3, 1 on day 4, and 2 on day 5). There is no significant difference between the CLO test read within 24 h or extended to 5 days (90% vs 97.5%; *P* = 0.098). Only 17 (21.3%) patients had positive UFT300 at 5 min, and the detection rate increased to 55% (44/80) when we extended the reading time to 30 min (21.3% vs 55%; *P* = 0.000). The detection rate of the

### Table 1

| Characteristics                      | Patients (n = 80) |
|--------------------------------------|------------------|
| Age (yr), mean ± SD                 | 52.6 ± 10.3 (24–74) |
| Gender (M/F)                        | 39/41            |
| Laboratory data, mean ± SD          |                  |
| GPT (IU/L)                           | 32.9 ± 28.9 (10–202) |
| T-bilirubin (mg/dL)                  | 0.62 ± 0.40 (0.2–2.7) |
| Creatinine (mg/dL)                   | 0.84 ± 0.21 (0.5–1.4) |
| Endoscopic findings                 |                  |
| Normal                               | 8                |
| Gastric ulcer/erosion               | 26 (12/14)       |
| Duodenal ulcer/douodenitis          | 25 (8/17)        |

Gastritis (antrum/corpus/cardia) †

A>B+C 14
A>B 4
A>C 3
B>C 23
A 9
B 12
C 5

†Distribution of gastritis: (A) antrum (n = 30), (B) corpus (n = 53), (C) cardia (n = 45).

### Table 2

| CLO                               | 24 h | 1–5 days | Detection rate |
|-----------------------------------|------|---------|----------------|
| Positive                          | 72   | 78      | 90%            |
| Negative                          | 8    | 2       | 2              |
| Detection rate*                   | 90%  | 97.5%   | 97.5%          |
| UFT300                            | 5 min | 30 min | 55%            |
| Positive                          | 17   | 44      | 44             |
| Negative                          | 63   | 36      | 36             |
| Detection rate**                  | 21.3%| 55%***  | 55%***         |

*P* = 0.098, between 24 h and 1–5 days CLO. **P** = 0.000, between 5 and 30 min UFT300. ***P*** = 0.000, between CLO and 5 min UFT300. ****P*** = 0.000, between CLO and 30 min UFT300.
Table 3 The detection rates of the CLO test between patients with and without endoscopic findings of carditis

|                | Carditis (+) | Carditis (−) |
|----------------|--------------|--------------|
| CLO (+)        | 41           | 31           |
| CLO (−)        | 4            | 4            |
| Detection rate*| 91.1%        | 88.6%        |

*P = 0.724, between patients with and without carditis.

The CLO test was significantly higher than that of the UFT300 at both 5 min (90% vs 21.3%; P = 0.000) and 30 min (90% vs 55%; P = 0.000). In a comparison of patients with and without carditis, the detection rates of the CLO test at 24 h were similar (91.1% vs 88.6%; P = 0.724) (Table 3). The detection rates of the UFT300 were higher in patients with carditis at 5 min (28.9% vs 11.4%; P = 0.097) and 30 min (60% vs 48.6%; P = 0.368) but without statistical significance (Table 4).

**Discussion**

_H. pylori_ colonization in the gastric mucus layer is key to the establishment of chronic infection. Two key factors are the production of urease enzyme and the possession of polar flagella, which confer motility on _H. pylori_. In subjects with intact acid secretion, _H. pylori_ in particular colonizes the gastric antrum, and this colonization pattern is associated with an antrum-predominant gastritis. Subjects in whom acid secretion is impaired have a more even distribution of bacteria in the antrum to corpus, leading to a corpus-predominant pangastritis. The impairment of acid secretion can result from atrophic gastritis or long-term use of acid-suppressive drugs. _H. pylori_-associated gastritis commonly involves the antrum as well as cardia, and lower bacterial density in the cardia has been noted. Another study demonstrated that 40 of 42 patients (95%) had _H. pylori_ colonization in the cardia, and the intensity of chronic active gastritis was similar in the antrum and cardia, higher than that in the corpus.4

In our study, we excluded patients taking antibiotics, PPI, H2RA, or bismuth salt during the previous 4 weeks. We found the rates of endoscopic gastritis were 37.5% (30/80) in the antrum, 66.3% (53/80) in the corpus, and 56.3% (45/80) in the cardia. The distribution of endoscopic gastritis was similar in the cardia and corpus (56.3% vs 66.3%; P = 0.256) but was significantly lower in the antrum than in the cardia (56.3% vs 37.5%; P = 0.026) and corpus (66.3% vs 37.5%; P = 0.000).

The rapid urease test is an indirect test to detect _H. pylori_ based on the presence of urease in the gastric mucosa. It has an advantage over serology in that it only detects the presence of active infection. Urease enzyme converts the urea test reagent to ammonia, leading to an increase in the pH value followed by a color change on the pH monitor. Several commercial RUT kits, including the gel-based test (CLOtest, HpFast), paper-based test (PyloriTek, ProntoDry), and liquid-based test (UFT300, EndoscHp), are available now, and different RUTs have different reaction times to provide results. The CLO test usually requires 24 h to yield accurate results, whereas PyloriTek takes 1 h and UFT300 takes only 5 min. The bacterial density present in the biopsy specimen will affect the reaction time and diagnostic accuracy of the RUT, while a minimum of 10^5 organisms is usually required for a positive finding. Other factors that may cause false negative results include PPI, bismuth compounds, antibiotics, intestinal metaplasia, and the presence of blood. In general, for the best diagnostic yield, 2 biopsy samples, 1 from the antrum avoiding areas of ulceration and intestinal metaplasia and another from normal-appearing corpus, are sufficient. A positive finding of the CLO test after 24 h may indicate the presence of a non-_H. pylori_ urease-containing organisms or could be a delayed positive result due to recent upper gastrointestinal (UGI) bleeding. In our study, the result of the CLO test was positive in 72 (90%) patients when read within 24 h, and an additional six patients had positive findings after 24 h.

A prospective controlled trial from Italy compared three RUTs to diagnose _H. pylori_ infection. One biopsy specimen was obtained from the antrum for the UFT300, and the sensitivity was 90.3, 94.5, 96.2, and 97.4% at 1, 5, 60 min, and 24 h, respectively (specificity 100%). The UFT300 approved for reading at 5 min provides a rapid and accurate determination of _H. pylori_ status. The time needed for color change is inversely proportional to bacterial density in the biopsy. As we already know, previous studies used histology or CLO tests for the diagnosis of _H. pylori_ colonization in the cardia. This is the first study to evaluate the role of the UFT300 for more rapid determination of _H. pylori_ status in the cardia. In our study, only 17 (21.3%) patients had positive findings with the UFT300 at 5 min, and the detection rate increased to 55% (44/80) when we extended the reading time to 30 min.

Because the bacterial density in the cardia is lower than that in the antrum, the UFT300 is not approved for reading at 5 min to evaluate _H. pylori_ status in the cardia. Our study demonstrated that the diagnostic yield of the CLO test was much higher than that of the UFT300 read at 5 min (90% vs 21.3%; P = 0.000), even when we extended the reading time to 30 min (90% vs 55%; P = 0.000). A higher false-negative rate of the UFT300 may result from low _H. pylori_ density, presence of blood, or sampling bias (we had excluded patients with recent administration of PPI or antibiotics). Presence of blood after biopsy may result in a false-negative result of the CLO test but not the UFT300 because we took the biopsy for the UFT300 prior to the CLO test. All biopsy specimens were taken from similar sites to avoid possible sampling bias. A previous study showed that _H. pylori_ density is lower in the cardia, and it could be the most reasonable explanation for a higher false-negative rate of UFT300 in our study. In other words, a positive result of

Table 4 The detection rates of the UFT300 between patients with and without endoscopic findings of carditis

|                | Carditis (+) | Carditis (−) |
|----------------|--------------|--------------|
| UFT300–5 min (+) | 13           | 4            |
| UFT300–5 min (−) | 32           | 31           |
| Detection rate* | 28.9%        | 11.4%        |
| UFT300–30 min (+) | 27           | 17           |
| UFT300–30 min (−) | 18           | 18           |
| Detection rate** | 60%          | 48.6%        |

*P = 0.097, between patients with and without carditis. **P = 0.368, between patients with and without carditis.
UFT300 might indicate a higher bacterial load in the cardia of \textit{H. pylori}-infected patients.

\textit{H. pylori} may persist in the gastric cardia, even following successful eradication from the antrum and corpus. This phenomenon has been attributed to an insufficient antibiotic concentration in the cardia.\textsuperscript{16} Several studies have revealed that high antral density of \textit{H. pylori} or intragastric bacterial load may affect the success of eradication therapy.\textsuperscript{17–19} A prospective case–control study demonstrated that the higher the \textit{H. pylori} density, the less effective triple therapy will be for \textit{H. pylori} eradication, and that quadruple therapy does not seem to be negatively affected by bacterial density.\textsuperscript{20} \textit{H. pylori} colonization with a high bacterial load in the cardia, especially for patients with a positive UFT300 test, could be considered a risk factor for treatment failure, and it warrants a more effective treatment such as a prolonged 14-day regimen and quadruple or concomitant therapy to improve the eradication rate.

A retrospective study from Japan studied the role of \textit{H. pylori} infection in chronic inflammation and gastric cardia cancer. Of 75 patients with cardiac cancer, \textit{H. pylori} was positive in 71 (95%), and cardiac inflammation was present in all cases with \textit{H. pylori} infection. These results suggest that gastric cardia cancer is mainly induced by \textit{H. pylori} infection in Japanese patients, and the treatment of chronic inflammation may lead to better control of this kind of gastric cancer.\textsuperscript{21}

Wang \textit{et al.} investigated the status of \textit{H. pylori} infection in the gastric cardia in high-risk populations in South China. The \textit{H. pylori} colonization rate was significantly higher in cardiac cancer (81.5%, \(P < 0.01\)) and carditis (80.1%, \(P < 0.01\)) than in a healthy control group (34.8%). These results suggest that persistent \textit{H. pylori} colonization with subsequent chronic inflammation may contribute to the high incidence of gastric cardia cancer in South China.\textsuperscript{22}

In conclusion, the CLO test is much more sensitive than the UFT300 in evaluating \textit{H. pylori} status of the cardia, and the detection rates were similar for patients with and without carditis (91.1% vs 88.6%). However, a positive result of the UFT300 may indicate a higher bacterial load in the cardia, and a more effective therapeutic strategy should be considered. Further randomized controlled trials will be needed to clarify the clinical impact of \textit{H. pylori} colonization at the cardia, especially for patients with higher bacterial density.

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