

## Predictive value of neutrophil infiltration as a marker of *Helicobacter pylori* infection

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**Supported by** The grant for Key Laboratory of Gastroenterology and Hepatology, Ministry of Health, Renji Hospital, Shanghai Jiao Tong University School of Medicine; and National Natural Science Foundation of China, No. 81170355

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Received: January 31, 2012 Revised: April 18, 2012

Accepted: May 5, 2012

Published online: September 28, 2012

*pylori* immunoglobulin G (IgG) antibody. Serum anti-*H. pylori* IgG antibody was measured by enzyme-linked immunosorbent assays (Biohit, Finland).

**RESULTS:** The sensitivity, specificity, positive predictive value and negative predictive value of neutrophil infiltration in the diagnosis of *H. pylori* infection were 92.3%, 83.5%, 77.4% and 94.7%, respectively. Neutrophil infiltration of gastric mucosa in the histological analysis was strongly associated with *H. pylori* infection (77.4% vs 5.3% in the neutrophil infiltration negative group,  $P = 0.000$ ). Moderate neutrophil infiltration was more frequent in *H. pylori* infection when compared to mild infiltration (81.8% and 75%, respectively), but did not reach statistical significance. For those patients with negative rapid urease test, *H. pylori* was detected in 73.2% of patients with positive neutrophil infiltration on histology. In patients with subtotal gastrectomy, the diagnostic accuracy of neutrophil infiltration in *H. pylori* infection was 50%.

**CONCLUSION:** Neutrophil infiltration is closely associated with *H. pylori* and may be recognized as a sign of this infection.

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**Key words:** *Helicobacter pylori*; Histology; Neutrophil; Sensitivity; Specificity

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Xu XQ, Wang ZH, Liao JX, Chen XY, Liu WZ, Xiao SD, Lu H. Predictive value of neutrophil infiltration as a marker of *Helicobacter pylori* infection. *World J Gastroenterol* 2012; 18(36): 5101-5105 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v18/i36/5101.htm> DOI: <http://dx.doi.org/10.3748/wjg.v18.i36.5101>

### Abstract

**AIM:** To evaluate the predictive value of neutrophil infiltration as a marker of *Helicobacter pylori* (*H. pylori*) infection.

**METHODS:** A total of 315 patients with dyspepsia symptoms who underwent upper gastrointestinal endoscopy were enrolled in this study. Biopsies were evaluated using the updated Sydney system. The medication history of all patients in the preceding 4 wk was recorded. The diagnosis of *H. pylori* infection was based on <sup>13</sup>C-urea breath test at least 4 wk after withdrawal of antisecretory drugs, antibiotics and related drugs. For the patients with subtotal gastrectomy, the diagnosis of *H. pylori* infection was based on anti-*H.*

## INTRODUCTION

Detection of *Helicobacter pylori* (*H. pylori*) infection is the first and the most important step in the treatment of *H. pylori*-associated diseases. Urease-based tests, including the rapid urease test (RUT) and  $^{13}\text{C}/^{14}\text{C}$  urea breath test (UBT), are common in the clinical practice of gastrointestinal (GI) diseases. Because of the high prevalence of *H. pylori* infection and high incidence of gastric cancer in China, endoscopy is recommended as the first-line management option for uninvestigated dyspepsia patients<sup>[1]</sup>. Endoscopy examination can not only diagnose pathological changes in the stomach, but the RUT based on gastric biopsy can detect *H. pylori* infection and has the advantages of speed and accuracy. The urea breath test as a non-invasive choice is universally accepted as the “gold standard” for the diagnosis of *H. pylori* infection. However, as urease-based tests, the RUT and UBT have some limitations. Many medications including acid suppressors [e.g., proton pump inhibitors (PPI),  $\text{H}_2$ -receptor antagonists ( $\text{H}_2\text{RA}$ )], antibiotics and bismuth influence these tests and cause false negative results<sup>[2-7]</sup>. The detection of *H. pylori* in histology requires experienced pathologists and special staining. It becomes very difficult in cases with a low number of organisms and in coccip-shaped organisms<sup>[5,7,8]</sup>.

In patients with subtotal gastrectomy due to gastric cancer, the examination and treatment of *H. pylori* are the key points in preventing the recurrence of gastric cancer. The detection of *H. pylori* in patients after gastrectomy is difficult due to low accuracy of the UBT in this situation<sup>[9,10]</sup>.

Some studies have reported that *H. pylori* infection is suggested by the presence of active inflammation<sup>[11,12]</sup>. Neutrophil infiltration is a hallmark of active inflammation. It is unknown whether neutrophil infiltration may be a marker of *H. pylori* infection. In this survey, we enrolled: (1) randomly-selected patients; (2) patients with neutrophil infiltration but negative-RUT; and (3) patients with subtotal gastrectomy and neutrophil infiltration on routine endoscopy and biopsy histology to explore the predictive value of neutrophil infiltration in the diagnosis of *H. pylori* infection.

## MATERIALS AND METHODS

### Patients

Patients presenting with upper gastrointestinal symptoms and endoscopically proven functional dyspepsia and scarred ulcer were enrolled into the study from June 2010 to September 2011 in Renji Hospital, Shanghai. Patients with active peptic ulcer and gastric cancer were excluded. A total of three biopsy specimens from the antrum or gastric remnant were taken during each endoscopy. One biopsy was used for the RUT to detect *H. pylori* and the other two biopsies were analyzed histologically. Informed consent was obtained from all patients in the study. Medication in the preceding 4 wk and previous *H. pylori* treatment before endoscopy ex-

amination were recorded.

### Study design

**Study 1:** Patients without previous gastric surgery or antibiotic therapy, bismuth, PPI or  $\text{H}_2\text{RA}$  in the preceding 4 wk were included in this study.

**Study 2:** Only patients with neutrophil infiltration on histological analysis, but negative RUT were candidates for entry into this study. Patients with previous gastric surgery were excluded.

**Study 3:** Ten subtotal gastrectomy patients with neutrophil infiltration on histological analysis were recruited into this study. Patients who had received previous *H. pylori* eradication therapy or antibiotic therapy, bismuth, PPI or  $\text{H}_2\text{RA}$  in the preceding 4 wk were excluded.

### Histology

All specimens for histological analysis were fixed in 10% formalin. An experienced pathologist analyzed the histological features of each sample using hematoxylin and eosin staining and made the diagnosis according to the updated Sydney classification<sup>[13]</sup>. The histological parameters included histological activity (neutrophil infiltration), chronic inflammation, glandular atrophy and intestinal metaplasia. Active inflammation meant the presence of neutrophil polymorphs in a background of chronic inflammation. Each category (mild, moderate, and severe) resulted in a score on a scale of 0-3 (none, 0; mild, 1; moderate, 2; severe, 3). The pathologist blinded to any clinical information counted the two specimens and calculated the average.

### Assessment of *H. pylori* infection

**$^{13}\text{C}$ -UBT:**  $^{13}\text{C}$ -UBTs were performed after endoscopy examination or 4 wk after withdrawal of antisecretory drugs, antibiotics and related drugs. *H. pylori* infection was considered positive when values were  $^{13}\text{CO}_2 \geq 4.0\text{‰}$  delta over baseline.

**Serological antibody test:** Blood samples (5 mL venous blood) were taken from each patient prior to endoscopy. These samples were stored before analysis and then centrifuged at  $-20^\circ\text{C}$ . Serum anti-*H. pylori* immunoglobulin G (IgG) antibody was measured by enzyme-linked immunosorbent assays (Biohit, Finland) according to the manufacturer's instructions. The IgG cut-off value which determined samples as Hp-positive was 2.5-80 ng/L.

## RESULTS

### Characteristics of patients included

A total of 315 patients were recruited in this study, including 261 with functional dyspepsia, 44 with scarred peptic ulcer and 10 with gastric remnant after distal gastrectomy (Table 1). Of the 10 patients with distal gastrectomy, 4 had a history of complicated peptic ulcer

**Table 1** Baseline demographic characteristics of subjects

	Study 1	Study 2	Study 3
No. of patients	137	168	10
Sex (male/female)	62/75	66/102	8/2
Age (average, range)	48.8 (21-79)	52.4 (21-81)	55.2 (50-77)
FD/scarred ulcer	123/14	138/30	N/A

FD: Functional dyspepsia; N/A: Not available.

**Table 2** Results of study 1

Neutrophil infiltration in gastric mucosa	<sup>13</sup> C- Urea breath test		
	Positive	Negative	Total
Positive	48	14	62
Negative	4	71	75
Total	52	85	137

**Table 3** Results of study 3

No. of positive patients	Anti-HP IgG antibody	RUT	<sup>13</sup> C-UBT
Mild neutrophil infiltration (n = 8)	4	1	0
Moderate neutrophil infiltration (n = 2)	1	1	1

Anti-HP IgG: Anti-*Helicobacter pylori* immunoglobulin G; RUT: Rapid urease test; UBT: Urea breath test.

disease and 6 had a history of gastric cancer.

### Accuracy of neutrophil infiltration in the diagnosis of *H. pylori* infection

**Study 1:** The diagnosis of *H. pylori* infection was based on <sup>13</sup>C-UBT. Sixty-two cases were positive for neutrophil infiltration, including 40 with mild and 22 with moderate infiltration. Of these 62 patients, 14 had a negative <sup>13</sup>C-UBT and 48 had a positive <sup>13</sup>C-UBT. Of the 40 patients with mild neutrophil infiltration, 10 had a negative <sup>13</sup>C-UBT and 30 had a positive <sup>13</sup>C-UBT. Of the 22 patients with moderate neutrophil infiltration, 4 had a negative <sup>13</sup>C-UBT and 18 had a positive <sup>13</sup>C-UBT. Seventy-five cases were negative for neutrophil infiltration. Of these patients, 71 had a negative <sup>13</sup>C-UBT and 4 had a positive <sup>13</sup>C-UBT (Table 2). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of neutrophil infiltration in the diagnosis of *H. pylori* infection were 92.3%, 83.5%, 77.4% and 94.7%, respectively. Neutrophil infiltration was strongly associated with *H. pylori* infection (77.4% *vs* 5.3% in the neutrophil infiltration negative group, *P* = 0.000). Moderate neutrophil infiltration was more frequent in *H. pylori* infection when compared to mild infiltration (81.8% and 75%, respectively), however, this difference failed to reach statistical significance.

**Study 2:** In 168 patients with negative RUT and positive neutrophil infiltration on histological analysis, the

diagnosis of *H. pylori* infection was based on positive <sup>13</sup>C-UBT. <sup>13</sup>C-UBT is the gold standard, and *H. pylori* was detected in 73.2% (123/168) of patients with negative RUT and positive neutrophil infiltration on histology. 27.6% (34/123) of patients had a history of medication use (antibiotic therapy, bismuth, PPI or H<sub>2</sub>RA) in the preceding 4 wk. Of 122 patients with mild neutrophil infiltration, 87 had a positive <sup>13</sup>C-UBT and the diagnostic accuracy was 71.3%. Of 46 patients with moderate neutrophil infiltration, 36 had a positive <sup>13</sup>C-UBT and the diagnostic accuracy was 78.2%.

**Study 3:** For the patients with subtotal gastrectomy and positive neutrophil infiltration on histological analysis, the diagnosis of *H. pylori* infection was based on positive anti-*H. pylori* IgG antibody. Serum anti-*H. pylori* antibody is the gold standard, and *H. pylori* was detected in 50% (5/10) of patients including 8 with mild neutrophil infiltration and 2 with moderate neutrophil infiltration. The diagnostic accuracy was 50% (Table 3).

## DISCUSSION

The accurate diagnosis of *H. pylori* infection is an important step in the treatment of *H. pylori*-associated diseases. However, the outcome of the most commonly used urease-based *H. pylori* tests (RUT and UBT) may be veiled by some drugs and gastrectomy resulting in false negative results. PPIs have a marked influence on gastric pH or *H. pylori* density, inducing bacteria to migrate to atypical sites, thus leading to false negative UBT results as well as false negative RUT results<sup>[3,14]</sup>. Antibiotics active against *H. pylori* can cause a temporary decrease in the bacterial load and hinder the detection of *H. pylori* infection<sup>[5]</sup>. Discontinuation of antisecretory drugs and antibiotics four weeks before detection of *H. pylori* is currently recommended<sup>[2]</sup>. However, it is impractical for some patients suffering from severe symptoms such as acid reflux and upper GI hemorrhage to discontinue drug treatment. Gastrectomy and reconstruction make the UBT unreliable<sup>[15]</sup>. *H. pylori* is also difficult to detect in cases of extensive intestinal metaplasia<sup>[16]</sup>. However, detection of *H. pylori* infection is very important for patients with early gastric cancer, peptic ulcer and chronic atrophic gastritis.

*H. pylori* is found within the mucous gel layer covering the gastric mucosa. It is characterized by infiltration of inflammatory cells into the gastric mucosa which are dependent on the production of proinflammatory cytokines, especially the potent neutrophil chemotactic and activating peptide interleukin (IL)-8<sup>[17]</sup>. IL-8 is produced by gastric epithelial cells and binds to the extracellular matrix producing a chemotactic gradient that directs neutrophil migration to the epithelial surface. The density of intraepithelial neutrophils is closely related to the extent of mucosal damage and to the intensity of *H. pylori* infection<sup>[18-21]</sup>. Some researchers have investigated the association between the activity of inflammation and



*H. pylori* infection and have shown that colonization of the human stomach by *H. pylori* can induce an inflammatory response that is characterized by dense mucosal infiltration by neutrophils<sup>[18,22,23]</sup>. According to the updated Sydney system, gastric specimens containing neutrophils indicate *H. pylori*-positive patients if a sufficient number of biopsies from both the antrum and corpus are taken<sup>[13]</sup>. A study by Warren *et al*<sup>[24]</sup> showed that neutrophils gradually disappeared after starting *H. pylori* treatment. Neutrophils were rapidly detected again if the treatment failed. Without treatment, the changes are life-long. However, there are no studies on the predictive value of neutrophil infiltration as a marker of *H. pylori* infection.

Serology testing is the preferred method for patients with bleeding ulcers and PPI consumption<sup>[8]</sup>. Fischbach *et al*<sup>[25]</sup> found that serum IgG, determined by ELISA, was correlated with the histological degree and the activity of gastritis. The antibody absorbance index was correlated with severe activity of gastritis in the antrum, but not with the severity of body gastritis<sup>[26]</sup>. Vorobjova *et al*<sup>[27]</sup> reported that seropositivity for CagA antibody was a sign of gastritis activity. In our study, we used anti-*H. pylori* IgG antibody as a standard to diagnose *H. pylori* infection in patients with subtotal gastrectomy. We found that the diagnostic accuracy was 50% for neutrophil infiltration as a marker of *H. pylori* infection in this situation.

Our study showed that the sensitivity, specificity, PPV and NPV of neutrophil infiltration in the diagnosis of *H. pylori* infection were 92.3%, 83.5%, 77.4% and 94.7%, respectively. Neutrophil infiltration was strongly associated with *H. pylori* infection. There was no significant difference between moderate and mild neutrophil infiltration in the diagnosis of *H. pylori* infection. For those with a negative RUT, *H. pylori* was detected in 73.2% of patients with positive neutrophil infiltration on histology.

In patients with subtotal gastrectomy due to a history of complicated peptic ulcer disease and gastric cancer, eradication of *H. pylori* infection can prevent ulcer relapse and metachronous gastric cancer in these patients. However, the UBT is not accurate in this situation and some patients are unable to discontinue medication. In our study, we used anti-*H. pylori* IgG antibody as a standard to diagnose *H. pylori* infection. We found that the diagnostic accuracy was 50% for neutrophil infiltration.

Detection of *H. pylori* infection is key step in the treatment of certain diseases. Medication and gastrectomy can result in false negative urease-based tests for *H. pylori*. Neutrophils are a sensitive indicator of the presence of *H. pylori*. In clinical practice, neutrophil infiltration in the gastric mucosa may provide the clinician with a clue for the diagnosis of *H. pylori* infection.

## COMMENTS

### Background

The accurate diagnosis of *Helicobacter pylori* (*H. pylori*) infection is the key role in the treatment of *H. pylori*-associated diseases. Urease-based tests, including the rapid urease test and the <sup>13</sup>C/<sup>14</sup>C urea breath test, are common in the diagnosis of *H. pylori* infection. However, medications and surgery can cause false

negative results in urease-based tests. Gastric mucosa with active inflammation on histology is highly suggestive of *H. pylori* infection and neutrophil infiltration is a hallmark of active inflammation.

### Research frontiers

The predictive value of neutrophil infiltration as a marker of *H. pylori* infection was studied, which may provide clinicians with a clue for the diagnosis of *H. pylori* infection in clinical practice.

### Innovations and breakthroughs

This study showed that neutrophil infiltration of gastric mucosa on histological analysis was strongly associated with *H. pylori* infection and suggested that neutrophil infiltration may be a sign of this infection.

### Applications

The association between neutrophil infiltration and *H. pylori* infection, shown in the present study, may provide clinicians with a clue for the diagnosis of *H. pylori* infection and help them identify false negative results in urease-based tests.

### Peer review

In this manuscript, the authors verified neutrophil infiltration of gastric mucosa in histology analysis was strongly associated with *H. pylori* infection and highlighted neutrophil infiltration can be considered as a sign of the infection, which may help the clinicians diagnose the infection of *H. pylori* more accurately.

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