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• *Helicobacter pylori* •

## Patients with *Helicobacter pylori* positive and negative duodenal ulcers have distinct clinical characteristics

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### Abstract

**AIM:** To assess the clinical characteristics of *Helicobacter pylori* (*H pylori*) negative duodenal ulcer.

**METHODS:** Patients with an endoscopic diagnosis of duodenal ulcer between 1996 and 2002 were included in the present study. Patients were considered to be negative for *H pylori*, if both histological examination and rapid urease test of biopsy specimens were negative. A comparison was made between patients with *H pylori* positive and negative duodenal ulcers.

**RESULTS:** A total of 1 343 patients were studied. Their mean age was 54.7±0.5 years. There was a male preponderance (M:F = 2.5:1). Three hundred and ninety-eight patients (29.6%) did not have *H pylori* infection. The annual proportion of patients with *H pylori* negative duodenal ulcers increased progressively from 1996 to 2002. On multivariate analysis, patients with *H pylori* negative duodenal ulcer were more likely to be older, have concomitant medical problem, pre-existing malignancy, recent surgery, underlying sepsis, or taken non-steroidal anti-inflammatory drugs. In terms of clinical presentations, patients with *H pylori* negative duodenal ulcer were more likely to present with bleeding, multiple ulcers and larger ulcers.

**CONCLUSION:** The proportion of patients with *H pylori* negative duodenal ulcers is on the rise because of a continued drop in incidence of *H pylori* positive duodenal ulcers in recent years. Such patients have distinct clinical characteristics and it is important to ascertain the *H pylori* status before starting eradication therapy.

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**Key words:** *Helicobacter pylori*; Duodenal ulcer

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### INTRODUCTION

Since the first description of *Helicobacter pylori* (*H pylori*), infection with this organism has been considered to be the most important cause of ulcer disease. Previous studies have reported that more than 90% and 60% of patients with duodenal ulcer and gastric ulcer, respectively, were infected with *H pylori*<sup>[1]</sup>. The use of non-steroidal anti-inflammatory drugs (NSAIDs) was suggested to be the major cause of the remaining *H pylori* negative ulcer disease<sup>[2]</sup>. The prevalence of *H pylori* infection in patients with duodenal ulcer was believed to be so high that confirmatory testing before eradication treatment was considered unnecessary by some centers<sup>[3]</sup>. It is now apparent that the prevalence of *H pylori* infection in patients with duodenal ulcer is not as high as what it used to be<sup>[4-6]</sup>.

It is, therefore, important to study the subset of patients with *H pylori* negative duodenal ulcer in order to assess any other etiologic factors associated with ulcer development and to establish appropriate management strategies. The present prospective study aimed to compare the differences between patients with *H pylori* positive and negative duodenal ulcer diseases.

### MATERIALS AND METHODS

#### Prospective database

Data from all patients with ulcer disease were prospectively fed into a computer database. This database contained data on patients' demographics, clinical presentations, past history of ulcer disease, concomitant medical problems, pre-existing malignancy, recent history of surgery or sepsis, past surgical history, drug history, family history, social history, vital signs and results of laboratory investigations on admission, amount of blood transfusion given, endoscopic findings (including the location, size and number of lesions), *H pylori* status, drug treatment prescribed, endoscopic or surgical therapy given, and treatment results. All patients presented to the Department of Surgery, University of Hong Kong Medical Center at Queen Mary Hospital with a diagnosis of ulcer disease were included into the database.

#### Upper endoscopy

Except for those with active gastrointestinal bleeding, patients were fasted for at least 8 h before endoscopic examination. Endoscopic examination was performed under local

pharyngeal anesthesia with the patient lying in a left lateral position. Endoscopic findings were prospectively recorded into the database. An ulcer was defined as a mucosal defect not less than 5 mm in at least one direction. Any mucosal defect of less than 5 mm was classified as erosion. Regardless of the endoscopic findings, three antral mucosal biopsy specimens were taken from within 3 cm of the pylorus and removed from the biopsy forceps (Olympus FB 25K, Olympus, Japan) with a needle. Two biopsy specimens were fixed with 40 g/L formaldehyde for histological examination, while one biopsy specimen was subjected to a rapid urease test<sup>†</sup>. In patients who have taken a proton pump inhibitor, an antibiotic, a bismuth compound, or eradication therapy for *H pylori*, two additional corpus mucosal biopsy specimens would be sent for histological examination. Patients were considered to be negative for *H pylori* if both histological examination and rapid urease test were negative. Patients were considered positive for *H pylori* if any one of the tests was positive.

**Patients**

Patients with an endoscopic diagnosis of duodenal ulcer between 1996 and 2002 were included in the present study. Patients were excluded if (1) they failed to provide an adequate history, including drug history, (2) their *H pylori* status was not assessed at the time of presentation, (3) they have taken an antibiotic, a bismuth compound, or eradication therapy for *H pylori* within 3 mo prior to the upper endoscopy, or (3) they refused upper endoscopy. Patients who have taken a proton pump inhibitor were not excluded.

**Statistical analysis**

All continuous values were expressed as mean±SE of mean unless otherwise stated. Univariate analysis was performed by Student's *t*-test for continuous variables and by  $\chi^2$  test (with Yates' correction where appropriate) for categorical variables. Fisher's exact test was used if any expected cell value in a (2×2) table was less than five. Significant factors identified on univariate analysis were subjected to multivariate stepwise logistic regression analysis. Data analyses were performed with a standard biomedical software package and differences with a *P* value of less than 0.05 were regarded as statistically significant.

**RESULTS**

From January 1996 to December 2002, 1 343 patients satisfied the inclusion criteria for this study. Their mean age was 54.7±0.5 years. There was a male preponderance (M:F = 2.5:1). Their main presentations included pain (249 patients, 18.5%), bleeding (1 074 patients, 80.0%), anemia (14 patients, 1.0%), and obstruction (6 patients, 0.4%).

Three hundred and fourteen patients (23.4%) were smokers, while 61 patients (4.5%) were alcoholics. Four hundred and thirty patients (32.0%) have one or more concomitant medical problems (Table 1). Of these 430 patients, 222 have one, 138 have two, 55 have three, 11 have four, and 4 have five concomitant medical problems. Fifty-five patients (4.1%) gave a past history of pulmonary tuberculosis.

Sixty-five patients (4.8%) have history of malignancy either currently or in the past, including colorectal cancer (13), urological cancer (10), lung cancer (10), gynecological cancer (8), cancer of nasopharynx (7), breast cancer (5), cancer of larynx (2), liver cancer (2), thyroid cancer (2), tongue cancer (1), lymphoma (1), cancer of maxilla (1), cancer of hypopharynx (1), sarcoma (1), and bone metastasis (1). Thirty-nine patients (2.9%) have undergone surgery within 3 mo before presentation. The natures of the operations are listed in Table 2. Twenty patients (1.5%) have underlying sepsis at the time of presentation, which included chest infection (11), intra-abdominal infection (4), urinary tract infection (3), and orthopedic infection (2). Current medications taken by the patients included NSAIDs (102), aspirin (67), corticosteroids (4), H<sub>2</sub> blockers (84), and proton pump inhibitors (15).

Seventy-six patients (5.7%) have multiple ulcers (more than two ulcers) on presentation. Three hundred and ninety-eight patients (29.6%) did not have *H pylori* infection. Although the annual proportion of patients with *H pylori* negative duodenal ulcers increased progressively from 1996 to 2002, the increase was due to an ongoing drop in the number of patients with *H pylori* positive duodenal ulcers; the annual number of patients with *H pylori* negative duodenal ulcers has remained relatively constant over the study period (Figure 1).

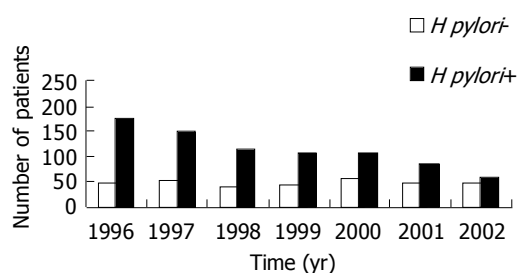
We analyzed the differences between *H pylori* positive and negative duodenal ulcers in terms of their pre-existing factors and their clinical presentations.

**Table 1** Concomitant medical problems

Concomitant medical problems	Number of patients (%)
Hypertension	279 (20.8)
Diabetes mellitus	127 (9.5)
Ischemic heart disease	79 (5.9)
Cerebral vascular accidents	62 (4.6)
Rheumatic diseases	54 (4.0)
Chronic obstructive airway disease	34 (2.5)
Congestive heart failure	27 (2.0)
Chronic renal failure	26 (1.9)
Cirrhosis	21 (1.6)
Asthma	18 (1.3)

**Table 2** Nature of recent surgery

Type of operation	Number of patients
Orthopedic	12
Cardiothoracic	10
Colorectal	5
Urology	4
Neurosurgery	1
Hepatobiliary	1
Head and neck	1
Vascular	1
Appendectomy	1
Gynecology	1
Endocrine	1
Ophthalmology	1



**Figure 1** Number of patients diagnosed to have duodenal ulcer with and without *H pylori* infection from 1996 to 2002.

### Differences in pre-existing factors

On univariate analysis, patients with *H pylori* negative duodenal ulcer were significantly more likely females, older, having concomitant medical problem, having pre-existing malignancy, having recent surgery, having underlying sepsis, taking NSAIDs, taking aspirin, or being non-smokers (Table 3).

On multivariate analysis, six factors were found to be independently associated with *H pylori* negative duodenal ulcer. These factors included older age, concomitant medical problem, pre-existing malignancy, recent surgery, underlying sepsis, and NSAIDs usage (Table 3).

On analyzing the relationship of each concomitant medical problem with the *H pylori* status, all except asthma were significantly associated with *H pylori* negative duodenal ulcer (Table 4).

**Table 3** Characteristics of patients according to their *H pylori* status

Characteristics	<i>H pylori</i> negative (n = 398)	<i>H pylori</i> positive (n = 945)	P
Sex (M/F)	268/130	693/252	<0.03
Age (yr)	65.3±0.9	50.3±0.6	<0.001 <sup>1</sup>
Concomitant medical problem (%)	50.8	24.1	<0.001 <sup>1</sup>
Pre-existing malignancy (%)	10.3	2.5	<0.001 <sup>1</sup>
Recent surgery (%)	8.0	0.7	<0.001 <sup>1</sup>
Recent sepsis (%)	5.0	0	<0.001 <sup>1</sup>
NSAIDs usage (%)	13.1	5.3	<0.001 <sup>1</sup>
Aspirin usage (%)	7.3	4.0	0.019
Corticosteroid usage (%)	0.8	0.1	0.08
Smoking (%)	18.1	25.6	0.003
Drinking (%)	3.5	5.0	0.315

<sup>1</sup>Significant factors on multivariate analysis.

**Table 4** Relationship of *H pylori* status and concomitant medical problem

Concomitant medical problem (%)	<i>H pylori</i> negative (n = 398)	<i>H pylori</i> positive (n = 945)	P
Hypertension	30.7	16.6	<0.001
Diabetes mellitus	15.3	7.0	<0.001
Ischemic heart disease	10.0	4.1	<0.001
Rheumatic diseases	7.8	2.4	<0.001
Cerebral vascular accidents	7.3	3.5	<0.005
Congestive heart failure	5.8	0.4	<0.001
Chronic renal failure	5.8	0.3	<0.001
Chronic obstructive airway disease	5.5	1.3	<0.001
Cirrhosis	4.0	0.5	<0.001
Asthma	1.0	1.5	NS

### Differences in clinical presentations

Patients with *H pylori* negative duodenal ulcer were more likely to present with bleeding, multiple ulcers (i.e., more than two ulcers), and larger ulcers (Table 5).

**Table 5** Clinical presentations of patients according to their *H pylori* status

Presentations	<i>H pylori</i> negative (n = 398)	<i>H pylori</i> positive (n = 945)	P
Presenting symptom			
Pain	59	190	
Bleeding	335	753	
Obstruction	4	2	<0.02
Multiple ulcers (%)	10.6	3.6	<0.001
Ulcer size (cm)	1.2±0.04	0.9±0.02	<0.001

## DISCUSSION

Previous studies have reported that more than 90% of patients with duodenal ulcer are infected with *H pylori*<sup>11</sup>. The use of NSAIDs was considered as the major cause of *H pylori* negative ulcer disease<sup>11,21</sup>. Owing to the high prevalence of *H pylori* infection in patients with duodenal ulcer, patients were given empirical eradication therapy without confirmatory testing of the infection in some centers<sup>13</sup>. Nevertheless, confirmatory testing of *H pylori* status is considered necessary today in view of a rising prevalence of *H pylori* negative duodenal ulcer<sup>14-61</sup>.

Nowadays it is evident that, apart from *H pylori* and NSAIDs usage, there remains a group of patients with ulcers of unknown etiology<sup>61</sup>. Besides, there were also arguments put forward to contend against *H pylori* as the primary cause of duodenal ulcer disease. Firstly, it has not fulfilled all the four Koch's postulates<sup>8-101</sup>. Secondly, the prevalence of ulcer disease is far lower than the prevalence of *H pylori* infection<sup>91</sup>. Thirdly, the Indians in Fiji have twice the number of duodenal ulcer than Fijians, although they have similar prevalence of *H pylori* infection<sup>11,121</sup>. Fourthly, there were numerous recent reports of a rising prevalence of *H pylori* negative duodenal ulcer<sup>14,5,12,131</sup>. Fifthly, a meta-analysis of North American studies revealed a 20% ulcer recurrence rate within 6 mo of successful eradication of *H pylori*<sup>141</sup>. The authors concluded that non-*H pylori*, non-NSAIDs-related ulcer disease may be more common in the USA than previously believed<sup>141</sup>.

In view of the significant proportion of *H pylori* negative duodenal ulcers and the possible existence of causal factors other than *H pylori*, it is necessary to study the differences between *H pylori* negative and positive ulcers in order to identify factors other than *H pylori*, which are involved in the development of ulcer disease.

In the present prospective study of 1 343 patients with endoscopically confirmed duodenal ulcer disease, only 70.4% of patients have *H pylori* infection. A similar prevalence of *H pylori* infection in patients with duodenal ulcer was reported by a number of recent studies<sup>5,151</sup>. In view of the current prevalence of *H pylori* infection in patients with duodenal ulcer, it is important to confirm the

*H pylori* status before prescribing eradication therapy.

It is clear from the present study that the rising proportion of *H pylori* negative duodenal ulcer was due to a progressive reduction in the number of patients with *H pylori* positive duodenal ulcer. This is most likely the result of widespread adoption of *H pylori* eradication for the treatment of *H pylori* related ulcer both in the primary and in the tertiary care settings in Hong Kong. The different extent in eradication of *H pylori* in different countries may account for the global variation in the prevalence of *H pylori* negative duodenal ulcer. The finding that the number of patients with *H pylori* negative duodenal ulcer has remained static suggested that duodenal ulcer might persist as a health problem unless we are able to identify other etiologic factors which are preventable.

*H pylori* negative duodenal ulcer was found to be associated with older age, concomitant medical problem, pre-existing malignancy, recent surgery, underlying sepsis, and NSAIDs usage. In the past, the majority of *H pylori* negative duodenal ulcers was believed to be related to NSAIDs usage<sup>[2]</sup>. The present study did confirm that NSAIDs is an independent factor associated with *H pylori* negative duodenal ulcer. However, only about 13% of patients with *H pylori* negative duodenal ulcer have taken NSAIDs (Table 3). Stress, as a result of recent surgical trauma or underlying sepsis, was also found to be another important risk factor for *H pylori* negative duodenal ulcer. In fact, it has been known for many years that trauma and sepsis are potent risk factors for the development of ulcer disease<sup>[16,17]</sup>. Such factors could therefore result in ulcer disease in the absence of *H pylori* infection.

The association of concomitant medical problem with *H pylori* negative duodenal ulcer could not be adequately explained. Apart from asthma, all medical problems were significantly associated with *H pylori* negative duodenal ulcer. Cirrhotic patients were known to have a higher risk of duodenal ulcer independent of *H pylori* infection<sup>[18]</sup>. On the other hand, patients with chronic renal failure were known to have a lower rate of *H pylori* infection<sup>[19,20]</sup>. The exact reason why concomitant medical problem is related to *H pylori* negative duodenal ulcer remains to be elucidated.

Older age was also found to be associated with *H pylori* negative duodenal ulcer in other published studies<sup>[13,21]</sup>. Physical inactivity was known to be associated with a higher chance of ulcer disease<sup>[22,23]</sup>. Whether physical inactivity is related to the development of duodenal ulcer in elderly individuals or individuals with underlying medical problem is currently unknown.

It is noteworthy that *H pylori* negative duodenal ulcer more commonly presented with bleeding, with larger ulcer, or with multiple ulcers. In an elderly patient requiring emergency surgery for bleeding duodenal ulcer, which is usually large in size, acid-reduction surgery may need to be considered in view of the likelihood that the ulcer is unrelated to *H pylori* infection.

It is unlikely that risk factors identified for *H pylori* negative duodenal ulcer will vanish in the future. In the presence of an aging population, therefore, it is possible that duodenal ulcer will persist worldwide even with the increasing use of eradication therapy and the availability of

more selective COX-2 inhibitors.

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