HELICOBACTER PYLORI INFECTION IN PEPTIC ULCER DISEASE: THE IMPORTANCE OF SMOKING AND ETHNICITY

KVK Pillay[1], M Htun[1], NN Naing[2] and B Norsa'adah[2]

[1]Department of Surgery, [2]Unit of Biostatistics and Research Methodology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia

Abstract. This study was conducted to determine the prevalence of *Helicobacter pylori* (*H. pylori*) and its associated factors among patients with peptic ulcer disease in Taiping Hospital. Consecutive peptic ulcer disease patients who had undergone esophagogastro-duodenoscopy were included. The *H. pylori* status was assessed by the rapid urease test. We excluded those who had active bleeding, a perforated peptic ulcer, severe vomiting, a history of gastric surgery, peptic ulcer disease or renal or liver diseases, carcinoma of the stomach, and recent use of antibiotics or proton pump inhibitors. Socio-demography, *H. pylori* status, medication history and other relevant clinical data were collected from case notes. A total of 416 subjects were selected, 49.7% were positive and 50.3% were negative for H*. pylori* infection. There were significant associations between *H. pylori* and age, ethnicity, smoking status and NSAID usage. However, there were no significant relationships between *H. pylori* status and gender or type of peptic ulcer. Multiple logistic regression showed that other ethnicities than Malays and smokers had a higher risk of *H. pylori*. Our prevalence rate was low and the identified risk factors were consistent with previous studies. Ethnic differences may be related to genetic and sociocultural behaviors. Quitting smoking may benefit peptic ulcer patients with *H. pylori* infection.

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is associated with a broad spectrum of gastroduodenal pathology ranging from asymptomatic gastritis to gastric malignancy. The importance of *H. pylori* as a causal agent in the development of peptic ulcer disease is now recognized worldwide and its eradication is considered an important issue in the management of peptic ulcer disease (Warren and Marshall, 1983; Kang *et al*, 1990; NIH Consensus Conference, 1994).

Correspondence: Dr Nyi Nyi Naing, Unit of Biostatistics and Research Methodology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia.
Tel: 609-7664899; Fax: 609-7653370
E-mail: nyi@kb.usm.my

H. pylori is a gram-negative curved or spiral, flagellated bacteria that can be found living in the mucus layer, that acts as the protective layer, overlying the gastric epithelium. *H. pylori* have an acid defense mechanism that generates local alkali ammonia by enzymatic cleavage of urea by the enzyme urease, in order to survive in a hostile acidic gastric environment (Vu and Ng, 2000). This is the basis of the diagnostic tests to diagnose the presence of the organism.

H. pylori is considered the most common bacterial infection in the world with an estimated 75% of the population in the developing world being infected with the organism even at an early age (Committee of Epidemic Disease, 1996). However, the majority of these people are asymptomatic for several decades due to the symbiotic nature of the organism which causes nothing more than minor gas-

tritis and inflammation (Vu and Ng, 2000). It can infect the stomach during childhood and cause a life-long chronic gastritis that can lead to gastroduodenal pathology (Graham *et al*, 1995). High rates of sero-positivity had been noted in children (Banatvala *et al*, 1995, Lin *et al,* 1997). *H. pylori* prevalence is high in South-east Asia, including Malaysia. Its prevalence in the Malaysian population has been estimated to be around 40% (Feldman *et al*, 1998). The incidence in Malaysia is higher among Chinese and Indians than Malays (Goh, 1997a). The same findings have also been noted in neighboring Singapore (Kang *et al*, 1990).

The infection is more prevalent in lower socioeconomic groups with poor living standards, such as crowded living conditions (Goodman and Correa, 1997), those with lower levels of education and poor hygiene (Graham *et al*, 1995). In more Westernized countries, the prevalence is low in children but increases with increasing age, paralleling the age related prevalence of chronic gastritis, found in 20% of those age 20 years old and 60% of those age 60 years old (Malaty and Evans, 1991). However, in poorer countries, such as Zaire, the prevalence of infection is as high as 70-90% in all age groups (Malaty and Evans, 1991). In developing countries, infection rates are higher in children; 85% of children below the age of 15 years old have been found to be infected, and this chronic infection continues into adult life (Graham *et al*, 1995). The assumption that *H. pylori* infection is more prevalent in low socioeconomic and low income groups has been confirmed by a study involving 247 children in Arkansas (Malaty and Evans, 1991). A comparable study was done in Wales where the age adjusted prevalence of *H. pylori* was the highest in the lowest social class, lower in the middle class and the lowest in the upper class (Sitas and Forman, 1991). A higher prevalence of *H. pylori* infection was seen among Irish soldiers with a low socioeconomic background (Basso and Clive, 1990). Similar trends were seen in a study done in Saudi Arabia which found an *H. pylori* infection rate of 77% in non-college graduates, higher than that found in those with a college degree, who had a 54% prevalence rate (Evan and Abdulghani, 1990). There was also high prevalence of *H. pylori* among an indigenous Indian population in the Andean mountains of Chile of 85%, compared to a 55% infection rate in the population living in urban Santiago (Steward and Hodas, 1997). Another epidemiological study confirmed a high prevalence of *H. pylori* infection among children with poor socioeconomic background in a suburban area of Bangladesh (Mohandas, 1997). This was supported by the high prevalence of *H. pylori* infection in children of West African countries (Gerald and Thumshin, 1995). In China, a high rate of *H. pylori* infection was reported among adults in suburban areas (Siow *et al*, 1995).

Most of these studies utilized serology methods, which are the most widely used methods for the diagnosis of *H. pylori* infection in epidemiological studies worldwide (Graham *et al*, 1995). The populations tested varied from blood donors and healthy volunteers to patients presenting to health centers. It is assumed that once *H. pylori* infection is acquired, it persists until old age, then there is a progressive increase in seroprevalence, which may be considered as a surrogate for incidence (Graham *et al*, 1995). If these figures are considered for adults in developed countries, the annual incidence of infection is only 1-2% (Malaty *et al*, 2002). Results from many of these studies have suggested that although the prevalence of infection among adults in developed countries is high, but the incidence rate is low, varying between 0.5-5.0% per year (Sitas and Forman, 1991).

As the data suggest, certain ethnic groups are more susceptible to infection with *H. pylori* than other ethnic groups. In America, healthy adult Hispanics and Blacks have se-

ropositivity to *H. pylori* several fold higher than the non-Hispanic white population (Dehesa and Dooley, 1991). The overall seropositivity of *H. pylori* among African Americans was 57%, compared with 26% in the Whites, and this association was independent of age, gender, diet and rural or urban location (Hopkin and Russel, 1990). In New Zealand, seropositivity with *H. pylori* among adults varies by ethnic origin with prevalence rates of 70% among Tongans, 44% in Samoans, 39% in Cook islanders and 15% in Caucasians (Morris and Nicholson, 1986). A study that was done in Australia among immigrants that showed a wide variation in the prevalence of *H. pylori* infection: 43% in Ethiopians, 40% in Salvadorans and 18% in Vietnamese (Dryger and Kaldar, 1988). The prevalence of *H. pylori* was reported to be 0.5% among the Australian Aborigine population who have a low incidence of peptic ulcer disease (Dwyer and Sun, 1988). This finding is similar to Malaysian aborigines where the prevalence of *H. pylori* infection is only 19% (Amry, 2003).

We conducted this study in view of the high prevalence of *H. pylori* infection and lack of epidemiological data among patients with peptic ulcer disease in Hospital Taiping. This study was performed to determine the prevalence of *H. pylori* infection among patients diagnosed with peptic ulcer disease and its associated factors.

PATIENTS AND METHODS

This study was conducted at Taiping Hospital, which is situated 65 km north of Ipoh, which is the capital of the state of Perak, in Malaysia. The area had a population of 306,478 in 2004. The availability of good surgical facilities in Taiping Hospital makes it a referral center for many dyspeptic and upper gastrointestinal pathology patients.

This retrospective study was carried out at Taiping Hospital among consecutive peptic ulcer disease patients who had undergone esophagogastro-duodenoscopy (EGD) from 1 January 2001 to 31 December 2002. In these patients, EGD was done as part of a diagnostic workup for symptoms, such as dyspepsia and epigastric pain. All patients underwent a rapid urease (CLO) test to confirm the presence of *H. pylori* (Al-Fadda *et al*, 2000). We excluded those who had active bleeding, a clinical presentation of a perforated peptic ulcer, severe vomiting, previous gastric surgery, a history of peptic ulcer disease or renal or liver diseases, carcinoma of the stomach, a history of recent use of antibiotics or proton pump inhibitors. Case notes of the patients were retrieved from the Medical Records Office and their socio-demographics, *H. pylori* status, drug history, smoking status, non-steroidal anti-inflammatory drug (NSAID) use and other relevant clinical data were recorded.

Data were entered and analyzed using SPSS for windows version 11.0. Univariate analysis was done using a chi-square test and Fisher's exact test for differences in proportions and associations between *H. pylori* status and other factors. An independent *t*-test was applied to test for differences in means. Univariate analysis was also done using simple logistic regression. Multivariate analysis was done by using multiple logistic regression to determine factors associated with *H. pylori* infection. Backward stepwise multiple logistic regression was applied with inclusion of variables in the model with a p-value less than 0.3. The fitness of the model was tested by the Hosmer-Lemenshow test and a classification table. The findings are presented as crude and adjusted odds ratios with 95% confidence intervals (CI) and corresponding p-values for the Wald test. The level of significance was set at 0.05.

RESULTS

A total of 416 subjects were included in

Table 1
Association of *H. pylori* with sex, ethnicity, smoking status, non-steroidal anti-inflammatory use and type of ulcer.

	H. pylori status n (%)		p-value
	Positive	Negative	
Age (years)	54.20 (15.84)[a]	59.60 (13.03)[a]	<0.001[b]
Sex			0.185[c]
Male	140 (48.1)	151 (51.9)	
Female	69 (55.2)	56 (44.8)	
Ethnicity			<0.001[d]
Malay	61 (29.6)	145 (70.4)	
Chinese	69 (57.5)	51 (42.5)	
Indian	69 (85.2)	12 (14.8)	
Other	8 (88.9)	1 (11.1)	
Smoking status			<0.001[c]
Yes	142 (73.6)	51 (26.4)	
No	65 (29.1)	158 (70.9)	
NSAID[e]			<0.001[c]
User	136 (57.4)	101 (42.6)	
Non-user	71 (39.7)	108 (60.3)	
Type of ulcer			0.829[c]
Duodenal	102 (50.2)	101 (49.8)	
Gastric	66 (47.8)	72 (52.2)	
Duodenal and gastric	39 (52.0)	36 (48.0)	

[a]Mean (Standard deviation); [b]independent *t*-test; [c]Chi-square test; [d]Fisher's exact test; [e]Non-steroidal anti-inflammatory drug

this study. Out 416 subjects, 207 (49.7%) were positive and 209 (50.3%) were negative for *H. pylori* infection. Table 1 shows the association between *H. pylori* and sex, ethnicity, smoking status, NSAID use and type of ulcer. There were no statistically significant relationships between *H. pylori* status and gender or type of peptic ulcer. However, there were statistically significant relationships between *H. pylori* and age, ethnicity, smoking status and NSAID usage.

Table 2 shows factors associated with *H. pylori* on multiple logistic regression. Other ethnicities had a higher risk of *H. pylori* infection than Malays. Smokers were 6 times more likely than non-smokers to be infected with *H. pylori*.

DISCUSSION

This study found the prevalence of *H. pylori* among patients with peptic ulcer disease in Taiping Hospital to be 49.7%. This rate is lower than previous studies among ethnic Malays which reported that 77% of peptic ulcerations were associated with *H. pylori* infection (Mazlam, 2002). It is unlikely the lower *H. pylori* prevalence obtained in this study is due to false negative results, since patients with a past history of peptic ulcer, bleeding, taking antibiotics and or proton pump inhibitors factors that may confound *H. pylori* prevalence by affecting the accuracy of the CLO test (Laine *et al*, 1998), were carefully excluded from this study. The method used in this study to determine the status of infection was the

Table 2
Factors associated with *H. pylori* infection.

	Simple logistic regression	Multiple logistic regression	p-value[b]
	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	
Ethnicity			
Malay	1 [a]	1[a]	
Chinese	3.22 (2.01, 5.14)	3.30 (1.96, 5.55)	<0.001
Indian	13.66 (6.91, 27.03)	12.69 (6.12, 26.34)	<0.001
Other	18.97 (2.33, 154.58)	9.85 (1.10, 87.91)	0.040
Smoking status			
No	1[a]	1[a]	<0.001
Yes	6.77 (4.40, 10.42)	6.29 (3.90, 10.12)	

Hosmer-Lemenshow test, p = 0.243, classification table overall percentage 73.6%.
[a]Reference category; [b]Wald test

CLO test. When endoscopy is performed, it is customary to check for *H. pylori* by taking a few biopsies from the antrum and the body of the stomach. The office based urease test, used by most endoscopists to detect the presence of urease enzyme in the biopsy specimen, is specific for *H. pylori.* Normal gastric mucosa is devoid of any urease activity. Hence the demonstration of urease activity in the stomach is a reliable indicator of active *H. pylori* infection. The CLO test is a highly sensitive (90-93%) and specific (93-95%) diagnostic test (Conwell *et al*, 1995). Randomized controlled trials performed by Goh *et al* (1996a) concluded there is no statistical difference in sensitivity and specificity compared to office based serological ELISA test for the *H. pylori*. Serological methods for the detection of *H. pylori* organisms are the most commonly used technique for population based epidemiological studies but are less reliable (Varghese, 2002). There are still some unresolved issues in defining the gold standard for the detection of *H. pylori* infection in various age groups, geographical areas and in persons with chronic infection (Amry, 2003). Culture of *H. pylori* organisms is still the gold standard for the diagnosis of *H. pylori* infection. Although it is very specific, it is not sensitive (Warren and Marshall, 1983).

Several epidemiological studies have reported the frequency of *H. pylori* in individuals increases with age. In the poorer countries, such as those in Africa, the prevalence of infection is as high as 70-90% in all age groups (Graham and Karen, 1991). In developing countries, the infection rate is higher in children than in developed countries, with 85% of them below the age of 15 years old being positive (Graham *et al*, 1995). In Singapore, the seroprevalence of *H. pylori* infection increases with age, from 3% in children below age 5 years to 71% in adults above age 65 (Fock, 1997). Increased ingestion of NSAIDs resulting in *H. pylori* negative peptic ulcer disease in the older population may be a contributory factor (Kachintorn *et al*, 1992). Moreover, the age related increase in *H. pylori* prevalence is due to the fact that the infection is usually acquired in childhood and carried for life, rather than a higher risk of *H. pylori* associated with peptic ulcer disease in older people (Vu and Ng, 2000). A study of school children of various ethnic groups in urban and rural areas of Selangor revealed a prevalence rate similar to that of adult subjects, suggest-

ing early exposure to the infection (Goh, 1997a). Despite *H. pylori* being more commonly found in older age groups, this age related increase in *H. pylori* prevalence was not found in our study, similar to some other studies (Kachintorn *et al*, 1992; Lee *et al*, 1993). We also found no significant association between gender and *H. pylori* infection. This result is similar to studies by Uyub *et al* (1994) and Goh (1997a).

The prevalence of *H. pylori* infection varies widely in Malaysia by ethnic group. Amongst the major races in Peninsular Malaysia, Malays consistently have a lower prevalence than Chinese and Indians on both endoscopic surveys and seroprevalence studies (Kang *et al*, 1990; Uyub *et al*, 1994; Goh *et al*, 1996b, 1997a). However, high prevalence rates of more than 50% have been reported in Sabah and Sarawak amongst indigenous populations (Goh *et al*, 1998; Mahendra *et al*, 1998). Available data suggest environmental factors probably account for at least some of the racial differences (Kang, 1985); these factors still remain unidentified. An assessment of the prevalence of *H. pylori* and peptic ulcer disease in the different races is therefore of interest. Ethnic differences in infection may be due to genetic differences, or transmission and perpetuation of infection within the same ethnic group resulting from varied habits and socio-cultural practices. Another contributory factor may be the Chinese and Indians in Malaysia are immigrant races that brought the infection from their home countries (Li *et al*, 1991).

In our study there was no statistically significant relationship between the type of ulcers and *H. pylori* status. Mazlam (2002) found the *H. pylori* infection rate were 56% in patients with gastric ulcers and 78% in patients with duodenal ulcers. Uyub *et al* (1994) found the *H. pylori* infection rate was 9% in non-ulcer dyspepsia patients, 5% in gastric ulcer patients and 50% in duodenal ulcer patients. Kuipers *et al* (1995) suggested that greater than 90% of all duodenal ulcers and greater than 80% of all gastric ulcers were associated with *H. pylori* infection. Furthermore, the prevalence of infection in bleeding ulcers ranged from 40-90% (Borody *et al*, 1991). In another study done in Singapore, the *H. pylori* prevalences in patients with gastric ulcers, duodenal ulcers and both gastric and duodenal ulcers were 67.9%, 85.1% and 85.7%, respectively (Vu and Ng, 2000). However this study was done on a small sample size. Conflicting data regarding *H. pylori* infection rates have been reported in acute and chronic duodenal ulcers (Reinbach *et al*, 1993; Sebastian *et al*, 1995; Ng *et al*, 1996). The nature of the ulcer, whether complicated or uncomplicated, active or chronic, when included in the study may influence the *H. pylori* prevalence (Vu and Ng, 2000).

Apart from genetic and socio-economic factors, another possibility which may account for the variations in prevalences in different studies, is the effect of NSAIDs. It has been reported that NSAIDs may be associated with an increase in the prevalence of *H. pylori* infection in relation to peptic ulcer disease (Vu and Ng, 2000). Low *H. pylori* prevalence in some geographical regions has been described (Jyotheeswaran *et al*, 1998; Schubert *et al*, 1999; Xia *et al*, 1999). The finding of increasing *H. pylori* negative ulcers may suggest a different pathogenesis in these patients. There is strong evidence that *H. pylori* infection may not be central to the pathogenesis of peptic ulceration in some patients. Host and environmental factors (smoking, alcohol and NSAIDs) may modulate clinical responses to *H. pylori* infection or cause peptic ulceration in the absence of *H. pylori* infection and warrants further study.

Our study did not find a significant relationship between NSAID consumption and *H. pylori* status. Other studies (Uyub *et al*, 1994; Goh, 1997a) have reported a high prevalence

of infection among endoscopy subjects taking NSAIDs. The use of NSAIDs seems to have a protective effect for the stomach mucosa against *H. pylori* infection (Matsukawa *et al*, 2003). It has been hypothesized that NSAIDs may have this protective effect on human gastric mucosal cells by inhibiting VacA channel activity required for vacuole genesis (Vittorio *et al*, 2002).

Our findings confirmed a significant relationship between smoking and *H. pylori* infection, which is consistent with previous studies (Goh, 1997a,b). This may be due to the fact that cigarette smoking predisposes an individual to peptic ulcer disease by a reduction in the protective bicarbonate layer over the gastric mucosa and may lead to increased susceptibility to *H. pylori* infection (Amry, 2003). A significant relationship between the number of cigarettes smoked and *H. pylori* infection has been reported by other studies (Goh, 1997b, Amry, 2003). This may be due to the fact that the more cigarettes smoked, the higher the incidence of peptic ulcer disease due to a reduction in gastric mucosal protective layer and a higher predisposition to *H. pylori* infection (Goh, 1997b). Another study found that *H. pylori* infection is more commonly found in patients with non-ulcer dyspepsia who smoked rather than in those patients who did not smoke cigarettes (Rajasekhar *et al*, 2000). This finding suggested the importance of quitting smoking in patients with *H. pylori.*

Our study had many limitations. Our study used the CLO test as the diagnostic method for *H. pylori* because of its simplicity and low cost, with high sensitivity and specificity (Goh *et al*, 1996a). Although the gold standard for diagnosing *H. pylori* infection is histological examination or culture of the organism, this is not performed at district government hospitals because of the complexity of the test, lack of trained staff, and cost. Culture of the organism may be used to determine antibiotic sensitivity when the initial treatment has failed (Varghese, 2002, Amry, 2003). Furthermore, we were using secondary data which had many missing variables. Many variables were not recorded, such as education level, income, family history, etc, therefore these could not be analyzed.

In conclusion, the prevalence of *H. pylori* infection among patients diagnosed with peptic ulcer disease at Hospital Taiping was low. Ethnicity and smoking were significant factors associated with the infection. Non-Malays and smokers should be more cautious with peptic ulcer symptoms, and testing for *H. pylori* infection is more needed than in Malays and non-smokers. Although these are the findings at a single hospital, it confirms previous studies conducted overseas and locally.

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