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Recurrence of Helicobacter Pylori Infection and Duodenal Ulcer Relapse, Following Successful Eradication in an Urban East Asian Population

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ABSTRACT

We aimed to determine the rate of Helicobacter pylori (HP) recurrence and duodenal ulcer relapse in patients of a hospital in Singapore over a period of at least one year from the time of eradication.

Ninety-six consecutive duodenal ulcer patients with biopsy-proven HP eradication and healed ulcer were seen at 3-month intervals, and follow-up endoscopy was performed when dyspepsia recurred, at the end of one year after eradication, or at the time of recall if the patient had been lost to follow-up. HP status was determined by antral and corpus biopsies and by antral cultures. Sixty-five had been given triple therapy, and 31 received dual therapy with omeprazole + amoxycillin or clarythromycin. Median time to follow-up endoscopy was 12 months.

Six patients (6.25%) were positive for HP infection after eradication. Recurrence of HP infection was detected at 9 and 10 months after confirmation of HP eradication in two patients, and at between 13 and 20 months in the remaining four. Two of these had recurrent duodenal ulcer; all but one had erosive duodenitis. Two other patients had recurrent duodenal ulcer despite absence of HP reinfection; they admitted to taking low-dose aspirin.

It was concluded that the recurrence of HP infection is low at the end of one year after successful eradication therapy in this urban East Asian population. Ulcer relapse occurred in 4.17% (4/96) of patients, and was associated with recurrent HP infection or NSAID exposure.

Keywords: Helicobacter pylori, Drug Therapy, Combination, Peptic Ulcer, Follow-up studies, Recurrence

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INTRODUCTION

Helicobacter pylori (HP) is now recognized as a major aetiological factor in the pathogenesis of type B gastritis and peptic ulcer disease. There is concrete evidence that eradication of the bacterium reverses histological gastritis, and results in significant reduction of duodenal and gastric ulcer recurrence. It has also been observed that ulcer relapse is associated with recurrence of HP infection in the absence of concurrent exposure to NSAIDs.

Recurrence of HP infection can occur through either (a) recrudescence of infection which has been temporarily suppressed by antibiotic therapy to an extent sufficient to render a test of cure negative or (b) reinfection after true eradication of the bacterium has been effected[1].

We sought to determine the rate at which recurrence of HP infection occurs in the local population, and also to determine the factors associated with duodenal ulcer relapse in this cohort.

MATERIALS & METHODS

This was a single-centre prospective cohort study. All patients with duodenal ulcer who had previously been treated at Toa Payoh Hospital (later renamed Changi General Hospital), Singapore between August 1993 and May 1995 for HP infection and with biopsy-proven eradication and ulcer healing were considered for inclusion. At the time the study was started in 1993, the hospital ethics committee had not yet been established, and therefore approval was not required.

The eradication regimens used were either Bismuth-based Triple Therapy for 2 weeks consisting of tripotassium dicitratobismuthate (DeNol), Tetracycline and Metronidazole, or Dual Therapy for 2 weeks with Omeprazole plus either Clarythromycin or Amoxycillin.

Entry criteria included Duodenal Ulcer and the presence of H pylori at pre-treatment antral biopsy as detected by Haematoxylin & Eosin staining or bacterial culture, documented ulcer healing on post-treatment endoscopy (defined as the first follow-up endoscopy), and successful eradication of H pylori. Successful eradication was defined by negative antral biopsies for both histology and culture, with at least 2 specimens taken for each modality at the first follow-up endoscopy performed at least 4 weeks after completion of eradication therapy.

Exclusion criteria were concomitant gastric ulcer, hypersecretory states, pregnancy, previous upper gastro-intestinal surgery, and the concomitant use of ulcerogenic drugs during the study.

All patients received either Triple Therapy or Dual Therapy with Omeprazole plus Amoxycillin or Clarythromycin for 2 weeks. A small number of patients received 2 or more different courses of eradication therapy because of adverse effects.

After the first follow-up endoscopy during the time period stated above, all patients who qualified for inclusion were enrolled into the study on a consecutive basis. Each patient was seen in the clinic at 3-monthly intervals. At each visit a standard questionnaire was administered, and specific information sought included dyspepsia or melaena since the previous visit. A history of all drugs consumed during the intervening period, and of NSAIDs in particular, was obtained each time. The end-point of the study was the performance of the second follow-up endoscopy.

The second follow-up endoscopy was performed at the end of one year from post-treatment endoscopy in asymptomatic patients, or within two weeks of the patient reporting a history of dyspepsia severe enough to warrant the use of any medication. Repeated attempts were made by telephone to contact patients who failed to attend follow-up appointments, and the reason for their non-attendance was enquired into. Endoscopy was performed for these individuals at their earliest convenience if they were asymptomatic and more than one year had elapsed since post-treatment endoscopy. If they were symptomatic they were invited to return for endoscopy regardless of the time since post-treatment endoscopy.

At follow-up endoscopy the presence or absence of duodenal and gastric ulcer was noted in particular. Two biopsies were taken from the gastric antrum and from the corpus for histology; two more were taken from the antrum for culture. Historical details ascertained on the same day included upper GI symptoms and medication taken within the last 4 weeks (in particular NSAIDs and antibiotics).

RESULTS

The eradication regimens used were a Bismuth-based triple therapy for two weeks and a dual therapy regimen of Omeprazole and Clarythromycin or Amoxycillin. The eradication rates obtained were 79.0% overall with Triple Therapy[2] and 68.1% with the Dual Therapy regimens[3].

A total of 96 patients returned for the second follow-up endoscopy and clinic review, out of 137 individuals eligible. The reasons for the failure of the 41 patients to return were (a) the inability to contact the individual (9 patients), (b) inability to take time off work (5 patients), or (c) unwillingness on the part of individuals to subject themselves to further endoscopy because of the absence of symptoms (27 patients). As such, this level of follow-up attendance may reflect over-representation of those positive for H pylori.

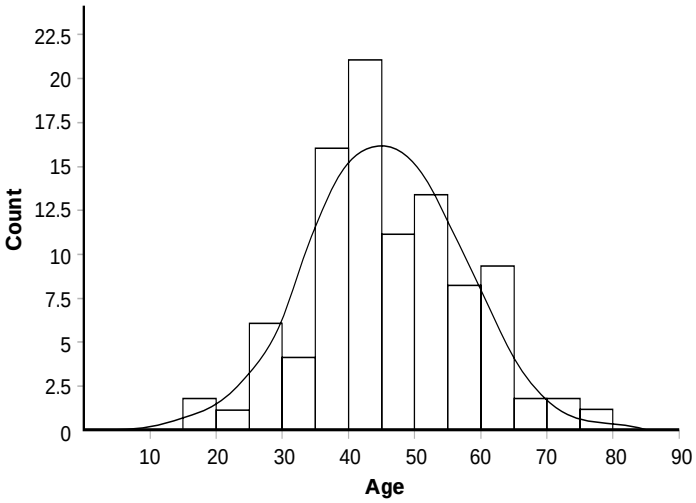

Fig. 1 Age Distribution of Cohort.

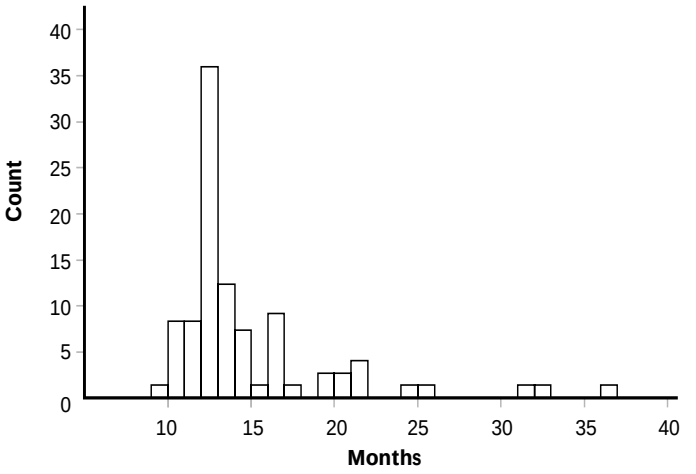

Fig. 2 Time to Follow-up Endoscopy.

Males accounted for 83.3% of the cohort, which ranged in age from 18 to 75 years (Fig. 1). Ethnic Chinese made up 88.5% of the cohort, while Indians, Malays and other ethnic groups accounted for 7.3, 3.1 and 1.0% respectively. Mean age was 45.96 years (1SD 11.72), and the median age was 44 years. Dyspepsia was the predominant mode of presentation, accounting for 68% of the cohort; the remaining 32% presented with symptoms referable to GI bleeding. The mean time to second follow-up endoscopy was 14.05 months, representing a total of 1349 patient-months or 112.4 patient-years. The median follow-up time was 12 months, with a range of 9 to 36 months. The distribution of time to follow-up endoscopy is given in Fig. 2.

Table I. Patients with recurrent H pylori infection

Patient	Sex	Age	Duodenitis	Ulcer	Time to OGD	Regimen	NSAID	Symptom
A	M	52	Yes	No	20 months	dual	No	Pain
B	M	26	Yes	No	16 months	dual	No	Nil
C	M	51	Yes	Yes	14 months	triple	No	Pain
D	F	49	Yes	Yes	13 months	dual	No	Pain
E	M	41	Yes	No	10 months	dual	No	Nil
F	M	39	No	No	9 months	triple	No	Pain

OGD – Oesophago-gastro-duodenoscopy

Six patients (6.25%) tested positive for HP infection after biopsy-proven eradication at post-treatment endoscopy. Recurrence of HP infection was detected endoscopically at 9 and 10 months after confirmation of HP eradication in two patients, and at between 13 and 20 months in the remaining four. Two of these had recurrent duodenal ulcer; all but one had erosive duodenitis. Six recurrences of infection occurred over 112 patient-years, giving an annual recurrence rate of 5.36%.

Recurrence of HP infection occurred in 2 patients given triple therapy and in 4 given dual therapy (3.12% vs. 12.90%, p=0.066). Two other patients had recurrent duodenal ulcer despite absence of HP reinfection; they admitted to taking low-dose aspirin. Recurrent duodenal ulcer was therefore seen in 4.17% (4/96) of patients, and was associated with either recurrence of H pylori infection or aspirin ingestion. No GI bleeding occurred in any of the patients followed up, regardless of their initial mode of presentation.

Details of the six patients with recurrence of H pylori infection are given in Table I. We found that 16.3% of patients who remained HP-negative were symptomatic at the end of the follow-up period, whereas 66.7% of patients with recurrent HP infection had recurrence of symptoms as well (p=0.0026).

DISCUSSION

Recurrence of Helicobacter pylori infection after apparently successful eradication may be the result of either recrudescence or reinfection[1]; the distinction between the two definitions is an important one. Recrudescence is the reappearance of the original infection after negative initial post-treatment assessment, and is defined in practical terms as reappearance of a HP strain identical to the pre-treatment strain. Reinfection has been defined as the post-treatment appearance of a HP strain that is genetically different from the pretreatment strain[4]. Strain typing is performed by any of a number of molecular techniques, which produces a DNA fingerprint unique to each strain isolated.

Most authors have reported recurrence rates of HP infection over 12 months or more following successful eradication. This figure is widely variable, and the annual rates reported have ranged from 0-41.5%[5]. A number of large longitudinal studies have shown that the rate of infection recurrence is highest immediately after eradication therapy, and diminishes with increasing follow-up time[6-11]. A landmark study found that when recurrences within one year were excluded, the rate of recurrent infection was 0.58% per year[6]. In the few studies where pre- and post-treatment strain typing was performed, only seven of the 25 patients in total yielded post-treatment strains different from the pre-treatment strain, and these included two patients proven to have endoscopically-transmitted HP reinfection[11-17]. This evidence has led to the conclusion that recrudescence of prior HP infection accounts for the vast majority of recurrences[4,5]. Where recurrent infection occurs with an identical strain, recrudescence of an old infection rather than reinfection from a close contact is likely to be responsible[5]. Factors associated with increased likelihood of recrudescent infection include (a) assessment performed too early after eradication therapy[16], (b) inadequate biopsies[5], and (c) the use of less efficacious eradication regimens[6]. A recent meta-analysis concluded that recurrent infection is rare when eradication rates exceed 90%[5].

The incidence, or rate of acquisition of HP infection is relatively low in developed countries, with a crude combined incidence of 0.4% per year. This rate is known to be higher in developing countries, at 3-10% per year[18]. The early childhood years are important with regards to exposure to HP infection, with higher rates of acquisition than during the adult years[19,20]. The rate at which HP infection is acquired is also influenced by individual susceptibility and environmental factors related to socio-economic status[18]. It has been suggested that if reinfection is distinguished from recrudescence, the rate of reinfection and that of natural acquisition of infection should be identical[4].

Our results demonstrate that recurrence of Helicobacter pylori infection and peptic ulcer is uncommon, and these are in agreement with work from other groups. This study was performed in a regional hospital in Singapore; a small, urban, and rapidly-developing country in South-East Asia that is fast approaching industrialized status. We determined previously the seroprevalence of HP in the local population[21]. Relatively few infections were found in children (12.5% under 14 were seropositive), and the seroprevalence rose progressively with age to 79.2% in those over 75, consistent with a pronounced birth-cohort effect. The pattern of seroprevalence was similar to that of the industrialized countries, as defined in another meta-analysis[22].

The eradication regimens used were a Bismuth-based triple therapy for two weeks and a dual therapy regimen of Omeprazole and Clarythromycin or Amoxycillin. The eradication rates obtained were 79.0% overall with Triple Therapy[2] and 68.1% with the Dual Therapy regimens[3]. Endoscopic biopsies were taken from the gastric antrum and corpus as a test of cure at least four weeks after cessation of therapy, to maximize sensitivity and specificity[5]. At at least one year after the endoscopy that documented HP eradication the patients were asked to return for a follow-up endoscopic study, at which time a similar biopsy protocol was performed. A standard questionnaire was administered to each individual within a week before that endoscopy. The vast majority (94%) of patients were asymptomatic, and there was a significantly higher proportion of HP recurrence (p=0.002) in symptomatic patients. We had great difficulty persuading some patients who were asymptomatic to attend follow-up review and endoscopy. Xia et al recognized this to be a problem in follow-up studies after HP eradication[5]. They suggest that the patients who dropped out were more likely to be asymptomatic and therefore free of HP, leading to over-estimation of the rate of HP recurrence in those who continued with follow-up; this too was our experience.

We found 6.25% (6/96) of the individuals who returned for follow-up endoscopy positive for HP, at a median interval of 12 months after the first follow-up endoscopy which confirmed eradication. Six recurrences of infection occurred over 112 patient-years, giving an annual recurrence rate of 5.36%. We did not have the means available to perform strain typing, but the evidence presented above indicates that the recurrences were almost certainly due to recrudescence of previous infection. A comparison of HP recurrence rates published in and after 1994 related to the geographical areas studied is given in Table II.

Table II. Annual recurrence rates of H pylori infection in industrialized countries and in emerging economies.

Country	Recurrence per pat. year	Annual Rate (%)	Eradication Rate (%)	HP assessment	Ref
Australia	2/550	0.36	Not given	14C	7
Australia	3/248	1.2	Not given	H	8
Netherlands	7/601	1.2	Not given	H, 13C	16
Austria	2/65	3.1	89	RUT, H, 13C	9
Ireland	29/320	9.1	84.3	RUT, H, 13C	14
Malaysia	0/70	0	Not given	RUT, H, 13C	23
China	4/356	1.08	Not given	RUT, H, 13C	11
South Africa	2/54	3.7	56.3	RUT, H, 13C	10
Chile	2/47	4.2	82	RUT, H, 13C	24
Hong Kong	6/59	10.1	94.6	RUT, H, 13C	25

14C – Carbon-14 Urea Breath Test *RUT – Rapid Urease Test*
H – Histopathology *13C – Carbon-13 Urea Breath Test*

CONCLUSION

The annual recurrence rate of HP infection is low in this population in Singapore at 5.36%, with six infection recurrences over 112 patient-years. Ulcer relapse occurred in 4.17% of patients, and was associated with recurrent HP infection or aspirin exposure. HP eradication in duodenal ulcer patients is a worthwhile exercise because it produces an aetiologic and symptomatic cure of ulcer disease in most patients. A trend was seen towards increased rates of recurrent HP infection in patients given the less efficacious dual therapy as opposed to triple therapy, but statistical significance was not reached. Previous studies have shown that the vast majority of patients with recurrent HP infection have recrudescent infection rather than re-infection.

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