SOCIETY REPORT

WORKING PARTY REPORT OF THE GASTROENTEROLOGICAL SOCIETY OF SINGAPORE PART I - *HELICOBACTER PYLORI* AND PEPTIC ULCER DISEASE IN SINGAPORE

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ABSTRACT

The Gastroenterological Society Working Party on Helicobacter pylori (H pylori) recommends eradication of H pylori in patients with peptic ulcer, provided H pylori infection has been demonstrated. H pylori treatment is not indicated for non-ulcer dyspepsia, histological gastritis or mere demonstration of H pylori infection. H pylori infection can be demonstrated by a urease test, culture or histological assessment on gastric antral biopsy or by a ^{13}C and ^{14}C urea breath test : serology is acceptable if validated in the local population. There are many eradication regimens for H pylori infection and follow-up assessments to demonstrate eradication is desirable.

Keywords: *non-ulcer dyspepsia, Helicobacter pylori*

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The Gastroenterological Society of Singapore, in response to requests from general practitioners and non-gastroenterologist specialists for information pertaining to *Helicobacter pylori* (*H pylori*) and peptic ulcer disease, decided in 1994 to form a working party to prepare a consensus on *H pylori* infection and treatment in Singapore. The members of the working party were gastroenterologists selected from both institutional and private sectors. The committee drafted a paper and presented their recommendations to gastroenterologists accredited by the Academy of Medicine in December 1994. This report has taken into consideration suggestions and criticisms made at that meeting and is a consensus reflecting the position of the Gastroenterological Society of Singapore. It is anticipated that with rapid advances in this field this report will have to be reviewed and updated regularly.

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Aims

The aims of this report are: (1) to inform our colleagues in general practice and general internal medicine about recent developments on *Helicobacter pylori* (*H pylori*) with particular reference to the situation in Singapore, and (2) to make recommendations on indications for investigation and treatment of *H pylori* infection in Singapore. There are two parts to this report: (1) *H pylori* and peptic ulcer disease, and (2) *H pylori* and non-ulcer dyspepsia. This report represents our views at this point in time. Periodic revisions in the light of new knowledge will be carried out in future.

Disease Associations[1,2]

H pylori infection is as common in Singapore as elsewhere in the world. The prevalence of infection increases with age. In Singapore, 50% of blood donors above the age of 50 have positive serology. Indians have higher prevalences of infection as judged by serology compared to Chinese and Malays.

H pylori is an important cause of duodenal ulcer and gastric ulcer. Other causes of ulcer disease include non-steroidal anti-inflammatory drugs and malignancy (especially for gastric ulcer) and gastrinoma (especially for duodenal ulcer). Eradication of *H pylori* in peptic ulcer patients dramatically reduces recurrence rates from 80% over one year to 10% for duodenal ulcer. *H pylori* infection increases the risks of subsequent development of gastric carcinoma fourfold. However it is not known whether this is reduced by eradication of *H pylori* in adulthood. *H pylori* is the main cause of histological gastritis but histological gastritis is

not correlated with symptoms. *H pylori* occurs in 30%-47% of patients with non-ulcer dyspepsia[3]. Again there is no evidence that *H pylori* causes non-ulcer dyspepsia, or that *H pylori* treatment relieves symptoms in non-ulcer dyspepsia (see addendum on *H pylori* and non-ulcer dyspepsia to be published in the next issue of SMJ). It is possible that peptic ulcer patients who have been treated with acid reducing agents could have healed their ulcers by the time they come to endoscopy. Such patients may then be diagnosed to have non-ulcer dyspepsia when the true diagnosis is that of healed peptic ulcer.

Diagnosis[1,2]

This can be divided into: (i) invasive methods involving endoscopy and gastric biopsy, or (ii) non-invasive methods including urea breath tests, and (iii) serology

i. During endoscopy, a biopsy can be taken from the gastric antrum and sent for the rapid urease test, histology, culture, or any combination of the above tests.

ii. Urea breath tests are non invasive and involve the ingestion of urea labelled with an isotope of carbon. *H pylori* produces large amounts of urease and, if present, results in release of labelled carbon in the breath. ^{13}C (non radioactive) or ^{14}C (radioactive) can be used. The former test is no longer available in Singapore but the latter may become available in the near future.

   Tests using gastric biopsy and the urea breath tests should only be performed if the patient has not been taking antibiotics, bismuth compounds or proton pump inhibitors within the preceding four weeks. Otherwise false negative results may occur.

iii. Serology involves the detection of IgG and/or IgA to *H pylori* and a high titre usually indicates active infection. Many commercial test kits are available. Most of them have not been validated in our local population. Care has therefore to be taken in the interpretation of serological tests. One test kit which was stated to be 96% sensitive and 93% specific by the manufacturers was found to be only 83% sensitive and 71% specific when tested in a local series of patients. Serology only indicate the presence or absence of *H pylori* infection. It cannot differentiate between non-ulcer dyspepsia, gastric carcinoma or peptic ulcer disease. It should not be used as the sole basis for therapy.

   Tests for *H pylori* antibodies in saliva are also under development but are less accurate than serological tests.

   In the West, serological testing for evidence of *H pylori* infection has been advocated by a few authors as a means of selecting dyspeptic patients for endoscopy. The chances of peptic ulcer and gastric cancer would be lower in those with negative serology and these people may not need endoscopy. This practice cannot be recommended in Singapore at the present time because: (1) the incidence of gastric carcinoma is higher in Singapore compared to the West and younger patients are affected, (2) Only 43%-62% of our gastric carcinoma cases have *H pylori* infection as determined histologically[3,4], although the serological status of these patients was not evaluated in those studies.

Treatment of *H pylori* in peptic ulcer disease

There is no ideal treatment for *H pylori* infection. The two regimens which have been most studied are:

1. Triple therapy using denol 1 tab qds, metronidazole 400 mg tds and tetracycline 500 mg qds. Amoxicillin can be used instead of tetracycline in cases of sensitivity to tetracycline.

2. Dual therapy with omeprazole 40-80 mg daily plus amoxicillin 1.5-2g/day. Clarithromycin 500 mg tds can be used instead of amoxicillin in patients who are sensitive to amoxicillin.

Each treatment course lasts for 2 weeks. Triple therapy has an eradication rate of about 80% while dual therapy with a proton pump inhibitor plus antibiotic has an eradication rate of 70%.

A third regime which was recently reported to be efficacious involves the use of metronidazole 500 mg tds, amoxicillin 750 mg tds, for two weeks together with a histamine 2 antagonist, ranitidine 150 mg bd for six weeks.

More recently, a one-week regime of omeprazole 20 mg daily, clarithromycin 250 mg and tinidazole or metronidazole 500 mg bd has been shown by several groups to give eradication rates in excess of 90%[5]. Many other treatment regimens involving different anti-microbial agents, the same agents in different combinations and different durations of treatment have also been described but are not mentioned here for the sake of brevity.

Triple therapy is associated with a high incidence of side effects including nausea and diarrhoea. Pseudomembranous colitis has been reported. The efficacy of eradication is markedly reduced by poor compliance and metronidazole resistance of *H pylori* which occurs in between 12% and 40% of our local isolates[6,7]. Dual therapy, in contrast, has fewer side effects which include diarrhoea and skin rashes.

Treatment for *H pylori* does not directly heal the ulcer craters. It is therefore important that anti-secretory or mucosal protective agents should be given concurrently with therapy for *H pylori*.

Follow-up

Since the efficacy of treatment is only 70%-80%, its success or failure should preferably be monitored. In the case of complicated ulcer, demonstration of ulcer healing and eradication is essential if withdrawal of maintenance histamine 2 receptor antagonist treatment is contemplated. Proof of eradication, although desirable, is not essential in the case of uncomplicated duodenal ulcer. Gastric ulcer should in any case be followed up to healing to exclude malignancy.

Assessment of the efficacy of treatment can be by repeat antral biopsy at endoscopy or by a urea breath test. These tests should be performed at least four weeks after use of antibiotics, bismuth preparations or proton pump inhibitors. Eradication can also be confirmed by the concurrent assay of pre-treatment and 6-month post-treatment sera for antibody to *H pylori*. A 50% reduction in titre of *H pylori* antibodies indicates successful eradication.

Incomplete or unsuccessful treatment can result in development of metronidazole resistance making subsequent eradication more difficult. Theoretically, resistance may also emerge for other antibiotics but this possibility has not been studied. The rate of re-infection after successful eradication is low in Western countries - about 1% per year. It is said to be high in developing countries. No data are as yet available for Singapore. A small proportion of ulcers does relapse despite initial successful eradication. This is relevant in the case of the ulcer which had initially presented with a complication.

We recommend *H pylori* eradication as first line treatment for peptic ulcer disease provided *H pylori* is demonstrable.

Summary of recommendations

a. Eradication of *H pylori* is recommended in patients with

peptic ulcer, provided *H pylori* infection has been demonstrated.

b. Treatment for *H pylori* should not routinely be given for non-ulcer dyspepsia, histological gastritis or demonstration of infection without peptic ulcer except in the context of a clinical trial. There is inadequate evidence at present to recommend eradication of *H pylori* in the prevention of gastric cancer.

c. *H pylori* infection can be demonstrated by urease test, culture or histological assessment on a gastric antral biopsy or by a ^{13}C or ^{14}C urea breath test. Serological assessment using a particular serological test would be acceptable provided sufficient sensitivity and specificity has been demonstrated for that assay system in our local population.

d. Triple therapy (bismuth, metronidazole, tetracycline) or dual therapy (proton pump inhibitor plus antibiotic) or a histamine 2 antagonist plus metronidazole and amoxycillin are the most commonly used regimens. Success rates vary from 70%-80% depending on compliance and sensitivity to metronidazole.

e. It is desirable that follow-up assessment be made to demonstrate eradication. This is essential in the case of complicated ulcer if maintenance acid suppressant treatment is to be ceased. Demonstration of eradication can be achieved by a repeat urease test, culture or histological study on a gastric antral biopsy or a repeat ^{13}C or ^{14}C urea breath test. Simultaneous measurement of pre-treatment and 6-month post-treatment serum samples for IgG antibody titres to *H pylori* is an alternative.

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