CONSENSUS STATEMENT

Management of Helicobacter Pylori Infection - A Working Party Report of the Malaysian Society of Gastroenterology and Hepatology

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Summary

The Working Party Report on the Management of *Helicobacter pylori* serves as a clinical practice guideline for Malaysian doctors. *H.pylori* is not uncommon in the Malaysian population. Marked racial differences and the consistently low prevalence rates amongst Malays are noted. The working party recommends that if endoscopy is to be performed, a rapid urease test should be used for diagnosis. Where suspicion of the infection is strong and the urease test is negative, histology should be performed on gastric biopsies. Culture should be used to monitor resistance patterns to antibiotics and regional laboratories should assume this responsibility. The urea breath tests are highly accurate tests for diagnosis of *H.pylori* but is as yet not widely available in Malaysia. The working party strongly recommends that all peptic ulcer patients infected with *H.pylori* whether active, in remission and complicated ulcers should be treated.for the infection. Patients with low-grade gastric mucosal lymphoid tisssue lymphoma should also be treated for *H.pylori* infection. It is considered advisable that patients on long term non-steroidal antinflammatory drug (NSAID) treatment with a history of peptic ulcers or dyspepsia and patients following resection of early gastric cancer or those with a family history of gastric cancer should also be tested and treated for *H.pylori*. The working party recommends, as first line treatment a 7-day combination therapy of a proton pump inhibitor, clarithromycin and metronidazole or amoxicillin. High metronidazole resistance rates locally may adversely affect regimens containing the antibiotic. It should also be noted that regimens that yield lower eradication rates may result in higher long term expenditure.

Key Words: *Helicobacter pylori*, Working party report, Recommendations, Management, Diagnosis, Treatment

Introduction

The discovery of *Helicobacter pylori* in 1983 by Warren and Marshall[1] ranks as perhaps one of the most important discoveries in gastroenterology to date. It has revolutionised our understanding of upper gastrointestinal disease and as a consequence our approach to the treatment of gastric diseases. *H.pylori* is now recognised as the cause of the majority of peptic ulcers and has been shown to play an important if not critical role in the pathogenesis of cancer of the stomach and gastric maltomas[2,3]. With the availability of new knowledge, treatment and diagnostic options have increased and this has led to confusion amongst medical practitioners as to the optimal management strategy for the patient.

In recognition of the need to review this new knowledge critically and to formulate firm guidelines for diagnosis and treatment, the National Institutes of Health (NIH) convened a Consensus Development Conference Panel in

February 1994 [4]. Since then the European "Maastricht" Consensus Meeting organised by the European Helicobacter Pylori Study Group, the American Digestive Health Initiative Update meeting and the Asia Pacific Consensus Workshop and Meeting have been held and their findings published [5,6,7].

In Malaysia, a Peptic Ulcer Consensus meeting was held in January 1996 under the auspices of the Malaysian Society of Gastroenterology and Hepatology, Ministry of Health and Academy of Medicine, Malaysia [8]. *H.pylori* related issues were discussed as part of this meeting. With further development in our understanding of *H.pylori* infection, the Malaysian Society of Gastroenterology and Hepatology convened a working party which met on 26th April and 14th May 1998 to review new and relevant information, and in particular local data, in order to update clinical practice guidelines.

Epidemiology in Malaysia

The prevalence of *H.pylori* varies widely in Malaysia. Prevalence of the infection appears to follow a "racial cohort pattern". Amongst the major races in Peninsula Malaysia, Malays consistently have lower prevalence rate compared to Chinese and Indians in both endoscopic surveys and seroprevalence studies [9,10]. This observation has also been reported in neighbouring Singapore [11,12]. The low prevalence amongst Malays is particularly seen in the East Coast of Peninsula Malaysia where exceptionally low rates have been reported [13]. On the other hand high prevalence rates of more than 50% have been reported in Sabah and Sarawak amongst the indigenous populations [14,15].

The close correlation of peptic ulcer disease and *H.pylori* infection is also observed in Malaysian patients[10]. *H.pylori* is found in more than 90% of duodenal ulcers and more than 70% of gastric ulcers. NSAIDs may be the cause of non-*H.pylori* infected ulcers and this may be more prevalent in some areas of the country [16].

A variety of host and bacterial factors have been thought as contributing to the pathogenesis of *H.pylori* associated gastrointestinal disease. Amongst the most frequently studied bacterial factor is the CagA protein. Studies have shown that the prevalence of this protein is higher in patients with peptic ulcer disease compared to non-ulcer patients [17]. However studies from Asia and Malaysia have reported contrasting results with a high prevalence of Cag A in both ulcer and non-ulcer patients [18-21]. Few studies have been performed locally, to investigate host risk factors. In a large cross-sectional survey of patients undergoing endoscopy, age, Indian and Chinese race and low social class were significant independent risk factors for the infection [10]. In another study [22] in local patients, Lewis blood group antigens A and B were not found to be correlated with *H.pylori* infection. The issue of reinfection has been increasingly clarified. It has been reported consistently in world literature as well as in long term follow-up studies locally [23-25] that following successful eradication, very low rates of reinfection occur, if at all. Higher reported rates are likely to represent recrudescence rather than true reinfection [26].

Diagnosis of H.plori

Diagnostic tests can be broadly divided into endoscopy based biopsy tests and non-invasive tests.

Endoscopy biopsy tests used include culture, histology and rapid urease test. Apart from culture which has a relatively lower sensitivity, all these tests have high diagnostic accuracy in excess of 90%, [27,28]. Rapid urease tests are convenient and useful tests; both the "home-made" test as well as the commercially available CLO test have high sensitivity and specificity [28]. Culture is generally not required for primary diagnosis of *H.pylori* infection but is useful in cases of treatment failures to determine bacterial resistance to antibiotics.

Laboratory based serological tests using the ELISA method are widely available as commercial kits. They give a high diagnostic accuracy and are in general reliable tests for the diagnosis of *H.pylori* infection. These tests, however, should be locally validated before use [16,29] as these tests vary considerably in their reported sensitivity and specificity. Finger prick office-based whole blood tests have the advantage of convenience and availability of immediate results but

have a lower diagnostic accuracy compared to the laboratory based serological tests. Validation of several such kits locally shows a high specificity but relatively low sensitivity of these tests [30,31].

Urea breath tests are not available in Malaysia for routine clinical testing. Local validation of the carbon^{14} and the carbon^{13} urea breath tests in the research setting have shown that both tests have excellent diagnostic accuracy and are convenient to use [32,33].

It is recommended that a rapid urease test be used for routine clinical testing. Where the suspicion of *H.pylori* infection is high and the rapid urease test is negative, histological examination of a gastric biopsy is recommended. In patients who have not received eradication therapy, 2 biopsies for each test from the gastric antrum is adequate. Following treatment, it is recommended that biopsies are obtained from both the antrum and corpus and that 2 tests be used to document successful eradication of infection. It must be appreciated that prior treatment with proton pump inhibitors, antibiotics and bismuth compounds will affect *H.pylori* status and result in false negative tests.

Table I
Testing For H.Pylori

Primary Diagnosis:

1. **Endoscopy biopsy tests**
   2 antral biopsies for urease test
   2 further antral biopsies for histological examination if suspicion is strong for *H.pylori* infection and urease test is negative

2. **Serology**
   Laboratory based serological tests (locally validated)

3. **Radiolabelled carbon^{13} or carbon^{14} urea breath tests**

Post Treatment:

1. **Endoscopy biopsy tests**
   2 antral biopsies for urease test and histology.
   In cases of treatment failures, biopsies for culture should be sent

2. **Radiolabelled carbon^{13} or carbon^{14} urea breath tests**

Not all patients need to be tested for successful *H.pylori* eradication following treatment. Patients with complicated ulcers should be tested following treatment. The urea breath tests are the best tests following therapy. Serological tests are not recommended, as the fall in antibody titers is variable over a given period of time. In Malaysia, endoscopy biopsy tests are likely to be the mainstay of post-eradication testing as the radio-labelled carbon urea breath tests are not yet widely available.

Where endoscopy is indicated following treatment for example in gastric ulcers to document ulcer healing, biopsies should be taken at the same time to test for *H.pylori* infection. Testing should be carried out at least 4 weeks after completion of therapy.

Emergence of bacterial resistance is of great concern where large numbers of patients are treated. Metronidazole resistance is of particular importance and has been shown in several studies to affect the eradication rates of nitroimidazole containing regimens [34,35]. Metronidazole resistance has been shown to have risen alarmingly over the past 7 years in Malaysia and a rate of over 50% has been reported [36-39]. Resistance to amoxicillin and clarithromycin has not been reported so far [40,41] but efforts must be made to monitor resistance rates to all three key antibiotics that are used in treatment.

It is recommended that monitoring be carried out by regional microbiology laboratories in the country. In keeping with the recommendation of the European *Helicobacter Pylori* Study Group (EHPSG), the working

party also recommends that the E-test and agar dilution methods should be employed for this purpose [42].

Recommendations for Testing of and Treatment of H.Pylori Infection

H.pylori infection when detected should be treated. Therefore, if treatment is not contemplated, testing should not be performed. In making these recommendations, the working party has adopted the classification of the European Maastricht consensus classification of recommendations: viz. *strongly recommended, advisable, uncertain and not recommended* [5].

Table II
Indications for Testing and Treating H.pylori Infection

	Recommendations
Peptic ulcers (active or healed)	Strongly recommended
Complicated peptic ulcers	Strongly recommended
Gastric MALT lymphomas	Strongly recommended
Previous history of ulcers or dyspepsia while on NSAID therapy	Advisable
Prior to starting NSAID therapy	Not recommended
Uninvestigated dyspepsia	Uncertain
Following resection of early gastric cancer	Advisable
Family history of gastric cancer	Advisable
Patients on long term PPIs	Uncertain
Screening of asymptomatic subjects	Not recommended

The working party strongly recommends that all *H.pylori* positive peptic ulcers whether, active, healed or complicated, should receive *H.pylori* eradication therapy. There is overwhelming evidence that *H.pylori* eradication results in marked decrease and in fact, virtual abolition of ulcer relapse. In effect, *H.pylori* eradication results in the cure of ulcer disease [43]. Reports have also shown clearly that the risk of complications from ulcer disease is also markedly diminished with *H.pylori* eradication [44].

Although gastric MALT lymphoma is an uncommon disease, the link between gastric MALT lymphoma and *H.pylori* is very strong and eradication of *H.pylori* has been shown to result in regression of the tumour [45]. The working party also strongly recommends treatment in this group of patients.

It is not recommended that patients being considered for NSAID treatment be routinely tested for *H.pylori*. It is recognized that NSAID use is widespread and it would be impractical to recommend testing for all patients embarking on treatment with these drugs. It is known that both *H.pylori* and NSAIDs are separate and independent risk factors for ulcer disease and that they may act synergistically. The working party, however, recommends that patients who have a past history of peptic ulcer should be approached as for peptic ulcers in general and be tested and treated for *H.pylori*. Patients with a recent history of dyspepsia and who are on NSAID therapy have been shown to have a high probability of ulcer disease [46] and it was considered advisable that these patients should also be tested and treated for *H.pylori* infection.

There is inconclusive evidence supporting primary testing for *H.pylori* and treating of patients with dyspepsia. Dyspepsia is a common clinical problem and can be broadly defined as pain or discomfort centered in the upper abdomen that has been persistent for two weeks or longer and is significant enough for an individual to seek medical attention [47]. A careful

clinical evaluation is imperative and patients with typical gastroesophageal reflux, irritable bowel syndrome and biliary symptoms should be recognized, investigated and treated appropriately. Older patients with a recent history of dyspepsia or those with alarm symptoms such as unexplained weight loss, anaemia, bleeding or dysphagia should undergo definitive diagnostic evaluation. For younger patients without alarm symptoms, an empiric therapeutic trial of treatment with acid-suppressing agents or prokinetics could be recommended or the patient receives further investigations. There are proponents for the "test and treat" approach for *H.pylori* infection. Treatment and eradication of *H.pylori* cures any underlying ulcer disease and may prevent against the development of further upper gastrointestinal disease. While results of controlled trials of *H.pylori* eradication in functional dyspepsia are inconclusive [48,49], clinical practice indicates a small undefined subset of patients with functional or non-ulcer dyspepsia who experience sustained improvement in symptoms with *H.pylori* eradication. The potential benefits of eliminating *H.pylori* probably outweighs the risk of treatment. The recommendation of the working party for testing and treatment of patients with dyspepsia is classified as uncertain and the choice of whether to test and treat should be made on an individual patient basis.

The working party recommends that *H.pylori* be tested and treated following resection of early gastric cancer. This recommendation is made on the evidence from Uemura's compelling study of *H.pylori* eradication in patients following resection of early gastric cancer [50]. On a similar note, it is also recommended that patients following partial gastrectomy for cancer of the stomach should also be tested and treated for *H.pylori* infection.

Testing and treating asymptomatic subjects with a family history of cancer of stomach was considered advisable. However, the working party does not recommend testing and treating asymptomatic healthy subjects for *H.pylori* in those with a family history of *H.pylori* infection and in those with a family history of peptic ulcer disease.

The working party considers it inappropriate and does not recommend screening of asymptomatic subjects for *H.pylori*. However testing and treatment may be offered on patient's request following discussion and counseling of the patients with respect to possible adverse drug events and the risk of promotion of bacterial resistance in the community, with widespread use of antibiotics.

Data on the development of atrophic gastritis in *H.pylori* infected on long term treatment with proton pump inhibitors (PPI) is conflicting. The working party classifies as uncertain the recommendation that patients with gastroesophageal reflux disease and on long term PPIs be tested and treated for *H.pylori* infection.

Table III
Recommended Treatment Regimens

1. PPI (in standard doses)* and amoxicillin 1gm and clarithromycin 500mg all taken b.d for 1 week

For patients who are allergic to penicillin antibiotics

2. PPI (in standard doses)* and metronidazole 400mg b.d and clarithromycin 500mg all taken b.d for 1 week

Where clarithromycin is not available

3. PPI (in standard doses)* and amoxicillin 1gm and metronidazole 400mg all taken b.d for 1 week

PPI in standard doses *:
Omeprazole 20mg
Lansoprazole 30 mg[1]
Pantoprazole 40mg[1]

[1] *(pending approval from Drug Control Authority, Malaysia for the treatment of H.pylori)*

Treatment Recommendations

The working party supports the recommendations that regimens achieving an 80% eradication rate on intention-to-treat (ITT) analysis and 90% on per protocol (PP) analysis be used in the treatment of *H.pylori* infection [5,6]. Treatment regimens however should not only be efficacious but safe and convenient to use.

Based on published world and local data and on local drug availability, the working party recommends that the one week regimen of PPI (given in standard doses), clarithromycin 500mg bd and amoxicillin 1 gm bd be recommended as the treatment of choice [51,52,53,54]. In patients who are allergic to penicillin, the PPI, clarithromycin, metronidazole therapy is recommended but it must be noted that in regions of high metronidazole resistance, this regimen may give a lower eradication rate than the former regimen. Where clarithromycin is not available, amoxicillin and metronidazole at a dose of 400mg b.d with a PPI may be used but it must be appreciated that this regimen will in general give an eradication rate that is 10-15% lower and that immediate cost-savings may result in increased long term expenditure [55].

Newer drugs and treatment regimens will become available and should be reviewed and considered for use when available.

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