

Guidelines for the Management of *Helicobacter Pylori* Infection

a report by

Peter Malfertheiner¹, Francis Mégraud² and Colm O'Morain³

1 Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University

Magdeburg; 2 INSERM ERI-10, Laboratoire de Bactériologie, Université Victor Segalen Bordeaux 2;

3 Adelaide and Meath Hospital

Introduction

The European *Helicobacter pylori* Study Group (EHSg) was founded in 1987 to promote multi-disciplinary research into the pathogenesis of *Helicobacter (H.) pylori*. Since then, the EHSg has organised successful annual meetings and arranged task forces on paediatric issues and clinical trials on *H. pylori*. Consensus meetings have convened on who, how and when to treat patients with *H. pylori* infection. The most active area of research is the link of *H. pylori* with gastric cancer, a major public health issue. The most recent consensus meeting held this year was divided into three panels:

- Who to treat?
- How to diagnose and treat *H. pylori*?
- Prevention of gastric cancer by *H. pylori* eradication.

Chairmen and selected experts were chosen to participate for each of these panels based on their contribution to the published literature. The chairmen met to choose topics relevant to their panel. They developed statements that needed clarification and debate. The international faculty that attended reflected on the global problem of *H. pylori* infection. Each of the panelists were asked to review different topics and provide key references on these topics.

Who to Treat?

The starting point when considering who to treat are the previous guidelines published by the European *Helicobacter* Study Group in Maastricht 2000 (see Table 1).

Dyspepsia

There is a need to define non-investigated and investigated dyspepsia and to consider them separately. Treatment of non-investigated dyspepsia may be different if the incidence of *H. pylori* is as low as occurs in developed countries. The increasing awareness of *H. pylori* as a pathogen in developing countries has stimulated interest in a test-and-treat approach in these areas. A test-and-treat approach

was recommended in adult patients below 45 years of age – the age cut-off may vary locally – presenting in primary care with persistent dyspepsia having excluded those with predominantly gastro-oesophageal reflux disease (GORD), non-steroidal anti-inflammatory drugs (NSAIDs) consumption and those with alarm symptoms. This recommendation has been vindicated in more recent publications. The definition of low prevalence is a population with an infection rate of less than 20%.

The Cochrane Systematic Review stated that the test-and-treat principle was as effective but less expensive than endoscopy in patients not at risk of malignant disease and likely to be more effective than acid-suppressive therapy; yet longer term studies have confirmed this statement. The majority of patients with dyspepsia have a normal endoscopy and in the absence of predominant reflux symptoms, these patients are considered to have non-ulcer dyspepsia. The Cochrane Systematic Review confirmed that there is a small benefit of eradicating *H. pylori* in this context. Empirical anti-secretory treatment may be less costly if the infection rate is less than 20%.

Statements and Recommendations

- *H. pylori* test and treat is an appropriate option for patients with non-investigated dyspepsia.
- *H. pylori* eradication is an appropriate option for patients infected with *H. pylori* and investigated non-ulcer dyspepsia.
- *H. pylori* test and treat is the strategy of choice in all (adult) patients with functional dyspepsia in high-prevalence populations.
- The effectiveness of *H. pylori* test and treat is low in populations with a low *H. pylori* prevalence. In this situation, the test-and-treat strategy or empirical acid suppression are appropriate options.

GORD

The second area of controversy that was reviewed was the link between *H. pylori* and reflux

Dr Peter Malfertheiner is Professor of Gastroenterology at Otto-von-Guericke University Magdeburg and Director of the Department of Gastroenterology, Hepatology and Infectious Diseases. Previously, he was Professor of Medicine at the University in Bonn. Dr Malfertheiner's research interests include *Helicobacter (H.) pylori* infection, main clinical outcomes, such as peptic ulcer disease and gastric cancer, gastro-oesophageal reflux disease and pancreatic pathology. Research includes studies on basic mechanisms and clinical trials. He went to Medical School in Bologna.

Dr Francis Mégraud is Professor of Bacteriology at Université Victor Segalen Bordeaux 2 and Hospital Pellegrin in Bordeaux. He is Head of the National Reference Center for *Helicobacters* in France and one of the founding members and current secretary of the European *Helicobacter* Study Group. His interest in *H. pylori* dates back to the early days after the discovery of the bacterium. He has been involved in epidemiological studies and clinical trials of *H. pylori* eradication. His main current interests are the role of *H. pylori* in gastric cancer and antimicrobial resistance.

Dr Colm O'Morain is Professor of Medicine at Trinity College Dublin and Academic Head of Department of Medicine at Adelaide and Meath Hospital. He is on the Editorial Board of ten peer-reviewed journals, has published over 200 peer-reviewed articles and has authored and co-authored six books. His research interests are in *H. pylori* and inflammatory bowel disease. Dr O'Morain was awarded an MD Thesis from the National University of Ireland and obtained an MSc, a Diploma in Immunology and a DSc from University of London. He received post-graduate training in Dublin, Nice, London and New York having studied medicine at University College Dublin.

Table 1: Strongly Recommended Indications for *H. Pylori* Eradication Therapy

Peptic ulcer disease – active or not including complicated ulcer

Mucosa-associated lymphoid tissue lymphoma (MALToma)

Atrophic gastritis

Post-gastric cancer resection

Patients who are first-degree relatives of gastric cancer patients

Patients' wishes – after full consultation with their physician

oesophagitis. In the previous guidelines, it was thought advisable to eradicate *H. pylori* when long-term anti-secretory treatment is necessary for the management of GORD. This recommendation was based on a report that such treatment may accelerate the progression of *H. pylori*-induced atrophic gastritis in the fundus of the stomach. Observational studies have suggested that *H. pylori* may protect against GORD, but the results could be due to bias or confounding factors.

In randomised controlled studies, the relapse rate in GORD symptoms was the same in the *H. pylori*-treated as the placebo-treated GORD patients (83% of both groups) and treatment of *H. pylori* did not affect the efficacy of proton pump inhibitors (PPIs). More recent studies fail to support the theory that *H. pylori* eradication leads to the development of erosive oesophagitis or worsening of symptoms in patients with pre-existing GORD.

Most *H. pylori*-positive GORD patients have a corpus-predominant gastritis, where treatment with a PPI eliminates gastric mucosal inflammation and induces regression of corpus glandular atrophy. *H. pylori* did not worsen reflux or lead to increased maintenance dose confirming the benefit of eradication of *H. pylori* in GORD patients.

Statements and Recommendations

- *H. pylori* eradication does not cause GORD.
- Profound acid suppression affects the pattern and distribution of gastritis favouring corpus-dominant gastritis and may accelerate the process of loss of specialised glands leading to atrophic gastritis.
- *H. pylori* eradication halts the extension of atrophic gastritis and may lead to regression of atrophy. The effect on intestinal metaplasia is uncertain.
- There is a negative association between the prevalence of *H. pylori* and GORD in Asia, but the nature of this relationship is uncertain.
- *H. pylori* eradication does not affect the outcome of PPI therapy in patients with GORD in Western populations. Routine testing for *H. pylori*

is not recommended in GORD; *H. pylori* testing should be considered in patients on long-term maintenance therapy with PPIs.

H. pylori and Non-steroidal Anti-inflammatory Drugs

The relationship between *H. pylori* and NSAIDs is complex. Both account for nearly all peptic ulcers. They are independent factors for peptic ulcer and peptic ulcer bleeding. *H. pylori* eradication is insufficient to prevent recurrent ulcer bleeding in high-risk NSAID users. It does not enhance the healing of peptic ulcer in patients taking anti-secretory therapy who continue to take NSAIDs.

In one study among patients with *H. pylori* infection and a history of upper gastrointestinal (GI) bleeding who are taking low-dose aspirin, the eradication of *H. pylori* was equivalent to treatment with a PPI in preventing recurring bleeding. However, PPI was superior to the eradication of *H. pylori* in preventing recurring bleeding in patients who are taking NSAIDs.

In a study from Hong Kong, *H. pylori* eradication reduced the risk of bleeding in *H. pylori*-positive patients or patients who had dyspepsia and a history of ulcer before beginning NSAID treatment. However, the eradication was insufficient to completely prevent NSAID ulcer disease. Clopidogrel is also associated with an increased risk of GI bleeding. The role of *H. pylori* in this situation has not been assessed. The combination of aspirin and clopidogrel merits further studies. These drugs have a synergistic beneficial effect on cerebral vascular disease. Among patients with a history of aspirin-induced ulcer bleeding whose ulcer had healed, aspirin and a PPI was superior to clopidogrel in the prevention of recurrent ulcer bleeding. Therefore, the current recommendation is that patients with GI intolerance to aspirin be given clopidogrel. However, this cannot be sustained.

An emerging topic was cyclooxygenase-2 (COX-2) inhibitor and *H. pylori*, but the recently published adverse events of these drugs has stopped all studies into this field.

Statements and Recommendations

- *H. pylori* eradication is of value in chronic NSAIDs users but is insufficient to completely prevent NSAID-related ulcer disease.
- Patients who are naïve NSAIDs users should be tested for *H. pylori* and, if positive, receive eradication therapy to prevent peptic ulcer and/or bleeding.

- Patients who are long-term aspirin users who bleed should be tested for *H. pylori* and, if positive, receive eradication therapy.
- In patients on long-term NSAIDs and peptic ulcer and/or ulcer bleeding, PPI maintenance therapy is superior to *H. pylori* eradication in preventing ulcer recurrence and/or bleeding.

Paediatrics

In paediatrics, it was agreed that there are other indications than peptic ulcer disease for eradication of *H. pylori*. Although recurrent abdominal pain of childhood is not an indication for a test-and-treat strategy, it was recognised that children who have a positive family history of peptic ulcer and gastric cancer should be tested after exclusion of other causes. Similar to adults, children with unexplained anaemia and no other obvious cause for it should be treated for *H. pylori* infection.

Statements and Recommendations

- There are other indications than peptic ulcer disease for eradication of *H. pylori* infection in children and adolescents.

Other Disease Areas

Data is accumulating on the association between *H. pylori* and idiopathic thrombocytopaenia (ITP). There is a significant increase in the platelet count after *H. pylori* eradication. In the published literature, 58% of patients with ITP were infected.

Eradication therapy was accompanied by a complete or partial platelet response in approximately half of the cases. The explanation for this is cross-reactivity of anti-geneticity of platelet surface and *H. pylori*. There is a need for placebo-controlled studies to confirm this benefit. The failure to identify a cause of iron deficiency anaemia in a substantial subset of patients with low iron stores raises the question of whether there are additional, yet unexplained causes of iron depletion.

Recently, there has been a growing body of evidence to suggest a relationship between *H. pylori* gastritis and iron deficiency anaemia in the absence of peptic ulcer disease.

Statements and Recommendations

H. pylori infection should be sought for and treated in patients with ITP and unexplained iron deficiency anaemia. *H. pylori* has no proven role in other extra-alimentary diseases.

How to Diagnose and Treat?

The management of *H. pylori* infection has been well established during the last 10 years. Recommendations were made in the Maastricht Conference in 1996 and were updated in 2000. Most of them have been used in other consensus conferences worldwide. Nevertheless, in the last four years, some points have emerged that led to questions and discussions at the Maastricht 3 Conference.

Diagnosis Pre-treatment

With regard to diagnostic tests, the discussion focused on the value of non-invasive tests other than the urea breath test (UBT). A first statement concluded that serology could be considered as a diagnostic test in some situations, such as bleeding ulcers, gastric atrophy, Mucosa-associated lymphoid tissue lymphoma (MALToma) and current use of PPIs or antibiotics. Indeed, PPIs are a source of false negative results for all diagnostic tests, except serology, and should be stopped at least two weeks before performing the test. In contrast, it was stated that neither the doctor tests (near-patient tests) nor the detection of *H. pylori* antibodies in urine and saliva had any current role in the management of *H. pylori* infection.

The situation is different for the stool test, which was considered acceptable on the same grounds as UBT for *H. pylori* diagnosis, especially in the case of implementation of the test-and-treat strategy.

With regard to invasive tests, the value of a positive, rapid urease test during initial endoscopy in patients without previous non-invasive testing or pre-treatment, was considered to be sufficient to initiate a therapy.

The importance of performing culture for clarithromycin susceptibility testing, before using clarithromycin-based treatment as a first-line treatment, was hardly debated. Culture was recommended if primary resistance to this antibiotic was higher than 15% to 20% in the respective geographical area or population, as well as after two treatment failures.

The importance of monitoring the primary antibiotic resistance in reference laboratories in different areas was also stressed. In the event that clarithromycin susceptibility testing under such circumstances is impossible, this antibiotic should not be used. In contrast, it was agreed that testing metronidazole susceptibility is not routinely necessary in the management of *H. pylori* infection. Metronidazole susceptibility testing needs further standardisation before being recommended as a first-line treatment.

How to Treat?

The recommended first-line therapy is therefore still PPI-clarithromycin-amoxicillin – or metronidazole, if the primary resistance to clarithromycin in the area is lower than 15% to 20%. However, it was agreed that there is a small advantage of using metronidazole instead of amoxicillin and, therefore, this combination was found to be preferable in areas where the prevalence of metronidazole resistance is lower than 40%. The consensus was also that a 14-day rather than a seven-day treatment had a slight advantage in terms of treatment success.

The other adaptation of this first-line therapy in various geographical regions of the world concerns the doses.

Another addition to the Maastricht 2 Consensus is that bismuth-based quadruple therapies, when available, are acceptable as alternative first-line therapies.

With regard to second-line therapies, bismuth-based quadruple therapies remain the best option. If unavailable, PPI-amoxicillin or tetracycline and metronidazole are recommended.

As previously proposed, the rescue therapy after a failure of two courses of different therapies should be based on antimicrobial susceptibility testing.

Follow-up After Treatment

With regard to patient follow-up after *H. pylori* eradication, UBT remains the preferred test. If unavailable, a laboratory-based stool test – preferably using monoclonal antibodies – could be used. The timing of this follow-up should be at least four weeks after the end of the eradication treatment.

At this stage, the detection of *H. pylori* pathogenic factors and host polymorphism was not considered helpful in the management of the infection.

H. pylori Infection and Risk of Gastric Cancer – Potential for Prevention

Gastric cancer is a major public health issue and the global burden of gastric cancer is increasing, largely at the expense of developing countries. *H. pylori* infection is the prime cause of human chronic gastritis, a condition that initiates the pathogenic sequence of events leading to atrophic gastritis, metaplasia, dysplasia and cancer. Pooled analyses of prospective sero-epidemiological studies have shown that individuals with *H. pylori* infection are at a statistically significant increased risk of subsequently developing non-cardia gastric cancer. It has also been well established that both histological types of gastric cancer, the intestinal and the diffuse type, are significantly associated with *H. pylori* infection. Non-

randomised clinical follow-up studies in Japan have shown that gastric cancer rates were significantly higher in patients with *H. pylori* infection than in those with no infection and that second tumour rates were higher in those with infection than those without, following endoscopic resection for early gastric cancer. Thus, it was agreed that *H. pylori* infection is the most common proven risk factor for human non-cardia gastric cancer.

Infection with *cagA*-positive strains of *H. pylori* increases the risk for gastric cancer over the risk associated with *H. pylori* infection alone. Interleukin-1 (IL-1) gene cluster polymorphisms are associated with higher risk of hypochlorhydria (odds ratio=9.1) and gastric cancer (odds ratio=1.9). Potential extrinsic and intrinsic environmental factors in gastric carcinogenesis include: heredity/family history, both direct and indirect (social inheritance); auto-immunity (*H. pylori* may trigger the onset of auto-immune atrophic gastritis in some patients with pernicious anaemia); occupational exposure/nitrate/nitrite/nitroso compounds (in diabetes type I); nutrition (salt, pickled food, red meat and smoking); general (low socio-economic status and geography, for example); and pharmacological (gastric acid inhibition). All these lines of evidence suggest that bacterial virulence factors, host genetic factors and environmental factors contribute to the risk of development of gastric cancer.

H. pylori eradication prevents development of pre-neoplastic changes (atrophic gastritis and intestinal metaplasia) of gastric mucosa. With regard to the possibility that *H. pylori* eradication may reduce the risk of gastric cancer, the following evidences are available: several non-randomised controlled studies in animals and humans showing the preventive effect of *H. pylori* eradication in reducing the occurrence of gastric cancer in very high-risk conditions; several randomised control studies showing regression of precancerous lesion or, at least, decrease of progression as compared to control group after *H. pylori* eradication; and one randomised control study failing to demonstrate reduction of cancer incidence at five years, but showing significant reduction in the group without pre-neoplastic lesions.

The consensus report concluded that eradication of *H. pylori* has the potential to reduce the risk of gastric cancer development. Moreover, the optimal time to eradicate *H. pylori* is before pre-neoplastic lesions (atrophy and intestinal metaplasia) are present. It was also agreed that the potential for gastric cancer prevention on a global scale is restricted by currently available therapies. Thus, new therapies are desirable for a global strategy of gastric cancer prevention. ■