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Peter Malfertheiner, Francis Megraud, Colm O'Morain, Franco Bazzoli, Emad El-Omar, David Graham, Richard Hunt, Theodore Rokkas, Nimish Vakil and Ernst Kuipers

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## Current concepts in the management of *Helicobacter pylori* infection –The Maastricht III Consensus Report

P. MALFERTHEINER<sup>1</sup>, F. MEGRAUD<sup>2</sup>, C. O'MORAIN<sup>3</sup>, F. BAZZOLI<sup>4</sup>, E. EL-OMAR<sup>5</sup>, D. GRAHAM<sup>6</sup>, R. HUNT<sup>7</sup>, T. ROKKAS<sup>8</sup>, N. VAKIL<sup>9</sup>, E.J. KUIPERS<sup>10</sup> & THE EUROPEAN HELICOBACTER STUDY GROUP (EHSG)

<sup>1</sup> Otto-von-Guericke University of Magdeburg, Magdeburg, Germany; <sup>2</sup> Hopital Pellegrin, Bordeaux, France; <sup>3</sup> Adelaide Meath Hospital, Trinity College, Dublin, Ireland; <sup>4</sup> University of Bologna, Bologna, Italy; <sup>5</sup> Aberdeen University, Aberdeen, UK; <sup>6</sup> VA Medical Center Houston, Texas, USA; <sup>7</sup> Mc Master University, Hamilton, Ontario, Canada, <sup>8</sup> Henry-Dunant Hospital, Athens, Greece, <sup>9</sup> University of Wisconsin Medical School, Milwaukee, USA, <sup>10</sup> Erasmus MC-University Medical Center, Rotterdam, Netherlands

Correspondence to: Professor P. Malfertheiner  
Otto-von-Guericke-Universität Magdeburg, Medizinische Fakultät  
Zentrum für Innere Medizin  
Klinik für Gastroenterologie, Hepatologie und Infektiologie  
Leipziger Straße 44  
D-39120 Magdeburg  
Germany  
Phone: +49 391 67 13 100  
Fax: +49 391 67 13 105  
E-mail: [peter.malfertheiner@medizin.uni-magdeburg.de](mailto:peter.malfertheiner@medizin.uni-magdeburg.de)

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**Keywords:** H. pylori, diseases, diagnosis, therapy, prevention

## List of abbreviations

EHSG	European Helicobacter Study Group
GORD	Gastro-oesophageal reflux disease
NSAID	Nonsteroidal anti-inflammatory drugs
PPI	Proton pump inhibitors
H2RA	Histamine 2 receptor antagonists
IDA	Iron deficiency anemia
ITP	Idiopathic thrombocytic purpura
RAP	Recurrent abdominal pain
UBT	<sup>13</sup> C-Urea Breath Test
CagA	Cytotoxin associated gene A
VacA	Vacuolating associated gene A
BabA2	Blood-group-antigen binding adhesion 2
OipA	Outer inflammatory protein A
SabA	Sialic acid binding adhesin
RUT	Rapid Urease test
AAG	Autoimmune chronic gastritis

## SUMMARY

The European Helicobacter Study Group (EHSG) convened the third Maastricht Consensus conference, to update guidelines on the management of *Helicobacter pylori*.

The guidelines cover indications for therapy, management and treatment strategies. The potential of *H. pylori* eradication for the prevention of gastric cancer was underlined.

The eradication of *H. pylori* infection is recommended in patients with (i) gastro-duodenal pathologies such as peptic ulcer disease and low-grade gastric mucosa-associated lymphoid tissue lymphoma (MALT lymphoma), (ii) atrophic gastritis, (iii) first-degree relatives of gastric cancer patients, (iv) unexplained iron deficiency anaemia (v) chronic idiopathic thrombocytopenic purpura. Recurrent abdominal pain in children is an indication for a test and treat strategy if other causes are excluded. The eradication of *H. pylori* infection (i) does not cause gastro-oesophageal reflux disease (GORD) or exacerbate GORD, and (ii) may prevent peptic ulcer in patients who are naïve non steroidal anti inflammatory drugs (NSAIDs) users. *H. pylori* eradication is less effective than proton pump inhibitor treatment in preventing ulcer recurrence in long term NSAID users.

In primary care a 'Test and Treat' strategy using a non invasive test is recommended in adult patients with persistent dyspepsia under the age of 45 (the age cut-off may vary locally). The non-invasive tests that should be used for the diagnosis of *H. pylori* infection are the urea breath test, stool antigen tests and serological kits with a high accuracy.

Triple therapy using a PPI with amoxicillin and clarithromycin or metronidazole given twice daily remains the recommended first choice therapy. Bismuth containing quadruple therapy, if available, is also a first choice treatment option. Rescue therapy should be based on antimicrobial susceptibility.

The global burden of gastric cancer is considerable but varies geographically. Eradication of *H. pylori* infection has the potential to reduce the risk of gastric cancer development.

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## INTRODUCTION

The European Helicobacter Study Group (EHSG) founded in 1987 to promote multidisciplinary research into the pathogenesis of *Helicobacter pylori* has organised successful annual meetings and arranged task forces on paediatric issues and clinical trials. Consensus meetings have been 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 Third Maastricht Consensus Conference was convened to update guidelines on the management of *H. pylori* infection. Fifty experts from 26 countries including primary care physicians were involved in formulating the consensus held in March 2005. The experts were chosen based on their expertise and contribution to the published literature.

## METHODOLOGY AND STRUCTURE OF CONFERENCE PROCESS

Current guidelines from Japan, China, North America and Europe were reviewed at an introductory plenary session.

Working groups addressed the following three topics relating to *H. pylori* infection:

- Indications/contraindications for eradication, focusing on dyspepsia, NSAIDs or aspirin use, GORD; and extra intestinal manifestations of the infection
- Diagnostic tests and treatment of infection;
- Prevention of gastric cancer and other complications.

The recommendations were debated and modified according to a standard template. The strength of recommendations and evidence to support them were graded (Table 1). Only for some statements the grade of recommendation did not match the level of evidence because either studies focussing on the same topic reported conflicting results, or the interpretation of the study by the experts led to a different grade of recommendation than expected from the level of evidence.

The statements and recommendations were edited and finally agreed at the concluding plenary session. Consensus was considered to have been reached if 70% or more supported the recommendation. The recommendations/statements resulting from this rigorous process are reported in this manuscript. A summary of all recommendations is attached at the end of the manuscript.

## INDICATIONS/CONTRAINDICATIONS FOR *H. PYLORI* ERADICATION

The indications for *H. pylori* eradication listed as a strong recommendation in Maastricht II-2000 guidelines<sup>1</sup> were reconfirmed at this update. (Table 2)

### ***H. pylori* and MALT lymphoma**

Subsequent to Maastricht II important new data has been published which has strengthened the indication for *H. pylori* eradication therapy in gastric MALT lymphoma.

Sixty two percent of patients with low-grade gastric MALT lymphoma have a complete remission following *H. pylori* eradication within 12 months<sup>2, 3</sup>. Predictors of response to eradication therapy in patients with low-grade gastric MALT lymphoma are: *H. pylori* positivity; Lugano classification stage I, lymphoma confined to the stomach; gastric wall invasion confined to mucosa / submucosa; and the absence of gene t (11, 18) (q21; q21), translocation with fusion of *API2* and *MALT1*. Fusion of both leads to suppression of apoptosis and strongly predicts failure to respond to eradication therapy. The Maastricht III-2005 consensus report concluded that *H. pylori* eradication is the treatment of first choice for *H. pylori* infected patients with stage I, low grade gastric MALT lymphoma.

### ***H. pylori* and dyspepsia**

A 'Test and Treat' strategy is recommended in adult patients under the age of 45 years presenting with persistent dyspepsia (the age cut-off may vary between countries, depending on the prevalence of gastric cancer). A test and treat strategy has been validated by a primary care study on uninvestigated dyspepsia in Canada<sup>4</sup>.

*H. pylori* eradication gives modest, but significant benefit in non-ulcer dyspepsia<sup>5</sup>. Economic modelling suggests that this benefit is cost-effective<sup>6</sup>. Twelve to fifteen infected patients need to be treated to cure one patient of non-ulcer dyspepsia<sup>6</sup>. This compares favourable to any other therapy available for non ulcer dyspepsia. The eradication of *H. pylori* infection is a once-off treatment that leads to long term symptom improvement, and also reduces the risk of developing peptic ulcer disease, atrophic gastritis and gastric cancer.

In areas of low *H. pylori* prevalence (< 20 %) PPI empirical therapy or a test and treat strategy were considered to be equivalent options<sup>7</sup>.

### **Recommendations:**

1. *H. pylori* eradication is appropriate for patients infected with *H. pylori* and investigated non ulcer dyspepsia.
2. *H. pylori* test and treat is appropriate for patients with uninvestigated dyspepsia.
3. The effectiveness of *H. pylori* test and treat is low in populations with a low *H. pylori* prevalence and in this situation empirical acid suppression is an equivalent option.

### ***H. pylori* and Gastro-Oesophageal Reflux Disease (GORD)**

The prevalence of *H. pylori* in patients with GORD is lower than in those without reflux disease<sup>8</sup>. Most countries with a high prevalence of *H. pylori* also show a low prevalence of GORD. The falling prevalence of *H. pylori* infection and related diseases, including peptic ulcer disease and gastric cancer in developed countries has been paralleled by an increase in GORD and its complications. The nature of this negative association is unclear<sup>9,10</sup>.

In a U.S. study on *H. pylori* infection and in particular infection with CagA positive strains was reported to be lower in patients with Barrett's oesophagus and adenocarcinoma of the cardia<sup>11</sup>. This association has been confirmed in most but not all studies<sup>12,13</sup>. Severe inflammation involving the fundus of the stomach is associated with reduced gastric acid secretion and is inversely correlated with GORD and its complications.

Eradication of *H. pylori* does not cause GORD<sup>14, 15, 16</sup>, and does not exacerbate symptoms in patients with GORD both when untreated<sup>17</sup> as well as when receiving PPI maintenance therapy<sup>18</sup>.

Screening for *H. pylori* in GORD patients needs more formal study including cost-effectiveness analysis and is currently not recommended.

### ***H. pylori* and PPIs**

Profound acid suppression affects the pattern and distribution of gastritis, favouring corpus dominant gastritis<sup>19</sup>. Profound acid suppression with PPIs or high dose H<sub>2</sub>RA in the presence of *H. pylori* positive corpus gastritis may accelerate the loss of specialized glands leading to atrophic gastritis and potentially gastric cancer. In patients with reflux oesophagitis on long term acid suppression, eradication of *H. pylori* infection decreases inflammation and gastritis activity, and reverses corpus gastritis<sup>18</sup>.

**Recommendations:** There is a negative association between the prevalence of *H. pylori* and GORD but the nature of this relationship is uncertain.

1. *H. pylori* eradication does not affect the outcome of PPI therapy in patients with GORD in western populations.
  2. Routine testing for *H. pylori* is not recommended in GORD
  3. *H. pylori* testing should be considered in patients on long-term maintenance therapy with PPIs\* Profound acid suppression affects the pattern and distribution of gastritis favouring corpus dominant gastritis. It may accelerate the process of loss of specialized glands leading to atrophic gastritis.
- H. pylori* eradication halts the progression of atrophic gastritis and may lead to regression of atrophy. The effect on intestinal metaplasia is uncertain.

### ***H. pylori* and Non Steroidal Anti Inflammatory drugs (NSAIDs)**

The relationship between *H. pylori* infection and NSAIDs in gastro-duodenal pathology is complex: *H. pylori* and NSAIDs independently and significantly increase the risk of peptic ulcer bleeding by 1.79 and 4.86 fold respectively. The risk of ulcer bleeding is increased by 6.13 fold when both factors are present<sup>20</sup>.

Results of *H. pylori* eradication in NSAIDs users are conflicting. Part of the problem is that both NSAIDs and *H. pylori* can cause peptic ulcers. *H. pylori* eradication can only be expected to prevent recurrence of *H. pylori* ulcers and while it may also reduce the incidence of ulcers among those with both *H. pylori* and NSAID use, the effect will vary depending on the proportion with true *H. pylori* ulcers in the population studied. In chronic NSAID users with peptic ulcer, *H. pylori* eradication was no better than placebo for maintaining a remission of peptic ulcer with PPI therapy at 6-months<sup>21</sup> PPI maintenance therapy is superior to *H. pylori* eradication alone in preventing upper gastro intestinal bleeding<sup>22</sup>. In contrast, in patients with *H. pylori* infection who are naive NSAID users, *H. pylori* eradication is superior to placebo in preventing peptic ulcer and upper gastrointestinal bleeding at 6-months<sup>23, 24</sup>. Patients who are on long-term aspirin and have ulcer disease and a history of significant bleeding should be tested for *H. pylori* infection and if positive be given eradication therapy<sup>22,25</sup>. Patients receiving long term PPI therapy for prevention of NSAID ulcers should be tested for *H. pylori* to reduce the PPI- *H. pylori* interaction leading to accelerated loss of specialized glands and atrophic gastritis.

**Recommendations:** *H. pylori* eradication is of value in chronic NSAID users but is insufficient to completely prevent NSAID-related ulcer disease

1. In naïve NSAID users *H. pylori* eradication may prevent peptic ulcer and bleeding

2 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.  
 3. Patients who are on long-term aspirin who bleed should be tested for *H. pylori*, and if positive receive eradication therapy.

### Extra-Intestinal Disease

There are studies that suggest that *H. pylori* infection may cause an iron deficiency anaemia (IDA) and idiopathic thrombocytopenic purpura (ITP). Possible pathogenetic mechanisms involved in IDA in patients with *H. pylori* infection include: occult blood loss secondary to chronic erosive gastritis; decreased iron absorption secondary to chronic gastritis of the corpus causing hypo- or achlorhydria; increased iron uptake and utilization by bacteria<sup>26</sup>. *H. pylori* eradication reverses iron deficiency anaemia in patients with asymptomatic gastritis<sup>27</sup> and improves oral iron absorption<sup>28</sup>.

In idiopathic thrombocytopenic purpura, some studies suggest that there is a higher prevalence of *H. pylori* infection in patients with ITP compared to controls<sup>29</sup>. Moreover, a review of published data on *H. pylori* infection and ITP confirms that eradication therapy induced a significant positive platelet response in a proportion of patients with ITP<sup>30-33</sup>. It was recommended that *H. pylori* infection should be sought for and treated in patients with unexplained iron-deficiency anaemia and in those with idiopathic thrombocytopenic purpura. *H. pylori* infection has no proven role in other extra-intestinal diseases.

**Recommendations:** *H. pylori* infection should be sought for and treated in patients with:

1. unexplained iron deficiency anemia and
2. idiopathic thrombocytopenic purpura
3. *H. pylori* has no proven role in other extra-intestinal diseases.

### *H. pylori* infection in children

Recurrent abdominal pain (RAP) is not an indication for a Test and Treat strategy for *H. pylori* infection in children. The primary goal of the diagnostic work up in RAP should be to determine the cause of the presenting gastrointestinal symptoms, and not the presence of *H. pylori* infection.

However, children with upper gastrointestinal symptoms should be tested for *H. pylori* infection (after exclusion of other causes of the symptoms) and should be treated if they have the infection.

In children and adolescents, iron deficient anaemia refractory to iron supplementation is an indication to test for *H. pylori* infection and for eradication therapy if positive. This should be after exclusion of other causes such as coeliac disease and inflammatory bowel disease (IBD). No other substantial aspects have been brought forward in respect to previously published guidelines<sup>34, 35</sup>.

### DIAGNOSTIC PROCEDURES

Non-invasive tests for the diagnosis of *H. pylori* infection include: <sup>13</sup>C-Urea Breath Test (UBT); Stool Antigen Tests (polyclonal antibody, monoclonal antibody and office-based); and immunological tests (laboratory tests and office-based and tests on saliva and urine).

The diagnostic accuracy of the UBT is >95% in studies. The UBT is an accurate, practical and readily available test<sup>36</sup>.

The stool antigen test is appropriate when multiple specimens are tested as a batch. However, it is necessary to store stool samples at -20°C before testing. The stool sensitivity decreased to 69% after 2-3 days at room temperature. In a systematic review of 89 studies evaluating stool antigen test the sensitivity and specificity test were 91% and 93% respectively<sup>37</sup>.

Serology is a widely available and an inexpensive non invasive test, but the diagnostic accuracy is low (80-84%)<sup>38</sup>. Tests that detect active infection although more expensive, are preferable to serology as these reduce the number of patients inappropriately treated for presumed *H. pylori* infection<sup>39, 40</sup>. Some kits for serology with a high accuracy (> 90%) are recommendable in validated settings.

### Special role of serology

PPI therapy can result in false negative invasive and non invasive diagnostic tests. PPI should be stopped for at least 2 weeks prior to testing. However, this does not apply to serology<sup>41-46</sup>. A positive serologic test with negative histology and urea blood test would suggest the presence of an unrecognized *H. pylori* infection and additional investigations to confirm whether the serologic test was false positive or reflected active infection. False positive non-invasive tests are more common in low prevalence populations requiring additional confirmation prior to treatment<sup>47, 48</sup>.

Serological tests are recommended to assess *H. pylori* in patients with a bleeding ulcer and conditions associated with a low bacterial density (extensive mucosal atrophy<sup>45</sup>, and MALT-lymphoma)<sup>46</sup>. The rapid urease test, culture and histology as well as UBT have shown a limited sensitivity in patients presenting with acute bleeding peptic ulcer. Polyclonal stool antigen tests have a low specificity due to cross reactivity with blood products.. Serology tests, and in particular detection of antibodies against the specific antigen CagA is very immunogenic and long lasting, link gastric cancer to *H. pylori* infection<sup>49</sup>.

#### Recommendation:

Serology should be considered as a diagnostic test

1. when others could be false negative such as in patients with bleeding ulcers, gastric atrophy, MALT-lymphoma and
2. recent or current use of PPI and antibiotics.

Office-based serological tests or near patient tests are extremely convenient, but they are not accurate and currently are not recommended<sup>50</sup>.

Kits are available to diagnose *H. pylori* antibodies in urine and saliva . Their main advantage is their non-invasiveness and convenience. Unfortunately their sensitivity is low. Therefore they are not useful in patient management but can be useful in epidemiological studies.

#### Recommendations:

1. Serology based office tests has no current role in the management of *H. pylori* infection.
2. The detection of specific *H. pylori* antibodies in urine and saliva has no current role in patient management but can be helpful for epidemiological studies.

### Detection of pathogenic factors

Some strains of *H. pylori* are more virulent than others<sup>51</sup>. Important pathogenic factors are CagA, a product of a gene of the *cag* pathogenicity island; VacA, a cytotoxin produced in various amounts; and BabA<sub>2</sub>, an adhesin which recognizes the blood group antigen A and allows *H. pylori* to adhere to gastric epithelial cells. Other factors, e.g. OipA and SabA, may also determine disease. Furthermore, host genetic factors may determine disease outcome<sup>52</sup> The association with *H. pylori* pathogenic factors and host genetic factors is real at the population level in Western countries, however the limited strength of the association does not allow a reliable prediction of the outcome at an individual level. Moreover, the tests are cumbersome and expensive and of little relevance in the management of *H. pylori* infection.

**Recommendation:** The detection of *H. pylori* pathogenic factors and the study of host genetic polymorphisms is not currently recommended in the management of *H. pylori* infection.

### Role for Urease test

The rapid urease test can detect the presence of *H. pylori*, within one hour with a satisfactory accuracy (>90%)<sup>53</sup>. False negatives can occur in patients taking antisecretory medication. It is acceptable to initiate eradication therapy on the basis of a positive rapid urease test.

**Recommendation:** A positive rapid urease test is sufficient to initiate treatment.

### Follow-up after treatment

Non-invasive tests should be employed for confirmation of eradication except in cases where repeat endoscopy is indicated, e.g. gastric ulcer patients. Systematic reviews of the studies performed in this context indicate that

UBT is the best option, with a sensitivity of 94% and a specificity of 95%<sup>36, 54</sup>. The accuracy of the stool antigen tests is inferior to that of UBT<sup>55-58</sup>. However, when UBT is not available, a stool test can be used. There are a number of stool tests available (one using monoclonal antibodies, lab and office based and the other polyclonal antibodies). The sensitivity of the test is lower if polyclonal antibodies<sup>59</sup> or if an office test is used. Confirmation of *H. pylori* eradication should be performed at least 4 weeks following treatment.

**Recommendation:** *H. pylori* eradication should be confirmed at least four weeks after treatment.

1. UBT is recommended if available.
2. If not available a laboratory-based stool test, preferably using monoclonal antibodies, could be used.

### TREATMENT OF *H. PYLORI* INFECTION

Numerous clinical trials have been published since the last Maastricht conference. Standard triple therapy composed of PPI, amoxicillin, and clarithromycin/ or metronidazole is more successful if extended to more than 7 days. Increased resistance to antibiotics used in the PPI triple therapy need to be considered in the selection of treatment. Recently sequential therapy consisting of 5 days of a PPI plus amoxicillin followed by 5 additional days of a PPI plus clarithromycin plus tinidazole has been shown to be superior to the combination of a PPI plus amoxicillin and clarithromycin for 7 days<sup>60,61</sup> and deserves further evaluation in different regions.

### Antimicrobial resistance

The mechanism of resistance of *H. pylori* strains to Clarithromycin is well understood. Its methods of detection are reliable and its clinical relevance has been proven.

The prevalence of clarithromycin resistance in Europe was measured in a European study in 1997-1998 and was overall 10%, with important differences between Northern European countries (4%) and Southern European countries (18.5%). There was a correlation between the prevalence of *H. pylori* clarithromycin resistance and the consumption of macrolides in the corresponding regions expressed in daily dose per 1000 inhabitants in 1997<sup>63</sup>.

Clarithromycin resistance is increasing. It is the main risk factor for treatment failure<sup>64-66</sup>. Treatment should achieve at least a  $\geq 80\%$  eradication rate<sup>67</sup>. The threshold of clarithromycin resistance at which this antibiotic should not be used or a clarithromycin susceptibility test should be performed is 15-20%.

*In vitro* resistance to metronidazole may not accurately reflect *in vivo* resistance<sup>68</sup>. For this reason Metronidazole testing is not recommended routinely in clinical practice.

### Recommendations:

1. The threshold of clarithromycin resistance at which this antibiotic should not be used or clarithromycin susceptibility testing performed is 15-20%.
2. Testing metronidazole susceptibility is not routinely necessary.
3. Metronidazole susceptibility testing needs further standardisation.

In susceptible strains the combination of PPI-clarithromycin-metronidazole is more successful than the combination of PPI-clarithromycin-amoxicillin (97% vs 88%, respectively). In the case of clarithromycin resistance alone, the eradication rates are also higher with PPI-clarithromycin-metronidazole than with PPI-clarithromycin-amoxicillin (50% vs 18%, respectively). In metronidazole resistance when a PPI-clarithromycin-metronidazole regimen is used, there is a 25% decrease in eradication rate (72% vs 97%)<sup>69</sup>.

Based on these data, the predicted eradication rates for the PPI-clarithromycin-metronidazole combination show a better efficacy than PPI-clarithromycin-amoxicillin which is nullified only when metronidazole resistance reaches 40%.<sup>70</sup>

A 14 day treatment lead to a (12% CI 7-17) higher eradication rate based on a single meta analysis<sup>71</sup> Few studies have compared the cost effectiveness of these different strategies<sup>72</sup>. Numerous studies with PPI triple therapy for 7 days mainly from European countries confirm that this is still a valid duration for this therapy<sup>70</sup>.



Bismuth containing quadruple therapy (10 or 14 days) is an option for the first line therapy . It leads to satisfactory eradication rates despite the increased resistance to both Clarithromycin and metronidazole.

First choice therapy in various geographical regions worldwide was also addressed and finally a global statement including the different points mentioned above was voted upon.

**Recommendation:**

1. For PPI (standard dose bid), clarithromycin (500 mg bid), amoxicillin (1000 mg bid) or metronidazole (400 or 500 mg bid), 14 day treatment is more effective than 7 days (by 12% 95% CI 7%-17%). A 7 day treatment may be acceptable where local studies show that it is very effective.
2. PPI-clarithromycin-amoxicillin or metronidazole therapy is the recommended first choice therapy in populations with less than 15-20% clarithromycin resistance. – In populations with less than 40% metronidazole resistance PPI-clarithromycin-metronidazole is preferable. – Quadruple therapies are alternative first choice therapies.
3. The same first-choice *H. pylori* therapies are recommended worldwide although different doses may be appropriate.

**Second choice therapy**

Bismuth based quadruple therapy is a preferred option as second choice therapy if not previously used. However, the participants highlighted the fact that bismuth is not currently available in many countries.

PPI triple therapies have been tested as second choice treatment. Clarithromycin should not be used unless phenotypic or genotypic tests show that the strain is susceptible. The eradication rate obtained with the combination of PPI-amoxicillin-metronidazole was 89% and 64% for metronidazole susceptible and resistant strains, respectively. In a clinical trial using this combination as a second choice therapy, the global eradication rate was 64%<sup>73</sup>. Another combination by which limited data exist is PPI-tetracycline-metronidazole with an eradication of 91%<sup>74</sup>.

**Recommendation:**

1. Bismuth-containing quadruple therapies remain the best second choice therapy, if available.
2. PPI-amoxicillin or tetracycline and metronidazole are recommended if Bismuth is not available.

**Third choice therapy**

Two other classes of antibiotics have emerged in the treatment of *H. pylori* infection: a fluoroquinolone, levofloxacin; and a rifamycin, rifabutin.

These antibiotics have been evaluated for the most part in first-choice therapies with PPI and amoxicillin rather than rescue therapies with a good success rate.

However, rifabutin is an antibiotic which can select resistance among Mycobacteria, so it must be used cautiously. *H. pylori* resistance to rifabutin may occur but is rare.

Many studies have included levofloxacin and led to good eradication rates<sup>75, 76</sup>. Unfortunately none of them tested for fluoroquinolone susceptibility. One can assume that the strains were susceptible. Recent data showed that levofloxacin resistance reached 20% in some areas and can result in eradication failure.

Due to the variety of clinical situations and antibiotics available in different countries, no specific recommendation was given for third choice therapy except to perform susceptibility testing.

Culture for the management of *H. pylori* infection has been neglected for a long time, despite the fact that several studies have shown that higher eradication rates are obtained when antibiotics are chosen based on susceptibility testing versus choosing empirically<sup>73,77, 78</sup>. This may be a cost-effective approach<sup>79</sup>. The high impact of clarithromycin resistance led to the proposal to perform culture and antimicrobial susceptibility testing when the resistance rate reaches 15-20%. Culture and sensitivity may help in decision making after failure of second choice therapy. We recommend that monitoring of primary antibiotic resistance be carried out in different regions in order to appreciate the risk of failure linked to antimicrobial resistance.

**Recommendation:** Rescue therapy should be based on antimicrobial susceptibility testing.

### PREVENTION OF GASTRIC CANCER

Gastric cancer is a major public health issue and the global burden of gastric cancer is increasing particularly in developing countries. *H. pylori* infection is the major cause of chronic gastritis, a condition that initiates the pathogenic sequence of events leading to atrophic gastritis, metaplasia, dysplasia and subsequently cancer. Pooled analyses of prospective sero-epidemiological studies have shown that individuals with *H. pylori* infection are at a statistically significant increased risk of developing non-cardiac gastric cancer<sup>80</sup>. It is also well established that both the intestinal and diffuse histological types of gastric cancer, are significantly associated with the *H. pylori* infection. Non-randomised clinical follow-up studies in Japan have shown that gastric cancers rates were significantly higher in patients with *H. pylori* infection than those in whom the infection was eradicated<sup>81</sup>. Metachronous tumour rates were also higher in those with persisting infection than those without, after endoscopic resection for early gastric cancer<sup>82</sup>.

Furthermore, follow-up studies in Sweden and Denmark of patient cohorts undergoing hip replacement procedures show statistically significantly lower rates of gastric cancer. This be explained by high doses of prophylactic antibiotics incidentally eradicating *H. pylori* infection.<sup>83</sup> 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. Determining the *cagA* status in *H. pylori* infection may confer additional benefit in identifying populations at greater risk for gastric cancer<sup>84</sup>. IL1 gene cluster polymorphisms are associated with a higher risk of hypochlorhydria (Odds Ratio = 9.1), and of gastric cancer (Odds Ratio = 1.9)<sup>52</sup>. Potential extrinsic and intrinsic factors in gastric carcinogenesis include: hereditary / family history, both direct and indirect (social inheritance); autoimmune (*H. pylori* may trigger the onset of autoimmune atrophic gastritis {AAG} in some patients with pernicious anemia; in diabetes type I, AAG is frequent and rarely associated with *H. pylori* infection); environmental (occupational exposure / nitrate / nitrite / nitroso-compounds); nutritional (salt, pickled food red meat, smoking); general (low socio-economic status, geography); pharmacological (gastric acid inhibition)<sup>85-90</sup>. All these lines of evidence suggest that bacterial virulence factors, host genetic factors, and environmental factors contribute to the risk of developing gastric cancer<sup>91</sup>. *H. pylori* eradication prevents development of pre-neoplastic changes (atrophic gastritis and intestinal metaplasia) of the gastric mucosa<sup>92-94</sup>. Evidence that *H. pylori* eradication may reduce the risk of gastric cancer is based on non-randomized controlled studies in animal and humans<sup>95, 96</sup>. Several randomized control studies show regression of pre-cancerous lesions or, at least, a decrease of progression as compared to control groups after *H. pylori* eradication<sup>97</sup>. One randomized control did not demonstrate reduction of cancer incidence at five years but showed a significant reduction in the group without pre-neoplastic lesions<sup>98</sup>. 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, 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<sup>96-99</sup>. Thus, new therapies are desirable for a global strategy of gastric cancer prevention

## Footnotes

- 1) The meeting was made possible by generous grants offered by Altana, AstraZeneca, Janssen Cilag, Takeda and Malesci (main sponsor for the local event).
- 2) Extracts in abstract form and comments have been published in Italian language. Short extracts published in GI Forefront, based on a presentation to the Japanese Society of Gastroenterology and an European short version release.
- 3) Since the Maastricht conference new additional literature was published in support of the recommendations and statements, and are included for updating of the manuscript.

Table 1. Grades of scientific evidence supporting the recommendations formulated in the Maastricht III-2005 Consensus Report

<b>Grade of recommendation</b>	<b>Evidence level</b>		<b>Type of studies</b>
A	1	1a	Systematic review of randomized controlled (RCT) of good methodological quality and with homogeneity
		1b	Individual RCT with narrow Confidence Interval
		1c	Non-controlled studies
B	2	2a	Systematic review of cohort studies (with homogeneity)
		2b	Individual cohort study (including low quality RCT, eg <80% follow-up)
		2c	Non-controlled cohort studies/Ecologic studies
	3	3a	Systematic review of case control studies (with homogeneity)
		3b	Individual case control study
C	4		Case series/Poor quality cohort or case control studies
D	5		Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"

Table 2. Strong recommendations for *Helicobacter pylori* eradication already considered in the Maastricht II-2000 Consensus Report.

Recommendation ( <i>H. pylori</i> positive)	Level of scientific evidence	Grade of recommendation
DU/GU (active or not, including complicated PUD)	1a	A
MALToma	1c	A
Atrophic gastritis	2a	B
Post gastric cancer resection	3b	B
Patients who are first degree relatives of gastric cancer patients	3b	B
Patients wishes (after full consultation with their physician)	5	D

Table 3. Recommendations for *Helicobacter pylori* eradication formulated in the Maastricht III-2005 Consensus Report, with levels of scientific evidence and grades of recommendation

Recommendations	Level of Evidence	Grade of Recommendation
<i>H. pylori</i> eradication is an appropriate option for patients infected with <i>H. pylori</i> and investigated non ulcer dyspepsia.	1a	A
<i>H. pylori</i> test and treat is an appropriate option for patients with uninvestigated dyspepsia.	1a	A
The effectiveness of <i>H. pylori</i> test and treat is low in populations with a low <i>Helicobacter pylori</i> prevalence. In this situation the test and treat strategy or empirical acid suppression are appropriate options.	2a	B
<i>H. pylori</i> eradication does not cause GORD.	1b	A
- <i>H. pylori</i> eradication does not affect the outcome of PPI therapy in patients with GORD in western populations. - Routine testing for <i>Helicobacter pylori</i> is not recommended in GORD; - <i>H. pylori</i> testing should be considered in patients on long-term maintenance therapy with PPIs*	1b 1b 2b	A A B
There is a negative association between the prevalence of <i>H. pylori</i> and GORD in Asia but the nature of this relationship is uncertain.	2b	B
In patients on long term NSAIDs and peptic ulcer and/or ulcer bleeding, PPI maintenance therapy is superior to <i>H. pylori</i> eradication in preventing ulcer recurrence and/or bleeding.	1b	A
<i>H. pylori</i> eradication is of value in chronic NSAID users but is insufficient to completely prevent NSAID-related ulcer disease.	1b	A
In naïve NSAID users, <i>H. pylori</i> eradication may prevent peptic ulcer and or bleeding.	1b	A

Table 4. Recommendations for diagnosis of *Helicobacter pylori* formulated in the Maastricht III Consensus Report, with levels of scientific evidence and grades of recommendation

Recommendations	Level of Evidence	Grade of Recommendation
The non-invasive tests that can be used for the test and treat strategy are UBT and the stool antigen tests. Certain kits for serology with high accuracy can also be applied.	1a	B
PPI is a source of false negative diagnostic tests except serology. PPI should be stopped for at least 2 weeks before performing a diagnostic test..	1b	A
Serology should be considered as a diagnostic test when other diagnostic tests could be false negative such as in patients with bleeding ulcers, gastric atrophy, MALT lymphoma and recent or current use of PPI and antibiotics..	2	B
The serological tests are not all equivalent and different tests may be applied in different situations.	2b	B
The detection of specific <i>H. pylori</i> antibodies in urine and saliva has no current role in patient management but can be helpful for epidemiological studies especially in children.	1b	A
Serology based near doctor-patient tests has no current role in the management of <i>H. pylori</i> infection.	1	A
The detection of <i>H. pylori</i> pathogenic factors and the study of host genetic polymorphisms is not helpful in the management of <i>H. pylori</i> infection.	3b	D
It is recommended that a follow-up evaluation to confirm successful eradication be performed after <i>H. pylori</i> eradication with UBT if available. If not available a laboratory-based stool test, preferably using monoclonal antibodies, could be used.	1b	A
Culture and antimicrobial sensitivity testing should be routinely performed – before clarithromycin-based treatment, if primary resistance to clarithromycin is greater than 15-20% in the respective area – after 2 treatment failures with different antibiotics. Monitoring of primary antibiotic resistance should be carried out in reference laboratories in different areas.	1b	B
In patients presenting for endoscopy without pre-treatment, a positive rapid urease test (RUT) is sufficient to initiate therapy.	2	A
There is a small advantage in using PPI CA or M for 14 days rather than 7 days, (evidence level 1a);	1a/5	A/D

Table 5. Recommendations of treatment for cure of *Helicobacter pylori* infection formulated in the Maastricht III Consensus Report, with levels of scientific evidence and grades of recommendation

Statement	Level of Evidence	Grade of Recommendation
The threshold of clarithromycin resistance at which empirical use of this antibiotic should be abandoned or pre-treatment clarithromycin susceptibility testing performed is 15-20%	1a	A
Testing for metronidazole susceptibility is not routinely necessary in the management of <i>H. pylori</i> infection. Metronidazole susceptibility testing needs further standardisation before it can be recommended..	1a-c	A
There is a small advantage of using PPI-clarithromycin-metronidazole combination instead of PPI-clarithromycin-amoxicillin as the first-choice treatment.	1a	A
- PPI-clarithromycin-amoxicillin or metronidazole therapy remains the recommended first-choice therapy in populations with less than 15-20% clarithromycin resistance prevalence. In populations with less than 40% metronidazole resistance prevalence PPI-clari-metro is preferable. – Quadruple therapies are alternative first-choice therapies.		
The same first-choice <i>H. pylori</i> therapies are recommended worldwide although different doses may be appropriate.	1b	A
- Bismuth-based quadruple therapies remain the best second-choice therapy, if available. If not, PPI amoxicillin or tetracycline and metronidazole are recommended..		
The rescue therapy should be based on antimicrobial susceptibility testing.	2c	B

Table 6. Statements concerning the relation between *Helicobacter pylori* and gastric cancer formulated in the Maastricht III-2005 Consensus Report, with levels of scientific evidence **and grades of recommendation**

Statement	Level of Evidence	Grade of Recommendation *1
The global burden of gastric cancer is increasing predominantly in developing countries.		A
<i>H. pylori</i> infection is the most common proven risk factor for human non-cardia gastric cancer.		A
The risk for gastric cancer development depends on bacterial virulence factors.		A
The risk for gastric cancer development depends on host genetic factors.		B
Environmental factors contribute to the risk of gastric cancer..		A
Evidence for <i>H. pylori</i> as important factor for gastric cancer development is shown by experimental animal models.		B
Eradication of <i>H. pylori</i> prevents development of pre-neoplastic changes of the gastric mucosa.	1b	A
Eradication of <i>H. pylori</i> has the potential to reduce the risk of gastric cancer development.	1c	B
The optimal time to eradicate <i>H. pylori</i> is before pre-neoplastic conditions (atrophy, intestinal metaplasia) are present, probably in early adulthood.	1b	A
<i>H. pylori</i> eradication for gastric cancer prevention is cost effective in economic analyses. Feasibility studies are required to evaluate further the benefits and risks of this strategy.	*2	B
The potential for gastric cancer prevention on a global scale is restricted by currently available therapies.	1b	A
New therapies are required for a global strategy of eradication to prevent gastric cancer.		A
<i>H. pylori</i> eradication for gastric cancer prevention in populations at risk should be evaluated and considered.	2a	B

\*1 grade of recommendation differs for some statements from the criteria presented in table 1, because the expert group interpreted the study results in a different way, or more studies on the same topic had conflicting results

\*2 Cost-analysis studies currently available are based on different economic models and scenarios.**REFERENCES**

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#### Participants to the conference

Andersen, Leif, Copenhagen, Denmark

Atherton, John, Nottingham, UK  
Asaka, Masahiro, Sapporo, Japan  
Bazzoli, Franco, Bologna, Italy  
Bytzer, Peter, Glostrup, Denmark  
Chan, Francio, Shatin, HongKong  
Coelho, Luiz Gonzaga Vaz, Belo Horizonte, Brazil  
de Wit, Niek, Utrecht, The Netherlands  
Delchier, Jean Charles, Paris, France  
Di Mario, Francesco, Padova, Italy  
El-Omar, Emad, Aberdeen, UK  
Fock, Kwong Ming, Singapore  
Forman, David, Leeds, UK  
Fujioka, Toshio, Oita, Japan  
Gasbarrini, Giovanni, Roma, Italy  
Genta, Robert, Geneva, Switzerland  
Goh, KL, Kuala Lumpur, Malaysia  
Graham, David Y., Houston, Texas, USA  
Hirschl, Alexander, Wien, Austria  
Hungin, Pali, Durham, UK  
Hunt, Richard, Ontario, Canada  
Isakov, Vassili A., Moscow, Russia  
Jones, Roger, London, UK  
Kist, Manfred, Freiburg, Germany  
Koletzko, Sibylle, München, Germany  
Kuipers, Ernst J., Amsterdam, The Netherlands  
Kupcinskis, Limas, Kaunas, Lithuania  
Ladas, Spiros, Athens, Greece  
Lanas, Angel, Zaragoza, Spain  
Machado, Jose, Porto, Portugal  
Malferteiner, Peter, Magdeburg, Germany  
McColl, Kenneth E. L., Glasgow, Scotland, UK  
Mégraud, Francio, Bordeaux, France  
Michetti, Pierre, Lausanne, Switzerland  
Moayyedi, Paul, Hamilton, Canada  
O'Morain, Colm, Dublin, Ireland  
Pilotto, Alberto, Vicenza, Italy  
Quina, Mario, Lisboa, Portugal  
Rokkas, Theodore, Athens, Greece  
Sharma, Patreek, Missouri, USA  
Simsek, Ylkay, Izmir, Turkey  
Sipponen, Pentti, Espoo, Finland  
Sollano, J., Manila, Philippines  
Stockbrügger, Reinold, Maastricht, The Netherlands  
Sugano, Kentaro, Yakushiji Tochigi, Japan  
Vaira, Dino, Bologna, Italy  
Vakil, Nimish, Milwaukee, WI, USA  
Vieth, Michael, Bayreuth, Germany  
Xiao, Shudong, Shanghai, China