Aliment Pharmacol Ther 2002; 16: 167–180.

Current concepts in the management of Helicobacter pylori *infection—The Maastricht 2-2000 Consensus Report*

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Accepted for publication 10 September 2001

SUMMARY

Significant progress and new insights have been gained in the 4 years since the first Maastricht Consensus Report, necessitating an update of the original guidelines. To achieve this, the European Helicobacter Pylori Study Group organized a meeting of specialists and experts from around the world, representatives from National Gastroenterology Societies and general practitioners from Europe to establish updated guidelines on the current management of *Helicobacter pylori* infection. The meeting took place on 21–22 September 2000.

A 'test and treat' approach is recommended in adult patients under the age of 45 years (the age cut-off may vary locally) presenting in primary care with persistent dyspepsia, having excluded those with predominantly gastro-oesophageal reflux disease symptoms, non-steroidal anti-inflammatory drug users and those with alarm symptoms. Diagnosis of infection should be by urea breath test or stool antigen test.

As in the previous guidelines, the eradication of *H. pylori* is strongly recommended in all patients with peptic ulcer, including those with complications, in those with low-grade gastric mucosa-associated lymphoid tissue lymphoma, in those with atrophic gastritis and following gastric cancer resection. It is also strongly recommended in patients who are first-degree relatives of gastric cancer patients and according to patients' wishes after full consultation.

It is advised that *H. pylori* eradication is considered to be an appropriate option in infected patients with functional dyspepsia, as it leads to long-term symptom improvement in a subset of patients. There was consensus that the eradication of *H. pylori* is not associated with the development of gastro-oesophageal reflux disease in most cases, and does not exacerbate existing gastro-oesophageal reflux disease. It was agreed that the eradication of *H. pylori* prior to the use of non-steroidal anti-inflammatory drugs reduces the incidence of peptic ulcer, but does not enhance the healing of gastric or duodenal ulcer in patients receiving antisecretory therapy who continue to take non-steroidal anti-inflammatory drugs.

Treatment should be thought of as a package which considers first- and second-line eradication therapies together. First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. Second-line therapy should use quadruple therapy with a proton pump inhibitor, bismuth, metronidazole and tetracycline. Where bismuth is not available, second-line therapy should be with proton pump inhibitor-based triple therapy.

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If second-line quadruple therapy fails in primary care, patients should be referred to a specialist. Subsequent failures should be handled on a case-by-case basis by the specialist. In patients with uncomplicated duodenal ulcer, eradication therapy does not need to be followed by further antisecretory treatment. Successful eradication should always be confirmed by urea breath test or an endoscopy-based test if endoscopy is clinically indicated. Stool antigen test is the alternative if urea breath test is not available.

INTRODUCTION

European guidelines on the management of *Helicobacter pylori* infection were published by the European Helicobacter Pylori Study Group (EHPSG) following a consensus meeting held in Maastricht in 1996,[1] and guidelines have also been developed subsequently in a number of regions around the world.[2–6] Significant progress and new insights have been gained in the 4 years since the first Maastricht meeting, including the results of studies conducted in an effort to answer some of the questions raised by the meeting. These new data necessitated an update of the original guidelines on the management of *H. pylori* infection. To achieve this, the EHPSG organized a multidisciplinary meeting of experts in the field, again held in Maastricht, The Netherlands.

The aim of the Maastricht 2-2000 Workshop was to revisit and update the original Maastricht guidelines, taking into account advances in our understanding of *H. pylori*, its role in disease pathology and new insights into the management of the infection. The adoption of *H. pylori* eradication therapy has broadened greatly since the original Maastricht Consensus Report, but confusion remains, particularly in primary care, over the management of *H. pylori* infection, the indications for eradication of the bacterium and the regimens that should be used to achieve this. This has been confirmed through research conducted among primary care physicians by specialist gastroenterologists.[7–9] An aim of the Maastricht 2-2000 Workshop was thus to provide practical management guidelines that are applicable across clinical practice, both in primary care and at the specialist level. A central element of this was to define who to treat and how to treat. The Maastricht 2-2000 Workshop also addressed *H. pylori* infection as a public health care issue, taking into account new epidemiological trends identified for the bacterium.

In addition, recommendations are included on the management of *H. pylori* infection in children, based on a previous consensus meeting organized by the EHPSG and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).[10]

STRUCTURE OF THE MEETING

The Maastricht 2-2000 Consensus Meeting involved 76 participants from 28 countries. The participants comprised specialists and experts from around the world, representatives from National Gastroenterology Societies and included primary care physicians from Europe.

Updates and perspectives on *H. pylori* guidelines around the world were given by participants from Africa, Asia/Australia, Japan and North and South America. These were followed by a series of reviews of the latest knowledge in specific areas, focusing on the management of *H. pylori* infection in primary care and the indications for eradication therapy. Four working groups each then focused on an individual area:

- *H. pylori* diagnosis and eradication in primary care;
- indications for eradication therapy;
- therapy and management of resistance;
- prevention of cancer and other *H. pylori*-related gastroduodenal pathologies.

Each workshop group formulated a series of consensus statements and recommendations according to a standard template. For each one, the strength of the recommendation was made at one of three levels: 1, strongly recommended; 2, advisable; 3, uncertain. The strength of the evidence supporting the recommendation was ranked according to one of five levels (1, well-designed and appropriately controlled studies; 2, well-designed cohort or case-controlled studies, somewhat flawed studies or persuasive indirect evidence; 3, case reports, seriously flawed studies or suggestive

indirect evidence; 4, clinical experience; 5, insufficient evidence to form an opinion).

Each workshop then reported their recommendations to the meeting for discussion, giving the rationale for the statement or recommendation, and overall consensus statements were agreed by voting. Agreement with the statement or recommendation by over 70% of the participants was used as the cut-off for consensus. In some circumstances, where 70% agreement was not achieved, statements were rephrased to reach this level of consensus.

PATIENT MANAGEMENT IN PRIMARY CARE

The majority of patients infected with *H. pylori* present initially in primary care, suffering from dyspeptic symptoms with or without alarm symptoms. This is where many of them can and should be treated for the infection, even though, in the absence of endoscopy, the primary care physician may not have an accurate diagnosis of the underlying disease pathology.

A further consideration is the increasing media, and hence patient, awareness of *H. pylori*, and its relationship to diseases such as gastric cancer. In this environment, primary care physicians need to have a clear understanding of the major role that they play in the management of the infection. The recommendations given here are particularly relevant to management in primary care, but many of them apply across clinical practice. The key management strategies in primary care are summarized in Table 1. The specific indications for *H. pylori* eradication are discussed in a later section, but two strongly recommended indications (Table 2) which should be noted here as particularly relevant in primary care are patients who are first-degree relatives of gastric cancer patients and eradication therapy in response to patients' wishes after full consultation.

Table 1. Summary of the key management strategies for *Helicobacter pylori* infection in primary care

Key management strategies in primary care
• A 'test and treat' approach should be used in adult patients under the age of 45 years (the age cut-off may vary locally) with persistent dyspepsia, having excluded those with predominantly GERD symptoms, NSAID users and patients with alarm symptoms
• Diagnosis of infection should be by urea breath test or stool antigen test
• Always test for successful eradication, by urea breath test or endoscopy-based test if endoscopy is clinically indicated. Stool antigen test is the alternative if urea breath test is not available
• In uncomplicated duodenal ulcer patients, eradication therapy does not need to be followed by further antisecretory treatment
• A 'search and treat' strategy is recommended for peptic ulcer patients on long-term and intermittent antisecretory therapy

GERD, gastro-oesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug.

Table 2. Strongly recommended indications for *Helicobacter pylori* eradication therapy and the strength of the supporting evidence

Indication (*H. pylori*-positive)	Strength of the supporting evidence
Peptic ulcer disease (active or not, including complicated ulcer)	1
MALToma	2
Atrophic gastritis	2
Post-gastric cancer resection	3
Patients who are first-degree relatives of gastric cancer patients	3
Patients' wishes (after full consultation with their physician)	4

MALToma, mucosa-associated lymphoid tissue lymphoma.

Whom to treat

As recommended in the original Maastricht Consensus Report, a 'test and treat' approach should be offered to adult patients under the age of 45 years (the age cut-off may vary locally according to the mean age of gastric cancer onset) presenting in primary care with persistent dyspepsia. Several studies have since been published which support this recommendation.[11–14] Patients presenting predominantly with gastro-oesophageal reflux disease (GERD) symptoms, such as heartburn and regurgitation, non-steroidal anti-inflammatory drug (NSAID) users and patients with alarm symptoms should be excluded first. Alarm symptoms and signs requiring prompt endoscopic investigation include unexplained weight loss, dysphagia, recurrent vomiting, digestive bleeding or anaemia, abnormal physical examination, malabsorption and concomitant disease with possible digestive involvement.

In practice, primary care physicians need to be prepared for the fact that, when applying a 'test and treat' strategy for dyspepsia patients, a significant

proportion may return with symptoms following the successful eradication of *H. pylori*. For example, despite excluding patients with predominant GERD symptoms, patients may return presenting with heartburn, but such symptoms may have existed before eradication therapy, masked by more severe symptoms such as epigastric pain.

The 'test and treat' approach is recommended exclusively for the dyspeptic patient under 45 years of age. The recommendation is advisable, based on level 2 scientific evidence. The strategy is effective, saves health care resources and is safe if properly adopted in areas where there is a low prevalence of gastric malignancy in the defined age group.[13, 15] A 'test and scope' approach is an alternative strategy that has been proposed, but it has not been shown to have any advantage over immediate endoscopy.[16] The prevalence of *H. pylori* infection and the waiting time for endoscopy are factors in the choice between 'test and treat' and immediate endoscopy. In patients under 45 years of age, initially managed without endoscopy, failure of eradication therapy or relapse of symptoms requires investigation.[11]

'Search and treat' for peptic ulcer disease

A 'search and treat' strategy is strongly recommended for peptic ulcer disease patients on long-term and intermittent antisecretory therapy, whereby patients are identified and given *H. pylori* eradication therapy. This is a particularly relevant recommendation in primary care. It is based on level 3 evidence, which shows cost-effectiveness benefits which accrue over time due to the discontinued use of antisecretory therapy following cure of the ulcer.[7, 8, 17]

Diagnosis of H. pylori *infection*

Inherent in a 'test and treat' approach is the need for a reliable, non-invasive diagnosis of *H. pylori* infection. For the diagnosis of the infection in primary care, it is strongly recommended that a urea breath test or stool antigen test be used.[18, 19] This is based on level 1 supporting evidence regarding the value of the two procedures, although such strong evidence is not specifically available in the primary care setting.

Enzyme-linked immunoabsorbent assay serology may be used as an alternative for diagnosis prior to treatment, but is inferior and requires local validation for appropriate accuracy. So far, whole blood tests and office-based serology tests have not reached acceptable accuracy for the diagnosis of *H. pylori* infection in primary care (level of evidence, 1).[20–22] In developing countries, the accessibility and cost of the urea breath test and stool antigen test are recognized problems, but such countries usually have a high prevalence of *H. pylori* infection, making laboratory serology a satisfactory alternative.

Confirmation of H. pylori *eradication following treatment*

It was recommended as advisable, based on level 2 evidence, that *H. pylori* eradication should be confirmed by urea breath test, which is the recommended first-line post-treatment diagnostic test.[23] If urea breath testing is not available, a stool antigen test is the alternative.[24, 25] Serology is an inappropriate means of determining cure of infection. Testing should be performed in all treated patients after a minimum of 4 weeks. Antisecretory drugs, and proton pump inhibitors in particular, should be discontinued for at least 1 week prior to the assessment of *H. pylori* status.

Confirmation of *H. pylori* eradication following treatment is recommended as it reassures the patient and provides confirmation that the risk of complications has been removed if eradication has been successful. Additionally, it facilitates the direction of any further management on an individual basis, be it re-treatment in the case of treatment failure, or switch to symptomatic therapy.

In the specialist setting, *H. pylori* eradication can be confirmed by a biopsy-based test as endoscopy is clinically indicated anyway in complicated duodenal ulcer, gastric ulcer, low-grade gastric mucosa-associated lymphoid tissue lymphoma and local resection of early gastric cancer. If endoscopy is clinically indicated, obtaining biopsy specimens from the body and antrum for histology and culture is recommended to exclude persistent infection.

PATIENT MANAGEMENT BY THE SPECIALIST

The role of the specialist is to handle all those patients referred from primary care because they are outside the recommendations above for the 'test and treat' strategy, for example because of alarm symptoms, or because

they are not managed by the strategy. Additionally, the specialist should manage patients presenting with complications such as acute gastrointestinal bleeding.

WHOM TO TREAT — THE INDICATIONS FOR *H. PYLORI* ERADICATION THERAPY

All the indications for *H. pylori* eradication strongly recommended in the first Maastricht Consensus Report were reinforced as strongly recommended at Maastricht 2-2000 (Table 2), and the reader is referred to the original guidelines for the rationale for these recommendations.[1] The recommendation to eradicate *H. pylori* in patients with peptic ulcer disease includes active and inactive disease, complicated disease and following gastric surgery for peptic ulcer.

H. pylori eradication is also strongly recommended in *H. pylori*-positive patients with low-grade mucosa-associated lymphoid tissue lymphoma, although subsequent lifelong surveillance is needed.[26–30] Individual patients with *H. pylori*-positive high-grade mucosa-associated lymphoid tissue lymphoma should undergo *H. pylori* eradication as first-line treatment.

Atrophic changes in the gastric mucosa are associated with an increased risk for possible progression to gastric cancer,[31, 93] and therefore this condition requires intervention by the eradication of *H. pylori*,[32] although there is no proof that progression to neoplasia occurs.

In addition, *H. pylori* eradication is now strongly recommended in infected patients who are first-degree relatives of gastric cancer patients, and in *H. pylori*-positive patients who wish to receive eradication therapy following full consultation with their physician. Although it has not been proven that the eradication of *H. pylori* will result in protection against gastric cancer in first-degree relatives of gastric cancer patients, this group is at a significantly higher risk than the general population.[33–37] Patients who are aware and concerned about the risks of *H. pylori* infection should be reassured and treated, but only after being given complete information, including the potential side-effects associated with current eradication therapies.

The relevance of *H. pylori* infection and the value of its eradication were considered in further disease areas, and the resultant statements, levels of recommendation and strength of supporting evidence are summarized in Table 3. Their basis is discussed in more detail in the following text.

H. pylori *and functional dyspepsia*

The recommendations in dyspepsia patients presenting in primary care have been addressed earlier. Additionally, *H. pylori* eradication is an advisable option in infected patients with functional (non-ulcer) dyspepsia. This was a controversial indication for which conflicting data were presented, and it was debated extensively. The recommendation is based on level 2 evidence, demonstrating that such intervention leads to long-term symptom improvement in a small subset of patients, even when negative results are taken into account.[38–44]

A recent meta-analysis has assessed all the relevant randomized controlled trials in functional dyspepsia available to date, with the main outcome measure being the relative risk reduction for remaining dyspeptic symptoms. The relative risk reduction at 12 months with *H. pylori* eradication was 9% compared with placebo, and economic modelling suggests that this will be cost-effective.[38] These results were robust under sensitivity analysis. It should be stressed, though, that the recommendation to eradicate *H. pylori* in patients with functional dyspepsia is made with the understanding that the likelihood of a symptomatic benefit is likely to be modest, with the recent meta-analysis indicating that 15 infected patients need to be treated to cure one case of non-ulcer dyspepsia.[38] However, such a response rate of 10% or less is equivalent to any other therapy available for functional dyspepsia, including antisecretory and antinociceptive therapies.[45, 46] In addition, the eradication of *H. pylori* is a one-off treatment which also removes a risk factor for subsequent peptic ulcer disease, atrophic gastritis and gastric cancer.

H. pylori *and GERD*

H. pylori eradication does not exacerbate pre-existing GERD[47–51] and, in most subjects, the eradication of the bacterium is not associated with the development of GERD, although there is a suggestion that patients with predominant corpus gastritis could be at risk.[52, 53] However, even in conditions with predominant corpus gastritis, such as gastric ulcer, there has been shown to be no increased risk of heartburn following *H. pylori* eradication.[54] These statements, based on level 3 evidence, are important as, to date, there has been confusion in this area, and concern that *H. pylori* eradication may cause or exacerbate GERD has limited

Table 3. Recommended indications for *Helicobacter pylori* eradication therapy, and related statements, in further disease areas, the level of the recommendation and the strength of the supporting evidence

Disease area	Level of the recommendation or statement	Strength of the supporting evidence
H. pylori-positive functional dyspepsia		
H. pylori eradication is an appropriate option	Advisable	2
This leads to long-term symptom improvement in a subset of patients	Strong	2
GERD		
H. pylori eradication:		
Is not associated with GERD development in most cases	Strong	3
Does not exacerbate existing GERD	Advisable	3
H. pylori should be eradicated, though, in patients requiring long-term profound acid suppression	Advisable	3
NSAIDs		
H. pylori eradication:		
Reduces the incidence of ulcer given prior to NSAID use	Advisable	2
Alone is insufficient to prevent recurrent ulcer bleeding in high-risk NSAID users	Strong	2
Does not enhance healing of gastric or duodenal ulcers in patients receiving antisecretory therapy who continue to take NSAIDs	Strong	1
H. pylori and NSAIDs/aspirin are independent risk factors for peptic ulcer disease	Advisable	2

GERD, gastro-oesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug.

its use in some instances. These concerns are now known to be largely unfounded, and should not prevent the adoption of *H. pylori* eradication therapy in appropriate patient groups.

However, in GERD patients who are in need of long-term acid suppressive therapy, *H. pylori* should be tested for and eradicated. This is an advisable recommendation based on level 3 evidence, which suggests that long-term profound acid suppression may accelerate the progression of *H. pylori*-induced corpus atrophic gastritis,[55–58] although not all studies agree.[59] The mechanisms contributing to accelerated progression of atrophic changes may include overgrowth of other bacteria, reduction in reactive oxygen metabolite scavengers and nitrosamine formation.

H. pylori *and NSAIDs*

The relationship between *H. pylori* and NSAIDs/aspirin in peptic ulcerogenesis is complex. The consensus meeting concluded that *H. pylori* and NSAIDs/aspirin are independent risk factors for peptic ulcer and peptic ulcer bleeding, based on level 2 evidence, and, additionally, that NSAIDs should be considered separately from aspirin in this respect.[60, 61]

Results with *H. pylori* eradication in NSAID users are conflicting, although one possible explanation is that differences between studies may relate to whether eradication therapy is given before or after NSAID use, and whether it is given when there are active ulcers or as a preventative measure. Maastricht 2-2000 recognized that *H. pylori* eradication reduces the incidence of peptic ulcers and concomitant symptoms when given prior to NSAID use.[62, 63] However, *H. pylori* eradication does not enhance the healing of gastric or duodenal ulcers in patients receiving antisecretory therapy who continue to take NSAIDs.[64–67] *H. pylori* eradication is advisable if NSAID therapy is planned in order to eliminate the infection as a confounding explanation of subsequent peptic ulcers and dyspeptic symptoms.

In patients with a history of peptic ulcer disease who are on low-dose aspirin, testing for *H. pylori* and eradication were recommended as advisable based on level 2 evidence. However, this was based on only a

single study which showed a benefit in patients with previous bleeding complications.[68] In any case, aspirin should be kept to a minimum dose in these patients. In high-risk users of NSAIDs, *H. pylori* eradication alone is insufficient to prevent recurrent ulcer bleeding,[68] and therefore long-term proton pump inhibitor therapy is needed. The relationship between cyclooxygenase-1, cyclooxygenase-2 and *H. pylori* at the mucosal level is unknown and requires investigation.

Management of H. pylori*-negative peptic ulcer*

There is debate as to the clinical significance of non-*H. pylori*- or non-NSAID-associated peptic ulcers, and their prevalence may vary in different parts of the world.[69] In *H. pylori*-negative duodenal and gastric ulcer, after ensuring that the *H. pylori* status is negative by multiple tests including serology, and ruling out NSAID use, the patient should have a blood test to exclude Zollinger–Ellison syndrome and systemic diseases which can be associated with peptic ulcer (i.e. mastocytosis and others). Any *H. pylori*-negative peptic ulcer should be carefully investigated and other possible aetiologies should be excluded. Empirical antisecretory therapy is then recommended.

Other disease areas

It was strongly recommended that *H. pylori* eradication is in general not indicated for extra-alimentary disease, based on level 3 evidence.[70–73] It may be considered in patients with cardiovascular disease where there are no other recognizable risk factors, and in anaemia and thrombocytopenia after full investigation.

While gastric cancer was recognized as a major public health issue, it was recommended that the asymptomatic general population should not be screened for *H. pylori* infection. This important area is discussed in more detail later in the section which specifically addresses the prevention of cancer and other *H. pylori*-related gastroduodenal pathologies.

HOW TO TREAT — THERAPY AND MANAGEMENT OF RESISTANCE

- As identified in the original Maastricht Consensus Report, treatment regimens should be simple, well tolerated, easy to comply with and cost-effective (Figure 1).
- First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. This is a modification of the recommendations in the original Maastricht Consensus Report, following numerous studies demonstrating similar efficacy with regimens based on ranitidine bismuth citrate as with those based on a proton pump inhibitor.[74, 75]
- Subsequent second-line therapy should use quadruple therapy with a proton pump inhibitor, bismuth, metronidazole and tetracycline.
- Where bismuth is not available, second-line therapy should be with proton pump inhibitor triple therapy.

These were all strong recommendations, based on level 1 or 2 evidence.[76–79] Subsequent failures should be handled on a case-by-case basis. If second-line quadruple therapy fails in primary care, patients should be referred to enable specialist assessment, including antibiotic susceptibility testing. Careful provision of information to the patient is necessary to achieve optimal compliance, particularly with quadruple therapies, which are cumbersome, but necessary to maximize the chances of success with second-line therapy in the light of antibiotic resistance. Therapy should not be denied by age alone, as proton pump inhibitor triple therapies are effective in the elderly.[80]

The specific dose regimens are given in Figure 1. The doses of proton pump inhibitors and ranitidine bismuth citrate which are approved for use in triple therapy regimens for the eradication of *H. pylori* are b.i.d. esomeprazole (20 mg), lansoprazole (30 mg), omeprazole (20 mg), pantoprazole (40 mg), rabeprazole (20 mg) and ranitidine bismuth citrate (400 mg). All drugs should be used as available and within locally approved indications which may vary between products and countries.

The combination of a proton pump inhibitor (or ranitidine bismuth citrate) in a triple therapy regimen with clarithromycin and amoxicillin should be preferred as first-line therapy, rather than the use of clarithromycin and metronidazole. Although there is not strong evidence for this, the recommendation was based on the opinion of the majority of participants that avoiding metronidazole in first-line therapy would favour better results with subsequent second-line quadruple therapy,

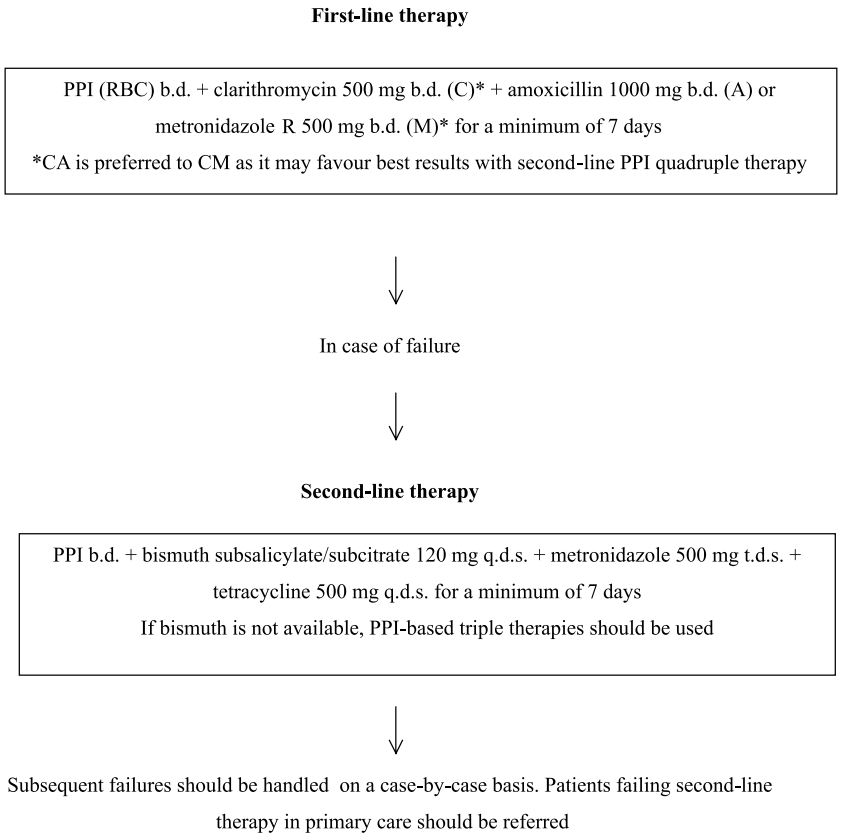

Figure 1. Summary of the recommended treatment strategy for the eradication of *Helicobacter pylori*. PPI, proton pump inhibitor; RBC, ranitidine bismuth citrate; R, metronidazole 400 mg, used adequately in many countries.

using metronidazole, in cases of treatment failure. This is a new principle guiding treatment in which it should be thought of as a 'treatment package' which considers first- and second-line eradication therapies together. When the clarithromycin–metronidazole combination is used, however, the lower dose of clarithromycin, 250 mg twice daily, is sufficient, but the variability of results appears to be less with 500 mg, which is therefore the recommended dose.[81] Amoxicillin should not be used in cases of penicillin allergy, while metronidazole should be avoided if alcohol consumption is an issue.

Looking to the future, *H. pylori*-specific antibiotics, probiotics and vaccines may become part of the armamentarium, but there are no practical recommendations at this stage.

Follow-up in uncomplicated duodenal ulcer

In uncomplicated duodenal ulcer patients, it is strongly recommended that *H. pylori* eradication therapy does not need to be followed by further antisecretory treatment, based on level 1 evidence, and this approach has recently been approved by the European regulatory authorities. The approval was based on a large, randomized, controlled trial which compared 1-week esomeprazole-based triple therapy, followed by placebo, with 1-week omeprazole-based triple therapy, followed by 3 weeks of omeprazole monotherapy, in patients with active duodenal ulcer.[82] Healing rates over 90% and similar control of symptoms were reported in both treatment arms.

Management of resistance

When proton pump inhibitor triple therapy is used as second-line therapy due to the unavailability of bismuth, the use of clarithromycin in this context should be based on susceptibility results. Patients failing second-line therapy should be managed in the specialist setting.

Routine testing for antibiotic susceptibility is not currently recommended. Implementation of resistance surveillance programmes is advisable as clarithromycin resistance affects the efficacy of first-line therapy.[83, 84]

In developing countries where resistance to metronidazole is usually at a very high level, furazolidone could be used.[85] Good eradication rates have been obtained

with this compound included in regimens and it has been recommended in the Latin American Consensus Conference.[5]

PREVENTION OF CANCER AND OTHER *H. PYLORI*-RELATED GASTRODUODENAL PATHOLOGIES

Gastric cancer is a major public health issue and *H. pylori* is an established aetiological factor for non-cardia gastric cancer. However, gastric cancer is a multifactorial disease and, although a substantial proportion of gastric cancer can be attributed to *H. pylori* infection, only a minority of infected subjects will develop gastric cancer. Additionally, there is a marked geographical variation in gastric cancer incidence and the risk associated with *H. pylori* infection, which is likely to be due to a combination of bacterial strain, host and environmental factors. All these were level 1 statements, based on level 2 evidence.[33, 36, 86–90] It was strongly recommended that the asymptomatic general population (other than in areas of high gastric cancer prevalence) should not be screened for *H. pylori* infection on the basis of a gastric cancer risk at present, based on level 3 evidence.

Development of LI intestinal type gastric cancer is a multistep process, proceeding from gastritis, through atrophy and intestinal metaplasia, to intestinal type carcinoma. Atrophic gastritis may improve on long-term follow-up after *H. pylori* eradication, which is thus strongly recommended in atrophic gastritis[32, 91–93] (Table 1), but intestinal metaplasia may not be reversible.[32, 94, 95] These statements are based on level 2 evidence. It should be noted that the diagnosis of atrophic gastritis can be observer dependent and this may be contributed to by sampling error.[96]

As discussed in the section on indications, *H. pylori* eradication is strongly recommended in patients who are first-degree relatives of gastric cancer patients and in infected patients who have early gastric cancer resection (Table 2). The recommendation in post-gastric cancer resection includes surgically resected stomachs, and there is a need for lifelong surveillance.[97]

H. PYLORI INFECTION IN CHILDREN

H. pylori infection is mainly acquired in childhood in both industrialized and developing countries, and persists throughout life unless treated. All the foregoing text and commentary relates to *H. pylori* infection in adults, but, for several reasons, guidelines developed for *H. pylori*-infected adults are not applicable to children.

In September 1998, a consensus conference was jointly organized by the EHPSG and an *H. pylori* working group of ESPGHAN. The consensus group consisted of paediatric gastroenterologists from 18 different European countries, and a number of other specialists, such as epidemiologists and microbiologists, working in the field. Statements on the indications for investigating children for *H. pylori* infection and on non-invasive tests in clinical practice were proposed, discussed and voted on. Publication of the meeting outcome was approved by all participants, presented to the council of ESPGHAN and published as a Medical Position Paper of the society.[10] The statements made in the Position Paper are in concordance with the consensus of the Canadian Helicobacter Study Group regarding *H. pylori* infection in children and adolescents,[98] and the conclusions have been summarized elsewhere.[99]

During the Maastricht 2-2000 Consensus Meeting, the final statements in the Position Paper were presented, voted on and accepted for inclusion in the Maastricht 2-2000 Consensus Report.

- In children, so far, there is no compelling evidence demonstrating a link between *H. pylori*-associated gastritis and abdominal pain or dyspeptic symptoms, except in those rare cases in which gastric or duodenal ulcer disease is present.
- In *H. pylori*-infected children with non-ulcer gastritis, treatment of the infection has no proven benefit in terms of symptom relief. Therefore, screening of children with dyspeptic symptoms for *H. pylori* infection with non-invasive tests is neither indicated nor recommended.
- Children should be investigated for *H. pylori* infection only when they present with symptoms or signs suggestive of organic disease which are severe enough to justify the risks of therapy.
- Upper gastrointestinal endoscopy with multiple biopsies is the optimal approach to investigation in children with upper digestive symptoms suggestive of organic disease, after exclusion of other causes (i.e. lactose maldigestion, coeliac disease, constipation, liver and biliary disease) with non-invasive methods.

- The urea breath test and stool antigen test are reliable in older children, but need further evaluation in younger children, especially in those less than 2 years of age.
- Serological tests for *H. pylori* infection are not reliable for use in children.
- Triple therapy using a proton pump inhibitor plus two antibiotics for 7–14 days is the treatment of choice in children. The higher antibiotic resistance rate against clarithromycin in *H. pylori* strains from children limits the efficacy.
- In children treated for *H. pylori* infection, the response to therapy should be monitored with a reliable non-invasive test.

It was emphasized that the main goals of *H. pylori* therapy in children are to heal peptic ulcer disease and to relieve symptoms. Therapy for the prevention of complications later in life (peptic ulcer disease or malignancy) in children with no or unspecific minor symptoms could be postponed to a later time when safer therapeutic options are available.

Antibiotic resistance in children

There are major concerns over the reports of increasing resistance against macrolides in *H. pylori* strains from children in different European countries (i.e. Belgium, France, Germany, Italy).[100] In children with double resistant strains, against clarithromycin and metronidazole, therapeutic options are limited as many second-line drugs (i.e. tetracycline, bismuth compounds, rifa butin, ciprofloxacin) are contraindicated or not released for use in children. The surveillance of the antibiotic susceptibility of *H. pylori* in the paediatric population is urgently required. In areas or populations with a high resistance rate against macrolides, an antibiogram prior to first therapy is recommended in *H. pylori*-infected children when clarithromycin is used as part of the treatment regimen.

ACKNOWLEDGEMENTS

The Maastricht 2-2000 Consensus Meeting was supported by an unrestricted educational grant from AstraZeneca, Byk Gulden, Janssen-Cilag and Takeda Chemical Industries. Special thanks to Dr Leodolter and Dr Peitz for scientific input and referencing, D. Marczak for secretarial support and T. Robinson for editorial work.

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APPENDIX

Participants in the Maastricht Consensus Meeting

Asaka M (Japan), Axon A (UK), Bazzoli F (Italy), Birkner B (Germany), Bureš J (Czech Republic), Burette A (Belgium), Bytzer P (Denmark), Castro L (Brazil), Culhane A (Ireland), de Boer W (The Netherlands), De Korwin J (France), De Koster E (Belgium), de Wit N (The Netherlands), Deltenre M (Belgium), Dent J (Australia), Di Mario F (Italy), Dragosics B (Austria), Färkkilä M (Finland), Forman D (UK), Freston J (USA), Gasbarrini G (Italy), Goh K (Malaysia), Graham D (USA), Hameeteman W (The Netherlands), Hawkey C (UK), Hirschl A (Austria), Hungin P (UK), Hunt R (Canada), Jaup B (Sweden), Jones R (UK), Kimura K (Japan), Kist M (Germany), Klotz P (France), Koletzko S (Germany), Kuipers E (The Netherlands), Labenz J (Germany), Ladas S (Greece), Lam SK (Hong Kong), Lauritsen K (Denmark), Lerang F (Norway), Lionis C (Greece), Loft D (UK), Louw J (South Africa), Malfertheiner P (Germany), McColl K (UK), Mégraud F (France), Mendonca-Santos J (Portugal), Michetti P (Switzerland), Misiewicz J (UK), Mössner J (Germany), Niv Y (Israel), Nowak A (Poland), O'Morain C (Ireland), Parajés-Garcia J (Spain), Pilotto A (Italy), Pounder R (UK), Quina M (Portugal), Rácz I (Hungary), Rauws E (The Netherlands), Rodrigo Saez L (Spain), Rokkas T (Greece), Segal

I (South Africa), Seifert B (Czech Republic), Sipponen P (Finland), Sjölundh C (Sweden), Solcia E (Italy), Stockbrügger R (The Netherlands), Sung J (Hong Kong), Surrenti C (Italy), Tulassay Z (Hungary), Tytgat G (The Netherlands), Unge P (Sweden), Vaira D (Italy), Vakil N (USA), Veldhuyzen van Zanten S (Canada), Wadström T (Sweden).

Educational grants were provided by AstraZeneca, Byk Gulden, Janssen and Takeda.