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Current view

Treatment of *H. pylori* infection: Current recommendations

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SUMMARY

***Helicobacter pylori (H. pylori)* was isolated twenty years ago, and since then a significant volume of literature concerning it's significance for gastric and extragastric pathology has been produced. The relevance of *H. pylori* infection and the value of its eradication in disease areas and the resultant statements with the corresponding level of recommendation, have been discussed in various consensus meetings. 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. 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 and therefore this condition requires intervention by the eradication of *H. pylori*, 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. 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.**

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Helicobacter pylori (H. pylori) was isolated twenty years ago, and since then a great amount of knowledge concerning it's significance for gastric and extragastric pathology has been gathered. The significant progress and the new insights into the management of *H. pylori* infection gained over these years were initially summarised in the European guidelines, published by the European Helicobacter Study Group (EHSG) following a consensus meeting held in Maastricht in 1996.[1] Subsequently guidelines were developed in a number of regions around the world.[2-6] In 2000 the Maastricht 2 Consensus meeting was again held in Maastricht in order to revisit and update the original Maastricht guidelines. The new guidelines, which among others included practical management recommendations, both in primary care and at the specialist level, were again published by the EHSG.[7] In this report recommendations were included on the management of *H. pylori* in children and this was based on a previous consensus meeting organised by the EHSG and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).[8]

The following current recommendations, on the management of *H. pylori* infection, were extracted mainly from the above mentioned consensus reports.

H. pylori *infection 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. The key management strategies in primary care, as discussed in the Maastricht 2-2000 Consensus Report,[7] are summarised as follows.

- A "test and treat" approach should be used in adult patients under the age of 45 years (the age cut-off

Table1. Strongly recommended indications for H. pylori eradication therapy.

Indication
• Peptic ulcer disease (active or not, including complicated ulcer)
• 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)

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.

When is eradication indicated?

All the main indications for *H. pylori* eradication, as strongly recommended at Maastricht 2-2000 Consensus Report[7], are shown in Table 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. 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[9,64] and therefore this condition requires intervention by the eradication of *H. pylori*,[10] 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

Table 2. Recommended indications for *H. pylori* eradication therapy and related statements, in disease areas other than those shown in Table 1 and the corresponding level of the recommendation.

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

relatives of gastric cancer patients, this group is at a significantly higher risk than the general population.[11-15] 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 in further disease areas and the resultant statements with the corresponding level of recommendation, as discussed in Maastricht 2-2000 Consensus meeting, are summarized in Table 2. According to this, *H. pylori* eradication is an advisable option in infected patients with functional (non-ulcer) dyspepsia. This is a controversial indication for which there are conflicting data, demonstrating that such intervention leads to long-term symptom improvement in a small subset of patients, even when negative results are taken into account.[16-22] A recent meta-analysis has assessed all the relevant randomized controlled trials in functional dyspepsia available, with the main outcome being the relative risk reduction for remaining dyspeptic symptoms. The relative risk at 12 months after *H. pylori* eradication was reduced to 9% compared with placebo, and economic modelling suggests that this will be cost-effective.[16] 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.[16] However, such a response rate of 10% or less is equivalent to any other therapy available for functional dyspepsia, including anti-secretory therapies.[23,24] 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 eradication does not exacerbate pre-existing GERD[25-29] 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.[30,31] 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.[32] 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, which suggests that long-term profound acid suppression may accelerate the progression of *H. pylori*-induced corpus atrophic gastritis,[33-36] although not all studies agree.[37] The mechanisms contributing to accelerated progression of atrophic changes may include overgrowth of other bacteria, reduction in reactive oxygen metabolite scavengers and nitrosamine formation.

The relationship between *H. pylori* and NSAIDs/aspirin in the pathogenesis of peptic ulcer disease is complex. The Maastricht 2-2000 consensus meeting concluded that *H. pylori* and NSAIDs/aspirin are independent risk factors for peptic ulcer and peptic ulcer bleeding, and, additionally, that NSAIDs should be considered separately from aspirin in this respect.[38,39] 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.[40,41] However, *H. pylori* eradication does not enhance the healing of gastric or duodenal ulcers in patients receiving antisecretory therapy who continue to take NSAIDs.[42-45] *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. However, this was based on only a single study, which showed a benefit in patients with previous bleeding complications.[46] 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,[46] 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.

H. pylori eradication is in general not indicated for extra-alimentary disease and this was strongly recommended in the Maastricht 2-2000 consensus meeting.[47-50] Eradication may be considered in patients with cardiovascular disease where there are no other recognizable risk factors, and in anaemia and thrombocytopenia after full investigation.

Treatment suggestions

The treatment of *H. pylori* infection can be likened

to the treatment of tuberculosis because multidrug regimens and an adequate length of treatment are needed to eradicate the organism. However, treatment regimens should be simple, well tolerated, easy to comply with and cost-effective.

First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. 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. 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.[51] 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. lansoprazole (30 mg), omeprazole (20 mg), pantoprazole (40 mg), rabeprazole (20 mg), esomeprazole (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 is based on the opinion that avoiding metronidazole in first-line therapy would favour better results with subsequent second-line quadruple therapy, using metronidazole, in cases of treatment failure. 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.[52] 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.

In uncomplicated duodenal ulcer patients, *H. pylori* eradication therapy does not need to be followed by further antisecretory treatment. This is 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.[53] Healing rates over 90% and similar control of symptoms were reported in both treatment arms.

Patient education about the need for effective eradication therapy and the necessity of completing the initial drug regimen is critical. A follow-up plan must be emphasized because further diagnostic testing may be needed to ensure eradication of the *H. pylori* organism, particularly if symptoms persist.

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 a resistance surveillance programme is advisable as clarithromycin resistance affects the efficacy of first-line therapy.[54,55] In developing countries where resistance to metronidazole is usually at a very high level, furazolidone could be used.[56] Good eradication rates have been obtained with this compound included in regimens and it has been recommended in the Latin American Consensus Conference.[5]

H. pylori *treatment and prevention of gastric cancer*

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.[11,14,57-61] In the Maastricht 2-2000 Consensus meeting, 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. The development of 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,[10,62-64] but intestinal metaplasia may not be reversible.[10,65,66] In the Maastricht 2-2000 Consensus meeting these statements were 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.[67] *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. The recommendation in post-gastric cancer resection includes surgically resected stomachs, and there is a need for lifelong surveillance.[68]

H. pylori *infection in pediatrics*

H. pylori infection is mainly acquired in childhood in both industrialized and developing countries, and persists throughout life unless treated. 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.[8] 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,[69] and the conclusions have been summarized elsewhere.[70] 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 as follows.

- 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.

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.

There are major concerns over the reports of increasing resistance against macrolides in *H. pylori* strains from children in different European countries.[71] In children with double resistant strains, against clarithromycin and metronidazole, therapeutic options are limited as many second-line drugs (i.e. tetracycline, bismuth compounds, rifabutin, 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.

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