Leading article

Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report

Summary
There is considerable confusion over the management of *Helicobacter pylori* infection, particularly among primary care physicians, and numerous European countries lack national guidelines in this rapidly growing area of medicine. The European Helicobacter Pylori Study Group therefore organised a meeting in Maastricht of *H pylori* experts, primary care physicians and representatives of National Societies of Gastroenterology from Europe to establish consensus guidelines on the management of *H pylori* at the primary care and specialist levels, and to consider general health care issues associated with the infection.

As in previous guidelines, eradication therapy was recommended in all *H pylori* positive patients with peptic ulcer disease. Additionally, at the primary care level in dyspeptic patients <45 years old and with no alarm symptoms, diagnosis is recommended by non-invasive means (^{13}C urea breath test, serology) and if *H pylori* positive the patient should be treated. Moreover, at the specialist level the indications for eradication of *H pylori* were also broadened to include *H pylori* positive patients with functional dyspepsia in whom no other possible causes of symptoms are identified by the specialist (after a full investigation including endoscopy, ultrasound and other necessary investigations), patients with low grade gastric mucosa associated lymphoid tissue (MALT) lymphoma (managed in specialised centres) and those with gastritis with severe macro- or microscopic abnormalities.

There was consensus that treatment regimens should be simple, well tolerated and achieve an eradication rate of over 80% on an intention to treat basis. It was strongly recommended, therefore, that eradication treatment should be with proton pump inhibitor based triple therapy for seven days, using a proton pump inhibitor and two of the following: clarithromycin, a nitroimidazole (metronidazole or tinidazole) and amoxycillin.

Introduction

Understanding of *H pylori* and its associated diseases continues to evolve at a rapid rate, and there have been significant advances in our knowledge since the guidelines of the US National Institutes of Health were produced in 1994.[1] Over the past two years, recommendations for the management of *H pylori* infection have been developed independently in several European countries. However, these are not identical in their recommendations and numerous countries lack national guidelines. Additionally, although there is increasing adoption of *H pylori* eradication therapy, there is also considerable confusion, particularly in primary care, with regard to the management of *H pylori* infection.[2 3]

It is timely, therefore, to develop European consensus guidelines for the management of *H pylori* infection, and, moreover, to ensure that such guidelines tackle the role of the primary care physician as well as the specialist gastroenterologist in patient management. The European Helicobacter Pylori Study Group (EHPSG) undertook this task at a meeting held in Maastricht, The Netherlands. The aim of the group was to develop European consensus guidelines on how advances in our understanding of *H pylori* should be applied in clinical practice, both in primary care and in specialised centres, and to tackle general health care issues related to *H pylori* infection.

Structure of the Meeting

The Maastricht Consensus Meeting involved 63 participants from 19 European countries as well as observers from Canada, Japan and the USA. The participants comprised primary care physicians, representative specialists from national gastroenterology societies and experts in the field of *H pylori* research.

Reviews of the latest knowledge in the area were provided by experts in the relevant fields of research before a series of key management questions were posed. These were considered by three working groups, each focusing on a specific area:

- the role of the primary care physician;
- patient management at the specialist level; and
- public health care issues.

Each management question was tackled using a standard template proforma on which the workshop:

- identified a specific concept, issue or question;
- formulated their consensus statement or recommendation;
- stated the strength of their statement or recommendation at one of three levels (strongly recommended, advisable or uncertain);
- ranked the strength of the evidence supporting the statement or recommendation as unequivocal, supportive, or equivocal;
- described the rationale for the statement or recommendation.

Each workshop then reported their recommendations to the meeting for discussion and overall consensus statements were agreed.

Patient management in primary care

A large proportion of subjects infected with *H pylori*, and for whom eradication therapy could be beneficial, initially present with dyspeptic symptoms to the primary care physician. Many of these patients can be diagnosed and treated in primary care.

SHOULD DIAGNOSIS OF *H PYLORI* START AT THE PRIMARY CARE LEVEL?

The management of *H pylori* infection requires a multidisciplinary approach and it is strongly recommended that there is close local collaboration and interaction between primary care physicians, specialist gastroenterologists, microbiologists, and possibly public health doctors. Such collaboration between these disciplines has been shown to be effective by the Suffolk and Gloucester groups in the United Kingdom.[4 5] Provided that there is a good working relationship between these parties, there is supportive evidence that testing for *H pylori* infection should be accessible to primary care physicians.

It is clear that not all dyspeptic patients presenting in primary care are currently referred to a specialist and are more likely to receive symptomatic treatment from the primary care physician. However, many of these patients will continue to seek medical attention repeatedly and thus it seems logical to consider *H pylori* infection, if present, as a possible aetiological factor even if its role in dyspepsia has not been definitively confirmed. Furthermore, a proportion of dyspeptic patients presenting in primary care for the first time are patients with peptic ulcer disease who are *H pylori* positive and will benefit from diagnosis and consequent treatment of the infection. In a community based study of 400 patients in Eastern Finland, for example, ulcers were found in 35 (8·7%) cases.[6] Additionally, as patients are increasingly aware of the existence of *H pylori* and that the bacterium may have a role in gastrointestinal complaints, primary care physicians need to be able to diagnose *H pylori* infection if they are to manage the patient effectively.

WHICH DIAGNOSTIC TESTS SHOULD BE DONE BY THE PRIMARY CARE PHYSICIAN?

In the absence of endoscopy facilities, primary care physicians require non-invasive methods to diagnose *H pylori* infection. There is unequivocal evidence that the ^{13}C-urea breath test (UBT) is an acceptable test for primary care use and it is strongly recommended that it should be more widely available, possibly provided as a central service to primary care practices. The test is easy to perform, does not require special transport conditions and is usually available at a reasonable cost, although it is more expensive than serology.

Laboratory serology is also strongly recommended as an acceptable test for primary care use, provided it is validated locally. Several ELISA based serological tests are commercially available and eight of these have been compared in a multicentre study involving 15 laboratories using the same serum samples.[7] The observed accuracy was acceptable, most tests having a sensitivity and specificity of 90–95%. The expertise to conduct these tests is generally available locally, the results can be obtained within a day and costs are reasonable. Local validation is recommended, however, as the antigenic properties of local bacterial strains may differ to those used in the tests.

With respect to currently available rapid ("office") serological tests using whole blood, sensitivities and specificities observed to date have been disappointing in independent validations performed in a specialist setting.[8–11] Values ranged from 63 to 97% and 68 to 92%, respectively. It is, therefore, too early to recommend their use and it is strongly recommended that they are further validated in primary care settings.

The need to test patients following eradication therapy in the primary care setting was considered but consensus was not reached as to whether to recommend it or not. As discussed later in the section on patient follow up, it may not be necessary to determine the outcome of attempted *H pylori* eradication in patients with uncomplicated peptic ulcer or non-ulcer dyspepsia when symptoms resolve.

Regional centres should follow patients to monitor changes in the efficacy of therapy and the emergence of *H pylori* resistance.

WHEN SHOULD A PATIENT BE TREATED IN PRIMARY CARE OR REFERRED TO A SPECIALIST?

The clinical presentation and the age of the patient are the main criteria to be taken into account. It is acceptable that patients with dyspeptic symptoms, under 40 years of age or in their early 40's, without alarm symptoms (anaemia, weight loss, dysphagia, palpable mass, malabsorption, etc) who test positive for *H pylori* for the first time can be treated, using eradication therapy if appropriate, by primary care physicians without further investigations (fig 1). It is important, however, that risk factors for gastric malignancy, such as a family history, are ruled out if the patient is not to be referred. This recommendation is cost effective and includes patients with uncomplicated duodenal ulcer disease. This was classed as advisable by the majority of participants in the Consensus Meeting but was not unanimous.

It is strongly recommended, however, that patients over 45 years who have severe dyspeptic symptoms, and those with alarm symptoms (irrespective of age) should be referred to a specialist for endoscopy. The evidence for this is unequivocal as the standardised incidence rate in the European Community of gastric cancer in the over 45's is 19 per 100 000 for men and 9 per 100,000 for women.[12] Note that the cut off age for referral may be below 45 years depending on regional differences in the incidence of gastric malignancy. Additionally, patients with a known history of gastric ulcer should be referred and undergo repeat endoscopy with biopsy until healed as malignancy may be present.

As discussed earlier, most patients with dyspepsia present initially in primary care, and a proportion of those who are *H pylori* positive have uncomplicated peptic ulcer disease which may be cured by eradication of the bacterium. Some patients, though, will be treated for their

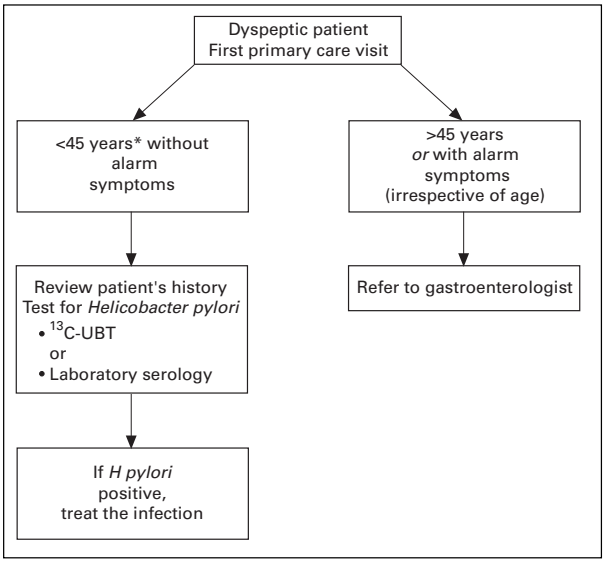

*Figure 1: Summary of the recommended approach to the management of dyspeptic patients in the community. *The cut off value may be below 45 years of age depending on regional differences in the incidence of gastric malignancy.*

infection per se but this may be viewed as preventive medicine given that *H pylori* infection always implies gastritis, which is a risk factor for further gastrointestinal disease. Preventive medicine is already common in community medicine where, for example, patients with high blood pressure receive life-long therapy even though only a small proportion would otherwise suffer cardiovascular problems.

There are also economic grounds to recommend treatment of *H pylori* infection in primary care. Several retrospective studies have provided evidence that by testing *H pylori* status in young patients with dyspepsia, endoscopy workload and costs can be reduced. This applies whether one then elects to perform an endoscopy in individuals found to be *H pylori* positive or in those found to be negative.[13–16] This has been confirmed by a prospective short term study.[17] There are now several rigorous decision analysis models which indicate substantial cost benefits if *H pylori* status is tested in young dyspeptic patients and all positive subjects then receive eradication therapy, though these benefits may take a number of years to accrue.[18–20]
It should be recognised that a potential negative aspect to widespread use of *H pylori* eradication therapy is that the resistance rate of *H pylori* to antibiotics may increase as may the resistance of other bacteria. This risk is indeed theoretically possible, but must be weighed against the benefits of eradicating *H pylori*. Additionally, it is not clear that the excess antibiotic consumption would be significant compared with the current general use of these compounds. It is important, however, that when *H pylori* eradication therapy is used, the risk of antibiotic resistance is minimised by avoiding use of inappropriate regimens, such as mono-antibiotic therapy, and by ensuring high patient compliance. Primary care physicians have considerable experience of the use of antibiotics and can be expected to use them appropriately.

Patient management by the specialist

When a patient is referred by a primary care physician, the specialist should review the history of the patient, the methods and results of previous *H pylori* tests and eradication therapy, and recent exposure to drugs which may affect the bacterium. After exclusion of other pathologies, using additional appropriate investigations, the specialist should decide on the need for endoscopy with biopsy. If the patient has already been treated and *H pylori* was not eradicated, they may be re-treated using a regimen avoiding antibiotics used previously to which the bacterium may be resistant. Alternatively, culture and sensitivity testing should be used to ensure choice of the appropriate antimicrobial therapy.[21 22]

The specialist should establish indications for *H pylori* eradication (see the recommendations below; table 1), treat as appropriate, and decide whether confirmation of *H pylori* eradication is necessary. This should either be by endoscopy with well taken, full thickness mucosal biopsy specimens for histological assessment (two from both the antrum and body in addition to one for a rapid urease test)[23] or by ^{13}C-UBT (see later).

How should the patient be followed up?

It is strongly recommended that eradication of *H pylori* be confirmed in complicated peptic ulcer disease, gastric ulcer, cases of low grade gastric MALT lymphoma, where treatment is incomplete or has a low efficacy, and when compliance is poor. When follow up tests for *H pylori* eradication are necessary, they should be performed no earlier than four weeks after cessation of treatment.

Non-recurrence of gastric and duodenal ulcer is strictly dependent on the success of *H pylori* eradication and the persistence of infection is a negative prognostic marker.[24] This is also true for relapses of ulcer complications such as bleeding.[25–27] Similarly, confirmation of successful eradication as an indicator of likely cure is also important in low grade gastric MALT lymphoma.

In complicated peptic ulcer, gastric ulcer and MALT lymphoma, the diagnostic assessment used to establish cure of *H pylori* infection should be endoscopy based, using biopsy specimens from the antrum and body. Additionally, after treatment for gastric ulcer, histological examination should also be performed to exclude malignancy as some gastric malignancies can only be detected during or following the healing process. Also, in MALT lymphoma histological assessment is required to evaluate the regression of malignancy. Indeed, endoscopy based testing is necessary in any situation when, in addition to confirming eradication, there is a need for histological assessment of any mucosal abnormalities. In such circumstances, multiple targeted biopsy specimens may be appropriate beyond the standard antral and body specimens.

Although it is generally advisable to determine the outcome of attempted *H pylori* eradication in uncomplicated peptic ulcer and non-ulcer dyspepsia, this may not be necessary where symptoms resolve. In duodenal ulcer disease, for example, symptom assessment at three and six months has been shown to be as valuable as the ^{13}C-UBT in determining ulcer cure following eradication therapy.[28] When eradication of *H pylori* is to be confirmed in these situations, non-invasive tests can be used, and the "gold standard" is the ^{13}C-UBT. With respect to serology, a 50% fall in antibody titres is indicative of successful elimination of the bacterium.[29 30] However, this takes up to six months to occur, requires a validated test kit, and all the relevant serum samples should be measured simultaneously in the same assessment. Serology should not, therefore, be used to assess early success or failure of therapy.

Is *H pylori* infection a health care issue?

There is unequivocal evidence that *H pylori* should be considered as a health care issue. This is based on the mortality associated with infection owing to the risk of bleeding and cancer. Additionally, other public health models which involve aggressive targeting of patients already exist, for example, hypertension and cervical cancer. Furthermore, the precise mode of transmission of *H pylori* has still to be determined.

TABLE 1 *Summary of the indications for* Helicobacter pylori *eradication therapy, the level of the recommendation and the strength of the supporting evidence*

Indications for H pylori *eradication therapy*	*Strength of supporting evidence*
Strongly recommended	
Peptic ulcer disease (whether active or not)	Unequivocal
Bleeding peptic ulcer	Unequivocal
Low grade gastric MALT lymphoma	Unequivocal
Gastritis with severe abnormalities	Supportive
Following early resection for gastric cancer	Supportive
Advisable	
Functional dyspepsia, after full investigation	Equivocal
Family history of gastric cancer	Equivocal
Long term treatment with proton pump inhibitors for GORD*	Supportive
Planned or existing NSAID therapy	Equivocal
Following gastric surgery for peptic ulcer	Supportive
The patient's wishes	Equivocal
Uncertain	
Prevention of gastric cancer in the absence of risk factors	Equivocal
Asymptomatic subjects	Equivocal
Extra-alimentary tract disease	Equivocal

*See text note on this recommendation.

Screening for *H pylori* infection is strongly recommended in the setting of clinical trials but not outside this. Studies should be performed which tackle the natural history of infection, and intervention studies are required, for example, in gastric cancer. Reliability of screening tests, treatment efficacy and safety, the development of secondary resistance and the risk of reinfection all need to be considered.

What are the indications for *H pylori* eradication therapy?

Table 1 summarises the indications for *H pylori* eradication therapy. As in previous guidelines,[1] *H pylori* eradication is strongly recommended in all infected patients with a diagnosis of duodenal or gastric ulcer disease, past or present, including those in remission or receiving antisecretory maintenance treatment. The evidence for this is unequivocal, on the grounds of both clinical and cost effectiveness, as eradication of *H pylori* will result in cure in over 90% of patients.[31–33]

Peptic ulceration may also be caused by the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and the causal relation between NSAIDs and infection with *H pylori* in the genesis of peptic ulcer disease requires further investigation. However, although the evidence to date is equivocal and more research is needed, initial studies suggest that *H pylori* eradication may prevent peptic ulceration after exposure to NSAIDs[34 35] and eradication of *H pylori* was thus classed as advisable when treatment with NSAIDs is planned or ongoing. Following eradication of the bacterium, NSAID associated ulcers have to be managed individually.

The recommendation for eradication in patients with peptic ulcer disease includes those with bleeding ulcers.[25–27] *H pylori* status should be determined in all such patients, and if infected, *H pylori* eradication therapy should begin with oral feeding after the acute bleeding phase. All of the controlled studies to date that have reported *H pylori* eradication rates of over 80% on an intention to treat basis have administered the drugs orally and no study has shown an advantage of giving eradication therapy during the bleeding phase. Moreover, drug pharmacokinetics at the gastric mucosal level are less predictable in the acute bleeding phase. It should be noted that pretreatment with proton pump inhibitors does not influence the success of proton pump inhibitor based triple therapy in eradicating *H pylori*.

H pylori eradication therapy is also strongly recommended in infected patients with low grade gastric MALT lymphoma based on unequivocal evidence—eradication of *H pylori* has been reported to lead to complete remission of the malignancy in 74% of patients.[36] This should be managed in specialist centres. Most importantly, accurate staging, including endoscopic ultrasound, is an essential prerequisite to treatment as advanced tumours do not regress after eradication of *H pylori*.

The natural history of *H pylori* infection is well known and although it is a multifactorial process, infection increases the risk of gastric cancer. Based on the data available, eradication therapy is strongly recommended in cases with advanced and progressively worsening forms of gastritis, such as in patients with intestinal metaplasia, glandular atrophy and those with erosive or hypertrophic forms of gastritis. Treatment of *H pylori* positive patients is also strongly recommended after resection of early gastric cancer or precancerous lesions. There are supportive data for this showing that *H pylori* eradication is associated with a decrease in the recurrence rate among patients in whom early gastric cancer is resected endoscopically.[37]

Although the evidence is equivocal, eradication therapy is advisable in *H pylori* positive patients with functional dyspepsia, established as such following careful exclusion of other pathologies with a potential for being cause of symptoms by the specialist. Treatment should be given for the reasons discussed earlier in the section on patient management in primary care. No specific dyspeptic symptoms have been shown to be associated with *H pylori* infection in the absence of macroscopic gastric abnormalities, such as ulcer, and the short term effects of *H pylori* eradication are not superior to symptomatic therapy.[38] However, this relation in the individual patient can only be clarified after cure of *H pylori* infection. Moreover, long term follow up data provide supportive evidence for a benefit of *H pylori* eradication therapy, resulting in amelioration of symptoms and a reduction in drug consumption,[39] and, indeed, eradication of *H pylori* avoids the long term sequelae of the infection. Eradication therapy is also advisable in *H pylori* positive patients with a family history of gastric cancer, after gastric surgery for peptic ulcer disease (subtotal gastric resection, vagotomy), and in response to the patient's wishes.

Eradication of *H pylori* may also be advisable when long term antisecretory treatment is necessary for the management of gastro-oesophageal reflux disease (GORD). This recommendation was based on a report that such treatment may accelerate the progression of *H pylori* induced atrophic gastritis in the corpus of the stomach.[40]

H pylori infection should be investigated and treated in paediatric patients with recurrent abdominal pain, but this should only be conducted by paediatricians in specialist centres. The evidence for this is equivocal and the recommendation was made at the uncertain level.

Treatment is not currently recommended for large scale gastric cancer prevention in people with no known risk factors, in extra-alimentary tract disease (for example, coronary artery disease), asymptomatic individuals or relatives of infected patients. In all cases the evidence is equivocal. Thus, there is no perceived benefit in giving *H pylori* eradication treatment to asymptomatic family members of patients with peptic ulcer disease. The only rationale would be reinfection, but this is very low. However, it is advisable to treat asymptomatic *H pylori* positive patients if they consult because of a family history of gastric cancer, not least because of the physician/patient relationship.

Which treatment regimen should be used?

The requirement is for a simple, well tolerated regimen, which is easy to comply with and is cost effective. Treatment should achieve an eradication rate of over 80% on a rigorous intention to treat basis. The regimens that have been studied to date have used a bismuth preparation, an H_2-receptor antagonist, ranitidine bismuth citrate, or a proton pump inhibitor, in combination with one, two or three antimicrobial agents.

A problem in assessing the studies currently available in the literature is that there is considerable heterogeneity in the methods used to calculate eradication rates. A comprehensive review of the studies published to date was therefore prepared for the Consensus Meeting, in which eradication rates were derived from all studies by a common, rigorous intention to treat analysis. Full description of this analysis is beyond the scope of this publication, but the key results have been published elsewhere.[41] Based on this analysis, the published literature and the participants' own clinical experience, it is strongly recommended that treatment should be with proton pump inhibitor based triple therapy, consisting of a proton pump inhibitor, and two of the following: clarithromycin,

a nitroimidazole (metronidazole or tinidazole) and amoxycillin, in various combinations. Classic bismuth based triple therapy (tripotassium dicitrato bismuthate plus metronidazole and tetracycline) has now been superseded by proton pump inhibitor based triple therapy regimens which are associated with higher efficacy, fewer side effects and better patient compliance. Additionally, no recommendation can be made regarding the role of ranitidine bismuth citrate until more convincing data are available.

The treatment regimens currently in use which have been shown to satisfy the criteria required above involve seven treatment days using a standard dose proton pump inhibitor, twice daily, and:

- metronidazole, 400 mg twice daily/tinidazole, 500 mg twice daily, plus clarithromycin, 250 mg twice daily;
- amoxycillin, 1000 mg twice daily, plus clarithromycin, 500 mg twice daily (advisable when metronidazole resistance is likely);
- amoxycillin, 500 mg three times daily, plus metronidazole, 400 mg three times daily (advisable when clarithromycin resistance is likely).

Standard doses of proton pump inhibitors are omeprazole (20 mg), lansoprazole (30 mg), and pantoprazole (40 mg). The evidence for use of these protocols comes largely from studies of seven day regimens with omeprazole.[42–47] More recently there have also been data for similar regimens using lansoprazole,[48] and some smaller studies using pantoprazole.[49 50]

In the case of treatment failure, a re-treatment regimen should be selected after consideration of previous treatment or microbial sensitivities, or both. Additionally, there are supportive data that quadruple therapy (omeprazole plus classic bismuth based triple therapy) can be used in the event of failure of triple therapy.

These variables may change in the light of future research, and specific regimens currently approved for use may vary between individual countries.

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Appendix

PARTICIPANTS IN THE MAASTRICHT CONSENSUS MEETING

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The pathology sections of the Consensus Report have also been reviewed by EHPSG members Sipponen P (Finland) and Price A (UK).

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