HELICOBACTER PYLORI

Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report

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Background: Guidelines on the management of *Helicobacter pylori*, which cover indications for management and treatment strategies, were produced in 2000.
Aims: To update the guidelines at the European Helicobacter Study Group (EHSG) Third Maastricht Consensus Conference, with emphasis on the potential of *H pylori* eradication for the prevention of gastric cancer.
Results: Eradication of *H pylori* infection is recommended in (*a*) patients with gastroduodenal diseases such as peptic ulcer disease and low grade gastric, mucosa associated lymphoid tissue (MALT) lymphoma; (*b*) patients with atrophic gastritis; (*c*) first degree relatives of patients with gastric cancer; (*d*) patients with unexplained iron deficiency anaemia; and (*e*) patients with chronic idiopathic thrombocytopenic purpura. Recurrent abdominal pain in children is not an indication for a "test and treat" strategy if other causes are excluded. Eradication of *H pylori* infection (*a*) does not cause gastro-oesophageal reflux disease (GORD) or exacerbate GORD, and (*b*) may prevent peptic ulcer in patients who are naïve users of non-steroidal anti-inflammatory drugs (NSAIDs). *H pylori* eradication is less effective than proton pump inhibitor (PPI) 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 urea breath test, stool antigen tests, and serological kits with a high accuracy are non-invasive tests which should be used for the diagnosis of *H pylori* infection. Triple therapy using a PPI with clarithromycin and amoxicillin or metronidazole given twice daily remains the recommended first choice treatment. Bismuth-containing quadruple therapy, if available, is also a first choice treatment option. Rescue treatment should be based on antimicrobial susceptibility.
Conclusion: 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.

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 to treat, and how and when to treat patients with *H pylori* infection. The most active area of research is into the link between *H pylori* and 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 examined the following three topics relating to *H pylori* infection:

- Indications/contraindications for eradication, focusing on dyspepsia, non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin use, gastro-oesophageal reflux disease (GORD); and extraintestinal 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). For some statements the grade of recommendation did not match the level of evidence because either studies focusing on the same topic reported conflicting results, or interpretation of the studies 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 of the experts supported the recommendation. The recommendations/statements resulting from this rigorous process are reported in this manuscript.

INDICATIONS/CONTRAINDICATIONS FOR *H PYLORI* ERADICATION

The indications for *H pylori* eradication listed as a strong recommendation in Maastricht II-2000 guidelines (table 2)[1] were reconfirmed at this update (table 3).

Abbreviations: BabA2, blood group antigen binding adhesin 2; CagA, cytotoxin associated gene A; EHSG, European Helicobacter Study Group; GORD, gastro-oesophageal reflux disease; IDA, iron deficiency anaemia; ITP, idiopathic thrombocytopenic purpura; MALT, mucosa associated lymphoid tissue; NSAIDs, non-steroidal anti-inflammatory drugs; OipA, outer inflammatory protein A; PPIs, proton pump inhibitors; RCT, randomised controlled trial; SabA, sialic acid binding adhesion; UBT, ^{13}C-urea breath test; VacA, vacuolating associated gene A

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

Grade of recommendation	Evidence level		Type of studies
A	1	1a	Systematic review of randomised controlled trials (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 studies (including low quality RCT, eg <80% follow-up)
		2c	Non-controlled cohort studies/ecological studies
	3	3a	Systematic review of case-control studies (with homogeneity)
		3b	Individual case-control studies
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"

H pylori and MALT lymphoma

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

Sixty two per cent of patients with low grade gastric MALT lymphoma have complete remission after *H pylori* eradication within 12 months.[2 3]

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 point 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.[4]

H pylori eradication gives modest, but significant benefit in non-ulcer dyspepsia.[5] Economic modelling suggests that this benefit is cost effective.[6] Twelve to 15 infected patients need to be treated to cure one patient with non-ulcer dyspepsia.[6] This compares favourably with any other treatment available for non-ulcer dyspepsia. The eradication of *H pylori* infection is carried out once and leads to long term symptom improvement; it also reduces the risk of developing peptic ulcer disease, atrophic gastritis, and gastric cancer.

In areas of low *H pylori* prevalence[7] (<20%) proton pump inhibitor (PPI) empirical treatment or a test and treat strategy were considered to be equivalent options (box 1).

Box 1: 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 GORD

The prevalence of *H pylori* in patients with GORD is lower than in those without reflux disease.[8] Most countries with a high prevalence of *H pylori* also have 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.[9 10]

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

Box 2: 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 treatment 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 receiving long term maintenance treatment with PPIs.

Profound acid suppression affects the pattern and distribution of gastritis favouring corpus dominant gastritis. It may accelerate the process of loss of specialised 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.

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

Recommendation (*H pylori* 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
After gastric cancer resection	3b	B
Patients who are first degree relatives of patients with gastric cancer	3b	B
Patients wishes (after full consultation with their physician)	5	A

DU, duodenal ulcer; GU, gastric ulcer; PUD, peptic ulcer disease; MALToma, mucosa associated lymphoid tissue lymphoma.

Eradication of *H pylori* does not cause GORD,[14–16] and does not exacerbate symptoms in patients with GORD either when untreated[17] or in those receiving PPI maintenance treatment.[18]

Screening for *H pylori* in patients with GORD needs more formal study, including a 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.[19] Profound acid suppression with PPIs or high dose histamine 2 receptor antagonists in the presence of *H pylori* positive corpus gastritis may accelerate the loss of specialised glands, leading to atrophic gastritis and, potentially, gastric cancer. In patients with reflux oesophagitis receiving long term acid suppression, eradication of *H pylori* infection decreases inflammation and gastritis activity, and reverses corpus gastritis (box 2).[18]

H pylori and NSAIDs

The relationship between *H pylori* infection and NSAIDs in gastroduodenal 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.[20]

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 treatment at six months.[21] PPI maintenance treatment is better than *H pylori* eradication alone in preventing upper gastrointestinal bleeding.[22] In contrast, in patients with *H pylori* infection who are naive NSAID users, *H pylori* eradication is better than placebo in preventing peptic ulcer and upper gastrointestinal bleeding at six months.[23 24]

Patients who are receiving 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.[22 25] Patients receiving long term PPI treatment for prevention of NSAID ulcers should be tested for *H pylori* to reduce the PPI-*H pylori* interaction leading to accelerated loss of specialised glands and atrophic gastritis (box 3).

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

Recommendations	Level of evidence	Grade of recommendation
H pylori eradication is an appropriate option for patients infected with *H pylori* and investigated non-ulcer dyspepsia	1a	A
H pylori test and treat is an appropriate option for patients with uninvestigated dyspepsia	1a	A
Effectiveness of *H pylori* test and treat is low in populations with a low *H pylori* prevalence. In this situation the test and treat strategy or empirical acid suppression is an appropriate option	2a	B
H pylori eradication does not cause GORD	1b	A
H pylori eradication does not affect the outcome of PPI treatment in patients with GORD in Western populations	1b	A
Routine testing for *H pylori* is not recommended in GORD	1b	A
H pylori testing should be considered for patients receiving long term maintenance treatment with PPIs	2b	B
There is a negative association between the prevalence of *H pylori* and GORD in Asia, but the nature of this relationship is uncertain	2b	B
In patients receiving long term NSAIDs and who have peptic ulcer and/or ulcer bleeding, PPI maintenance treatment is better than *H pylori* eradication in preventing ulcer recurrence and/or bleeding	1b	A
H pylori eradication is of value in chronic NSAID users but is insufficient to prevent NSAID related ulcer disease completely	1b	A
In naïve users of NSAIDs, *H pylori* eradication may prevent peptic ulcer and or bleeding	1b	A

Box 3: Recommendations

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

1. In naïve NSAID users *H pylori* eradication may prevent peptic ulcer and bleeding.
2. In patients receiving long term NSAIDs and with peptic ulcer and/or ulcer bleeding, PPI maintenance treatment is better than *H pylori* eradication in preventing ulcer recurrence and/or bleeding.
3. Patients who are receiving long term aspirin who bleed should be tested for *H pylori* and, if positive, receive eradication therapy.

Extraintestinal disease

Some studies suggest that *H pylori* infection may cause 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 use by bacteria.[26] *H pylori* eradication reverses IDA in patients with asymptomatic gastritis[27] and improves oral iron absorption.[28]

Some studies suggest that there is a higher prevalence of *H pylori* infection in patients with ITP than in controls.[29] Moreover, a review of published data on *H pylori* infection and ITP confirmed that eradication therapy induces a significant positive platelet response in a proportion of patients with ITP.[30–33] It was recommended that *H pylori* infection should be sought for and treated in patients with unexplained IDA and in those with ITP. *H pylori* infection has no proven role in other extraintestinal diseases (box 4).

H pylori infection in children

Recurrent abdominal pain is not an indication for a test and treat strategy for *H pylori* infection in children. The primary goal of a diagnostic investigation in recurrent abdominal pain 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, IDA refractory to iron supplementation is an indication to test for *H pylori* infection and for eradication therapy if positive. This should be carried out after exclusion of other causes, such as coeliac disease and inflammatory bowel disease.

No other substantial aspects have been brought forward in respect of the previously published guidelines.[34 35]

Box 4: Recommendations

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

1. Unexplained iron deficiency anemia.
2. Idiopathic thrombocytopenic purpura.

H pylori has no proven role in other extraintestinal diseases.

Box 5: Recommendations

Serology should be considered as a diagnostic test when others could be false negative, such as in patients with:

1. Bleeding ulcers, gastric atrophy, MALT lymphoma.
2. Recent or current use of PPIs and antibiotics.

DIAGNOSTIC PROCEDURES

Non-invasive tests for the diagnosis of *H pylori* infection include: the ^{13}C-urea breath test (UBT); stool antigen tests (polyclonal antibody, monoclonal antibody, and office based); and immunological tests (laboratory and office based tests and tests on saliva and urine) (table 4).

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

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 sensitivity of the stool antigen test decreased to 69% after 2–3 days at room temperature. In a systematic review of 89 studies evaluating the stool antigen test the sensitivity and specificity were 91% and 93%, respectively.[37]

Serology is a widely available and inexpensive non-invasive test, but the diagnostic accuracy is low (80–84%).[38] 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.[39 40] Some kits for serology with a high accuracy (>90%) are recommended in validated settings.

Special role of serology

PPI treatment can result in false negative invasive and non-invasive diagnostic tests. PPI should be stopped for at least two weeks before testing. However, this does not apply to serology.[41–46] A positive serological test with negative histology and UBT suggests the presence of an unrecognised *H pylori* infection, and additional investigations to confirm whether the serological test is false positive or reflects active infection should be carried out. False positive non-invasive tests are more common in low prevalence populations, requiring additional confirmation before treatment.[47 48]

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[45] and MALT lymphoma)[46] (box 5). 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 owing to cross reactivity with blood products. Serological tests, and in particular detection of antibodies against the specific antigen CagA, which is immunogenic and long lasting, are also the best method to document the link of gastric cancer with *H pylori* infection.[49]

Office based serological tests or near patient tests are extremely convenient, but they are not accurate and are currently not recommended[50] (box 6).

Box 6: Recommendations

1. Serology based office tests have 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.

Box 7: Recommendation

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

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.

Detection of pathogenic factors

Some strains of *H pylori* are more virulent than others.[51] Important pathogenic factors are CagA, a product of a gene of the *cag* pathogenicity island; VacA, a cytotoxin produced in various amounts; and $BabA_2$, an adhesin which recognises the blood group antigen A and allows *H pylori* to adhere to gastric epithelial cells. Other factors, for example, OipA and SabA, may also determine disease. Furthermore, host genetic factors may determine disease outcome[52] The association with *H pylori* pathogenic factors and host genetic factors is real in Western populations, but 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 (box 7).

Role for urease test

The rapid urease test can detect the presence of *H pylori*, within one hour with a satisfactory accuracy (>90%).[53] False negative results can occur in patients taking antisecretory drugs. It is acceptable to initiate eradication therapy on the basis of a positive rapid urease test (box 8).

Box 8: Recommendation

A positive rapid urease test is sufficient to initiate treatment.

Box 9: Recommendations

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

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

Follow-up after treatment

Non-invasive tests should be employed for confirmation of eradication except in cases where repeat endoscopy is indicated, for example in patients with gastric ulcer. 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%.[36 54] The accuracy of the stool antigen tests is less than that of the UBT.[55–58] However, when a UBT is not available, a stool test can be used. There are a number of stool tests available (one using monoclonal antibodies, laboratory and office based and the other polyclonal antibodies). The sensitivity of the test is lower if polyclonal antibodies[59] or an office test is used. Confirmation of *H pylori* eradication should be performed at least four weeks after treatment (box 9).

Table 4 Recommendations for diagnosis of *H 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. PPIs 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 might be false negative, such as in patients with bleeding ulcers, gastric atrophy, MALT lymphoma, and recent or current use of PPIs 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 *H pylori* antibodies in urine and saliva has no current role in patient management but can he helpful for epidemiological studies	1b	A
Serology based near doctor-patient tests have no current role in the management of *H pylori* infection	1	A
Detection of *H pylori* pathogenic factors and the study of host genetic polymorphisms is not helpful in the management of *H pylori* infection	3b	D
It is recommended that a follow-up evaluation to confirm successful eradication be performed after *H pylori* 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 two 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 pretreatment, a positive rapid urease test is sufficient to initiate treatment	2	A

Box 10: 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.

TREATMENT OF *H PYLORI* INFECTION

Numerous clinical trials have been published since the last Maastricht conference. Table 5 shows the recommendations for treatment of *H pylori* infection formulated at the Maastricht III Consensus Conference. Standard triple therapy composed of PPI, clarithromycin and amoxicillin/or metronidazole is more successful if extended to more than seven days. Increased resistance to antibiotics used in the PPI triple therapy needs to be considered in the selection of treatment. Recently, sequential treatment consisting of five days of a PPI plus amoxicillin followed by five additional days of a PPI plus clarithromycin plus tinidazole has been shown to be better than the combination of a PPI plus amoxicillin and clarithromycin for seven days[60 61] 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 proved.

The prevalence of clarithromycin resistance in Europe was measured in a European study in 1997–98 and was, overall, 10%, with important differences between northern (4%) and southern European countries (18.5%).[62] There was a correlation between the prevalence of *H pylori* clarithromycin resistance and the consumption of macrolides in the corresponding regions expressed as the daily dose per 1000 inhabitants in 1997.[63]

Clarithromycin resistance is increasing. It is the main risk factor for treatment failure.[64–66] Treatment should achieve an eradication rate of ⩾80%.[67] The threshold of clarithromycin resistance at which this antibiotic should not be used, or a clarithromycin susceptibility test should be performed, is 15–20%.

Box 11: Recommendations

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 seven days (by 12% (95% confidence interval 7% to 17%). A seven day treatment may be acceptable where local studies show that it is effective.
2. PPI-clarithromycin-amoxicillin or metronidazole treatment is the recommended first choice treatment in populations with less than 15–20% clarithromycin resistance. In populations with less than 40% metronidazole resistance PPI-clarithromycin-metronidazole is preferable. Quadruple treatments are alternative first choice treatments.
3. The same first choice *H pylori* treatments are recommended world wide, although different doses may be appropriate.

Box 12: Recommendations

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

In vitro resistance to metronidazole may not accurately reflect in vivo resistance.[68] For this reason metronidazole testing is not recommended routinely in clinical practice (box 10).

In susceptible strains the combination of PPI-clarithromycin-metronidazole is more successful than the combination of PPI-clarithromycin-amoxicillin (97% *v* 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% *v* 18%, respectively). In cases of metronidazole resistance when a PPI-clarithromycin-metronidazole regimen is used, there is a 25% decrease in eradication rate (72% *v* 97%).[69]

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%.[70]

A 14 day treatment led to a 12% (95% confidence interval 7 to 17%) higher eradication rate based on a single meta-analysis.[71] Few studies have compared the cost effectiveness of these different strategies.[72] Numerous studies with PPI triple therapy for seven days, mainly from European countries, confirm that this is still a valid duration for this treatment.[70]

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

First choice treatment in various geographical regions world wide was also examined and finally, a global statement including the different points mentioned above was voted upon (box 11).

Second choice treatment

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

PPI triple treatments 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 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 treatment, the global eradication rate was 64%.[73] Another combination, for which limited data exist, is PPI-tetracycline-metronidazole with an eradication of 91% (box 12).[74]

Third choice treatment

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

Box 13: Recommendation

Rescue treatment should be based on antimicrobial susceptibility testing.

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

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

These antibiotics have been evaluated for the most part in first choice treatments with PPI and amoxicillin rather than rescue treatments, 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 obtained good eradication rates.[75 76] 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.

Owing to the variety of clinical situations and antibiotics available in different countries, no specific recommendation was given for third choice treatment 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 rather

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

Statements	Level of evidence	Grade of recommendation
The global burden of gastric cancer increasing, predominantly in developing countries	*1	A
H pylori infection is the most common proven risk factor for human non-cardiac 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 *H pylori* as an important factor for gastric cancer development is shown by experimental animal models		B
Eradication of *H pylori* prevents development of pre-neoplastic changes of the gastric mucosa	1b	A
Eradication of *H pylori* has the potential to reduce the risk of gastric cancer development	1c	B
The optimal time to eradicate *H pylori* is before pre-neoplastic conditions (atrophy, intestinal metaplasia) are present, probably in early adulthood	1b	A
H pylori 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 treatments	1b	A
New treatments are required for a global strategy of eradication to prevent gastric cancer		A
H pylori eradication for gastric cancer prevention in populations at risk should he 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.

than chosen empirically.[73 77 78] This may be a cost effective approach.[79] 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 the failure of a second choice treatment. 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 (box 13).

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 (table 6). *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 seroepidemiological studies have shown that people with *H pylori* infection are at a statistically significantly increased risk of developing non-cardiac gastric cancer.[80] 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 cancer rates are significantly higher in patients with *H pylori* infection than in those in whom the infection was eradicated.[81] Metachronous tumour rates are also higher in those with persisting infection than in those without, after endoscopic resection for early gastric cancer.[82]

Furthermore, follow-up studies in Sweden and Denmark of patient cohorts undergoing hip replacement procedures show statistically significantly lower rates of gastric cancer. This may be explained by the possibility that high doses of prophylactic antibiotics incidentally eradicate *H pylori* infection.[83] Thus, it was agreed that *H pylori* infection is the most common proven risk factor for human non-cardiac gastric cancer.

Infection with *cag*A positive strains of *H pylori* increases the risk for gastric cancer over the risk associated with *H pylori* infection alone. Determining the *cag*A status in *H pylori* infection may confer additional benefit in identifying populations at greater risk for gastric cancer.[84] Interleukin 1 gene cluster polymorphisms are associated with a higher risk of hypochlorhydria (odds ratio = 9.1) and of gastric cancer (odds ratio = 1.9).[52] 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 in some patients with pernicious anaemia in diabetes type I, autoimmune chronic gastritis is common and rarely associated with *H pylori* infection); environmental (occupational exposure/nitrate/nitrite/nitroso compounds); nutritional (salt, pickled food, red meat, smoking); general (low socioeconomic status, geography); pharmacological (gastric acid inhibition).[85–90] All these lines of evidence suggest that bacterial virulence factors, host genetic factors, and environmental factors contribute to the risk of developing gastric cancer.[91]

H pylori eradication prevents development of pre-neoplastic changes (atrophic gastritis and intestinal metaplasia) of the gastric mucosa.[92–94] Evidence that *H pylori* eradication may reduce the risk of gastric cancer is based on non-randomised controlled studies in animal and humans.[95 96] Several randomised control studies show regression of precancerous lesions or, at least, a decrease of progression as compared with control groups after *H pylori* eradication.[97] One RCT did not demonstrate reduction of cancer incidence at five years but showed a significant reduction in the group without pre-neoplastic lesions.[98] 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 globally is restricted by currently available treatments.[96–99] Thus, new treatments are desirable for a global strategy of gastric cancer prevention.

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Since the Maastricht conference new additional publications in support of the recommendations and statements, are included to update the manuscript.

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APPENDIX

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From the question on page 755

The CT scan showed a 3.4×2.3 cm paracolic mass near to the left kidney without associated lymphadenopathy. The tumour was hypodense with an enhanced wall of the lesion (fig 1).

The histological examination of the CT-guided biopsy of the lesion demonstrated numerous *Aspergillus fumigatus* hyphae (H&E ×400; fig 2), which could be cultured on Sabourauds's medium.

Most Aspergillus infections are found in immunosuppressed patients and, typically, involve the lungs. This case documents a highly unusual extrapulmonary aspergilloma without secondary focus. The management is surgical. Our patient had a smooth postoperative course and was symptom free at a follow-up 5 years after the resection of the aspergilloma.

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