EDITOR'S CHOICE

Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report

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ABSTRACT

Management of *Helicobacter pylori* infection is evolving and in this 4th edition of the Maastricht consensus report aspects related to the clinical role of *H pylori* were looked at again in 2010. In the 4th Maastricht/Florence Consensus Conference 44 experts from 24 countries took active part and examined key clinical aspects in three subdivided workshops: (1) Indications and contraindications for diagnosis and treatment, focusing on dyspepsia, non-steroidal anti-inflammatory drugs or aspirin use, gastro-oesophageal reflux disease and extraintestinal manifestations of the infection. (2) Diagnostic tests and treatment of infection. (3) Prevention of gastric cancer and other complications. The results of the individual workshops were submitted to a final consensus voting to all participants. Recommendations are provided on the basis of the best current evidence and plausibility to guide doctors involved in the management of this infection associated with various clinical conditions.

Management of *Helicobacter pylori* infection is evolving and so is our understanding of the role of the bacterium in various clinical conditions.

The European Helicobacter Study Group first took the initiative in 1996 in Maastricht to gather dedicated experts in the field and to review and discuss all relevant clinical data to arrive at recommendations for the clinical management of *H pylori* infection.[1] The Maastricht conference has since been repeated at intervals of 4–5 years.[2 3]

Aspects related to the clinical role of *H pylori* were re-examined in Florence 2010 with the Maastricht methodology. The meeting focused on indications, diagnostics and treatments of *H pylori* infection with additional emphasis on disease prevention—in particular, prevention of gastric cancer.

In the 4th Maastricht/Florence Consensus Conference 44 experts from 24 countries took active part. Experts invited were chosen for their expertise and contribution to *H pylori* research and/or guideline methodology.

METHODOLOGY AND STRUCTURE OF CONFERENCE PROCESS

Current guidelines from Japan, Asia-Pacific, North America and Europe, as well as the 'Maastricht methodology' were reviewed at an introductory plenary session.

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

- Indications and contraindications for diagnosis and treatment, focusing on dyspepsia, non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin use, gastro-oesophageal reflux disease and extraintestinal manifestations of the infection.
- Diagnostic tests and treatment of infection.
- Prevention of gastric cancer and other complications.

Individual questions were submitted to all participants, debated and modified according to a standard template. After a thorough discussion of each statement in one of the three working groups the strength of recommendations and the strength of the supporting evidence were graded according to the slightly modified system, used in our previous report[3] (table 1). In a few statements where there are only experimental studies in support of the biological plausibility but no treatment studies, we did not quote the evidence, but graded the recommendation for the statement. 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 the interpretation of the studies by the experts led to a different grade of recommendation than expected from the level of evidence. Aspects related to the implementation of recommendations in daily clinical practice have also been taken into account.

The statements and recommendations were edited and finally agreed at the concluding plenary session. Consensus was defined as support by 70% or more of the experts. The recommendations resulting from this rigorous process are reported in the manuscript.

Commentaries on statements were written by the chairmen of individual workshops based on the data presented by the person assigned to elaborate the question; they include the conclusion of discussions held at the meeting. Coauthors were involved in the final editing of the commentaries. The previous strong recommendations for *H pylori* eradication, such as in patients with peptic ulcer disease,[3] has been reconfirmed.

THE TEST-AND-TREAT STRATEGY (WORKSHOP 1)

Statement 1: A test-and-treat strategy is *appropriate* for uninvestigated dyspepsia in populations where the *H pylori* prevalence is high (≥20%). This approach is subject to local cost–benefit considerations and is not applicable to patients with alarm symptoms, or older patients (age to be determined locally according to cancer risk)

Evidence level: 1a **Grade of recommendation: A**

Statement 2: The main non-invasive tests that can be used for the test-and-treat strategy are the UBT and monoclonal stool antigen tests. Certain validated serological tests can also be used.

Evidence level: 2a **Grade of recommendation: B**

H pylori is the most successful human pathogen infecting an estimated 50% of the global population. It is a common and potentially curable cause of dyspepsia and peptic ulcer disease. Test and treat is a strategy involving a non-invasive test being carried out in patients with dyspepsia to assess whether *H pylori* is present and then treatment of the infection if it is found; it thus avoids the cost, inconvenience and discomfort of endoscopy. The test-and-treat strategy is appropriate in situations where the risk of the patient having gastric cancer is low; in most countries this means dyspeptic patients below a locally determined age cut-off point (depending on local incidence of gastric cancer in different age groups) and without so-called 'alarm' symptoms or signs which are associated with an increased risk of gastric cancer. These include weight loss, dysphagia, overt GI bleeding, abdominal mass and iron deficient anaemia. In young patients with dyspepsia, testing for and treating *H pylori* is preferable to a strategy of just prescribing a proton pump inhibitor where the *H pylori* prevalence is ≥20%. The Urea Breath Test (UBT) and stool antigen testing are acceptable non-invasive tests for *H pylori* infection in this setting. For UBT, sensitivity is 88–95% and specificity 95%–100%.[4] Stool antigen testing may be somewhat less acceptable to patients in some cultures but is equally valid, with a sensitivity of 94% and a specificity of 92%.[5] A significant symptom benefit can be obtained from a test-and-treat strategy. This has been validated in a primary care cohort, which is the setting where most dyspeptic patients present.[6] Test and treat must be used cautiously in populations with a low *H pylori* prevalence as it becomes less accurate in this setting.[7] In patient groups with an increased risk of gastric cancer (over a local age cut-off point or with alarm symptoms or signs), the test-and-treat strategy is not recommended and a strategy of 'endoscope and treat' is preferred.[8] In addition, non-invasive tests are less accurate in older adults.[9]

Acid and functional dyspepsia

Statement 3: H pylori eradication produces long-term relief of dyspepsia in one of 12 patients with *H pylori* and functional dyspepsia; this is better than any other treatment.

Evidence level: 1a **Grade of recommendation: A**

Statement 4: H pylori can increase or decrease acid secretion depending on the intragastric distribution of inflammation.

Evidence level: 2b **Grade of recommendation: B**

Many dyspeptic patients found to be infected by *H pylori* have functional dyspepsia (FD) rather than peptic ulcer disease. The benefit from eradication treatment is less clear in these patients than in those with peptic ulcer. At a population level, there is a significant improvement in the resolution of persistent symptoms in the *H pylori* eradication group (95% CI 6% to 14%) compared with placebo, with a number needed to treat of 12.[10] Treatment response is difficult to predict for the individual patient. *H pylori* eradication led to a 25% reduction in dyspepsia consultations between 2 and 7 years of follow-up in a randomised controlled trial.[11] Another study suggested that *H pylori* eradication provides a similar long-term symptom reduction in patients with dyspepsia and duodenal ulcer.[12] The cost-effectiveness of *H pylori* eradication in FD varies between regions. In Europe *H pylori* eradication is cost-effective compared with offering no treatment but in the USA it is less certain that this is a cost-effective approach owing to the higher cost of eradication treatment.[13] Overall response, however, is much better in regions where *H pylori* is highly prevalent and this is where it may be most cost-effective. Patients with FD in Asia would benefit from treatment for *H pylori* infection with an increased chance of symptom resolution as high as 3.6–13 after its eradication.[14 15]

Successful treatment of *H pylori* infection may increase, decrease or have no overall effect on acid secretion. The effect on acid secretion depends upon the initial pattern of gastritis. People with an antral-predominant, body-sparing, non-atrophic gastritis have high stimulated acid production due to low somatostatin production in the antrum, higher gastrin levels compared with non-infected controls and so higher acid production by the uninflamed gastric corpus. Clinically, duodenal ulcer and non-ulcer dyspepsia are common in this group. In contrast, people with body-predominant and atrophic gastritis affecting the gastric body have low acid production despite the same hormonal changes. This phenotype is associated with premalignant gastric lesions and with an increased

Table 1 Grades of recommendation and evidence levels in support of the recommendations formulated in the Maastricht IV / Florence Consensus Report

Grade of recommendation*	Evidence level		Type of studies
A	1	1a	Systematic review of randomised controlled trial (RCT) of good methodological quality and with homogeneity
		1b	Individual RCT with narrow CI
		1c	Individual RCT with risk of bias
B	2	2a	Systematic review of cohort studies (with homogeneity)
		2b	Individual cohort study (including low quality RCT, eg <80% follow-up)
		2c	Non-controlled cohort studies/ecological studies
	3	3a	Systematic review of case–control studies (with homogeneity)
		3b	Individual case–control study
C	4		Case series/poor quality cohort or case–control studies
D	5		Expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles'

*The highest grade of recommendation does not always correspond to the highest evidence level.

risk for gastric cancer.[16 17] Therefore it can be concluded that the pattern of gastritis and associated disturbance in acid secretion determine disease outcomes. In both situations, treatment of *H pylori* resolves the gastritis and leads to an, at least partial, correction of the high or low acid state. While interesting, these changes in acid production after *H pylori* treatment have no proven clinical relevance and they should not be used as an argument to treat or not to treat *H pylori*.

H pylori and gastro-oesophageal reflux disease (GORD)

Statement 5: On average, *H pylori* status has no effect on symptom severity, symptom recurrence and treatment efficacy in GORD. *H pylori* eradication does not exacerbate pre-existing GORD or affect treatment efficacy.

Evidence level: 1a **Grade of recommendation: A**

Statement 6: Epidemiological studies show a negative association between the prevalence of *H pylori* and the severity of GORD and incidence of esophageal adenocarcinoma.

Evidence level: 2a **Grade of recommendation: B**

At a population level, *H pylori* and GORD are negatively associated,[18] and this is most marked for cytotoxin-associated gene product (CagA)-positive strains of *H pylori*. A review of 26 studies showed a rate of *H pylori* infection in patients with GORD of 39% compared with 50% in controls.[19] Similarly, the sequelae of GORD, such as Barrett's oesophagus and oesophageal adenocarcinoma, are also less common in infected individuals.[20] However, eradication of *H pylori* in populations of infected patients, on average, neither causes nor exacerbates GORD.[21–23] Therefore the presence of GORD should not dissuade practitioners from *H pylori* eradication treatment where indicated. In addition, the long-term efficacy of proton pump inhibitor (PPI) maintenance treatment for GORD is not influenced by *H pylori* status.[24] An interesting phenomenon has been observed whereby some *H pylori*-positive patients may develop a sudden-onset, transient epigastric pain shortly after the start of PPI treatment for reflux, but this again should not affect decisions on management, and more studies are needed to confirm and explore this phenomenon.[25]

H pylori, aspirin and NSAIDs

Statement 7: H pylori infection is associated with an increased risk of uncomplicated and complicated gastroduodenal ulcers in NSAID and low-dose aspirin (acetosalicylic acid (ASA)) users.

Evidence level: 2a **Grade of recommendation: B**

Eradication reduces the risk of complicated and uncomplicated gastroduodenal ulcers associated with either NSAID or low-dose ASA use.

Evidence level: 1b **Grade of recommendation: A**

Statement 8: H pylori eradication is beneficial before starting NSAID treatment. It is mandatory in patients with a peptic ulcer history.

Evidence level: 1b **Grade of recommendation: A**

However, *H pylori* eradication alone does not reduce the incidence of gastroduodenal ulcers in patients already receiving long-term NSAID treatment. They require continued PPI treatment as well as eradication treatment.

Evidence level: 1b **Grade of recommendation: A**

Statement 9: Testing for *H pylori* should be performed in ASA users with a history of gastroduodenal ulcer. The long-term incidence of peptic ulcer bleeding is low in these patients after receiving eradication even in the absence of gastroprotective treatment.

Evidence level: 2b **Grade of recommendation: B**

Both *H pylori* infection and NSAID use are independent risk factors for the development of peptic ulcer disease and associated bleeding and these conditions are uncommon in those who do not have either risk factor. It has been shown that there is an increased risk when these factors are both present.[26] There is a difference between naive users and those receiving long-term NSAID treatment in the benefits of searching for, and eradicating, *H pylori*. In naive users it is clearly beneficial to eradicate *H pylori*.[27 28] In those who are already long-term users there is no clear benefit.[29–31] A meta-analysis showed, however, that eradication seems less effective than treatment with a maintenance PPI for preventing NSAID-associated ulcers.[32] Further research is needed on whether selective cyclo-oxygenase-2-inhibiting NSAIDs may be safer options. For aspirin, even given at low dose, *H pylori* eradication can prevent gastropathy and should be undertaken in patients with a history of peptic ulcers.[33 34] In such patients, the residual risk of peptic ulcer bleeding due to continued aspirin use after *H pylori* has been successfully treated is very low.[35]

H pylori and PPIs

Statement 10a: Long-term treatment with PPIs in *H pylori*-positive patients is associated with the development of a corpus-predominant gastritis. This accelerates the process of loss of specialised glands, leading to atrophic gastritis.

Evidence level: 1c **Grade of recommendation: A**

Statement 10b: Eradication of *H pylori* in patients receiving long-term PPIs heals gastritis and prevents the progression to atrophic gastritis. However, there is no evidence that this reduces the risk of gastric cancer.

Evidence level: 1b **Grade of recommendation: A**

Acid suppression affects the pattern and distribution of gastritis and favours corpus-predominant gastritis. It may accelerate the process of loss of specialised glands, leading to atrophic gastritis. In *H pylori*-positive patients, active inflammation increases in the corpus and decreases in the antrum during PPI treatment.[36 37] This shift in gastritis appears to be accompanied by an increase in corpus atrophy.[38 39] Studies in *H pylori*-infected Mongolian gerbils showed that PPI treatment accelerated the progression to gastric cancer.[40 41] But there are no such data in humans.

H pylori and intestinal metaplasia

Statement 11a: There is accumulating evidence that after *H pylori* eradication, corpus function may improve. However, whether this is associated with regression of atrophic gastritis remains equivocal.

Evidence level: 2a **Grade of recommendation: B**

Statement 11b: There is no evidence that *H pylori* eradication can lead to regression of intestinal metaplasia.

Evidence level: 2a **Grade of recommendation: B**

H pylori eradication has the potential to prevent gastric cancers.[42] A study on the effect of *H pylori* eradication on patients with premalignant lesions showed that eradication may prevent their progression.[43] It is thought though that a so-called 'point of no return' may exist in the histological cascade from chronic gastritis to adenocarcinoma after which eradication is unlikely to prevent gastric cancer. It appears that by the time intestinal metaplasia (IM) has become established eradication, although retarding the progression of IM, cannot completely prevent gastric cancer.[44 45] This is not necessarily true for gastric atrophy, where there appears to be a discrepancy between the effect of eradication in the corpus and in the antrum. A meta-analysis of 12 studies on 2658 patients concluded that eradication of *H pylori* results in significant improvement in atrophy in the corpus but not in the antrum, but has no effect on gastric IM.[46]

H pylori and gastric mucosa-associated lymphoid tissue (MALT) lymphoma

Statement 12: H pylori eradication is the first-line treatment for low-grade gastric marginal zone (MALT) lymphoma.

Evidence level: 1a **Grade of recommendation: A**

Low-grade MALT lymphoma accounts for approximately 50% of cases of gastrointestinal non-Hodgkin's lymphoma. Most are linked to *H pylori* infection and in the early (lugano I/II) stage low-grade MALT lymphoma can be cured by *H pylori* eradication in 60–80% of cases.[47–49] When the t(11,18) translocation is present, however, *H pylori* eradication is usually ineffective and these patients need adjunctive and alternative treatments.[50] All patients should be followed up intensively after *H pylori* treatment and given alternative treatments (chemotherapy or radiotherapy) if the lymphoma fails to respond or progresses.[51]

H pylori and extragastric diseases

Statement 13: There is evidence linking *H pylori* to the aetiology of otherwise unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura (ITP) and vitamin B12 deficiency. In these disorders, *H pylori* should be sought and eradicated.

Iron-deficiency anaemia

Evidence level: 1a **Grade of recommendation: A**

ITP

Evidence level: 1b **Grade of recommendation: A**

Vitamin B12 deficiency

Evidence level: 3b **Grade of recommendation: B**

The evidence available shows no unequivocal causative association between *H pylori* and other extragastric disorders, including cardiovascular and neurological disorders.

Statement 14: The evidence available shows no definite causative protective effect of *H pylori* against the following disorders nor that its eradication causes or worsens them. However, further research is needed.

1. Asthma and atopy

2. Obesity and related illnesses

Statement 15: In *H pylori*-positive patients eradication treatment improves the bioavailability of thyroxine and l-dopa.

Evidence level: 2b **Grade of recommendation: B**

The association of *H pylori* with unexplained iron-deficiency anaemia has been conclusively proved in adult and paediatric populations. Two separate meta-analyses in recent years have supported this association with one illustrating a clear link between *H pylori* infection and iron- deficiency anaemia and the other showing that *H pylori* eradication increases haemoglobin levels in these patients.[52 53] Similarly, for adults with ITP, systematic reviews of past literature have shown an overall platelet response in more than 50% of the patients successfully treated for the infection and increased response rates in countries with a high prevalence of *H pylori* infection in background populations.[54–56]

Interesting associations have been noted between *H pylori* and several neurological conditions, including stroke, Alzheimer's disease and idiopathic Parkinson's disease. However, these are insufficient to make a clear causal or therapeutic link.[57–59] A similar situation pertains with respect to ischaemic heart disease, with several studies showing an association with disease.[60–62] The strongest link between these conditions and *H pylori* infection pertains to infection with a CagA-positive strain. One study showed that seropositivity to CagA was significantly associated with the occurrence of acute coronary events.[63] Inverse associations have been observed between the declining rates of *H pylori* infection in some communities and the increasing prevalence of certain diseases such as asthma and obesity. Childhood infection with *H pylori* was negatively associated with asthma and allergy in a widely reported US cohort.[64] However, this phenomenon was not observed in a longitudinal community-based study which looked at serological markers of *H pylori* infection in Europe.[65] A large, population-based US cohort failed to show an association between *H pylori* status and body mass index (BMI).[66]

H pylori infection has been linked with impaired absorption of certain drugs. The mechanism for this probably lies in decreased acid secretion in infected patients.[67] Clear associations have been observed between *H pylori* infection and poor bioavailability of both thyroxine and l-dopa, whereas *H pylori* treatment improves the bioavailability of both these drugs.[68 69] However, there is no evidence that this is of direct clinical benefit to patients.

H pylori virulence factors and host genetic polymorphisms

Statement 16: Certain *H pylori* virulence factors and certain host genetic polymorphisms are known to affect the risk of any specific individual developing H. *pylori*-associated disease. However, there is no evidence that strategies based on testing for these factors are useful for an individual patient.

Across populations, numerous studies have linked bacterial virulence factors and host genetic polymorphisms to patterns of gastritis and risk of disease, particularly peptic ulcer and gastric cancer.[70–74] When combined, these markedly affect disease risk—for instance, one study showed an increased risk of gastric cancer with an OR of 87 when patients who were infected with strains with a particular vacuolating cytotoxin genotype (*vacA* s1) also happened to have a specific interleukin 1β genotype (the T carrier polymorphism of IL-1B-511).[75] However, it is not yet possible to define a clinical role for testing for either bacterial virulence factors or host genetic polymorphisms in the management of individual patients.

MANAGEMENT OF *H PYLORI* INFECTION (WORKSHOP 2)

Diagnosis non invasive tests

Statement 1: The diagnostic accuracy of the stool antigen test (SAT) is equivalent to the UBT if a validated laboratory-based monoclonal test is used.

Evidence level: 1a **Grade of recommendation: A**

Several non-invasive *H pylori* tests are established in clinical routine.

The UBT using essentially [^{13}C]urea remains the best test to diagnose *H pylori* infection, has a high accuracy and is easy to perform.[76] During recent years new formats of the SAT using monoclonal antibodies instead of polyclonal antibodies, which lead to a constant quality of the reagents have been developed. The two formats available are: (1) laboratory tests (ELISAs) and (2) rapid in-office tests using an immunochromatographic technique. A meta-analysis of 22 studies including 2499 patients showed that laboratory SATs using monoclonal antibodies have a high accuracy both for initial and post-treatment diagnosis of *H pylori*.[77] These data have been confirmed by more recent studies.[78 79] In contrast, the rapid in-office tests have a limited accuracy.[80 81]

Therefore, when a SAT has to be used the recommendation is to use an ELISA format with a monoclonal antibody as reagent.

Statement 2: The serological tests are not all equivalent. Only validated IgG serology tests should be used owing to variability in the accuracy of different commercial tests.

Evidence level: 1b **Grade of recommendation: B**

Statement 3: A validated IgG serology may be used in the setting of recent use of antimicrobial* and antisecretory drugs, or ulcer bleeding, atrophy and gastric malignancies.

Evidence level: 1b **Grade of recommendation: B**

*Expert opinion (5D).

Serology is the third method commonly used as a non-invasive method to diagnose *H pylori* infection. Given that this infection is a chronic infection, IgG detection is only considered and the favoured method is ELISA.

Commercial tests use different antigen extracts. It appears that those with high and low molecular weight are more specific. The accuracy of the various commercial tests has been compared using well-documented serum samples,[82 83] and showed marked variability. There are, however, several kits with an accuracy >90%. Only these validated commercial tests should be used.

As was already stated at previous Maastricht conferences, serology is the only test which is not affected by local changes in the stomach that could lead to a low bacterial load and to false-negative results of the other tests. This is owing to the fact that antibodies against *H pylori* and especially against its most specific antigen CagA, remain elevated despite transient decreases of the bacterial load and even for long periods (months, even years) after the disappearance of *H pylori* from the stomach.[84]

Decreases of the gastric *H pylori* bacterial load arise from the use of antimicrobial agents, of antisecretory drugs and ulcer bleeding (see also the 'Treatment' section). Also, bacterial load may be permanently low in premalignant and malignant lesions, including extensive IM or MALT lymphoma.[85 86]

H pylori serology combined with serum pepsinogen I/II ratio may constitute a non-invasive method to detect premalignant conditions, although it has a limited sensitivity.[87]

- Test-and-treat strategy (cf. Statement 1, workshop 1)

This approach proposed at the Maastricht 2 Conference[2] is reviewed in the first part of this article.

- Diagnosis of *H pylori* infection in patients treated with PPI

Statement 4: In patients treated with PPIs: (1) if possible, PPI should be stopped for 2 weeks before testing by culture, histology, rapid urease test, UBT or stool test.

Evidence level: 1b **Grade of recommendation: A**

(2) if it is not possible, validated IgG serology can be performed.

Evidence level: 2b **Grade of recommendation: B**

PPIs are now widely available since some are generic drugs and even over-the-counter drugs in some countries. Because of their efficacy in treating pain and heartburn, they are widely used for symptomatic treatment of dyspepsia. As a consequence, when a patient consults for dyspeptic symptoms, there is a good chance that she/he is receiving a PPI treatment.

Several studies have shown that by increasing the gastric pH, PPI use leads to local changes in the stomach. The bacterial load decreases, especially in the antrum, causing false-negative results of the diagnostic tests, with the exception of serology.

Most of the studies have been carried out with UBT and showed a 10–40% rate of false-negative results.[88 89] Similar results were obtained with the SAT[90 91] and it has also proved to be the case with biopsy based tests (including culture, rapid urease test and histology)[92] but PCR has not been evaluated.

Histology leads to more controversial results: the pathologists specialised in this field still consider this method suitable for diagnosing *H pylori* in the absence of detectable bacteria but in the presence of surrogate features (ie, polymorphonuclear cells), whereas other pathologists may not share the same opinion.

Given that *H pylori* antibodies remain present for months after suppression and even eradication of *H pylori*, serology is the only test not to be affected.

However, stopping PPIs 2 weeks before testing allows the bacteria to repopulate the stomach and the tests previously negative (UBT, SAT, rapid urease test, histology, culture) can once again become positive. Furthermore, no study has evaluated the washout period necessary after long-term PPI treatment. For UBT a study claimed that the use of a more acidic test meal would overcome the problem of false-negative tests.[93] Anti H_2 drugs may also lead to some false-negative results but to a much lesser extent[94 95] and the panel did not find it necessary to stop them before testing if using citric acid.

Endoscopy-based strategy

Statement 5: (1) It is important to perform culture and standard susceptibility testing to antimicrobial agents in a region or population of high clarithromycin resistance before prescription of the first-line treatment if the standard clarithromycin-containing triple therapy is being considered. Furthermore, culture and standard susceptibility testing should be considered in all regions before second-line treatment if endoscopy is carried out for another reason and generally when a second-line treatment has failed.

Evidence level: 5 **Grade of recommendation: D**

(2) If standard susceptibility testing is not possible, molecular tests can be used to detect *H pylori* and clarithromycin and/or fluoroquinolone resistance directly on gastric biopsies.

Evidence level: 1b **Grade of recommendation: A**

When an endoscopy is performed, biopsy-based tests such as a rapid urease test, histology and culture can be carried out. The interest of culture is mainly due to the possibility of performing antimicrobial susceptibility testing. The rationale relates to the fact that in the case of clarithromycin resistance the rate of success of the clarithromycin-containing triple therapy is very low, in the range of 10–30%.[96 97] Several studies using tailored treatments based on *H pylori* susceptibility to antibiotics in comparison with standard empirical triple therapy have shown a better eradication rate[98] and may be cost-effective. While the cost-effectiveness may vary according to the cost of care in a given country, it is the expert's opinion that this approach is economically and ecologically sound in countries of high clarithromycin resistance or in specific populations in some areas.

After a first failure, if an endoscopy is carried out, culture (and standard susceptibility testing) should be considered in all regions before giving a second-line treatment because the chance of having a resistant organism is high, in the range of 60–70% for clarithromycin.

After a second failure, it should be performed in all cases as already recommended at the previous Maastricht conference.[3]

If culture (and standard susceptibility testing) is not possible, molecular tests (including fluorescence in situ hybridisation) can be used to detect *H pylori* and clarithromycin and/or fluoroquinolone resistance in gastric biopsies. Such tests have been developed recently[99–101] and kits are commercially available,[102 103] but it must be noted that the accuracy of fluoroquinolone molecular testing is not as reliable as for clarithromycin.

Attempts have been made to use stools instead of gastric biopsy specimens.[104] Owing to an improved sensitivity, molecular tests may detect resistant organisms when they constitute a small proportion of the total bacterial load present. Further studies will determine if molecular tests predict failure more accurately or not than phenotypic tests.[105]

It must be stated that there is a cross-resistance in each family of antibiotics because the same resistance mechanism occurs: resistance to clarithromycin indicates resistance to all macrolides, resistance to levofloxacin indicates resistance to all fluoroquinolones including moxifloxacin, for example. There is no cross-resistance between different families of antibiotics which have different resistance mechanisms.[106] However, it is important to use the compound indicated—that is, clarithromycin for macrolides, tetracycline HCl and not doxycycline, levofloxacin or moxifloxacin but not ciprofloxacin for fluoroquinolones to get good results.

Statement 6: (1) If *H pylori* is cultured from gastric biopsy specimens, antibiotic susceptibility testing should include metronidazole.

Evidence level: 1b **Grade of recommendation: A**

(2) If susceptibility for clarithromycin is assessed by molecular tests, the addition of culture for the assessment of metronidazole resistance is not justified.

Evidence level: 5 **Grade of recommendation: D**

The rationale is that standard metronidazole susceptibility testing lacks reproducibility[107] and no molecular alternative exists.

It was shown, however, that globally metronidazole resistance, as determined, is associated with a lower *H pylori* eradication rate (from 5% to 25%)[96] also in sequential treatment[108] compared with cases where the strain is metronidazole susceptible and that increasing metronidazole dosage and treatment duration may partially overcome resistance.

Treatment

Regimens available

- The triple treatment including PPI-clarithromycin and amoxicillin or metronidazole proposed at the first Maastricht conference[1] to treat *H pylori* infection has become universal since it was recommended by all the consensus conferences held around the world. However, the most recent data show that this combination has lost some efficacy and often allows the cure of only a maximum of 70% of the patients, which is less than the 80% rate aimed for at the beginning and far below what should be expected for an infectious disease.[109]
- While no new drug has been developed for this indication, a number of studies have been carried out in recent years using different combinations of known antibiotics. Most data were obtained with the so-called 'sequential treatment' which includes a 5-day period with PPI amoxicillin, followed by a 5-day period with PPI-clarithromycin-metronidazole (or tinidazole).[110 111]
- It was also proposed that the three antibiotics should be taken simultaneously together with a PPI (non-bismuth quadruple therapy).[112 113]
- There was also a renewal of the old recipe—that is, the bismuth-containing quadruple therapy following the development of a gallenic formulation including bismuth salts, tetracycline and metronidazole in the same pill.[114–116] A summary of treatment strategies is shown in tables 2 and 3.

Statement 7: PPI-clarithromycin-containing triple therapy without prior susceptibility testing should be abandoned when the clarithromycin resistance rate in the region is more than 15–20%.

Evidence level: 5 **Grade of recommendation: D**

There are several explanations for the decrease in efficacy of the standard triple therapy: compliance, high gastric acidity, high bacterial load, type of strains, but by far the most important is the increase in *H pylori* resistance to clarithromycin. The global clarithromycin resistance rate in Europe increased from 9% in 1998[117] to 17.6% in 2008–9.[118] Resistance increased in most parts of Europe, but it has now reached a prevalence >20% in most countries in Central, Western and Southern Europe, which is considered a high resistance rate. In Northern European countries it is <10%, which is considered a low resistance rate.[97]

Following the European Medicines Agency recommendation on evaluation of medicinal products indicated for treatment of bacterial infection, three categories of bacterial species can be defined according to their susceptibility to a given antibiotic: usually susceptible (0–10% resistant), inconstantly susceptible (10–50% resistant) and usually resistant (>50% resistant). *H pylori* now falls into the second category, except for Northern Europe.[119]

In order to take into account the CIs of the prevalence obtained and the regional differences in a given country, a threshold of 15–20% was recommended to separate the regions of high and low clarithromycin resistance (figure 1).

Regions of low clarithromycin resistance

First-line treatment.

Statement 8: In areas of low clarithromycin resistance, clarithromycin-containing treatments are recommended for first-line empirical treatment. Bismuth-containing quadruple therapy is also an alternative.

Evidence level: 1a **Grade of recommendation: A**

In these regions the standard PPI-clarithromycin-containing regimen is still recommended as the first-line treatment as well as bismuth-containing regimens.

Different ways of improving the PPI-clarithromycin-amoxicillin/metronidazole regimens have been proposed:

- Increase the dose of PPI.

Table 2 Summary of treatment strategies

Statement	Level of evidence	Grade of recommendation
Proton pump inhibitor (PPI)-clarithromycin containing triple therapy without prior susceptibility testing should be abandoned when the clarithromycin resistance rate in the region is over 15–20%	5	D
In areas of low clarithromycin resistance, clarithromycin- containing treatments are recommended for first-line empirical treatment. Bismuth-containing quadruple treatment is also an alternative	1a	A
In areas of high clarithromycin resistance, bismuth-containing quadruple treatments are recommended for first-line empirical treatment. If this regimen is not available sequential treatment or a non-bismuth quadruple treatment is recommended	1a	A
The use of high-dose (twice a day) PPI increases the efficacy of triple therapy	1b	A
Extending the duration of PPI-clarithromycin-containing triple treatment from 7 to 10–14 days improves the eradication success by approximately 5% and may be considered	1a	A
PPI-clarithromycin-metronidazole (PCM) and PPI-clarithromycin-amoxicillin (PCA) regimens are equivalent	1a	A
Certain probiotics and prebiotics show promising results as an adjuvant treatment in reducing side effects	5	D
PPI-clarithromycin-containing treatments do not need to be adapted to patient factors except for dosing	5	D
After failure of a PPI-clarithromycin containing therapy, either a bismuth containing quadruple therapy of Levofloxacin containing triple therapy are recommended.	1a	A
Rising rates of Levofloxacin resistance should be taken into account	2b	B
After failure of second-line treatment, treatment should be guided by antimicrobial susceptibility testing whenever possible	4	A
The urea breath test or a laboratory based validated monoclonal stool test are both recommended as non-invasive tests for determining the success of eradication treatment. There is no role for serology	1a	A

Statement 9: The use of high-dose (twice a day) PPI increases the efficacy of triple therapy.

Evidence level: 1b **Grade of recommendation: A**

There is indirect and direct evidence that high-dose PPI can improve the cure rates of *H pylori* treatment.

Indirect evidence comes from old multiple studies showing that high-dose PPI was necessary for the efficacy of dual therapies and the meta-analysis showing that twice-a-day PPI was better than a single daily dose in triple therapy.[120] In addition, cure rates of standard triple therapy depend on the availability of PPI, which itself depends on the CYP2C19 and MDR polymorphisms. A meta-analysis showed that extensive PPI metabolisers had lower eradication rates, while the difference was only seen with omeprazole.[121] A lower eradication rate was also obtained when the MDR T/T genotype was present compared with the T/C and C/C genotypes.[122]

Direct evidence comes from a meta-analysis showing that high-dose PPIs increase cure rates by around 6–10% in comparison with standard doses.[123] A subanalysis of these data showed that the maximal effect was seen in the studies comparing high doses of the more potent second-generation PPIs—namely, 40 mg of esomeprazole twice a day, with a standard dose of a first-line PPI also twice a day.[123] The rationale for this finding is that the difference in the degree of gastric secretion between arms is more important when using double doses of more potent PPIs. According to the data of this last subanalysis, increasing the dose of PPI from, for example, 20 mg omeprazole twice daily to 40 mg of esomeprazole or rabeprazole twice daily may increase cure rates by 8–12%.

- Increase the length of treatment.

Statement 10: Extending the duration of PPI-clarithromycin-containing triple therapies from 7 to 10–14 days improves the eradication success by about 5% and may be considered.

Evidence level: 1a **Grade of recommendation: A**

Four meta-analyses have been carried out and yielded very similar results, that is, a 10-day treatment improves the eradication rate by 4% and a 14-day treatment improves the eradication rate by 5-6%, in comparison to a 7-day treatment.[124–127] There was no difference regarding the rate of side effects. While the difference in efficacy is statistically significant, they may be considered relevant or not, according to other factors such as cost.

- use metronidazole instead of amoxicillin as the second antibiotic.

Statement 11: PPI-clarithromycin-metronidazole (PCM) and PPI-clarithromycin-amoxicillin (PCA) regimens are equivalent.

Evidence level: 1a **Grade of recommendation: A**

The meta-analysis of Gisbert *et al*[128] was updated for the Maastricht IV conference. A subanalysis was performed on the trials using the same high dose of clarithromycin (500 mg) in both arms, showing an eradication of 71% for PCM and 65% for PCA, but the difference did not reach statistical significance (OR=0.82 (95% CI 0.58 to 1.16)).

When the PCM and PCA regimens were compared in patients with clarithromycin-resistant strains, a statistically significant difference was seen ($p<0.001$), but this difference may be due to the heterogeneity of the studies. The few comparative studies analysed could not ascertain whether the differences observed were truly due to an effect of treatment or to confounders.

- Adding an adjuvant treatment.

Statement 12: Certain probiotics and prebiotics show promising results as an adjuvant treatment in reducing side effects.

Evidence level: 5 **Grade of recommendation: D**

Lactoferrin has been used to improve *H pylori* treatment. Two meta-analyses obtained the same results and showed that lactoferrin increases the efficacy of PPI-clarithromycin-containing triple therapies.[129 130] However, the poor quality of many trials and the limited number of centres involved should be emphasised and preclude giving a positive recommendation.

Meta-analyses on the studies where Lactobacilli were used are heterogeneous as they mix different species and strains. Additional work needs to be performed to determine the strain, dose and administration to be used.[131 131a]

A meta-analysis on the use of *Saccharomyces boulardii* as adjuvant to triple therapy showed promising results (OR=0.46 (95% CI 0.3 to 0.7)).[132]

All these treatments are most likely to lead to a decrease of adverse events, especially diarrhoea and indirectly may help to improve the eradication rate. More studies need to be performed.

- Other factors.

Statement 13: PPI-clarithromycin-containing treatments do not need to be adapted to patient factors except for dosing.

Evidence level: 5 **Grade of recommendation: D**

Besides the CYP2C19 and MDR1 polymorphisms, which affect the availability of the PPI administered, and the interleukin (IL)-1β polymorphisms, which affect the intragastric acidity present in the stomach in the case of *H pylori* infection, other factors have been considered: type of disease, BMI and smoking status.

Treating patients with peptic ulcer disease shows a consistently better outcome than treating patients with FD. Several studies have shown an association between clarithromycin resistance and FD status of the patients[133] without pinpointing the causes.

In patients with high BMI, especially obese people, the distribution volume of the drugs being higher, it is most likely that the concentration at the gastric mucosal level will be lower and the risk of failure higher.[134] In contrast, Asian patients who usually have a lower BMI will have a better outcome.

Smoking is also a risk factor for failure. The summary OR for eradication failure among smokers versus non-smokers was 1.95 (95% CI 1.55 to 2.45) corresponding to a mean difference of 8.4% in eradication rate in a meta-analysis.[135] The reason may be a reduction of antibiotic delivery due to a decreased gastric blood flow, a decrease in intragastric pH in cases of smoking, and nicotine could potentiate the vacuolating toxin activity of *H pylori* in gastric cells. It may also be a marker of poor compliance.

Second-line treatment.

Statement 14: (1) After failure of a PPI-clarithromycin-containing treatment, either a bismuth-containing quadruple therapy or levofloxacin-containing triple therapy is recommended.

Evidence level: 1a **Grade of recommendation: A**

(2) Rising rates of levofloxacin resistance should be taken into account.

Evidence level: 2b **Grade of recommendation: B**

The rationale is to abandon clarithromycin in an empirical second-line-treatment because there is a likelihood that selection of a clarithromycin-resistant strain occurred. Three pragmatic studies have evaluated the Maastricht 3 guidelines—that is, the sequence of triple therapy followed by quadruple therapy, in routine clinical practice.[136–138] The three studies show that a high rate of eradication success can be achieved with the Maastricht 3 approach. Studies from Asia suggest that quadruple therapy is also effective as a second-line treatment in Asia.[139] A recent meta-analysis of quadruple therapy showed that metronidazole resistance had limited effect on the outcome when adequate dosages and durations are used. This meta-analysis also showed that compliance with quadruple therapy is high.[116 140] Recent studies of quadruple therapy using a single capsule preparation have shown good efficacy[114–116] This treatment meets the proposed criteria for a second-line treatment[136]: it does not contain the key antibiotic of the original regimen (clarithromycin),[137] the treatment is not affected by clarithromycin resistance,[139] metronidazole resistance in vitro does not affect the outcome of quadruple therapy significantly,[140] compliance with the regimen is high[115] and the regimen is effective in most parts of the world.

Use of 10-day PPI-levofloxacin-amoxicillin is the other alternative second-line treatment based on the results obtained in recent years.[141 142] However, the rapid acquisition of resistance may jeopardise its future efficacy. It is strongly advised that levofloxacin should not be used in a patient with chronic infectious bronchopneumopathy who may have received fluoroquinolones. Whenever possible it is recommended to test levofloxacin susceptibility before to prescribe it.

Third-line treatment.

Statement 15: After failure of second-line treatment, treatment should be guided by antimicrobial susceptibility testing whenever possible.

Evidence level: 4 **Grade of recommendation: A**

After two treatment failures, it appears recommendable to empirically prescribe antibiotics not previously used but, whenever possible, to obtain gastric biopsy specimens to culture *H pylori* and perform susceptibility testing.[143 144] It will enable the best choice to be made among the various antibiotics that can be used and to which *H pylori* may develop resistance. Besides clarithromycin and levofloxacin already mentioned, rifabutin is another candidate that may be used.[138 145 146]

Regions or populations of high clarithromycin resistance

First-line treatment.

Statement 16: In areas of high clarithromycin resistance, bismuth-containing quadruple therapies are recommended for first-line empirical treatment. If this regimen is not available, sequential treatment or a non-bismuth quadruple therapy is recommended.

Evidence level: 1a **Grade of recommendation: A**

In regions of high clarithromycin resistance, bismuth-containing quadruple therapies are the first choice. It appears mandatory to avoid clarithromycin use in the standard regimen under such circumstances if this antibiotic cannot be tested. The treatment recommended contains bismuth salts for which no resistance has been described, tetracycline for which resistance is seldom found in Europe and metronidazole for which in vitro resistance is common but can be overcome by increasing the length of treatment.

Several studies have shown good results with such regimens. Furthermore, despite the number of pills, the compliance was satisfactory and the bismuth-containing regimens do not lead to more adverse events than the standard clarithromycin-containing triple therapy.[147]

However, bismuth drugs may not be available in some areas. It is then necessary to prescribe sequential treatment. While not ideal because it contains clarithromycin, it has been shown that clarithromycin resistance could be overcome in a number of cases. Indeed, the success rate with clarithromycin-resistant strains was 75%.[110] Non-bismuth quadruple therapy (the so called 'concomitant' treatment) is also an option.

Second line therapy.

Statement 17: (1) In areas of high clarithromycin resistance after failure of bismuth-containing quadruple therapy, levofloxacin containing triple therapy is recommended.

Evidence level: 5 **Grade of recommendation: D**

(2) Rising rates of levofloxacin resistance should be taken into account.

Evidence level: 2b **Grade of recommendation: B**

After failure of the second-line treatment (with bismuth-containing quadruple regimen), it is recommended to use the PPI-containing levofloxacin regimen.[141 142] However, given the rise in resistance to this antibiotic, the prevalence must be taken into account.

Third-line therapy.

Statement 18: After failure of second-line therapy, treatment should be guided by antimicrobial susceptibility testing, whenever possible.

Evidence level: 4 **Grade of recommendation: A**

The recommendation is the same as in areas of low clarithromycin resistance.

Treatment options in patients with penicillin allergy

Statement 19: In patients with penicillin allergy, in areas of low clarithromycin resistance, for a first-line treatment, a PPI-clarithromycin-metronidazole combination may be prescribed and in areas of high clarithromycin resistance, the bismuth-containing quadruple therapy should be preferred.

As a rescue regimen, in areas of low fluoroquinolone resistance, a levofloxacin-containing regimen (together with a PPI and clarithromycin) represents a second-line alternative in the presence of penicillin allergy.

Evidence level: 2c **Grade of recommendation: B**

In this relatively common subgroup of patients, a triple therapy including a PPI, clarithromycin and metronidazole represents one of the most frequently recommended regimens in areas of low clarithromycin resistance.[148] A PPI, tetracycline, metronidazole regiment[149] is a better alternative in areas with high clarithromycin resistance, as well as the bismuth-containing quadruple therapy.

As a rescue treatment, levofloxacin is a good alternative[150] but its efficacy might be jeopardised by high resistance rates in some areas.

Follow-up after *H. pylori* treatment

Statement 20: The UBT or a laboratory-based validated monoclonal stool test are both recommended as non-invasive tests for determining the success of eradication treatment. There is no role for serology.

Evidence level: 1a **Grade of recommendation: A**

Statement 21: The time for testing the success of *H pylori* eradication after the end of treatment should be at least 4 weeks.

Evidence level: 2b **Grade of recommendation: B**

In special cases where a gastric ulcer or gastric MALT lymphoma has been diagnosed, follow-up is necessary with upper digestive endoscopy and then biopsy-based tests can be performed for

confirmation of *H pylori* eradication. In other situations, a non-invasive test is used.

There is now overwhelming evidence that UBT is an excellent test for follow-up after *H pylori* eradication.[76] The discussion concerns the timing after the end of eradication treatment. The relapse rate seen in the 6 months or the year after *H pylori* eradication is mainly related to recurrence of the same infection rather than a true reinfection. The proposed period of 4 weeks has therefore been questioned and proposals have been made to extend it to 6 or 8 weeks. However, recent data do not support this proposal.

Statement 22: (1) In uncomplicated duodenal ulcer (DU), prolonging acid inhibition with PPI is not recommended after *H pylori* treatment.

Level: 1a **Grade of recommendation: A**

(2) In gastric ulcers (GUs) and complicated DUs, prolonging PPI is recommended.

Level: 1b **Grade of recommendation: A**

H pylori is the key factor in peptic ulcer development and eradication is recommended for both DUs and GUs, as it has been shown that *H pylori* eradication effectively achieves ulcer healing rates of >90%.[151 152] Moreover, prolonged acid inhibition with PPI is not required after successful *H pylori* eradication in uncomplicated DU.[153 154]

On the other hand, data on the need to prolong PPI for GU healing after successful eradication are controversial.[154–156] GU requires longer acid inhibition for healing than DU and endoscopic follow-up is needed to ensure complete GU healing. *H pylori* eradication should be confirmed in GU. However, prolonged PPI is also beneficial for improving healing when eradication has failed. Similarly, studies on complicated DU and GU also recommend prolonged PPI treatment after eradication.[157 158] Therefore, PPI treatment should be continued after eradication treatment in GU until complete healing is achieved and in complicated DU until *H pylori* eradication is confirmed.

Statement 23: H pylori eradication treatment should be started at reintroduction of oral feeding in cases of bleeding ulcer.

Evidence level: 1b **Grade of recommendation: A**

Bleeding is a common and severe complication of peptic ulcer disease. It is well established that *H pylori* eradication can effectively prevent bleeding recurrence in infected patients.[3 159] As the effect of PPI in preventing recurrent bleeding seems to be greater in *H pylori*-positive patients, the possibility of leaving *H pylori* infection untreated until the ulcer is completely healed has been hypothesised.[160] However, it has been shown that *H pylori* infection/eradication has no effect on early rebleeding rate in patients with peptic ulcer bleeding after endoscopic haemostasis.[161 162] On the other hand, delaying treatment to after discharge leads to reduced compliance or loss to follow-up without receiving treatment.[163] Based on a decision analytic model, it has been recently proposed that empirical treatment of *H pylori* infection in patients with bleeding peptic ulcer, immediately after feeding is restarted, is the most cost-effective strategy for preventing recurrent haemorrhage.[164] The most influential variable in this analysis was the prevalence of *H pylori* infection in patients with peptic ulcer bleeding. In patients with peptic ulcer bleeding the prevalence of *H pylori* infection appears to be lower than in patients with uncomplicated peptic ulcer disease, varying, in recent European studies, from 43% to 56%, possibly explained by NSAID use.[165]

In areas of low *H pylori* infection, instead of an empirical treatment, a test-and-treat strategy should be considered. In the setting of peptic ulcer bleeding, histology and rapid urease test maintain a high specificity, but are affected by a low sensitivity, possibly leading to undertreatment.[166 167] Serology seems not to be influenced by upper gastrointestinal (GI) bleeding and has been recommended in this setting by previous Maastricht consensus reports. The accuracy of the UBT remains very high in these patients, despite PPI treatment.[168] Current consensus in upper gastrointestinal bleeding recommends performing a delayed test, 4—8 weeks after the bleeding episode.[169]

Table 3 Treatment of *Helicobacter pylori*-positive peptic ulcer diseases

Statement	Level of evidence	Grade of recommendation
In uncomplicated DU, prolonging acid inhibition with PPI is not recommended after *Helicobacter pylori* treatment	1a	A
In GU and complicated DU, prolonging PPI is recommended	1b	A
H pylori eradication treatment should be started at reintroduction of oral feeding in cases of bleeding ulcer	1b	A

DU, duodenal ulcer; GU, gastric ulcer; PPI, proton pump inhibitor.

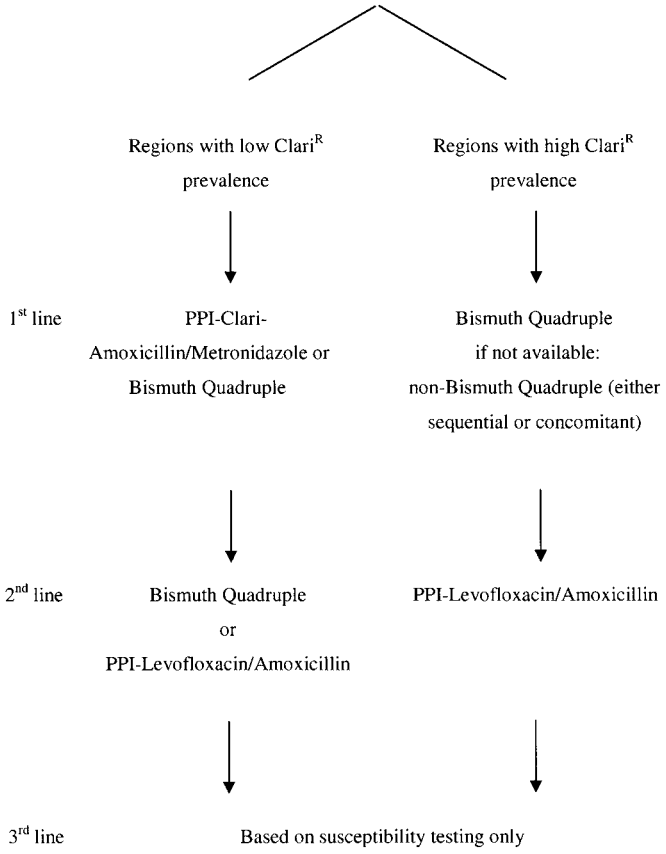

Figure 1 Treatment regimen should be selected according to areas of low and high clarithromycin resistance (Clari-R). Low prevalence of Clari-R if <20%, high prevalence if >20%. In case of failure of first-line treatment, second-line treatment is selected without resistance testing, whereas with further failure, third-line treatment should be chosen based on *Helicobacter pylori* cultures and antibiotic susceptibility testing. PPI, proton pump inhibitor.

PREVENTION OF GASTRIC CANCER AND OTHER COMPLICATIONS (WORKSHOP 3)

Statement 1: H pylori infection is the most consistent risk factor for gastric cancer. Its elimination is therefore the most promising strategy to reduce the incidence of gastric cancer

Evidence level: 1a **Grade of recommendation**: A

Based on unequivocal scientific evidence, this statement was first released in the Maastricht 3 consensus report and has since been adopted by several international guidelines, including a recent S3-guideline.[3 170–172] Scientific data collected since then reinforce the statement that *H pylori* infection is the most common proven risk factor for human non-cardiac gastric cancer.

The evidence is based on epidemiological data, experimental models in vitro and in vivo. There is biological plausibility from clinical observations and in therapeutic trials.[173 174]

In the original epidemiological reports the risk for non-cardiac gastric cancer in *H pylori* infection was estimated to be threefold but based on more accurate methodologies and with proper controls epidemiological studies indicate the risk to be 20-fold or even higher.[84 175] *H pylori* is confirmed to be a risk factor if the lesion is gastric in nature and to originate from below the cardia.[176]

In vivo experimental models have demonstrated the causal role of *H pylori* infection in the cascade leading to gastric cancer.[40 177] The transgenic expression of IL-1β (a proinflammatory and acid-suppressive cytokine) in parietal cells lead to spontaneous gastritis, mobilisation of myeloid-derived suppressor cells and gastric dysplasia. These lesions progress to carcinoma when infected with *Helicobacter felis*.[178] In a mouse model of Helicobacter-induced gastric cancer bone marrow-derived cells were implicated as the potential origin for gastric cancer.[179]

Observational and controlled trials

Eradication treatment is effective in preventing gastric cancer if it is given before preneoplastic conditions/ lesions have had time to develop. Intervention studies completed in Columbia,[180] China[181] and Japan[182] all suggest that *H pylori* eradication is the most effective approach to gastric cancer prevention, but that it is more effective in those who do not have atrophic gastritis or IM at baseline. A pooled analysis of six studies with a total of 6695 (mostly Asian) participants followed up for 4–10 years showed that the RR for gastric cancer after *H pylori* eradication was 0.65 (95% CI 0.43 to 0.98).[183] After eradication a significant reduction in cancer incidence was seen only in subjects with normal serum pepsinogen levels. This suggests that cancers developing after eradication are related to the presence of extensive atrophic gastritis present before the eradication treatment was given. *H pylori* eradication is beneficial in most subjects who have normal serum pepsinogen I and those with only mild atrophy.[184]

Early eradication of *H pylori* in gastric cancer prevention has also been shown to be successful in experimental studies using Mongolian gerbils and mice.[185 186]

Statement 2: There is strong evidence that *H pylori* infection exerts direct mutagenic effects in animal models and cell lines.

Evidence level: not quotable **Grade of recommendation: C**

H pylori causes direct mutagenic effects in mice.[187 188] This is related to the duration of infection and the gender of the animal.[189] Genetic instability of nuclear and mitochondrial DNA has also been reported in studies conducted on gastric cell lines.[190 191] *H pylori* causes preneoplastic lesions and cancer in experimental in vivo models, demonstrating the causal role of *H pylori* infection in the cascade leading to gastric cancer. The most important single carcinogenic factor of *H pylori* may be CagA, which is injected by the bacteria into the host mucosal epithelial cells. Recently, transgenic expression of CagA has been shown to lead to carcinoma in the absence of coexisting gastritis in mice. This indicates that CagA is a bacterial oncogene.[192]

There is no supportive human evidence to date, mainly because transgenic CagA expression is too artificial to be extrapolated into the human situation.

Statement 3: The risk for gastric cancer development is influenced by bacterial virulence factors, but no specific bacterial virulence markers can be recommended for clinical practice.

Evidence level: 1a **Grade of recommendation: A**

Among bacterial pathogenetic factors that carry an increased risk for gastric cancer, CagA and VacA[75 193 194] are by far the most important.

The oncogenic potential of bacterial virulence factors relates to distinct polymorphisms of CagA and VacA.[195–197] EPIYA repeats of CagA enable differentiation to be made between Eastern and Western CagA-positive strains. This work indicates that Eastern strains have a much higher virulence than Western ones. The importance of geographical variability in the oncogenic potential of bacterial virulence is reflected by the difference in cancer incidence.[198 199]

Statement 4: The risk of gastric cancer is influenced by host genetic factors but in clinical practice no specific marker can be recommended for genetic testing at present.

Evidence level: 1b **Grade of recommendation: A**

The impact of a familial risk driven by the presence of *H pylori* infection is well established[200] and is associated with host cytokine gene polymorphisms. The first observation of a polymorphism leading to an increased risk of atrophy and gastric cancer was IL-1β. Since then other genes have been reported in this context, including tumour necrosis factor α, IL-10, interferon γ, IL-8.[201–203]

Studies in a variety of geographical areas have shown wide variation in the OR for gastric cancer development that is related to altered gene expression of defined cytokine haplotypes.[204–206]

Also, polymorphisms of immune regulatory genes, including pattern recognition factors initiating the innate immune system, are reported to be associated with an increased risk for gastric cancer.[207]

Statement 5: The influence of environmental factors is subordinate to the effect of *H pylori* infection.

Evidence level: 1a **Grade of recommendation: A**

A number of nutritional and environmental elements contribute to the development of gastric cancer to various degrees. They include N-nitroso compounds, sodium and salted foods, tobacco, alcohol and others.[208–213] There is a strong association between smoking and gastric cardia adenocarcinoma.

In contrast, the association between smoking and gastric non-cardia adenocarcinoma is less consistent.[212] Most studies analysing the relationship between gastric cancer and environmental factors have not dealt with the presence or absence of *H pylori* infection.

Some nutritional substrates are claimed to provide some degree of protection against gastric cancer but there is little prospective evidence to support this.[214 215] The essential information gathered from a more recent European study is that the effect of all nutritional components is strictly dependent on the presence of *H pylori* infection and that nutrition has only a small contributing role in the absence of the infection.[216 217]

In October 2009, the International Agency for Research on Cancer, which forms part of the World Health Organization, classified acetaldehyde included in, and generated endogenously from, alcoholic beverages as a group I human carcinogen. This compound is found in alcoholic beverages and is also generated endogenously from them. Acetaldehyde which is also related to *H pylori* is a relevant carcinogen especially in patients with atrophic gastritis.[218]

Regular NSAID intake may be beneficial in preventing gastric cancer. There is some evidence for this in patients with gastric ulcer, particularly in those infected by *H pylori*.

A recent meta-analysis concluded that the regular use of aspirin was associated with a reduced risk of non-cardiac gastric cancer, especially among Caucasians.[219]

Statement 6: Histopathological changes at the morphological level indicate that:

1. gastric cancer is rare in the absence of chronic active gastritis;

2. the extent and severity of the gastritis together with atrophy and IM is positively associated with cancer.

Evidence level: 2b **Grade of recommendation**: A

Gastric cancer is a multistep and multifactorial disease. *H pylori* infection is the most important factor in the pathogenesis of chronic gastritis[42 43 220] and is an essential factor in 71–95% of all gastric cancers.[84] *H pylori* induces chronic active gastritis in all those infected.[221] Patients with corpus-dominant *H pylori* gastritis are at a substantially increased risk for gastric cancer.[222] Prospective data indicate that *H pylori*-infected subjects with atrophy and IM (5–6 × risk), pan-gastritis (15 × risk) and corpus-dominant gastritis (34 × risk) have a significantly increased risk developing gastric cancer.[223] IM and atrophy are indicators of an increased risk of malignant transformation and serve as precancerous markers.[224] IM, which occurs as a result of *H pylori* infection and after the development of atrophic gastritis,[225] is common in the human stomach and is associated with an increased risk of gastric cancer.[226 227] Intestinal-type adenocarcinoma is often preceded or accompanied by metaplastic changes, whereas diffuse-type adenocarcinoma can arise in non-metaplastic gastric mucosa. However, some cases of intestinal-type adenocarcinoma do arise from the gastric mucosa without IM.[228]

Less than 1% of gastric carcinomas can be attributed to hereditary diffuse gastric cancer. This is an autosomal dominant condition and is not related to *H pylori* infection or gastritis. The lifetime risk for gastric carcinoma for individuals with mutation of the CDH-1 gene is 40–70% for men and 60–80% for women.[229–232]

Statement 7: Mechanisms at the functional level indicate:

1. atrophic corpus gastritis causes hypochlorhydria;

2. hypochlorhydria allows the overgrowth of non-*H pylori* organisms that are capable of producing metabolites with a carcinogenic potential.

Evidence level: 2c **Grade of recommendation**: A

There is direct and indirect evidence of atrophic corpus gastritis leading to hypochlorhydria.[233] Patients with a hypochlorhydria have an overgrowth of salivary and faecal-type organisms in the gastric lumen. Studies that have compared individuals receiving acid suppression or after truncal vagotomy with controls confirm that hypochlorhydria also leads to bacterial overgrowth. Some of these organisms can reduce nitrate to nitrite, causing a rise in intraluminal nitrite. Nitrosating bacteria present in the lumen are capable of generating potentially carcinogenic N-nitrosamines and reactive oxygen species.[234–240]

Overgrowth in several bacterial species cohabiting with *H pylori* has been shown in conditions of hypochlorhydria and pharmacological acid suppression.[241 242]

The hypochlorhydric stomach contains reduced or absent concentrations of the free oxygen scavenger ascorbic acid.

Ascorbic acid is an antioxidant that scavenges carcinogenic N-nitrosamines and reactive oxygen species. It is concentrated in the gastric mucosa, and in the healthy stomach luminal concentrations are higher than in plasma. Infection with *H pylori* causes the luminal concentration to fall. In the achlorhydric stomach it disappears almost completely.[243–249]

Statement 8: H pylori eradication abolishes the inflammatory response and slows or may arrest the progression of atrophy. In some cases it may reverse atrophy.

Evidence level: 1a **Grade of recommendation**: A

In the absence of preneoplastic conditions successful *H pylori* eradication restores the inflamed gastric mucosa to normal. The active inflammatory process characterised by infiltration with polymorphonuclear cells is usually abolished within 4 weeks but chronic inflammation with lymphocytic infiltration often persists for up to 1 year.[250]

The changes associated with atrophy do regress to a certain extent, but reports are conflicting.[46 251 252] Data are limited because usually only a small number of biopsy specimens have been taken and this may lead to observer bias in its assessment. A recent meta-analysis indicated that gastric atrophy may be reversible only in the corpus, but not in the antrum. There is uniform agreement that IM is irreversible.[46 250 251 253–266]

Statement 9: There is strong evidence that *H pylori* eradication reduces the risk of gastric cancer development.

Evidence level: 1c **Grade of recommendation: A**

The plausibility of *H pylori* eradication in the prevention of gastric cancer was initially suggested based on the evidence obtained from epidemiological and interventional studies in animals and from observational studies in humans.[42] Randomised controlled trials have further proved the beneficial effect of *H pylori* eradication on preneoplastic conditions[43 44 180] and in primary and secondary gastric cancer prevention.[45 267] Moreover, several important cohort studies have all confirmed the positive effect of *H pylori* eradication in the prevention of gastric cancer,[182 184 223 268–272] and related aspects have been critically evaluated in meta-analyses[183 251] and reviews.[252 273]

Statement 10: The risk of gastric cancer can be reduced more effectively by employing eradication treatment before the development of preneoplastic conditions.

Evidence level: 1a **Grade of recommendation: A**

A number of cohort studies have shown a decreased risk of gastric cancer development after *H pylori* eradication. A recent meta-analysis demonstrated that *H pylori* eradication leads to the reduction of gastric cancer risk.[183] In one study a significant

Table 4 *Helicobacter pylori* and gastric cancer—key statements relevant for prevention strategies

Statement	Level of evidence	Grade of recommendation
Helicobacter pylori infection is the most consistent risk factor for gastric cancer. Its elimination is therefore the most promising strategy to reduce the incidence of gastric cancer	1a	A
The influence of environmental factors is subordinate to the effect of *H pylori* infection	1a	A
H pylori eradication abolishes the inflammatory response and slows or may arrest the progression of atrophy. In some cases it may reserve atrophy	1a	A
There is strong evidence that *H pylori* eradication reduces the risk of gastric cancer development	1c	A
The risk of gastric cancer can be reduced more effectively by employing eradication treatment before the development of preneoplastic conditions	1a	A
H pylori eradication for gastric cancer prevention is cost-effective in certain communities with a high risk for gastric cancer	3	B
H pylori eradication offers additional clinical and financial benefits in addition to gastric cancer prevention	varies with disease (1a to 4)	A
A screen-and-treat strategy of *H pylori* should be explored in communities with a significant burden of gastric cancer	2c	A
Validated serological tests for *H pylori* and markers of atrophy (ie, pepsinogens) are the best available non-invasive tests to identify subjects at high risk of gastric cancer	1a	B
H pylori eradication to prevent gastric cancer should be undertaken in populations at high risk	1c	A
Preneoplastic high-risk conditions require endoscopic follow- up. Prospective studies are needed to determine the correct timing of follow-up	2c	A

reduction of gastric cancer after treatment was shown only in the group without preneoplastic conditions (lesions).[45] Early eradication of *H pylori* was shown to prevent gastric cancer in patients with peptic ulcer disease.[182 272] The more advanced the preneoplastic condition is the more likely it is that the development of gastric cancer cannot be halted.[172 274] The exact point of no return has not been identified.

Statement 11: H pylori eradication for gastric cancer prevention is cost-effective in certain communities with a high risk for gastric cancer.

Evidence level: 3 **Grade of recommendation: B**

The incidence of gastric cancer differs widely between populations and there is a wide range in the prevalence of *H pylori* infection between children and adults.[275] When considering a *H pylori* eradication strategy, differences in *H pylori* virulence factors must be taken into account together with the effects of global population migration patterns and the available healthcare resources.

Screening young adults for *H pylori* could prevent one in every four to six gastric cancers in China and would represent a cost-effective strategy.[276] In selected populations at very high risk of developing gastric cancer (eg, resected early gastric cancer), *H pylori* eradication should be reimbursed to prevent subsequent cancer and in order to reduce healthcare costs.[277] Early once-in-a-lifetime *H pylori* eradication is more cost-effective than a surveillance strategy. However, this approach is still subject to the risk of reinfection, the ability to detect early gastric cancer and the timing of intervention.[278] *H pylori* eradication for gastric cancer prevention is cost-effective in certain communities at high risk for gastric cancer.

Statement 12: H pylori eradication offers additional clinical and financial benefits in addition to gastric cancer prevention.

Evidence level: varies with disease (1a to 4) **Grade of recommendation: A**

H pylori eradication treatment offers additional clinical and financial benefits besides gastric cancer prevention, as outlined in the section on indications.

Eradication prevents future *H pylori*-induced peptic ulceration of the stomach and/or duodenum.[279] Patients with GI risk factors taking ASS are often not provided with concomitant gastroprotective drugs and thus at increased risk for mucosal lesions in the presence of H. pylori.[280] Furthermore, because prophylactic eradication reduces the risk of ASS, ulcer eradication indirectly prevents possible interaction between PPIs and dual antiplatelet treatment.[281] Eradication treatment reduces the risk of FD and prevents gastric MALT lymphoma. Iron-deficiency anaemia, ITP, lymphocytic gastritis and Morbus Menetrier may be prevented by eradication treatment as well. Finally, *H pylori* eradication heals gastritis (ICD-10) and may prevent the spread of the infection and reduces future costs arising from treatment of later *H pylori* associated disease. One prospective study has shown that a community test-and-treat policy in a developed country would pay for itself over 10 years.[282–284]

Statement 13: A screen-and-treat strategy of *H pylori* should be explored in communities with a significant burden of gastric cancer

Evidence level: 2c **Grade of recommendation: A**

Population-based screening is probably the best option for the primary prevention of gastric cancer. However, there are large differences in incidence between populations and this is mainly attributable to differences in *H pylori* virulence and dietary factors.[199 217 285] The Asian-Pacific consensus[172] has already recommended a policy of *H pylori* eradication in populations at high risk of gastric cancer. This approach should be considered in other high-risk areas around the world, including Europe.

Statement 14: Validated serological tests for *H pylori* and markers of atrophy (ie, pepsinogens) are the best available non-invasive tests to identify subjects at high risk of gastric cancer.

Evidence level: 1a **Grade of recommendation: B**

Measurement of serum pepsinogen I detects severe preneoplastic conditions (ie, severe atrophy) and has gained attention as a candidate screening test for gastric cancer.[286] Most cases detected by the pepsinogen method in Japan are asymptomatic early gastric cancers limited to the mucosa and these are particularly well suited for endoscopic treatment.[287 288]

Serological screening is suitable for clinical use in countries with a relatively low incidence of gastric cancer because it enables endoscopic follow-up of cases with an abnormal serological profile suggestive of atrophic gastritis.[289] Regionally validated serological testing for *H pylori* and markers of atrophy (ie, pepsinogens) together are therefore the best non-invasive

tests to identify subjects at high risk for gastric cancer. Subjects with severe gastric atrophy, in whom *H pylori* has disappeared and who are therefore serologically negative for *H pylori*, are at a particularly high risk.

The combination of *H pylori* infection and atrophic gastritis determined by serological examination is suitable for the identification of subjects with a high risk of gastric cancer.

Statement 15: Risk stratification of patients with premalignant gastric conditions is useful and should be based on the severity and distribution of lesions.
Evidence level: 2b **Grade of recommendation: B**

Patients with preneoplastic changes of the gastric mucosa are at an increased risk of developing gastric cancer.[274] *H pylori* eradication treatment has the potential to prevent gastric cancer. However, recent reports after long-term follow-up have suggested that *H pylori* eradication does not prevent gastric cancer development in all infected patients, especially in those who have preneoplastic changes of the gastric mucosa before eradication treatment is given.[45] Therefore, risk stratification of patients with premalignant gastric conditions is useful and should be based on the severity and distribution of lesions.

The gastritis OLGA-staging conveys useful information on the potential clinicopathological outcome of the gastritis—in particular, the likelihood of progression to gastric cancer. The adoption of this system is therefore useful for patient management. According to OLGA-staging and *H pylori* status, patients with gastritis can be confidently stratified and managed according to their cancer risk. This has been shown for separate populations with different gastric cancer risk.[290–292] More recently the OLGIM histological staging has been shown to be of similar value. In this histological system IM is used as the preneoplastic marker instead of atrophy.[293]

Statement 16: H pylori eradication to prevent gastric cancer should be considered in the following:

first-degree relatives of family members with a diagnosis of gastric cancer;

patients with previous gastric neoplasia already treated by endoscopic or subtotal gastric resection;

patients with a risk of gastritis: severe pan-gastritis, corpus-predominant gastritis, severe atrophy;

patients with chronic gastric acid inhibition for more than 1 year;

patients with strong environmental risk factors for gastric cancer (heavy smoking, high exposure to dust, coal, quartz, cement and/or work in quarries);

H pylori-positive patients with a fear of gastric cancer.

Evidence level: 1a to 4 **Grade of recommendation: A**

H pylori eradication to prevent gastric cancer should be undertaken in patients at high risk. A first-degree relative of a family member with a diagnosis of gastric cancer is at high risk.[294] First- degree relatives have a two to three times increased risk of developing gastric cancer.[295–300] If more than one first-degree relative has contracted gastric cancer the risk for others is increased by a factor of 10. Patients with the CDH-1 mutation should be offered genetic consultation and prophylactic gastrectomy.[301–307]

There is an absolute indication for eradication treatment in patients at high risk, but they also require follow-up. Patients who have had a previous gastric operation, prior gastric neoplasia (MALT lymphoma, adenoma, cancer), pan-gastritis, corpus-dominant gastritis and in conjunction with IM and atrophy are all at high risk.[308–311]

Patients who have been receiving acid inhibition for >1 year and those who will be given long-term acid inhibition for >1 year are at increased risk.[312] Patients exposed to one or more strong environmental risk factors for gastric cancer such as heavy smoking, a high exposure to dust, coal, quartz, cement and/or work in quarries and those who live in a geographical area with a high incidence of gastric cancer should undergo eradication treatment.[172 313 314]

Finally, *H pylori*-positive patients with fear of gastric cancer should receive eradication treatment.

Statement 17: H pylori eradication to prevent gastric cancer should be undertaken in populations at high risk.
Evidence level: 1c **Grade of recommendation: A**

H pylori infection is a necessary but not sufficient cause for gastric cancer. Recent *H pylori* guidelines recommend population screening and treatment for *H pylori* in high-risk regions.[172] This strategy would be cost-effective where gastric cancer rates are high and most effective before the development of gastric atrophy. *H pylori* eradication for gastric cancer prevention should be undertaken in populations at high risk.

Statement 18: Factors to be considered for prevention strategies include:
the incidence of gastric cancer in the community to be targeted;
likely future trends in cancer incidence if intervention is not employed;
the availability of primary care facilities and other logistics;
the likely compliance of the chosen population;
the availability of funding;
the possibility of retesting and re-treatment in the event of eradication failure.
Evidence level: not quotable **Grade of recommendation: A**

Several factors should be considered when identifying populations in whom a prevention strategy is planned. The incidence of gastric cancer in the community to be targeted is relevant.[199] The likely future trends in the incidence of gastric cancer if intervention is not provided must be considered and the general availability of primary care facilities and other logistics such as funding are also important.[315–317]

The likely compliance of the target population is another factor to be taken into consideration. Reinfection with *H pylori* after eradication is rare in developed countries but more common in developing countries at around 13%. So the need for retesting and re-treatment in the event of eradication failure or reinfection must be kept in mind when considering a preventive strategy.[318]

Statement 19: The antibiotic combination should be chosen according to local *H pylori* antibiotic resistance patterns.
Evidence level: 2b **Grade of recommendation: B**

Antibiotic resistance is the most important factor responsible for the falling success rate of *H pylori* eradication treatment.[319 320] Local surveillance of *H pylori* antibiotic resistance is mandatory and the antibiotic combination for *H pylori* eradication treatment should be chosen according to the local resistance patterns. A wider range of effective treatments is urgently required.

Statement 20: Vaccination would be the best option for eliminating *H pylori* infection in the population. A major effort to develop a vaccine should be made.
Evidence level: 4 **Grade of recommendation: A**

In 2010, the worldwide prevalence of *H pylori* infection ranged between 7% and 87%. The average prevalence in Europe is around 30%, a high immigration background needs to be taken into account.[321] A vaccination strategy would be the best option for eliminating *H pylori* infection in the population.[322] A vaccine

against *H pylori* is feasible in animals both for prevention and treatment. Its potential in humans requires further research.[323 324]

A major effort should be made to develop a vaccine against *H pylori* in humans.

Statement 21: (a) Preneoplastic high-risk conditions require endoscopic follow-up. (b) Prospective studies are needed to determine the correct timing of follow-up.
Evidence level: 2c **Grade of recommendation: A**

Patients with high-risk conditions such as atrophic gastritis and IM are at an increased risk of developing gastric cancer.[17 223 325]

Whether these lesions merit endoscopic follow-up and the optimal timing for this, require evaluation in prospective studies.

- Preneoplastic conditions to be considered for endoscopic follow-up
  - when there is a firm diagnosis of pernicious anaemia with histological confirmation of type A autoimmune atrophic gastritis;
  - if there are histological and/or serological signs of subtotal or total atrophic gastritis with hypo- or achlorhydria;
  - if there has been a diagnosis/removal of gastric adenoma(s).
- Regular follow-up should be considered in moderate to severe atrophy at 2–3 years intervals and 3–6 month intervals where there is dysplasia.

Key aspects related to gastric cancer prevention strategies involving *H pylori* are listed in table 4.

Author footnote

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