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

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ABSTRACT

Important progress has been made in the management of *Helicobacter pylori* infection and in this fifth edition of the Maastricht Consensus Report, key aspects related to the clinical role of *H. pylori* were re-evaluated in 2015. In the Maastricht V/Florence Consensus Conference, 43 experts from 24 countries examined new data related to *H. pylori* in five subdivided workshops: (1) Indications/Associations, (2) Diagnosis, (3) Treatment, (4) Prevention/Public Health, (5) *H. pylori* and the Gastric Microbiota. The results of the individual workshops were presented to a final consensus voting that included all participants. Recommendations are provided on the basis of the best available evidence and relevance to the management of *H. pylori* infection in the various clinical scenarios.

INTRODUCTION

Nearly 4 years after publication of the Maastricht IV/Florence Consensus Report[1] the content has been updated by maintaining the traditional interval considered appropriate for capturing progress in the field of *Helicobacter pylori* related clinical issues and adapting the management to current demands.

Among the challenges, the increasing *H. pylori* resistance to previously efficacious antibiotic regimens is of great concern and requires modification of therapeutic strategies. Furthermore, new studies have been conducted to demonstrate the feasibility and efficacy of primary and secondary gastric cancer prevention. A recent important evolution has taken place by the publication of the Kyoto consensus report.[2] Key outcomes of this consensus report include the designation of *H. pylori* gastritis as an infectious disease with the recommendation of treatment of all *H. pylori* infected subjects. This represents a paradigm shift, as the indication for treatment is no longer reserved for patients with clinical manifestations of the infection. In the same consensus, *H. pylori* gastritis with dyspeptic symptoms was designated as a specific entity outside the 'umbrella' definition of functional dyspepsia. Both these aspects have been carefully re-examined. The role of *H. pylori* infection has also been assessed with the perspective of potential interactions with other microbiota in the upper and lower digestive system, as the gut microbiome has emerged as an essential player in human health and disease. A comprehensive and updated overview on the complexity of gastric functions in health and disease has recently addressed this issue.[3]

The aim of this report is to serve as a state-of-the-art guide for the management of *H. pylori* infection and related clinical manifestations and also as an inspiration for new clinical research in the area.

In the Maastricht V/Florence Consensus Report 43 experts from 24 countries convened for 2 days for a face-to-face meeting after having been actively involved in a previously started Delphi process as described below.

The working groups were set up according to the following topics:

Working group 1: Indications/Associations
Working group 2: Diagnosis
Working group 3: Treatment
Working group 4: Prevention/Public Health
Working group 5: *H. pylori* and the Gastric Microbiota

METHODOLOGY

The evidence-based Delphi process developed consensus statements following proposals by designated coordinators. The process allowed individual feedback and changes of views during the process regulated by the coordinators and the consensus chair.

The principal steps in the process were: (a) selection of the consensus group; (b) identification of areas of clinical importance; (c) systematic literature reviews to identify evidence to support each statement, draft statements and discussions supported by the evidence specific to each statement.

Two rounds of voting were conducted.

The delegation was asked to choose one of the following ratings for each statement:

- agree strongly
- agree with reservation
- undecided
- disagree or
- disagree strongly.

When no strong agreement was reached, the statement was rephrased and the vote was repeated. Evidence-based discussions with key references were provided for each statement on which participants voted. Consensus had to be reached by 80% of respondents who (a) strongly agreed or (b) agreed with reservation.

The level of evidence and strength of the recommendations were completed only after the individual working group meetings. Based on the type of

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studies, evidence levels and grade of recommendation were either based on the system used in the previous consensus reports (see online supplementary appendix)[1] or, if statements were suitable for grade assessment, based on so called PICO questions (PICO: population, intervention, comparator, outcome) they have been graded accordingly.[4]

The Face to Face meeting was held in 8–9 October 2015 and reviewed the statements in individual working groups first which were then presented to all delegates for final voting.

Statements that have passed the 80% consensus threshold are reported in here.

WORKING GROUP 1: INDICATIONS/ASSOCIATIONS

Statement 1: H. pylori gastritis is an infectious disease irrespective of symptoms and complications.

Level of evidence: 1B **Grade of recommendation: A**

H. pylori is a human pathogen that is transmitted from human to human, and causes chronic active gastritis in all colonised subjects. This can lead to peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma, and MALT (mucosa-associated lymphoid tissue) lymphoma. *H. pylori* eradication cures gastritis and can alter the progression to long-term complications, or recurrence of disease. For these reasons, *H. pylori* is considered an infectious disease irrespective of an individual's symptoms and stage of disease.[2]

Statement 2: A test-and-treat strategy is appropriate for uninvestigated dyspepsia. This approach is subject to regional *H. pylori* prevalence and cost-benefit considerations. It is not applicable to patients with alarm symptoms or older patients.

Level of evidence: high **Grade of recommendation: strong**

In young patients with uninvestigated dyspepsia the 'test-and-treat' strategy with non-invasive tests is preferred rather than prescribing proton pump inhibitor (PPI) or direct oesophago-gastro-duodenoscopy (OGD), avoiding cost, inconvenience and discomfort.[5 6]

The rationale for guidelines recommending a 'test-and-treat' over an 'endoscope-and-treat' policy is based on the outcome of five randomised controlled trials (RCTs).[7–10] These five studies were included in a meta-analysis[6] and four were included in a Cochrane report.[11] There was a small but significant benefit for the 'endoscope-and-treat' strategy in terms of improvement of symptoms and patient satisfaction.[6] But this was negated by a cost saving of US$389 per patient in the test-and-treat arm. This economic benefit was achieved in the short- and long-term by reducing the number of endoscopies.

Based on economic evaluations, some guidelines advocate initial empiric treatment with a PPI if the *H. pylori* prevalence in a population is below 20%. These economic analyses may not apply to all countries. Screening for *H. pylori* may not be appropriate when the population prevalence of *H. pylori* decreases to 10% as this may result in a significant proportion of false positives, leading to unnecessary treatments.[12] This is more likely to occur with the less sensitive and specific serology tests than with the urea breath test (UBT).

There is a close correlation between the prevalence of *H. pylori* and the incidence of its related diseases, including peptic ulcer and gastric cancer. This implies that in an environment with low *H. pylori* prevalence, the chance of a positive test as well as *H. pylori*-related disease are both low. A lower prevalence of *H. pylori* in the population increases the chance that a positive *H. pylori* serology test is false. This implies that the positive predictive value of the test declines with decreasing *H. pylori* prevalence. In such a population, a chance of non-*H. pylori*-related pathology is higher than the risk of *H. pylori*-related disease. The use of an endoscope and treat approach in regions of low *H. pylori* prevalence may be considered as it may offer additional benefit by ruling out significant oesophageal pathology.

When alarm symptoms are present—weight loss, dysphagia, overt gastrointestinal (GI) bleeding, abdominal mass or iron deficiency anemia—an OGD is needed.[13] When the risk of gastric cancer is high, the 'test-and-treat' strategy is not recommended, and OGD is preferred, especially in older adults in whom non-invasive tests are less accurate.[14] The threshold varies between regions depending on the age of the subject with gastric cancer.

Statement 3: An endoscopy-based strategy should be considered in patients with dyspeptic symptoms, particularly in low prevalence *H. pylori* populations.

Level of evidence: very low **Grade of recommendation: weak**

Endoscopy should include visualisation of the whole upper GI tract— that is, oesophagus, cardia, fundus in retroflexion, corpus, antrum, duodenal bulb, and descending duodenum—in order to detect any pathology and to biopsy any visible lesion. Biopsies according to standardised protocols need to be taken. If endoscopy is performed it should be quality assured, and in countries with low *H. pylori* prevalence, it rules out significant oesophageal pathologies.

Statement 4: *H. pylori* gastritis may increase or decrease acid secretion. Treatment may reverse or partially reverse these effects.

Level of evidence: high **Grade of recommendation: high**

People with non-atrophic antral-predominant gastritis have high stimulated acid production due to decreased somatostatin in the antrum, and increased gastrin levels compared with non-infected controls. Clinically, duodenal ulcer and non-ulcer dyspepsia are common in this group.[15–17] In contrast, people with atrophic gastritis (involving both antrum and corpus mucosa) have impaired acid production. This phenotype is associated with gastric proximal ulcers, more advanced precancerous lesions, and with an increased risk for gastric cancer.[18 19] In both of these patterns of gastritis, treatment of *H. pylori* resolves the gastritis and leads to partial correction of the high or low acid state. Such reversal is not noted in cases within extensive atrophic changes.[20–23] The increased acid secretion after treatment has been described as worsening aspects of gastro-oesophageal reflux disease (GORD) in people who already have a weak lower oesophageal sphincter.[23–28] However, in most populations, the changes in acid production after *H. pylori* treatment have no proven clinical relevance and should not be used as an argument to treat or not to treat *H. pylori*.

Statement 5: *H. pylori* gastritis is a distinct entity and causes dyspeptic symptoms in some patients. *H. pylori* eradication produces long-term relief of dyspepsia in about 10% of patients in comparison to placebo or acid suppression therapy.

Level of evidence: moderate **Grade of recommendation: strong**

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The latest WHO ICD-11β version under development and the Kyoto Global Consensus of *H. pylori* gastritis[2] recommend that the classification of gastritis is based on causative factors, which includes (a) *H. pylori*-induced, (b) drug-induced, and (c) autoimmune gastritis. *H. pylori* gastritis is a distinct cause of dyspepsia and is therefore an organic disease.[29 30] This is in contradiction to the Rome III consensus that considered *H. pylori*-associated dyspepsia to be 'functional dyspepsia'.[31]

Many *H. pylori*-positive subjects do not have symptoms, but in a subset of patients *H. pylori* is the cause of symptoms. Acute iatrogenic or self-administered infection with *H. pylori* can induce acute dyspeptic symptoms.[32 33] However, while persistent colonisation virtually always leads to chronic gastritis, in the majority of subjects the symptoms are transient.

Epidemiological studies show an association between *H. pylori* infection and dyspeptic symptoms,[34–37] although some point to other factors as being more important. The most convincing evidence showing a causal link, however, comes from *H. pylori* eradication studies in infected patients with uninvestigated or functional dyspepsia.[11 38–40] In these studies, eradication is associated with a small but statistically significant benefit for symptom control over no eradication (estimated number needed to treat (NNT)=14). The symptomatic gain takes at least 6 months to become significant over no eradication, and this has been attributed to the time it takes for gastritis to recover.[38 40]

Sustained symptom abolition or improvement provides the rationale for considering *H. pylori* gastritis as a distinct disease entity causing dyspeptic symptoms.

Statement 6: *H. pylori* gastritis has to be excluded before a reliable diagnosis of functional dyspepsia can be made.

Level of evidence: high **Grade of recommendation: high**

Dyspeptic symptoms are very common, and can occur as a result of a range of different upper GI conditions. When a dyspeptic patient has no diagnostic work-up, the condition is classified as 'non-investigated dyspepsia'. If patients have an endoscopic work-up, this may yield different diagnoses, including GORD or peptic ulcer. Patients with dyspepsia but without endoscopic lesions are classified as having 'functional dyspepsia'.

H. pylori gastritis is an infectious disease that leads to chronic active gastritis of varying severity in all infected subjects.[41] Cure of *H. pylori* infection heals the inflamed gastric mucosa.[3 42–44]

For these reasons, a diagnosis of true 'functional' dyspepsia can only be made in the absence of *H. pylori*. This can be either by primary exclusion of *H. pylori* gastritis, or confirmation of successful eradication.

Statement 7: The use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of ulcer disease in *H. pylori* infected subjects. Anticoagulants (aspirin, coumarines, new oral anticoagulants) increase the risk of bleeding in patients with peptic ulcer.

Level of evidence: high **Grade of recommendation: strong**

NSAIDs, aspirin, and *H. pylori* infection are independent risk factors for peptic ulcer and peptic ulcer complications.[45 46] A meta-analysis showed that NSAIDs use increases the risk of peptic ulcer in *H. pylori*-infected patients.[45] A recent epidemiological study has shown that *H. pylori* infection and NSAIDs use have additive effects on the risk of peptic ulcer bleeding.[46] Another meta-analysis[47] of five randomised clinical trials and additional studies reported more recently[48] have shown that *H. pylori* eradication is associated with a reduced incidence of peptic ulcer in new users but not in chronic users. No evidence is available for the effect of *H. pylori* eradication in coxib users.

The effect of *H. pylori* infection on the risk of peptic ulcer or peptic ulcer bleeding in low-dose aspirin (acetylsalicylic acid, ASA) users is more controversial. Although *H. pylori* eradication has been shown to reduce peptic ulcer bleeding in ASA users,[49–51] a more recent meta-analysis pointed out that the evidence was not enough to conclude that this infection was a risk factor for peptic ulcer bleeding in ASA users.[52] Furthermore, a recent epidemiological study found neither an additive nor a potentiating effect between ASA and *H. pylori* infection, although both were independent risk factors for peptic ulcer bleeding.[46]

New evidence shows that therapy with non-aspirin antiplatelet agents or anticoagulants also increases the risk of peptic ulcer bleeding.[53]

Since *H. pylori* infection is an independent risk factor for peptic ulcer bleeding, it seems reasonable to assume that *H. pylori*-infected individuals may be exposed to a greater risk for ulcer bleeding with these non-ulcerogenic compounds than non-infected individuals.

Statement 8: Testing for *H. pylori* should be performed in aspirin and NSAIDs users with a history of peptic ulcer.

Level of evidence: moderate **Grade of recommendation: high**

NSAIDs, aspirin, and *H. pylori* infection are independent risk factors for peptic ulcer and peptic ulcer complications.[45 46] Patients with a history of peptic ulcer or peptic ulcer bleeding are at the highest risk of upper GI bleeding if treated with NSAIDs, coxibs or aspirin.[46 54] A few clinical trials[49 55 56] and one observational study,[50] conducted in these high risk patients of Chinese origin, have shown that *H. pylori* eradication reduces but does not eliminate that risk, and that PPI co-therapy seems still necessary to reduce further the risk of upper GI bleeding. Therefore, PPI treatment is mandatory for those who receive NSAIDs, coxibs or even low-dose aspirin after a peptic ulcer bleeding event and *H. pylori* eradication if tested positive for the infection.[49 55 56]

Statement 9: Long-term treatment with PPIs alters the topography of *H. pylori* gastritis. Eradication of *H. pylori* heals gastritis in long-term PPI users.

Level of evidence: low **Grade of recommendation: strong**

The patterns of *H. pylori* colonisation and associated gastritis depend on the level of acid output. In situations with normal to increased acid output, bacterial colonisation and gastritis are predominantly confined to the gastric antrum. In situations of decreased acid output, bacterial colonisation and gastritis also affect the gastric body, leading to corpus-predominant pangastritis. This pattern is solely related to the level of acid output, irrespective of the underlying cause such as gland loss, vagotomy, or profound acid suppressive therapy. In case of the latter, the conversion from antral-predominant gastritis to corpus-predominant pan-gastritis occurs within days to weeks after initiation of therapy,[57] and remains throughout the duration of treatment.[58–60] Eradication of *H. pylori* cures gastritis irrespective of the continuation of acid suppressive drugs.[42 61]

At a population level, *H. pylori* and GORD are negatively associated, and this is most marked for cytotoxin-associated gene product (CagA)-positive strains of *H. pylori*.[62] A review of

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26 studies showed a rate of *H. pylori* infection in patients with GORD of 39% compared with 50% in controls.[63] Similarly, the sequelae of GORD, such as Barrett's oesophagus and oesophageal adenocarcinoma, are also less common in infected individuals.[64] However, eradication of *H. pylori* in populations of infected patients, on average, neither causes nor exacerbates GORD.[65–68] Therefore the presence of GORD should not dissuade practitioners from *H. pylori* eradication treatment where indicated. In addition, the long-term efficacy of PPI maintenance treatment for GORD is not influenced by *H. pylori* status.[42 69] 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,[70] but this again should not affect decisions on management, and more studies are needed to confirm and explore this phenomenon.

Statement 10: There is evidence linking *H. pylori* to unexplained iron deficiency anaemia (IDA), idiopathic thrombocytopenic purpura (ITP), and vitamin B12 deficiency. In these disorders, *H. pylori* should be sought and eradicated.

Level of evidence: very low **Grade of recommendation: weak**

The association of *H. pylori* with unexplained IDA has been conclusively proven in adult and paediatric populations.[71] Recent meta-analyses have shown that *H. pylori* eradication improves anaemia and increases haemoglobin levels, in particular in those with moderate to severe anaemia.[72 73] Indeed recent national guidelines on the management of IDA recommend eradication of *H. pylori*, where present, in patients with recurrent IDA with normal OGD and colonoscopy results.[74]

For adults with ITP, recent studies have shown increased platelet counts in some patients treated for *H. pylori* and increased response rates in countries with a high prevalence of *H. pylori* infection in the background population.[75] ITP patients with atrophic gastritis are reportedly more likely to respond to *H. pylori* eradication therapy.[5] Consensus guidelines on the management of ITP recommend eradication therapy in ITP patients who are *H. pylori* positive (based on UBTs, stool antigen tests (SATs) or endoscopic tests) and that *H. pylori* screening should be considered in patients with ITP in whom eradiation therapy would be used if testing is positive.[76 77] These guidelines currently recommend against routine testing for *H. pylori* in children with chronic ITP based on conflicting reports in the literature, although there are some studies that suggest that *H. pylori* eradication may prove effective in paediatric ITP patients.[78]

Studies have shown a link between chronic *H. pylori* infection and malabsorption of vitamins, including deficiencies in the absorption of vitamin B12, which results in the accumulation of serum homocysteine.[79]

Statement 11: *H. pylori* has been positively and negatively associated with a number of other extra-gastroduodenal conditions. The causality of these associations is not proven.

Level of evidence: moderate **Grade of recommendation: moderate**

In addition, *H. pylori* infection and CagA positivity have been associated with atherosclerosis.[80–83] Interesting associations have also been noted between *H. pylori* and several neurological conditions, including stroke, Alzheimer's disease, and idiopathic Parkinson's disease.[84–87] However, these associations are not sufficient to make a clear causal or therapeutic link. Inverse associations have been described between the declining rates of *H. pylori* infection in some countries and the increasing prevalence of obesity and asthma.[88] In a large, population-based Japanese study *H. pylori* eradication was associated with a subsequent significant increase in body mass index.[89]

A range of studies have reported negative associations between *H. pylori* colonisation and asthma and other atopic conditions (see online supplementary table S1 and S2).

Statement 12: *H. pylori* eradication is the first-line treatment for localised stage gastric MALToma.

Level of evidence: moderate **Grade of recommendation: strong**

Localised stage gastric MALToma are strongly associated with *H. pylori* infection. In the early (Lugano I/II) stage low-grade MALT lymphoma can be cured by *H. pylori* eradication in 60–80% of cases.[90] When the lymphoma contains a t(11,18) translocation, however, *H. pylori* eradication is usually ineffective[90] and these patients need adjunctive and alternative treatments. Patients with gastric MALToma are at increased risk for development of gastric adenocarcinoma,[91] with the majority having signs of premalignant gastric lesions.[92] All patients should be followed up intensively after *H. pylori* treatment[93] and given alternative treatments (chemotherapy or radiotherapy) if the lymphoma fails to respond or progresses.

WORKING GROUP 2: DIAGNOSIS

Statement 1: UBT is the most investigated and best recommended non-invasive test in the context of a 'test-and-treat strategy'. Monoclonal SAT can also be used. Serological tests can be used only after validation. Rapid ('office') serology tests using whole blood should be avoided in this regard.

Level of evidence: 2a **Grade of recommendation: B**

The ^{13}C-UBT is the best approach to the diagnosis of *H. pylori* infection, with high sensitivity and specificity, and excellent performances.[94–96] Out of 12 RCTs comparing the 'test-and-treat' strategy to OGD or PPI therapy, eight (66%) were performed with UBT, four (33%) with serology, and none with SAT.

^{14}C UBT has also been proposed because of its lower cost, but as it exposes patients to radiation it cannot be used in children and pregnant women.[97] SAT may be less acceptable in some societies but also has a high sensitivity and specificity, provided a monoclonal antibody-based ELISA is used.[98] There is no RCT comparing the 'test-and-treat' strategy with OGD or PPI therapy that used SAT.[94]

Some serology tests have high sensitivity and specificity,[99 100] but these tests may perform differently in different geographic locations according to the antigenic composition of the circulating strains. Thus, only locally validated tests should be used. This can be done by testing the serum of patients known to be *H. pylori* positive by invasive methods (histology, culture, PCR). As for other tests, predictive values are highly dependent on the prevalence of the infection.

Rapid ('office' or 'near-patient') serological tests using whole blood could facilitate application of the test-and-treat strategy in general practice. However, these tests have not yet been

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approved, as their sensitivities and specificities observed to date have generally been disappointing.[101]

Statement 2: PPI should be discontinued at least 2 weeks before testing for *H. pylori* infection. Antibiotics and bismuth compounds should be discontinued at least 4 weeks before the test.

Level of evidence: 2b **Grade of recommendation: B**

PPIs have an anti-*H. pylori* activity and decrease the load of *H. pylori* leading to false-negative results on urease test, UBT, and SAT.[102] Furthermore the bacterium may inhibit urease activity.[103] The 14 days are considered a 'safety' interval, while a 7-day withdrawal has been shown to be sufficient.[104]

H2 receptor antagonists have been shown to have minimal effect on the sensitivity of UBT, and antacids do not impair the sensitivity of UBT or SAT. H2-blockers do not have anti-*H. pylori* activity.[105–107] In contrast, the antibacterial activity of antibiotics and bismuth compounds necessitate their discontinuation for 4 weeks to allow an increase of a detectable bacterial load.

Statement 3: In clinical practice when there is an indication for endoscopy, and there is no contraindication for biopsy, the rapid urease test (RUT) is recommended as a first-line diagnostic test. In the case of a positive test, it allows immediate treatment. One biopsy should be taken from the corpus and one from the antrum. RUT is not recommended as a test for *H. pylori* eradication assessment after treatment.

Level of evidence: 2b **Grade of recommendation: B**

The sensitivity of biopsy urease tests is approximately 90%, and specificity is in the range of 95–100%.[108 109] False-positive tests are unusual; false-negative results can occur in patients with recent GI bleeding or with the use of PPIs, antibiotics, or bismuth-containing compounds or with excessive atrophy and intestinal metaplasia. If RUT is to be performed, patients should be off antibiotics or bismuth for 4 weeks and off PPI therapy for 2 weeks.[102 110 111]

Obtaining tissue samples from the antrum and the fundus may increase the sensitivity of the test.[111 112] False-negative tests are more frequent than false-positive tests and thus a negative result should not be used to exclude *H. pylori*. False-positives are rare and when present may be due to the presence of other urease containing bacteria such as *Proteus mirabilis*, *Citrobacter freundii*, *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Staphylococcus aureus*.[113]

The main interest for performing the RUT is to obtain a quick result, which is practical as it allows an eradication treatment to be prescribed immediately.

Statement 4: For assessment of *H. pylori* gastritis, a minimum standard biopsy setting is two biopsies from the antrum (greater and lesser curvature 3 cm proximal to the pyloric region) and two biopsies from the middle of the body. Additional biopsy from the incisura is considered for detection of precancerous lesions.

Level of evidence: 2b **Grade of recommendation: B**

It is known that atrophy and intestinal metaplasia are found to be more severe close to the lesser than the greater curvature.[114] These lesions, especially in the antrum, can have several causes besides *H. pylori* infection, while within the corpus mucosa most are caused by ongoing or cured *H. pylori* infection.[115–117] According to the updated Sydney System, biopsies are required from the lesser and greater curvature[118] and from the antrum and corpus.[119] Others showed that two antral biopsies only[120] (lesser at the incisura region and greater curvature) were sufficient to detect *H. pylori*. Satoh *et al*[121] reported that even one biopsy from the greater curvature suffices and that in individuals with severe atrophy of the antrum it is more suitable at the greater curvature, which is superior to a biopsy from the lesser curvature and/or incisura. Additionally, in patients with duodenal ulcer, *H. pylori* colonisation is denser in the antrum than in the corpus.[122–126] Antral biopsies are recommended to assess the density of colonisation of *H. pylori*.

It has been shown that the best biopsy sites for detection of *H. pylori* and assessment of atrophy are the lesser and greater curvature of the mid antrum, and the middle gastric body at the lesser and greater curvature.[121] This is supported by the updated Sydney System as well[118] and corresponds to the best biopsy site for the rapid urease test, that is, corpus and incisura region.[120] In conclusion, a maximum approach for gastric biopsies includes the incisura region at the lesser curvature.

In the case of detection of gastric polyps, besides the biopsies for gastritis assessment, a set of a few targeted biopsies from such polyps are sufficient for a correct histopathological diagnosis. The decision for eventual further intervention can be planned according to the histopathological result.[109 127 128]

For ulcerations and suspicious focal lesions further biopsies are necessary. The development of new endoscopic techniques (eg, narrow band imaging (NBI) and blue light imaging (BLI)) with magnifying endoscopy allow targeted biopsies with higher accuracy and may change the standard recommendation.[129]

Statement 5: Most cases of *H. pylori* infection can be diagnosed from gastric biopsies using histochemical staining alone. In cases of chronic (active) gastritis in which *H. pylori* is not detected by histochemistry, immunohistochemical testing of *H. pylori* can be used as an ancillary test. In the case of normal histology no immunohistochemical staining should be performed.

Level of evidence: 2b **Grade of recommendation: A**

Histochemical staging is the standard for *H. pylori* gastritis assessment. An argument for the use of immunohistochemistry (IHC) is that it may shorten the time required for the search of the bacteria, especially in cases with a low level of organisms. However, the IHC staining procedure is more expensive than histochemical stains and it is not available in all laboratories. Some studies support the use of IHC routinely, since haematoxylin and eosin (H&E) staining has been shown to be 42–99% sensitive and 100% specific when compared to IHC,[130–135] while other studies do not, since they found sensitivity/specificity of IHC to be 97/98% and 90/100%, when compared to Genta and H&E stains, respectively.[136 137] On the other hand, IHC staining for *H. pylori* has a lower inter-observer variation when compared to histochemical stains.[136–138]

Cases missed by histological stains are typically those with a low level of *H. pylori*,[131] while samples without chronic gastritis (active or inactive) are negative for the organism even when using IHC.[131–133] Use of IHC could thus be restricted to cases with chronic gastritis (active or inactive), atrophic gastritis (extensive intestinal metaplasia) or in follow-up biopsies after eradication treatment for *H. pylori*, when no organisms are identified by using histochemical stains. *H. pylori* density may

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also be low and patchy or the organism may appear as coccoid forms in patients who receive PPIs.

Statement 6: It is recommended to perform clarithromycin susceptibility testing when a standard clarithromycin-based treatment is considered as the first-line therapy, except in populations or regions with well documented low clarithromycin resistance (<15%). This test can be performed either by a standard method (antibiogram) after culture or by a molecular test directly on the gastric biopsy specimen.

Level of evidence: very low **Grade of recommendation: weak**

Statement 7: After a first failure, if an endoscopy is carried out, culture and standard antimicrobial susceptibility testing (AST) are recommended to tailor the treatment, except if a bismuth-based quadruple therapy is considered.

Level of evidence: weak **Grade of recommendation: strong**

The value of culture is primarily to perform AST for clarithromycin, levofloxacin, metronidazole, rifamycin, and eventually amoxicillin and tetracycline. 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 and may be cost-effective.[139 140] The cost-effectiveness may vary according to the cost of care in a given country.

The correlation between AST performed by culture and antibiogram versus a molecular test, essentially real-time PCR, is not perfect. Molecular tests are able to detect more cases of heteroresistance (a mixed population of susceptible and resistant organisms) but at this stage we do not have quantitative data on the proportion of resistant organisms, which can still be eradicated with the different combinations.

In the case of concomitant therapy, if the strain is clarithromycin resistant the other antibiotics will cure the infection.[141] However, in the context of a prudent use of antibiotics, it appears unjustified to prescribe an antibiotic which will lack efficacy and will induce adverse events and higher cost. Therefore, if possible it is better to test for clarithromycin resistance.

After a first failure, if an endoscopy is carried out, culture (and standard AST) 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.[142] AST must then use the standard method (antibiogram) because it is the only way to test the susceptibility to all antibiotics and not only to clarithromycin. It is especially important if a levofloxacin-based therapy is planned because resistance to fluoroquinolones is high in some regions and has a major impact on the success of treatment. In contrast, if a bismuth-based quadruple therapy is used in these different situations it is not recommended to perform AST because the risk of having a tetracycline resistant strain is extremely low and it was shown that metronidazole resistance has no impact.[143]

Statement 8: Serological tests presenting high accuracy, and locally validated, can be used for non-invasive *H. pylori* diagnosis.

Level of evidence: 2a **Grade of recommendation: B**

Serology is a non-invasive diagnostic method for the detection of *H. pylori* infection. Under certain clinical circumstances there are important local changes that may lead to a low bacterial load in the stomach and to a decreased sensitivity of all diagnostic methods except serology. These clinical situations include GI bleeding, atrophic gastritis, gastric MALT lymphoma, and gastric carcinoma.

A recent comparative study of 29 commercially available *H. pylori* serological kits came to the conclusion that some of the available kits are excellent, with performance parameters such as sensitivity and specificity above 90%.[100] These results show considerable improvement over previously published comparative analysis.[144–146] In general terms ELISA-based methods are preferred over rapid near-patient tests whose performances are not currently satisfactory.

Because serology is able to detect past infection with *H. pylori* it should not be used as a method to monitor effectiveness of eradication. Moreover, because of the low levels of antibodies, fluids such as saliva and urine should not be used to perform *H. pylori* serology assays.

Given that regional differences in prevalence of infection, infection load, and strain distribution are likely to exist, the development of *H. pylori* serology kits should ideally be done using local *H. pylori* strains, local titres should be established, and all *H. pylori* serology kits should be locally validated. New rapid near-patient tests currently being evaluated may fulfil the accuracy criteria to be used in the future. Looking specifically for CagA antibodies, which remain positive for a very long period of time, may allow detection of *H. pylori* infection in gastric cancer patients when other tests are negative.

Statement 9: The available data consistently recognise pepsinogen (Pg) serology as the most useful non-invasive test to explore the gastric mucosa status (non-atrophic vs atrophic). The PgI/PgII ratio can never be assumed as a biomarker of gastric neoplasia.

Level of evidence: 2a **Grade of recommendation: A**

The predictive value of Pg testing is limited in patients harbouring antrum-restricted atrophy.[147] Moreover, as observed by Shiotani *et al*., the reliability of Pg testing "clearly depends on the cut-off of serum Pg levels as well as the definition used to identify atrophy".[148]

A panel of serological tests (GastroPanel) including serum Pg (PgI and PgII), gastrin 17 (G-17), and anti-*H. pylori* antibodies has recently been proposed as 'serological biopsy' in dyspeptic patients.[149 150] In populations with a low prevalence of atrophic gastritis, the negative predictive value of the GastroPanel in identifying atrophic gastritis is as high as 97% (95% CI 95% to 99%).[151]

One of the most recent steps in Pg's validation as markers of atrophic gastritis was made at the Kyoto Global Consensus Conference[2] where the experts involved unequivocally agreed on the following statement: "Serological tests (pepsinogen I and II and anti-*H. pylori* antibody) are useful for identifying patients at increased risk for gastric cancer."

Statement 10: UBT is the best option for confirmation of *H. pylori* eradication and monoclonal SAT is an alternative. It should be performed at least 4 weeks after completion of therapy.

Level of evidence: high **Grade of recommendation: strong**

UBT is a valid and reliable test in the assessment of *H. pylori* eradication in the post-treatment evaluation[152] and SAT can be used as an alternative.[153] False-negative results can occur in patients taking PPI and antibiotics. Testing to prove eradication should be performed at least 4–8 weeks after completion of *H. pylori* therapy. PPI should be discontinued for at least 2 weeks as it interferes with the sensitivity of UBT and SAT.[95 153–155] Antibiotics and PPI contribute to the false-

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negative results obtained with post-eradication UBT by inhibiting growth and by their bactericidal activity against *H. pylori*.

Statement 11: *H. pylori* eradication results in significant improvement of gastritis and gastric atrophy but not of intestinal metaplasia.
Level of evidence: moderate **Grade of recommendation: strong**

H. pylori infection is a crucial factor in the multistep carcinogenic process of gastric cancer. In this process the gastric mucosa evolves through the stages of acute gastritis, chronic gastritis, gastric atrophy, intestinal metaplasia and dysplasia known as the Correa Cascade before developing gastric adenocarcinoma. Over the years one question has prevailed: are there any long-term benefits for the gastric mucosa after *H. pylori* eradication?

In recent years (2007, 2011, and 2016) three meta-analyses[156–158] systematically reviewed the long-term effects of *H. pylori* eradication on gastric histology (ie, effects on gastric atrophy and intestinal metaplasia for both antrum and corpus) by meta-analysing all relevant studies. In all three meta-analyses the results were consistent, showing significant improvement of gastric atrophy, whereas improvement was not shown for intestinal metaplasia.

WORKING GROUP 3: TREATMENT

Statement 1: *H. pylori* resistance rates to antibiotics are increasing in most parts of the world.
Level of evidence: moderate **Grade of recommendation: strong**

Although regionally variable, all areas of the world which have been studied on more than one occasion show increasing resistance rates to antibiotics in both high and middle/low income countries. A recent review on the global emergence of *H. pylori* antibiotic resistance confirms that eradication rates have been declining while the prevalence of antibiotic resistance rates have been increasing.[159] Such evidence comes from studies in Europe, Japan, Korea, China, Iran, Greece, Bulgaria and others.[160–165] Moreover, clarithromycin resistance rates have now reached ~30% in Italy and Japan, ~40% in Turkey, and ~50% in China, although rates in Sweden and Taiwan were ~15%.[159] A recent study from Taiwan has studied the impact of a government introduced restrictive antibiotic policy on *H. pylori* resistance rates, indicating the rise in levofloxacin resistance since the restriction of macrolides.[166]

Statement 2: PPI-clarithromycin-containing triple therapy without prior susceptibility testing should be abandoned when the clarithromycin resistance rate in the region is more than 15%.
Level of evidence: very low **Grade of recommendation: weak**

There are several explanations for the decrease in efficacy of standard triple therapy: compliance, high gastric acidity, high bacterial load, and bacterial strains, but the most important is the increase in *H. pylori* resistance to clarithromycin. 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 in Northern Europe. In order to take into account the confidence intervals of the prevalence and regional differences in a given country, a threshold of 15% was recommended to separate regions of high and low clarithromycin resistance.

Statement 3: For any regimen, the eradication rate can be predicted if the cure rates are known for susceptible and resistant strains and the prevalence of resistance in the population.
For an individual patient a history of any prior use of one of the key antibiotics proposed will identify likely antibiotic resistance despite low resistance rates in the population. Susceptibility based results simultaneously provide results that are both population- and individual-based.
Level of evidence: low **Grade of recommendation: strong**

Population results are not transferable to other geographical areas with different patterns of resistance. Success for an individual depends on his chance of having a resistant infection, which is ultimately related to local resistance patterns and previous antibiotic intake. Most available treatment data are thus population-specific and lack the data required to be directly linked to the patterns of resistance and susceptibility in other populations. These data are thus not generalisable. Clinically useful information must be susceptibility-based which provides results that are simultaneously population- and individual-based. This is relevant for clarithromycin, metronidazole, and levofloxacin but not for amoxicillin or tetracycline.

Statement 4: In areas of high (>15%) clarithromycin resistance, bismuth quadruple or non-bismuth quadruple, concomitant (PPI, amoxicillin, clarithromycin and a nitroimidazole) therapies are recommended.
In areas of high dual clarithromycin and metronidazole resistance, bismuth quadruple therapy (BQT) is the recommended first-line treatment.
Level of evidence: low **Grade of recommendation: strong**

In settings with high clarithromycin resistance, the choice of therapy should be based on the frequency of metronidazole and dual clarithromycin and metronidazole resistance. In geographical areas where metronidazole resistance is almost negligible (eg, Japan), replacing clarithromycin for metronidazole in triple therapy (ie, PPI-metronidazole-amoxicillin) still shows excellent cure rates.[167]

Dual resistance to clarithromycin and metronidazole >15% will impair the efficacy of all non-BQTs.[168] The expected rate of dual resistance according to the individual resistance of both antibiotics is displayed in online supplementary table S3. If metronidazole resistance remains stable between 30% and 40%, clarithromycin resistance would have to be 50% and 40% to undermine the efficacy of concomitant therapy.

In regions with high clarithromycin resistance (15–40%) but low to intermediate metronidazole resistance (<40%) (a pattern common for most central and southern European countries and the USA),[164 169] non-bismuth quadruple concomitant therapy, prescribed for 14 days,[170] can be an effective alternative as the prevalence of dual resistant-strains will always be <15%. Recent studies in Spain,[171–174] Greece,[175 176] and Italy[174 177] have consistently shown cure rates ranging from 85% to 94% with concomitant therapy.

BQT has proven high efficacy in spite of metronidazole resistance in Europe.[143]

In regions of high (>15%) dual clarithromycin and metronidazole resistance, bismuth-containing quadruple therapies are the treatment of choice. Ideally, clarithromycin should be

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avoided and a combination of alternative antibiotics for which resistance does not become problematic (eg, amoxicillin, tetracycline, furazolidone, rifabutin) or can be successfully overcome with increasing doses, dosing interval and duration (eg, metronidazole) should be recommended. In China (with estimated *H. pylori* resistance to clarithromycin 20–40% and to metronidazole >60%),[178] quadruple therapy with a PPI, bismuth and a combination of two antibiotics, among furazolidone, tetracycline, metronidazole, and amoxicillin, has been successfully tested (>90% cure rates) against *H. pylori* strains resistant to metronidazole, fluoroquinolones, and clarithromycin[179] and currently is the recommended first-line treatment.[178]

If bismuth is not available in high dual clarithromycin and metronidazole resistance areas, levofloxacin,[180] rifabutin,[181] and high dose dual (PPI+amoxicillin)[182] treatments can be considered. If tetracycline is not available in high dual resistance areas, bismuth-containing quadruple therapy combining furazolidone plus metronidazole or amoxicillin plus metronidazole can be considered[178 179] as well as bismuth plus triple therapy (PPI, amoxicillin, and either clarithromycin or levofloxacin).[183 184]

A therapeutic algorithm for geographical areas with high clarithromycin resistance is provided in figure 1.

Statement 5: The treatment duration of bismuth quadruple therapy should be extended to 14 days, unless 10 day therapies are proven effective locally.

Level of evidence: very low **Grade of recommendation: weak**

The doses of bismuth used in *H. pylori* eradication are usually administered for 7–14 days; a meta-analysis involving 35 studies with 4763 patients showed that bismuth salts, on their own or associated with other antimicrobials used in eradicating *H. pylori* infection, are safe and well tolerated.[185] Fischbach *et al*[186] performed a meta-analysis evaluating the efficacy, adverse events, and adherence related to first-line *H. pylori* quadruple eradication therapies. The efficacy of BQT for 1–3 days, 4 days or 7 days was less effective than when given for 10–14 days. The combination of PPI, bismuth, metronidazole, and tetracycline lasting 10–14 days achieved ≥85% eradication rate, even in areas with a high prevalence of metronidazole resistance.

A Cochrane systematic review involving 75 studies was performed to study the optimum duration for *H. pylori* eradication regimens.[187] Only six studies (n=1157) provided data for PPI +bismuth+two antibiotics quadruple therapy. The antibiotic combination included tetracycline and metronidazole, furazolidone and amoxicillin, and clarithromycin and amoxicillin. *H. pylori* eradication was compared for 14 days versus 7 days, 10 days versus 7 days, and 14 days vs 10 days. None of the comparisons suggest that increased duration significantly improved treatment effect for bismuth-based quadruple therapy, but numbers in studies were small. A single large trial provided data to compare the efficacy and tolerability of a twice-a-day BQT for 14 and 10 days.[188] The *H. pylori* eradication rate was not significantly different between 14 days (91.6%) and 10 days (92.6%). Metronidazole resistance data were not available, but in that area, metronidazole resistance in previous studies was 29%[188] and was 30% in a previous European multicentre study.[164]

Recent studies performed in different regions have achieved ≥85% eradication with 14 days BQT.[189–191] Two RCTs tested a triple capsule with a combination of bismuth, metronidazole, tetracycline plus omeprazole for 10 days and reported an intention-to-treat (ITT) eradication rate ≥90%.[143 192] A further study reported a 93% eradication rate as rescue therapy after failure of standard triple therapy.[193]

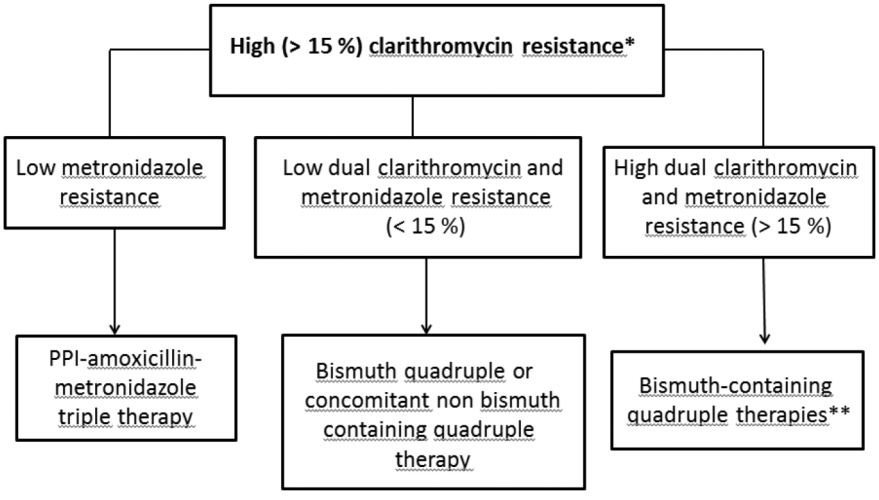
Currently, BQT should be considered effective provided the doses are sufficient and the duration is at least 10 days, preferably 14 days in areas of high metronidazole resistance.[186 194] A 2-week metronidazole use may overcome the negative influence of metronidazole resistance.[195]

Korean studies also suggest some benefit with longer treatment duration.[196–199]

Statement 6: Clarithromycin resistance undermines the efficacy of triple and sequential therapy, metronidazole resistance undermines the efficacy of sequential therapy, and dual clarithromycin and metronidazole resistance undermines the efficacy of sequential, hybrid and concomitant therapy.

Level of evidence: moderate **Grade of recommendation: strong**

Figure 1



* Regardless of their population expectations, individuals who have previously taken clarithromycin and/or metronidazole should be considered high risk patients for dual resistance.

** If bismuth is not available, levofloxacin, rifabutin and high dose dual (PPI + amoxicillin) therapies might be considered. If tetracycline is not available, bismuth-containing quadruple therapy combining furazolidone-metronidazole or amoxicillin-metronidazole can be considered.

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Currently, therapeutic expectations with clarithromycin-containing treatments and BQT can be predicted, depending on the rate of clarithromycin and metronidazole resistance (see online supplementary table S4).[168] All non-BQTs are believed to perform better than triple therapy and be highly effective against clarithromycin resistance. Sequential therapy achieves higher cure rates against clarithromycin-resistant strains than 7- and 10-day triple therapy, but is not superior to 14-day triple therapy.[200 201] Of note, sequential therapy achieves lower cure rates compared to concomitant therapy against clarithromycin-resistant strains, as shown in head-to-head trials (see online supplementary table S5) and in the recent literature (see online supplementary table S6).

Metronidazole resistance is another key factor impairing the efficacy of sequential therapy. Unlike clarithromycin resistance, metronidazole resistance can be partially overcome by increasing the dose, frequency, and duration of the antibiotic. Sequential therapy provides metronidazole for 5–7 days, hybrid therapy for 7 days, and concomitant therapy for 10–14 days. When comparing the efficacy of sequential and concomitant therapy against metronidazole-resistant and clarithromycin-susceptible *H. pylori* strains, cure rates for sequential therapy have been lower in head-to-head trials (see online supplementary table S7) and in the recent literature (see online supplementary table S8). A trial evaluating the advantage of 14-day sequential over 14-day triple therapy in Taiwan reported a decision model to predict the outcome of both therapies. This suggested that sequential therapy was more effective than 14-day triple therapy only when metronidazole resistance was <40%.[200] This premise has been fully corroborated in several further systematic reviews and meta-analyses,[201–204] consistently showing the lack of advantage of sequential therapy over 14-day triple therapy when sequential therapy was evaluated in settings with increasing metronidazole (and dual) resistance.[200] Dual (clarithromycin and metronidazole) resistance is the main factor influencing the efficacy of all non-BQTs (see online supplementary table S9). It has been proposed that cure rates with sequential, hybrid, and concomitant therapy will always be <90% when the rate of dual resistant strains is >5%, >9% or >15%, respectively.[168] Cure rates for sequential therapy against dual clarithromycin- and metronidazole-resistant *H. pylori* strains were considerably lower than that of concomitant therapy in head-to-head trials (see online supplementary table S9) and the recent literature (see online supplementary table S10). As for hybrid therapy, we currently only have data from two recent trials with a small number of patients,[174 205] where treatment was effective against clarithromycin-susceptible and metronidazole-resistant strains ((47/48 (97%)) and, to a lesser extent, against dual resistant strains ((2/4 (50%)).[201]

Statement 7: Currently, concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) should be the preferred non-bismuth quadruple therapy, as it has shown to be the most effective to overcome antibiotic resistance.

Level of evidence: moderate **Grade of recommendation: strong**

All non-BQTs (concomitant, hybrid, triple, and sequential) lead to excellent cure rates against susceptible *H. pylori* strains, but results may differ when facing populations with different patterns of resistance.[168] Three meta-analyses have shown a similar efficacy for sequential and concomitant therapy,[201 206 207] as well as a further one suggesting non-inferiority for hybrid therapy.[208] The results of these meta-analyses should be viewed with caution due to methodological issues. In the first meta-analysis, two of six (33%) included studies compared 5-day concomitant to 10-day sequential therapy, whereas studies comparing both treatments for 14 days were excluded.[201] In the second meta-analysis, three of eight (37%) included studies compared 5-day concomitant to 10-day sequential therapy. In the third, treatment duration was 5, 7, 10, and 14 days for concomitant therapy and 10 and 14 days for sequential therapy.[207] Of note, the study with the largest sample size (n=975) which was included in all of these meta-analyses compared 5-day concomitant to 10-day sequential therapy (in Latin America, with high clarithromycin and metronidazole resistance).[209] Moreover, meta-analyses have consistently shown that the efficacy of concomitant therapy is duration-dependent.[210 211] The efficacy of concomitant therapy was significantly higher than that of sequential therapy when both treatments were compared with a similar duration (see online supplementary figure S2).

Sequential therapy is more complex and requires changing antibiotic drugs during the treatment course, which can be confusing for patients. Concomitant therapy therefore is more easy to meet patients' adherence compared to sequential therapy and tolerability is similar to standard triple therapy.

Data on hybrid therapy are scarce. Possibly due to geographical differences in resistance patterns, good results have been published from Spain, Iran, and Taiwan,[171 174 205 212 213] but unsatisfactory reports from Italy and Korea.[177 214–216]

Statement 8: The recommended treatment duration of non-bismuth quadruple therapy (concomitant) is 14 days, unless 10 day therapies are proven effective locally.

Level of evidence: very low **Grade of recommendation: weak**

Early studies from Europe and Japan suggested that a short course of 3–5 days with three antibiotics and a PPI could achieve reasonable eradication rates.[217] In a first meta-analysis including nine studies, very short treatment durations of some of the trials with concomitant therapy yielded excellent results but the duration of therapy became a significant variable.

Gisbert and McNicholl, in a meta-analysis involving 55 studies (n=6906), were unable to find clear evidence for higher eradication results with longer treatments. However, several RCTs compared, in the same study and with the same protocol, two different durations of concomitant therapy, and demonstrated that the longer duration is more effective.[215 218–220] Moreover, suboptimal results have been observed with a 5-day treatment duration in Latin America[209] (73.5%) and South Korea (58.6%),[221] but also in two studies of 14-day treatment from Turkey (75%)[222] and South Korea (80.8%).[223] These inferior results have been attributed to the high prevalence of *H. pylori* strains resistant to clarithromycin and especially metronidazole in these populations.[168 170] A recent study has compared the efficacy and tolerability of the standard and the so called 'optimised' concomitant regimen (new generation PPIs at high doses of esomeprazole 40 mg twice daily and longer treatment duration 14 days), demonstrating higher eradication rates with the optimised regimen (91% vs 86%).[224] Although the incidence of adverse events was higher with the optimised treatment, these were mostly mild and did not negatively impact the compliance.

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In another multicentre study, the OPTRICON trial,[172] the authors compared the effectiveness and safety of two 'optimised' triple and concomitant therapies (with esomeprazole 40 mg twice daily) for 14 days. The optimised concomitant therapy achieved significantly higher eradication rates. Adverse events were significantly more common with optimised concomitant therapy, but full compliance with therapy was similar between groups.

Statement 9: In areas of low clarithromycin resistance, triple therapy is recommended as first-line empirical treatment. Bismuth-containing quadruple therapy is an alternative.

Level of evidence: high **Grade of recommendation: strong**

In these regions the standard PPI-clarithromycin-containing regimen is still recommended as the first-line treatment. Bismuth-based quadruple regimens are valid first-line alternatives.

Statement 10: The use of high dose PPI twice daily increases the efficacy of triple therapy. Esomeprazole and rabeprazole may be preferred in Europe and North America where the prevalence of PPI extensive metabolisers is high.

Level of evidence: low **Grade of recommendation: weak**

H. pylori is more likely in a non-replicative state when gastric pH is low (pH 3–6); by raising pH, bacteria enter the replicative state and become susceptible to amoxicillin and clarithromycin.[225] The role of PPIs is supported by the results of several meta-analyses, where significantly higher eradication rates were found with clarithromycin and amoxicillin or metronidazole-containing triple-therapy regimens and twice-daily PPI compared with once-daily PPI.[226–228]

Response to PPI is strongly determined by the capacity of the patient to metabolise the drug, which is determined by the cytochrome 2C19 and MDR polymorphisms. These polymorphisms can affect the success rate of eradication therapy; higher PPI doses, controlling gastric pH adequately, can be crucial for eradication in extensive metabolisers. Caucasian subjects show a higher prevalence of high metabolisers (56–81%) compared to Asian, and in particular Japanese people.[170 229–233] Some meta-analyses show that the success rates of omeprazole- and lansoprazole-containing triple therapies are affected by CYP2C19 polymorphisms whereas there is no impact on regimens that include rabeprazole and esomeprazole. Rabeprazole has been suggested as the PPI least affected by CYP2C19 genotype, being mainly metabolised through a non-enzymatic process. Esomeprazole and rabeprazole provide better overall *H. pylori* eradication rates, especially esomeprazole 40 mg twice daily, whereas rabeprazole 10 and 20 mg twice daily maintained results compared to first-generation PPIs.[234–239]

Statement 11: The treatment duration of PPI-clarithromycin based triple therapy should be extended to 14 days, unless shorter therapies are proven effective locally.

Level of evidence: moderate **Grade of recommendation: strong**

Several meta-analyses with similar results have been published to date.[187 240–242] All consistently show that 14-day triple therapies increase cure rates when compared to 7 days. Ten-day therapies were also superior to 7-day therapies. The increases in cure rates were superior with 14 day than with 10 day therapy in all meta-analyses and no differences in side-effect rates were observed in any of the reviews. Ultimately it has to depend on the physician prescribing in each particular area, taking into account the local efficacy, tolerability adverse events and costs. Cardiovascular outcomes need to be considered in the context of prolonged clarithromycin use.[243] In general, shorter duration should be reserved only for regions where equally high treatment success is demonstrated.[244]

Statement 12: After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing triple or quadruple therapy may be recommended. In cases of high quinolone resistance, the combination of bismuth with other antibiotics, or rifabutin, may be an option.

Level of evidence: very low **Grade of recommendation: weak**

In theory, any treatment could be used after failure of BQT, including repeating the same BQT with longer duration and high metronidazole dosage. However, it seems wiser never to repeat a treatment that has already failed. Studies evaluating the efficacy of a third-line combination of a PPI, amoxicillin, and levofloxacin for the eradication of *H. pylori* infection after two eradication failures, with the second-line treatment including a bismuth quadruple regimen, are summarised in online supplementary table S11.[245–248] Moxifloxacin triple therapy has been recently reported to achieve a 67% eradication rate as second-line treatment after first-line bismuth quadruple failure in 28 patients in Korea.[249] In a study from China, bismuth therapy was effective as first-line treatment in 99% of patients, and in the two patients who failed, sequential therapy was effective.[250] Using a clarithromycin-containing treatment as second-line therapy after failure of a BQT does not seem to be practical since bismuth therapies are usually proposed as first-line treatments for areas of high clarithromycin resistance. Levofloxacin-based triple therapy, that is known to be effective as second-line therapy after clarithromycin-containing therapy,[251 252] should also be recommended after failure of a bismuth-containing quadruple regimen.

Statement 13: After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy are recommended as a second-line treatment.

Level of evidence: low **Grade of recommendation: weak**

After failure of PPI-clarithromycin-amoxicillin triple therapy, either primary or acquired clarithromycin resistance should be expected, therefore repeating the same regimen must be avoided. Indeed, a pooled analysis of eight studies showed a very low eradication rate of 46% when repeating a clarithromycin-based therapy.[253] Based on previous meta-analyses demonstrating a similar effectiveness with the two regimens,[251 252 254] Maastricht IV guidelines recommended either a bismuth-containing quadruple therapy or a levofloxacin-containing triple therapy. A recent meta-analysis of RCTs supports the use of either a levofloxacin-containing triple therapy (see online supplementary figure S3) or a bismuth-containing quadruple therapy (see online supplementary figure S4) as an effective second-line therapy for *H. pylori* eradication.[253] Moreover, a similar efficacy of PPI-levofloxacin-amoxicillin triple therapy and bismuth-containing quadruple therapy after a first-line treatment failure with a PPI-amoxicillin-clarithromycin was shown, providing cure rates of 76% and 78%, respectively. However, the incidence of side effects was lower with levofloxacin-containing triple therapy than with bismuth-containing quadruple therapy.[255] A sub-group analysis showed similar eradication rates with 500 mg (either once a day or

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250 mg twice a day) and 1000 mg (500 mg twice a day) of levofloxacin, thus suggesting that the low-dose regimen should be preferred.[255] Conversely, an increased prevalence of primary levofloxacin resistance has been recently reported and this may affect the efficacy of levofloxacin-based regimens.[256] Therefore, bismuth-containing quadruple therapy continues to represent a valid second-line treatment for *H. pylori* eradication, particularly in areas with high fluoro quinolones resistance. In second line, a 14-day bismuth quadruple treatment provides higher eradication rates than 7-day treatment.[257] A potential role for quadruple therapy with the novel '3 drugs in one pill' is foreseeable in this setting.[143]

Recent data have confirmed that combining bismuth and levofloxacin in a 14-day quadruple therapy is an effective (≥90% cure rate), simple, and safe second-line strategy in patients whose previous standard triple has failed.[258] Several studies previously evaluated this quadruple regimen (PPI, amoxicillin, levofloxacin, and bismuth) as reported in online supplementary table S12.

The use of a triple therapy with a PPI, amoxicillin, and metronidazole has provided encouraging results with an overall eradication rate of 87%; moreover, the inclusion of studies where PPI-amoxicillin-metronidazole treatments were administered three times daily may explain the superiority, even in shorter regimens.[253] However, there are no clinical trials comparing this treatment with BQT and only two small comparative studies with PPI-levofloxacin-amoxicillin-triple therapy are available.[259 260]

Statement 14: After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing triple or quadruple therapy are recommended.

Level of evidence: very low **Grade of recommendation: weak**

A systematic review and meta-analysis has been performed to explore effective second-line treatments after an unsuccessful attempt to eradicate *H. pylori* infection with non-BQTs (updated meta-analysis for the consensus). Sixteen studies were selected: seven treating patients after concomitant failure, 15 after sequential failure, and one after hybrid failure. Most studies evaluated a rescue therapy with levofloxacin, amoxicillin, and a PPI, which obtained an overall 78% eradication rate (201 patients) after the failure of a non-BQT (see online supplementary figure S5).[176 177 261–264] This triple therapy (levofloxacin-amoxicillin-PPI) was similarly effective after failure of both sequential (81%) (see online supplementary figure S6) and concomitant (78%) (see online supplementary figure S7) treatment. Only one study reported results of the levofloxacin triple therapy after failure of hybrid therapy, with a 50% cure rate. Tolerance of this regimen was acceptable. Four patients stopped the treatment due to side effects.

Some authors have included moxifloxacin instead of levofloxacin in this triple rescue regimen (moxifloxacin-amoxicillin-PPI), achieving an overall eradication rate of 71%[249 265 266] after failure of non-BQTs. These results should be interpreted with caution, due the heterogeneity of the data and the differences between study characteristics.

An important caveat of the levofloxacin-containing therapy is that it is markedly less effective in the presence of fluoroquinolone resistance.[267] The efficacy of levofloxacin-containing therapy is decreasing, most likely due to increased primary quinolone resistance.[268] Bismuth has a synergistic effect with antibiotics, and overcomes clarithromycin and levofloxacin resistance.[269 270] A quadruple regimen adding bismuth (PPI, amoxicillin, levofloxacin, bismuth) showed encouraging results.[270–273] In patients randomly assigned to receive PPI, amoxicillin, and levofloxacin with or without bismuth for 14 days, the eradication rate was slightly higher with the bismuth-based regimen (87% vs 83%); but in levofloxacin-resistant strains, the bismuth combination was still relatively effective (71%) while the non-bismuth regimen achieved *H. pylori* eradication in only 37% of the patients.[270] With a second-line quadruple regimen containing bismuth, levofloxacin, amoxicillin, and esomeprazole for 14 days in patients who failed *H. pylori* eradication treatment, cure rates were similar.[258] Therefore, the levofloxacin/bismuth-containing quadruple therapy constitutes an encouraging second-line strategy not only in patients failing previous standard triple therapy but also non-bismuth quadruple 'sequential' or 'concomitant' treatments. BQT (PPI-bismuth-tetracycline-metronidazole) after failure of a non-BQT (after failure of a sequential regimen in both cases) is effective (see online supplementary figure S8). Little experience is available with other treatment options.[200 274 275]

Statement 15: After failure of second-line treatment, culture with susceptibility testing or molecular determination of genotype resistance is recommended in order to guide treatment.

Level of evidence: very low **Grade of recommendation: weak**

After failure of a second-line strategy, treatment should be guided by AST, whenever possible. Resistance to clarithromycin, levofloxacin or rifabutine has a major negative impact on the results of triple therapies. Resistance to metronidazole has a less marked negative effect. Susceptibility-guided triple therapies proved more effective than empirical triple therapies in first-line treatment.[139 276] In a systematic review, benefits of tailored treatment in second-line treatment remain uncertain, and there is no comparative data for third-line treatment. In most of these studies, strains were only tested for clarithromycin susceptibility.

There are no data comparing empirical with susceptibility-guided sequential therapy. However, an optimal efficacy of a genotype resistance-guided sequential therapy in third-line treatment of refractory *H. pylori* infection has been reported.[277]

Non-bismuth-containing quadruple treatment had a significant impact on dual resistance.[176] Better results with susceptibility-guided triple therapy than with empirical concomitant therapy were obtained in a region of high clarithromycin resistance.[278] Bismuth-containing quadruple therapy is the least dependent treatment on antibiotic resistance. Tetracycline resistance is very rare and not expected to develop despite treatment failures. Metronidazole resistance does not decrease eradication rates.[143 192 279]

Statement 16: After failure of the first-line treatment (clarithromycin based) and second-line treatment (with bismuth-containing quadruple regimen), it is recommended to use the fluoroquinolone-containing regimen. In regions with a known high fluoroquinolones resistance, a combination of bismuth with different antibiotics or a rifabutin-containing rescue therapy should be considered.

Level of evidence: very low **Grade of recommendation: weak**

This scenario reflects the therapeutic approach as recommended first- and second-line regimens proposed by the Maastricht IV Consensus conference. A study tested this approach in clinical practice and used as third-line empirical therapy a levofloxacin-based regimen. This achieved high cumulative *H. pylori* eradication rates.[247] Several studies have

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confirmed the efficacy of a third-line combination of a PPI, amoxicillin, and levofloxacin for the eradication of *H. pylori* infection after two eradication failures.[245 247 251 252] However, given the rise in levofloxacin resistance, the prevalence of resistance must be taken into account.[280] In known high local fluoro quinolones resistance, rifabutin-containing rescue therapy likely represents the better therapeutic option.[281] Studies evaluating the efficacy of a third-line combination of a PPI, amoxicillin, and levofloxacin for eradication of *H. pylori* infection after two eradication failures (first-line with a PPI-clarithromycin-amoxicillin, and second-line with a bismuth quadruple regimen), are summarised in online supplementary table S13.

Statement 17: After failure of the first-line treatment (triple or non-bismuth quadruple) and second-line treatment (fluoroquinolone-containing therapy), it is recommended to use the bismuth-based quadruple therapy.

Level of evidence: very low **Grade of recommendation: weak**

A quadruple regimen of bismuth, metronidazole, and tetracycline plus omeprazole produces a high eradication rate in patients previously failing *H. pylori* eradication regimens. This bismuth-based regimen offers an effective option as rescue therapy.[143 193 282 283] Furthermore, BQT is not influenced by clarithromycin and fluoroquinolone resistance.[284]

Statement 18: After failure of first-line treatment with bismuth quadruple and second-line treatment (fluoroquinolone-containing therapy), it is recommended to use a clarithromycin-based triple or quadruple therapy. A combination of bismuth with different antibiotics may be another option.

Level of evidence: very low **Grade of recommendation: weak**

In this scenario, no clarithromycin has been used previously. Therefore, clarithromycin-based triple therapy (in areas of low clarithromycin resistance) or non-BQTs (in areas of high clarithromycin resistance) are effective options. Another therapeutic option is the repeat-use of bismuth plus a combination of two antibiotics not previously used.[191]

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, BQT should be preferred.

Level of evidence: very low **Grade of recommendation: weak**

Only a minority of patients presenting with a history of penicillin allergy have evidence of immune-mediated hypersensitivity. Negative allergy testing enables the use of penicillin as first-line treatment when necessary so that these patients are not excluded from the best therapy.[285–288] The substitution of amoxicillin by metronidazole is not an effective option because of dual resistance.[289 290]

A 10-day treatment with PPI-tetracycline and metronidazole was effective in patients with documented penicillin allergy.[291 292] This triple combination was better with the addition of bismuth (resulting in a quadruple regimen), and may be a better alternative for first-line treatment in the presence of penicillin allergy (especially in areas with high metronidazole and/or clarithromycin resistance).[293] A 10 to 14 days eradication regimen in penicillin-allergic patients and failure of previous PPI, clarithromycin, metronidazole with classical BQT (PPI-bismuth-tetracycline-metronidazole) or a modified bismuth quadruple regimen with PPI-bismuth-tetracycline-furazolidone is very effective.[193 294]

Statement 20: Rescue regimen: A fluoroquinolone-containing regimen may represent an empirical second-line rescue option in the presence of penicillin allergy.

Level of evidence: very low **Grade of recommendation: weak**

Fluoroquinolone-containing regimens in various combinations are effective;[242 293] however, resistance to quinolones is acquired easily, and in countries with high consumption of these drugs the resistance rate is relatively high.[294]

A sitafloxacin-based regimen is an option, successfully tested in Japan.[295 296]

WORKING GROUP 4: PREVENTION/PUBLIC HEALTH

Statement 1: *H. pylori* infection is accepted as the major aetiological factor for gastric cancer.

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

This is now established beyond doubt from numerous strands of evidence, including epidemiology, molecular studies, animal studies, and eradication studies in humans, showing a reduced incidence of gastric cancer in those receiving eradication therapy. While Epstein-Barr virus and other rare causes (including hereditary ones) might account for a small proportion of gastric cancers worldwide, it is acknowledged that at least 90% of cancers are related to *H. pylori* infection. The risk of cancer arising from *H. pylori* infection is identical for gastric cancer of both intestinal and diffuse type.[297–302]

Statement 2: *H. pylori* infection is also a risk factor for proximal gastric cancer (PGC) provided that oesophageal and junctional adenocarcinoma have been properly excluded.

Level of evidence: 2c **Grade of recommendation: B**

The initial epidemiological studies that assessed the risk of *H. pylori* in the development of gastric cancer exclusively focused on distal gastric cancer (non-cardia gastric cancer, NCGC).[303 304]

In nearly all epidemiological reports the traditional distinction between PGC and NCGC is not addressed; they also fail to distinguish adenocarcinoma originating from or proximal to the gastroesophageal junction from that originating in the cardia mucosa and thus do not address the distinction between Barrett's cancer, true junctional gastric cancer, and PGC. The distinction has been made in only a few studies. In these where the correct origin of PGC has been made the prevalence of *H. pylori* is the same as for NCGC.[305–307] Accordingly, *H. pylori* is the principal risk factor for gastric adenocarcinoma in all sites.

Statement 3: *H. pylori* eradication reduces the risk of gastric cancer development.

Level of evidence: low **Grade of recommendation: moderate**

Although cohort investigations consistently suggest that *H. pylori* infection is a powerful risk factor for gastric cancer, the evidence that the risk is reduced by *H. pylori* eradication is based so far on two randomised interventional trials.[301 308] Pooled data from the most recent published meta-analysis shows

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the incidence rate ratio=0.53 (CI 0.44 to 0.64). Eradication provided significant benefit for asymptomatic infected individuals and individuals after endoscopic resection of early gastric cancer.[309] The overall gastric cancer risk reduction can be estimated at 34%. Several trials are ongoing in China, UK, and Korea currently, including a large one with 184 786 participants; these should provide more reliable data relating to any benefit or adverse consequences that accrue from *H. pylori* eradication in the prevention of gastric cancer.[310 311]

Statement 4: The influence of environmental factors is subordinate to the effect of *H. pylori* infection.
Level of evidence: 2a **Grade of recommendation: A**

Although the International Agency for Research on Cancer (IARC) monographs classify *H. pylori* as a group 1 carcinogen that causes NCGC,[312] several authors have postulated that *H. pylori* is a necessary but not sufficient cause.[313] Case–control studies that have corrected for the observation that the bacterium and its markers may be lost from the stomach when severe atrophy is present, have established either past or present *H. pylori* in almost all non-cardia cancers. Cohort studies have similarly documented that there was exposure to *H. pylori* in the vast majority of cases. A Japanese cohort study showed that all of the cancers had developed in *H. pylori*-positive subjects with none in the negatives.[314] A recent re-analysis of the Eurgast-EPIC cohort has been undertaken. The study comprised a follow-up of 500 000 subjects from 10 European countries aged 40–65 years. The Western blot assay was used to test for *H. pylori* exposure before diagnosis. It found that 93.2% of the cancer cases were positive compared with 58.9% of the controls.[315] Factors such as excessive salt intake and cigarette smoking, different from epidemiological studies that did not take into account the role of *H. pylori*, had only a low 'add-on effect' in the presence of *H. pylori* infection. The attributable risk fraction of *H. pylori* to gastric cancer, based on a pooled analysis of three cohort studies in Europe and Australia, was recently estimated at 89%.[316]

It is unclear whether the small fraction of cases where *H. pylori* is not detectable is associated with other aetiologic factors (eg, Epstein-Barr virus) or is related to misclassification. Moreover, it is unknown whether cofactors are necessary in all cases or whether infection alone leads to gastric cancer.

Statement 5: *H. pylori* eradication abolishes the inflammatory response and early treatment prevents progression to preneoplastic lesions.
Level of evidence: 1b **Grade of recommendation: B**

A rapid decrease of active inflammation in gastric mucosa occurs following *H. pylori* eradication. This can be demonstrated by morphological improvement of mucosa both in the antrum and corpus of the stomach[317] or biomarker results, in particular a rapid decrease in PgII (indicator for active inflammation) levels following successful *H. pylori* eradication. A decrease in PgII has been demonstrated within 1–2 months following *H. pylori* eradication.[318 319] Improvement of the mucosal status has also been demonstrated with high-resolution endoscopy 3 months after eradication.[320]

Epidemiological evidence shows that *H. pylori* eradication prevents progression towards precancerous lesions; in Matsu Island (Taiwan) there was a 77.2% reduction in atrophy (but not intestinal metaplasia).[321] The observation that *H. pylori* eradication prevents the progression of preneoplastic lesions is also supported by a recent meta-analysis on prevention of metachronous gastric lesions by eradication after endoscopic resection of gastric neoplasms.[322]

Statement 6: *H. pylori* eradication reverses gastric atrophy if intestinal metaplasia is not present and arrests the progression of preneoplastic to neoplastic lesions in a subset of patients.
Level of evidence: 1b **Grade of recommendation: A**

H. pylori eradication heals chronic active gastritis. This may be associated with a certain restitution of glands with specialised cells, and thus a reduction of atrophic gastritis.[42 323 324]

Several meta-analyses have shown that gastric atrophy can be reversed to a degree in both the antrum and corpus.[157 325–327] This is not the case once intestinal metaplasia becomes established. Intestinal metaplasia cannot be reversed although its progression is halted in a large subset of patients.

Statement 7: The risk of developing gastric cancer can be reduced more effectively by employing eradication treatment before the development of atrophy and intestinal metaplasia.
Level of evidence: 2b **Grade of recommendation: B**

There remains a considerable gap in knowledge as to how early, in terms of the degree and extent of the preneoplastic lesion, eradication of *H. pylori* may still be successful in preventing progression to gastric cancer.

A systematic review of the literature, of randomised trials, and of population *H. pylori* screening and treatment has shown that eradication therapy reduces the risk of developing gastric cancer.[327] In this review, two randomised trials[301 308] evaluated gastric cancer incidence in participants with and without preneoplastic lesions at baseline. The relative risk of gastric cancer in 2060 participants with preneoplastic lesions at baseline in those receiving *H. pylori* eradication therapy was 0.78 (95% CI 0.46 to 1.34). This compared with a relative risk of 0.24 (95% CI 0.04 to 1.52) in the 1812 participants without preneoplastic lesions. There was a non-significant trend to suggest that the efficacy of *H. pylori* eradication was greater in those without preneoplastic lesions. This potential difference was driven by one study[308] with no trend seen in the other trial.[301]

Statement 8: *H. pylori* eradication for gastric cancer prevention is cost-effective in communities with a high risk for gastric cancer.
Level of evidence: moderate **Grade of recommendation: strong**

Nine economy-based modelling studies have evaluated the cost-effectiveness of population *H. pylori* screen-and-treat policies for the prevention of gastric cancer. They employed different assumptions and methods, but concluded that *H. pylori* screening and treatment was cost-effective. The key assumption is that *H. pylori* eradication reduces gastric cancer risk and this is now supported by a systematic review.[327] The benefit is likely to be highest in communities with a high risk of gastric cancer (where all these randomised trials were conducted.) However, it may also be cost-effective in developed countries because randomised trials have shown that population *H. pylori* screening and treatment reduces dyspepsia costs.[327 328] This could result in the programme being cost neutral.

Statement 9: *H. pylori* eradication offers clinical and economic benefits other than gastric cancer prevention and should be considered in all communities.
Level of evidence: low **Grade of recommendation: weak**

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While there is ample evidence for cost-effectiveness in high prevalence countries and specific high risk groups in gastric cancer prevention, a benefit is also reported for low prevalence countries.[329]

The clinical and economic benefits of *H. pylori* eradication extend to its role in peptic ulcer prevention, a disease that is responsible for a serious burden of morbidity and mortality throughout the world.[18 47 330] *H. pylori* eradication also reduces peptic ulcer bleeding relapses, the development of NSAID induced ulcers, and unexplained dyspeptic symptoms. Additional beneficial health outcomes have also been considered. From an economic perspective the test-and-treat policy may be cost-effective within 10 years.

Statement 10: *H. pylori* 'screen-and-treat' strategies are recommended in communities at high risk of gastric cancer.
Level of evidence: moderate **Grade of recommendation: strong**

So far such strategies have been conducted in few countries (Taiwan, China).[301 321] Screen-and-treat strategies are recommended in high-risk populations and are considered to be cost-effective as to the expected level of adverse events and compliance;[331] a large population-based Chinese screen-and-treat trial undertaken in a rural area at high risk of gastric cancer reported excellent compliance, minor adverse effects and low cost, altogether indicating good feasibility. Long-term follow-up in gastric cancer prevention trials will provide a final answer.[310]

Statement 11: A screen-and-treat strategy of *H. pylori* gastritis should be considered in communities with intermediate to low risk for gastric cancer
Level of evidence: low **Grade of recommendation: weak**

Maastricht IV guidelines indicated that screen-and-treat should be explored in communities with a significant burden of gastric cancer[1] because several randomised clinical trials had shown a 30–40% reduction in gastric cancer risk in those in whom *H. pylori* had been successfully eradicated.[327] However, the burden of disease is important in lower risk areas as well.

There were an estimated 12 000 deaths from gastric cancer in the USA in 2012 and 58 000 in the 28 countries of the European Union. Gastric cancer mortality remains high because in most cases the condition is incurable at the time the diagnosis is made, so prevention is the most appropriate way forward.[332] Another concern in these countries at intermediate or relatively low risk is that there may be areas, populations or ethnic groups where the incidence is high (eg, migrants from high incidence areas).

H. pylori screen-and-treat is cost-effective in published reports, even though the majority of models have been elaborated for developed countries (eg, USA, UK.) The economic benefit of *H. pylori* eradication is greater if reductions in dyspepsia and peptic ulcer disease are considered. However, the potential deleterious effects of *H. pylori* eradication, including antibiotic resistance/adverse events, need to be taken into consideration.

The IARC working group meeting of December 2013 concluded that countries should explore the possibility of introducing population-based *H. pylori* screen-and-treat programmes, taking account of disease burden and other health priorities such as cost-benefit analysis and possible adverse consequences.[332]

They should also include a scientifically valid assessment of programme process and feasibility.

Statement 12: Screen-and-treat for *H. pylori* is recommended in individuals at increased risk for gastric cancer.
Level of evidence: moderate **Grade of recommendation: strong**

Individuals with the 'gastric cancer phenotype' are at increased risk of cancer. This is characterised by corpus predominant gastritis, gastric atrophy/intestinal metaplasia, hypochlorhydria, and evidence of current or past *H. pylori* infection. Screening on a population-wide basis by invasive approaches is not feasible but the gastric cancer phenotype can be detected by a combination of non-invasive markers including *H. pylori* serology and pepsinogen levels (Pgl or Pgl/II ratio).[333 334] Genomic approaches are also promising but require validation in prospective studies.[335] Some indigenous sub-populations and immigrants from high incidence countries may also be at increased risk and could be targeted for screening and prevention.[336 337] Those with a positive family history have a modestly increased risk and in the presence of *H. pylori* infection have an increased prevalence of preneoplastic abnormalities including atrophy and hypochlorhydria.[338 339] They should also be screened and treated.

Statement 13: Endoscopy-based screening should be considered as an option in communities and individuals at increased risk of gastric cancer.
Level of evidence: very low **Grade of recommendation: weak**

Certain countries and communities have a considerably increased risk of gastric cancer compared with others and in these screening endoscopy is a valid option.[18 340 341]

Individuals within those communities who are at a much higher risk of developing gastric cancer may be identified by serological screening and offered endoscopic screening and surveillance.[342 343]

Statement 14: Advanced preneoplastic lesions (atrophy/intestinal metaplasia) require follow-up by endoscopic staging.
Level of evidence: very low **Grade of recommendation: moderate**

This recommendation was first released within a guideline based on the evidence that the risk of progression is maximised in the presence of preneoplastic lesions.[149 344–348] The selection of patients for follow-up should be based on histological classification criteria (OLGA/OLGIM: operative link for gastritis assessment/operative link for gastric intestinal metaplasia assessment).[344 346]

Statement 15: Public awareness campaigns for prevention of gastric cancer should be encouraged.
Level of evidence: D **Grade of recommendation: A**

Public awareness campaigns in a number of countries have focused on the prevention of colorectal cancer and have led to the introduction of national screening programmes based on colonoscopy and/or stool blood positivity. They target individuals in the at-risk age range (50–65 or 70 years.) It is largely accepted that acceptance rates for screening are related to the extent of public awareness on the topic. The methodology used in public awareness campaigns differ in their communication

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strategies: paid media, public service announcements, public relations, media advocacy, government relations, and community activities. Communication strategies can be assessed on three levels of evaluation: (1) short-term outcomes (awareness, attitude shifts); (2) intermediate outcomes (knowledge, attitude/policy shifts); (3) long-term outcomes (changes in behaviour, disease rate changes).

Public awareness of gastric cancer risk factors and disease screening in high risk regions should be encouraged but public awareness campaigns on gastric cancer may lead to over-investigation.

Statement 16: Mass eradication using a 'screen-and-treat' strategy with commonly used antibiotics may create additional resistance selection pressure on pathogens other than *H. pylori*.

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

The widespread use of antibiotics for gastric cancer prevention that are commonly used for treating life-threatening diseases (eg, amoxicillin, clarithromycin, levofloxacin) may select resistance in bacteria other than *H. pylori*.[349 350]

Use of a single macrolide in the dose and duration of the shortest *H. pylori* eradication regimen (clarithromycin 500 mg twice daily for 7 days) increased the resistance of macrolide-resistant pharyngeal *Streptococcus pneumoniae* in a placebo-controlled study in healthy volunteers. The difference was statistically significant over the entire study period of 180 days.[289]

Use of macrolides has been associated with an increase in resistance of *Streptococcus pyogenes* and *Staphylococcus aureus* that are frequent causes of community-acquired infections.

Extensive use of fluoroquinolones is associated with a marked increase in resistance of uropathogenic *Escherichia coli* and circulation of ESBL (extended-spectrum beta-lactamases)-producing multi-drug resistant bacterial strains. The same applies to the use of amoxicillin that already has very high resistance rates in most countries. The spread of highly pathogenic *Clostridium difficile* ribotype 027 that is resistant to fluoroquinolones can be facilitated by use of these drugs.

Alternative treatment regimens could be considered in public health campaigns to minimise this undesirable ecological side effect. Bismuth, tetracycline, and metronidazole are less important antibacterial agents in managing life-threatening disease, and therefore are more appropriate in public health settings. Resistance to rifabutin can develop after several months of prolonged use of the drug, therefore short-duration treatment is not expected to increase the resistance of *Mycobacterium tuberculosis* substantially.

Statement 17: An effective vaccine against *H. pylori* would be the best public health measure against the infection.

Level of evidence: 4 **Grade of recommendation: D**

A successful *H. pylori* vaccine field trial from China[351] has recently been reported. This is a promise for the future and demands increased efforts for further development of a vaccine.

WORKING GROUP 5: *H. PYLORI* AND THE GASTRIC MICROBIOTA

Statement 1: Gastric microbiota includes other microbes beyond *H. pylori*.

Level of evidence: 2c **Grade of recommendation: B**

The stomach, as with other parts of the GI tract, harbours its own microbiota, of which *H. pylori* is its best known component, but certainly not the only one. Up to now, only a few studies have investigated the composition of gastric microbiota through culture-independent, molecular approaches (eg, 16S rDNA sequencing analysis), focusing mainly on the analysis of bacteria. In healthy conditions, the main phyla of gastric microbiota are Proteobacteria, Firmicutes, Bacteroidetes, and Actinobacteria, whereas the most commonly found genus in the stomach is *Streptococcus*.[352–356] The composition of the gastric microbiota appears to be substantially different from that of the oral and throat microbiota.[357] This indicates that the gastric microbiota is composed of resident microbes rather than those derived from the passage of microorganisms from upper organs.

Statement 2: The composition of a healthy gastric microbiota and how *H. pylori* affects this microbiota have not yet been fully defined.

Level of evidence: 5 **Grade of recommendation: D**

In spite of an increasing body of evidence,[352–357] the exact composition of a healthy gastric microbiota remains uncharacterised and the relationship between *H. pylori* and other gastric microorganisms is yet to be fully defined.[355 358] Nevertheless, some evidence shows that *H. pylori* decreases the diversity of the gastric microbiota,[352] suggesting a predominance of *H. pylori* over other microbes.

Statement 3: Components of the gastric microbiota may play a role in the development of *H. pylori*-related diseases.

Level of evidence: low **Grade of recommendation: weak**

Alterations of the human gastric microbiota have been found in different gastric diseases, including those arising as a complication of *H. pylori*-related gastritis. The reduced acid secretion of the atrophic stomach supports the growth of a number of microorganisms whose development is retarded by the low gastric pH in healthy conditions. To date, there are few data on the microbial pattern of atrophic gastritis. Overall, lower microbial richness is significantly associated with a lower serum PgI/PgII ratio in Chinese patients.[359] Furthermore, a shift in the predominant bacterial communities, from *Prevotella* to *Streptococcus*, has been identified in atrophic gastritis.[360]

16S rRNA gene sequencing analysis showed that gastric microbiota of patients with gastric cancer is dominated by different species of the genera *Streptococcus* (among them, the predominant species were *S. mitis* and *S. parasanguinis*), *Lactobacillus*, *Veillonella*, and *Prevotella*.[361]

The use of microarray G3 PhyloChip in patients with, respectively, non-atrophic gastritis, intestinal metaplasia, and gastric cancer, has shown that the gastric microbiota of patients with gastric cancer displays significantly lower diversity but a higher abundance of members of the *Pseudomonas* genus than that of patients with non-atrophic gastritis (with nine families representing 50% of all operational taxonomic units); furthermore, both a trend towards the decrease of six taxa (two species from *TM7* phylum, two *Porphyromonas* species, *Neisseria* species, and *Streptococcus sinensis*) and an opposite trend towards the increase of two taxa (*Lactobacillus coleohominis* and *Lachnospiraceae*) was observed from non-atrophic gastritis to intestinal metaplasia to gastric cancer.[362]

Another assessment of the gastric microbiota of patients with chronic gastritis, intestinal metaplasia and gastric cancer, performed through 16S rrDNA sequencing using a high-

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throughput sequencing platform (454 GS FLX Titanium), has obtained totally different data, that includes a greater microbial diversity, a relative increase of *Bacilli* and *Streptococcaceae*, and a relative decrease of *Helicobacteraceae* in the gastric cancer group than other groups.[363] In both studies, the analysis of Unifrac distance between the three groups showed a clear separation between the gastric cancer group and the gastritis group, whereas the intestinal metaplasia group overlapped with the two groups.

These studies suggest that *H. pylori* may represent the main but not the only microbial trigger for different gastric diseases, and that microorganisms other than *H. pylori* may play a relevant role in the development of complications in *H. pylori*-related gastritis.[355 356 364]

Statement 4: Non-*H. pylori Helicobacter* species can cause human gastric disease.
Level of evidence: 2c **Grade of recommendation: B**

Numerous *Helicobacter* species other than *H. pylori* have been identified over recent years. Some of them have been found in humans, including *H. bilis*, *H. cinaedi*, and *H. fennelliae*. Besides occasional associations with gastroenteritis,[365] infection with these and other enterohepatic *Helicobacter* species have been associated with extraintestinal diseases, including extrahepatic cholangiocarcinoma for *H. bilis* and *H. hepaticus*[366 367] and bacteraemia.[368] In addition to these enterohepatic *Helicobacter* species, gastric non-*H. pylori Helicobacter* species have also been detected in humans. These patients have been reported to suffer from gastritis, peptic ulcer disease, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma.[369–374] Although these bacteria are often erroneously referred to as '*H. heilmannii*', a number of similar but distinct zoonotically important bacterial species are in fact involved, including *H. bizzozeronii*, *H. felis*, *H. heilmannii s.s.*, *H. salomonis*, and *H. suis*.[367 368 373 375–379] Diagnosis of infection with one of these non-*H. pylori Helicobacter* species is not always straightforward, in part due to their patchy colonisation in the human stomach.[373 380]

Statement 5: *H. pylori* eradication therapy can impair the healthy gut microbiota, leading to short-term clinical consequences.
Level of evidence: 2c **Grade of recommendation: B**

Antibiotic treatments, including those for *H. pylori* eradication, are known to cause a number of short-term side effects. Mouse models and human studies have shown that antibiotic treatment can alter gut microbiota in terms of richness, diversity, and composition.[381–385] The recent improvement in diagnostic technologies has allowed us to detect changes in gut microbiota which occur after antibiotic therapy. In a recent study, antibiotic-associated microbiota impairment was assessed by high-throughput sequencing. Observed qualitative changes were drug and dose dependent. The most relevant shifts involved, respectively, *Bacteroides, Bifidobacterium, Clostridium, Enterobacteriaceae, and Lactobacillus*.[386] Probiotics may counteract the harmful effects of antibiotics on gut microbiota.[384]

Antibiotic-associated microbiota impairment can lead to a number of clinical manifestations. The most common GI side effects correlated with antibiotic therapy include diarrhoea, nausea, vomiting, bloating, and abdominal pain[387] that may lead to the discontinuation of treatment, with consequent risk of therapeutic failure and/or development of antibiotic resistance.

Furthermore, antibiotic administration is the main risk factor for the development of *C. difficile* infection, an important cause of morbidity and increased healthcare costs.[388]

Statement 6: *H. pylori* eradication should be used with care in subjects with undeveloped or unstable gut microbiota to avoid long-term clinical consequences.
Level of evidence: 2c **Grade of recommendation: B**

Evidence in animals and humans suggest that the alteration of microbiota induced by antibiotics may be responsible for long-term clinical consequences, that may persist after drug administration.[381–385] In a number of animal models, antibiotic therapy was able to drive metabolic and weight changes, and to affect intestinal expression of genes involved in the immune regulation.[389 390] Several epidemiological studies have shown a positive association between exposure to antibiotics in early years of life and increased risk of weight and fat gain.[391–395] Therefore, *H. pylori* eradication in subjects with unconsolidated gut microbiota (eg, during weaning) should be considered with care.

Statement 7: Antibiotic-based *H. pylori* eradication therapy can select antibiotic-resistant components of gut microbiota.
Level of evidence: 2c **Grade of recommendation: B**

Overall, treatment with antibiotics increases the risk for selection of antibiotic resistant members of host gut microbiota. In particular, several studies showed that antibiotic-based eradication therapy against *H. pylori* could select antibiotic-resistant components of gut microbiota. Different triple therapies against *H. pylori*, including omeprazole in combination with amoxicillin and metronidazole or with clarithromycin and metronidazole, led to the rise of resistant streptococci and staphylococci and to an increase in the number of resistant *Enterococcus* species, *Enterobacteriaceae* species, and *Bacteroides* species.[396] Results of a cohort study have demonstrated that triple therapy consisting of omeprazole, clarithromycin, and metronidazole selects for resistance to macrolides within the gut microbiota of the host.[397] The same eradication regimen was demonstrated to promote the selection of resistant enterococci and resistant strains of *Staphylococcus epidermidis*, that persisted within the human gut microbiota for several years after the end of antibiotic therapy.[398 399]

Finally, a history of fluoroquinolone-based therapies has been shown to increase the risk for emergence of MRSA (methicillin-resistant *Staphylococcus aureus*)[400 401] and extended specturm beta lactamase (ESBL)-producing strains of *E. coli* or *K. pneumoniae*.[402]

Statement 8: Additional studies are required to address the long-lasting impact of *H. pylori* eradication on the composition of gut microbiota.
Level of evidence: 5 **Grade of recommendation: D**

Currently, there is insufficient evidence on the effect of different eradication regimens upon gut microbiome. Therefore, optimally, mass eradication programmes should be implemented by means of well-designed studies, including the evaluation of the effects on gut microbiome. Other potential adverse events and approaches to deal with such effects could also be addressed in such studies.

Statement 9: Only certain probiotics have been shown to be effective in reducing GI side effects caused by *H. pylori* eradication therapies. Specific strains should be chosen only upon the basis of a demonstrated clinical efficacy.
Level of evidence: moderate **Grade of recommendation: strong**

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Several meta-analyses of RCTs have assessed the efficacy of probiotic supplementation in reducing side effects associated with antibiotic-based *H. pylori* eradication therapies, with overall encouraging results.[403–412] Some of these have focused on the *Lactobacillus* genus, either including only studies investigating *Lactobacillus*-containing probiotics or by subgroup analysis of pooled data, and have shown positive results,[403–406 412] One meta-analysis highlighted the importance of a duration exceeding 2 weeks of the probiotic treatment.[404] However pooling data from studies which differ with regards to species/strains, dosages and duration of probiotic therapies may lead to misleading conclusions and therefore should be avoided.[413]

The efficacy of adjuvant treatment with *Saccharomyces boulardii* has been extensively investigated. In 2010, a first meta-analysis showed that *S. boulardii* reduced the risk or overall adverse events (RR 0.46, 95% CI 0.3 to 0.7).[414] In 2015, the same group reported an updated meta-analysis, with comparable results: *S. boulardii* decreased the risk and overall adverse effects (RR 0.44, 95% CI 0.31 to 0.64).[415] Encouraging data on other probiotics, such as *Bacillus clausii*, have emerged from double-blind RCTs.[416]

In conclusion, certain probiotics appear to be effective in reducing adverse events related to *H. pylori* eradication therapy. Several questions remain, including the effectiveness of specific probiotic strains, dosages and duration of adjuvant probiotic therapy, geographical differences, and the influence of lifestyle (eg, diet, alcohol or smoke consumption). These should be addressed by future research.

Statement 10: Certain probiotics may have a beneficial effect on *H. pylori* eradication.

Level of evidence: very low **Grade of recommendation: weak**

Probiotics may inhibit *H. pylori* through several mechanisms, including the release of antimicrobial products or the competition with *H. pylori* for colonisation and survival. A number of meta-analyses of RCTs have assessed the capacity of probiotics to increase the efficacy of *H. pylori* eradication therapies, with positive results.[403–412] Nevertheless, in meta-analyses in which sub-group analysis was performed, only certain strains maintained significance, including different *Lactobacillus* strains,[403 404 408 410] *Bifidobacterium* strains,[403 404] and *S. boulardii*.[404]

These data highlight the impropriety of pooling the data from studies investigating different probiotic species and strains.[413] In two meta-analyses, *S. boulardii* was shown to increase the *H. pylori* eradication rate, with, respectively, RRs of 1.13 (95% CI 1.05 to 1.21)[414] and 1.11 (95% CI 1.06 to 1.17).[415]

Despite these encouraging data, probiotics appear to increase the *H. pylori* eradication rate by reducing side-effects related to eradication therapy, rather than through direct effects on *H. pylori*. Consequently, more data are definitely needed to assess the direct efficacy of probiotics against *H. pylori*.

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