

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

P Malfertheiner,¹ F Megraud,² C A O'Morain,³ J P Gisbert,^{4,5} E J Kuipers,⁶ A T Axon,⁷ F Bazzoli,⁸ A Gasbarrini,⁹ J Atherton,¹⁰ D Y Graham,¹¹ R Hunt,^{12,13} P Moayyedi,¹⁴ T Rokkas,¹⁵ M Rugge,¹⁶ M Selgrad,¹⁷ S Suerbaum,¹⁸ K Sugano,¹⁹ E M El-Omar,²⁰ on behalf of the European Helicobacter and Microbiota Study Group and Consensus panel

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/gutjnl-2016-312288>).

For numbered affiliations see end of article.

Correspondence to Professor P Malfertheiner, University of Magdeburg, Department of Gastroenterology, Hepatology and Infectious Diseases, Leipziger Str. 44, Magdeburg 39120, Germany; peter.malfertheiner@med.ovgu.de

Received 19 May 2016
Accepted 9 August 2016
Published Online First
5 October 2016

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 Report¹ 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



To cite: Malfertheiner P, Megraud F, O'Morain CA, et al. *Gut* 2017;**66**:6–30.

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-analysis⁶ 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

The latest WHO ICD-11 β version under development and the Kyoto Global Consensus of *H. pylori* gastritis² 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-analysis⁴⁷ of five randomised clinical trials and

additional studies reported more recently⁴⁸ 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 pan-gastritis. 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

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 eradication 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-gastrointestinal 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 ineffective⁹⁰ 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* treatment⁹³ 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 ¹³C-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.

¹⁴C 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

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 curvature¹¹⁸ and from the antrum and corpus.¹¹⁹ Others showed that two antral biopsies only¹²⁰ (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 well¹¹⁸ 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

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 anti-biogram 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 Pgl/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 (Pgl 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 Conference² 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 evaluation¹⁵² 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-

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

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 clarithromycin¹⁷⁹ 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

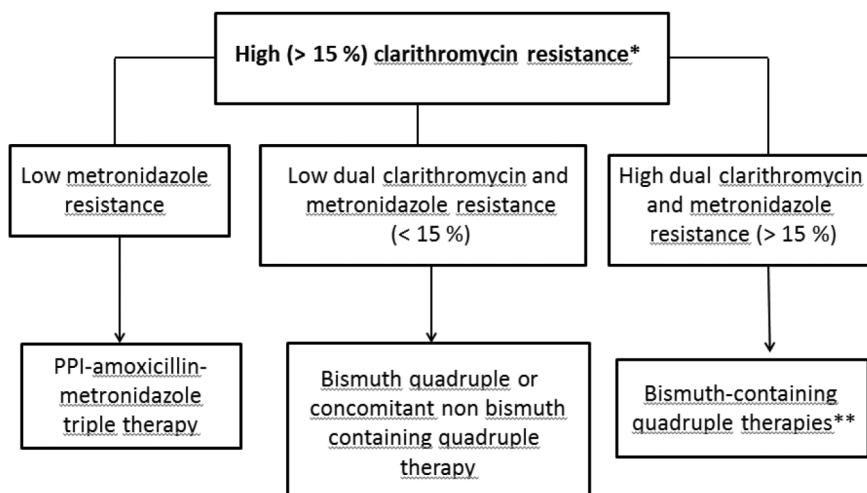
Korean studies also suggest some benefit with longer treatment duration.^{196–199}

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.

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 America²⁰⁹ (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.

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

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 fluoroquinolones 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 ($\geq 90\%$ 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 rifabutin 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

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 fluoroquinolones 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

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 aetiological 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 stomach³¹⁷ 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 study³⁰⁸ 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**

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 cancer¹ 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

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 short-term *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 China³⁵¹ 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 Pgl/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-

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 pain³⁸⁷ 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 spectrum 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

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*.

Author affiliations

¹Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

²Laboratoire de Bactériologie, Inserm U853, Université de Bordeaux, Bordeaux, France

³Faculty of Health Sciences, Trinity College, Dublin, Ireland

⁴Department of Gastroenterology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IP), Madrid, Spain

⁵Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREH), Madrid, Spain

⁶Erasmus University Medical Center, Rotterdam, The Netherlands

⁷General Infirmary Leeds, UK

⁸Internal Medicine and Gastroenterology, University of Bologna Italy, Bologna, Italy

⁹Gastroenterology, and Liver Unit, Internal Medicine, Roma, Italy

¹⁰Nottingham, UK

¹¹Department of Medicine (111D), Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA

¹²Department of Medicine, McMaster University, Hamilton, Canada

¹³Hillcroft, Beaconsfield, Buckinghamshire, UK

¹⁴Department of Gastroenterology, McMaster University, Hamilton, Canada

¹⁵Department of Gastroenterology, Henry Dunant Hospital, Athens, Greece

¹⁶Department of Diagnostic Sciences, University of Padova, Padova, Italy

¹⁷Regensburg, Germany

¹⁸Medizinische Hochschule Hannover, Institut für Medizinische Mikrobiologie, Hannover, Germany

¹⁹Department of Medicine, Jichi Medical School, Tochigi, Japan

²⁰St George and Sutherland Clinical School, University of New South Wales, Sydney, Australia

Acknowledgements We acknowledge the editorial assistance of Mrs. D. Deutschländer.

Contributors L. Agreus (Sweden), L.P. Andersen (Denmark), J. Atherton (UK), A. Axon (UK), F. Bazzoli (Italy), L. Coelho (Brazil), J.C. Delchier (France), F. Di Mario (Italy), M. Dinis-Ribeiro (Portugal), E. El-Omar (UK), W. Fischbach (Germany), B. Flahou (Belgium), K.M. Fock (Singapore), A. Gasbarrini (Italy), G. Gasbarrini (Italy), G. Gensini (Italy), J. Gisbert (Spain), K.L. Goh (Malaysia), D.Y. Graham (USA), R. Herrero (France), R. Hunt (UK), E.J. Kuipers (The Netherlands), L. Kupcinskas (Kaunas), A. Lanas (Spain), M. Leja (Latvia), J.C. Machado (Portugal), V. Mahachai (Thailand), P. Malfertheiner (Germany), F. Megraud (France), T. Milosavljevic (Serbia), P. Moayyedi (Canada), J. Molina-Infante (Spain), Y. Niv (Israel), C. O'Morain (Ireland), A. Ristimaki (Finland), T. Rokkas (Greece), M. Rugge (Italy), M. Selgrad (Germany), S. Suerbaum (Germany), K. Sugano (Japan), B. Tepes (Slovenia), D. Vaira (Italy), M. Vieth (Germany), W. You (China).

Funding This study was supported by an unrestricted grant of Malesci/Menarini Foundation.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection—the Maastricht IV/ Florence Consensus Report. *Gut* 2012;61:646–64.
- Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on Helicobacter pylori gastritis. *Gut* 2015;64:1353–67.
- Hunt RH, Camilleri M, Crowe SE, et al. The stomach in health and disease. *Gut* 2015;64:1650–68.
- Robinson KA, Saldanha II, Mckoy NA. *Frameworks for Determining Research Gaps During Systematic Reviews*. Agency for Healthcare Research and Quality (US), 2011.
- Howden CW, Hunt RH. Guidelines for the management of Helicobacter pylori infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol* 1998;93:2330–8.
- Ford AC, Qume M, Moayyedi P, et al. Helicobacter pylori 'test and treat' or endoscopy for managing dyspepsia: an individual patient data meta-analysis. *Gastroenterology* 2005;128:1838–44.
- Arents NLA, Thijs JC, van Zwet AA, et al. Approach to treatment of dyspepsia in primary care: a randomized trial comparing 'test-and-treat' with prompt endoscopy. *Arch Intern Med* 2003;163:1606–12.
- Duggan AE, Elliott CA, Miller P, et al. Clinical trial: a randomized trial of early endoscopy, Helicobacter pylori testing and empirical therapy for the management of dyspepsia in primary care. *Aliment Pharmacol Ther* 2009;29:55–68.
- Lassen AT, Pedersen FM, Bytzer P, et al. Helicobacter pylori test-and-eradicate versus prompt endoscopy for management of dyspeptic patients: a randomised trial. *Lancet* 2000;356:455–60.
- McColl KEL, Murray LS, Gillen D, et al. Randomised trial of endoscopy with testing for Helicobacter pylori compared with non-invasive H pylori testing alone in the management of dyspepsia. *BMJ* 2002;324:999–1002.
- Delaney B, Ford AC, Forman D, et al. Initial management strategies for dyspepsia. *Cochrane Database Syst Rev* 2005;(4):CD001961.
- Moayyedi P, Axon AT. The usefulness of the likelihood ratio in the diagnosis of dyspepsia and gastroesophageal reflux disease. *Am J Gastroenterol* 1999;94:3122–5.
- Ikenberry SO, Harrison ME, Lichtenstein D, et al. The role of endoscopy in dyspepsia. *Gastrointest Endosc* 2007;66:1071–5.
- Niv Y, Niv G, Koren R. 13C-urea breath test for diagnosis of Helicobacter pylori infection in the elderly. *Dig Dis Sci* 2004;49:1840–4.

- 15 Levi S, Beardshall K, Haddad G, *et al.* Campylobacter pylori and duodenal ulcers: the gastrin link. *Lancet* 1989;1:1167–8.
- 16 Moss SF, Legon S, Bishop AE, *et al.* Effect of Helicobacter pylori on gastric somatostatin in duodenal ulcer disease. *Lancet* 1992;340:930–2.
- 17 Gillen D, El-Omar EM, Wirz AA, *et al.* The acid response to gastrin distinguishes duodenal ulcer patients from Helicobacter pylori-infected healthy subjects. *Gastroenterology* 1998;114:50–7.
- 18 de Vries AC, van Grieken NCT, Looman CWN, *et al.* Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology* 2008;134:945–52.
- 19 Malfertheiner P. The intriguing relationship of Helicobacter pylori infection and acid secretion in peptic ulcer disease and gastric cancer. *Dig Dis* 2011;29:459–64.
- 20 El-Omar EM, Oien K, El-Nujumi A, *et al.* Helicobacter pylori infection and chronic gastric acid hyposecretion. *Gastroenterology* 1997;113:15–24.
- 21 Haruma K, Mihara M, Okamoto E, *et al.* Eradication of Helicobacter pylori increases gastric acidity in patients with atrophic gastritis of the corpus-evaluation of 24-h pH monitoring. *Aliment Pharmacol Ther* 1999;13:155–62.
- 22 Iijima K, Ohara S, Sekine H, *et al.* Changes in gastric acid secretion assayed by endoscopic gastrin test before and after Helicobacter pylori eradication. *Gut* 2000;46:20–6.
- 23 Fukuchi T, Ashida K, Yamashita H, *et al.* Influence of cure of Helicobacter pylori infection on gastric acidity and gastroesophageal reflux: study by 24-h pH monitoring in patients with gastric or duodenal ulcer. *J Gastroenterol* 2005;40:350–60.
- 24 Hamada H, Haruma K, Mihara M, *et al.* High incidence of reflux oesophagitis after eradication therapy for Helicobacter pylori: impacts of hiatal hernia and corpus gastritis. *Aliment Pharmacol Ther* 2000;14:729–35.
- 25 Takeuchi R, Kato K, Mizuno S, *et al.* Abnormal gastroesophageal flap valve is highly associated with endoscopic reflux esophagitis after Helicobacter pylori eradication. *Helicobacter* 2004;9:1–8.
- 26 Inoue H, Imoto I, Taguchi Y, *et al.* Reflux esophagitis after eradication of Helicobacter pylori is associated with the degree of hiatal hernia. *Scand J Gastroenterol* 2004;39:1061–5.
- 27 Kawanishi M. Development of reflux esophagitis following Helicobacter pylori eradication. *J Gastroenterol* 2005;40:1024–8.
- 28 Toyoda M, Shirasaka D, Aoyama N, *et al.* Helicobacter pylori eradication therapy on histologic change in the distal esophagus. *Helicobacter* 2006;11:217–23.
- 29 Sugano K. Should we still subcategorize Helicobacter pylori-associated dyspepsia as functional disease? *J Neurogastroenterol Motil* 2011;17:366–71.
- 30 Suzuki H, Nishizawa T, Hibi T. Can Helicobacter pylori-associated dyspepsia be categorized as functional dyspepsia? *J Gastroenterol Hepatol* 2011;26(Suppl 3):42–5.
- 31 Tack J, Talley NJ, Camilleri M, *et al.* Functional gastroduodenal disorders. *Gastroenterology* 2006;130:1466–79.
- 32 Marshall BJ, Armstrong JA, McGeachie DB, *et al.* Attempt to fulfil Koch's postulates for pyloric Campylobacter. *Med J Aust* 1985;142:436–9.
- 33 Morris A, Nicholson G. Ingestion of Campylobacter pyloridis causes gastritis and raised fasting gastric pH. *Am J Gastroenterol* 1987;82:192–9.
- 34 Bode G, Brenner H, Adler G, *et al.* Dyspeptic symptoms in middle-aged to old adults: the role of Helicobacter pylori infection, and various demographic and lifestyle factors. *J Intern Med* 2002;252:41–7.
- 35 Moayyedi P, Forman D, Braunholtz D, *et al.* The proportion of upper gastrointestinal symptoms in the community associated with Helicobacter pylori, lifestyle factors, and nonsteroidal anti-inflammatory drugs. Leeds HELP Study Group. *Am J Gastroenterol* 2000;95:1448–55.
- 36 Wildner-Christensen M, Hansen JM, De Muckadell OBS. Risk factors for dyspepsia in a general population: non-steroidal anti-inflammatory drugs, cigarette smoking and unemployment are more important than Helicobacter pylori infection. *Scand J Gastroenterol* 2006;41:149–54.
- 37 Nandurkar S, Talley NJ, Xia H, *et al.* Dyspepsia in the community is linked to smoking and aspirin use but not to Helicobacter pylori infection. *Arch Intern Med* 1998;158:1427–33.
- 38 Moayyedi P, Soo S, Deeks J, *et al.* Eradication of Helicobacter pylori for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2006;(2):CD002096.
- 39 Makris N, Barkun A, Crott R, *et al.* Cost-effectiveness of alternative approaches in the management of dyspepsia. *Int J Technol Assess Health Care* 2003;19:446–64.
- 40 Suzuki H, Moayyedi P. Helicobacter pylori infection in functional dyspepsia. *Nat Rev Gastroenterol Hepatol* 2013;10:168–74.
- 41 Sonnenberg A, Lash RH, Genta RM. A national study of Helicobacter pylori infection in gastric biopsy specimens. *Gastroenterology* 2010;139:1894–901.
- 42 Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, *et al.* Cure of Helicobacter pylori infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. *Gut* 2004;53:12–20.
- 43 van der Hulst RW, van der Ende A, Dekker FW, *et al.* Effect of Helicobacter pylori eradication on gastritis in relation to cagA: a prospective 1-year follow-up study. *Gastroenterology* 1997;113:25–30.
- 44 Tulassay Z, Stolte M, Engstrand L, *et al.* Twelve-month endoscopic and histological analysis following proton-pump inhibitor-based triple therapy in Helicobacter pylori-positive patients with gastric ulcers. *Scand J Gastroenterol* 2010;45:1048–58.
- 45 Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002;359:14–22.
- 46 Sostres C, Carrera-Lasfuentes P, Benito R, *et al.* Peptic ulcer bleeding risk. The role of Helicobacter pylori infection in NSAID/low-dose aspirin users. *Am J Gastroenterol* 2015;110:684–9.
- 47 Vergara M, Catalán M, Gisbert JP, *et al.* Meta-analysis: role of Helicobacter pylori eradication in the prevention of peptic ulcer in NSAID users. *Aliment Pharmacol Ther* 2005;21:1411–18.
- 48 de Leest HTJL, Steen KSS, Lems WF, *et al.* Eradication of Helicobacter pylori does not reduce the incidence of gastroduodenal ulcers in patients on long-term NSAID treatment: double-blind, randomized, placebo-controlled trial. *Helicobacter* 2007;12:477–85.
- 49 Lai KC, Lam SK, Chu KM, *et al.* Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002;346:2033–8.
- 50 Chan FKL, Ching JYL, Suen BY, *et al.* Effects of Helicobacter pylori infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. *Gastroenterology* 2013;144:528–35.
- 51 Fletcher EH, Johnston DE, Fisher CR, *et al.* Systematic review: Helicobacter pylori and the risk of upper gastrointestinal bleeding risk in patients taking aspirin. *Aliment Pharmacol Ther* 2010;32:831–9.
- 52 Lanás A, Carrera-Lasfuentes P, Arguedas Y, *et al.* Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. *Clin Gastroenterol Hepatol* 2015;13:906–12.e2.
- 53 Holster IL, Valkhoff VE, Kuipers EJ, *et al.* New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 2013;145:105–112.e15.
- 54 González-Pérez A, Sáez ME, Johansson S, *et al.* Risk factors associated with uncomplicated peptic ulcer and changes in medication use after diagnosis. *PLoS One* 2014;9:e101768.
- 55 Chan FKL, Wong VWS, Suen BY, *et al.* Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet* 2007;369:1621–6.
- 56 Chan FK, Chung SC, Suen BY, *et al.* Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. *N Engl J Med* 2001;344:967–73.
- 57 Kuipers EJ, Uytterlinde AM, Peña AS, *et al.* Increase of Helicobacter pylori-associated corpus gastritis during acid suppressive therapy: implications for long-term safety. *Am J Gastroenterol* 1995;90:1401–6.
- 58 Kuipers EJ, Lundell L, Klinkenberg-Knol EC, *et al.* Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996;334:1018–22.
- 59 Eissele R, Brunner G, Simon B, *et al.* Gastric mucosa during treatment with lansoprazole: Helicobacter pylori is a risk factor for argyrophil cell hyperplasia. *Gastroenterology* 1997;112:707–17.
- 60 Lundell L, Havu N, Miettinen P, *et al.* Changes of gastric mucosal architecture during long-term omeprazole therapy: results of a randomized clinical trial. *Aliment Pharmacol Ther* 2006;23:639–47.
- 61 Schenk BE, Kuipers EJ, Nelis GF, *et al.* Effect of Helicobacter pylori eradication on chronic gastritis during omeprazole therapy. *Gut* 2000;46:615–21.
- 62 Warburton-Timms VJ, Charlett A, Valori RM, *et al.* The significance of cagA+ Helicobacter pylori in reflux oesophagitis. *Gut* 2001;49:341–6.
- 63 O'Connor HJ. Review article: Helicobacter pylori and gastro-oesophageal reflux disease—clinical implications and management. *Aliment Pharmacol Ther* 1999;13:117–27.
- 64 Rokkas T, Pistiolas D, Sechopoulos P, *et al.* Relationship between Helicobacter pylori infection and esophageal neoplasia: a meta-analysis. *Clin Gastroenterol Hepatol* 2007;5:1413–17, 1417.e1–2.
- 65 Laine L, Sugg J. Effect of Helicobacter pylori eradication on development of erosive esophagitis and gastroesophageal reflux disease symptoms: a post hoc analysis of eight double blind prospective studies. *Am J Gastroenterol* 2002;97:2992–7.
- 66 Yaghoobi M, Farrokhyar F, Yuan Y, *et al.* Is there an increased risk of GERD after Helicobacter pylori eradication?: a meta-analysis. *Am J Gastroenterol* 2010;105:1007–13; quiz 1006, 1014.
- 67 Qian B, Ma S, Shang L, *et al.* Effects of Helicobacter pylori eradication on gastroesophageal reflux disease. *Helicobacter* 2011;16:255–65.
- 68 Moayyedi P, Bardhan C, Young L, *et al.* Helicobacter pylori eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. *Gastroenterology* 2001;121:1120–6.

- 69 Klinkenberg-Knol EC, Nelis F, Dent J, *et al.* Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 2000;118:661–9.
- 70 Di Mario F, Ingegnoli A, Dal Bò N, *et al.* Early epigastric pain after PPI administration: exacerbation of Helicobacter pylori corpus gastritis? *Helicobacter* 2004;9:92–4.
- 71 Queiroz DMM, Harris PR, Sanderson IR, *et al.* Iron status and Helicobacter pylori infection in symptomatic children: an international multi-centered study. *PLoS One* 2013;8:e68833.
- 72 Yuan W, Li Yumin, Yang Kehu, *et al.* Iron deficiency anemia in Helicobacter pylori infection: meta-analysis of randomized controlled trials. *Scand J Gastroenterol* 2010;45:665–76.
- 73 Qu X-H, Huang X-L, Xiong P, *et al.* Does Helicobacter pylori infection play a role in iron deficiency anemia? A meta-analysis. *World J Gastroenterol* 2010;16:886–96.
- 74 Goddard AF, James MW, McIntyre AS, *et al.* Guidelines for the management of iron deficiency anaemia. *Gut* 2011;60:1309–16.
- 75 Sato R, Murakami K, Okimoto T, *et al.* Development of corpus atrophic gastritis may be associated with Helicobacter pylori-related idiopathic thrombocytopenic purpura. *J Gastroenterol* 2011;46:991–7.
- 76 Neuner C, Lim W, Crowther M, *et al.* The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011;117:4190–207.
- 77 Provan D, Stasi R, Newland AC, *et al.* International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;115:168–86.
- 78 Russo G, Miraglia V, Branciforte F, *et al.* Effect of eradication of Helicobacter pylori in children with chronic immune thrombocytopenia: a prospective, controlled, multicenter study. *Pediatr Blood Cancer* 2011;56:273–8.
- 79 Stabler SP. Vitamin B12 deficiency. *N Engl J Med* 2013;368:2041–2.
- 80 Franceschi F, Tortora A, Gasbarrini G, *et al.* Helicobacter pylori and extragastric diseases. *Helicobacter* 2014;19(Suppl 1):52–8.
- 81 Huang B, Chen Y, Xie Q, *et al.* CagA-positive Helicobacter pylori strains enhanced coronary atherosclerosis by increasing serum OxLDL and HsCRP in patients with coronary heart disease. *Dig Dis Sci* 2011;56:109–14.
- 82 Ikeda A, Iso H, Sasazuki S, *et al.* The combination of Helicobacter pylori- and cytotoxin-associated gene-A seropositivity in relation to the risk of myocardial infarction in middle-aged Japanese: The Japan Public Health Center-based study. *Atherosclerosis* 2013;230:67–72.
- 83 Hughes WS. An hypothesis: the dramatic decline in heart attacks in the United States is temporally related to the decline in duodenal ulcer disease and Helicobacter pylori infection. *Helicobacter* 2014;19:239–41.
- 84 Bu XL, Yao XQ, Jiao SS, *et al.* A study on the association between infectious burden and Alzheimer's disease. *Eur J Neurol* 2015;22:1519–25.
- 85 Roubaud-Baudron C, Krolak-Salmon P, Quadrio I, *et al.* Impact of chronic Helicobacter pylori infection on Alzheimer's disease: preliminary results. *Neurobiol Aging* 2012;33:1009.e11–19.
- 86 Bu XL, Wang X, Xiang Y, *et al.* The association between infectious burden and Parkinson's disease: a case-control study. *Parkinsonism Relat Disord* 2015;21:877–81.
- 87 Dobbs SM, Charlett A, Dobbs RJ, *et al.* Antimicrobial surveillance in idiopathic parkinsonism: indication-specific improvement in hypokinesia following Helicobacter pylori eradication and non-specific effect of antimicrobials for other indications in worsening rigidity. *Helicobacter* 2013;18:187–96.
- 88 Engler DB, Reuter S, van Wijck Y, *et al.* Effective treatment of allergic airway inflammation with Helicobacter pylori immunomodulators requires BATF3-dependent dendritic cells and IL-10. *Proc Natl Acad Sci USA* 2014;111:11810–15.
- 89 Lane JA, Murray LJ, Harvey IM, *et al.* Randomised clinical trial: Helicobacter pylori eradication is associated with a significantly increased body mass index in a placebo-controlled study. *Aliment Pharmacol Ther* 2011;33:922–9.
- 90 Nakamura S, Sugiyama T, Matsumoto T, *et al.* Long-term clinical outcome of gastric MALT lymphoma after eradication of Helicobacter pylori: a multicentre cohort follow-up study of 420 patients in Japan. *Gut* 2012;61:507–13.
- 91 Capelle LG, de Vries AC, Looman CWN, *et al.* Gastric MALT lymphoma: epidemiology and high adenocarcinoma risk in a nation-wide study. *Eur J Cancer* 2008;44:2470–6.
- 92 Capelle LG, den Hoed CM, de Vries AC, *et al.* Premalignant gastric lesions in patients with gastric mucosa-associated lymphoid tissue lymphoma and metachronous gastric adenocarcinoma: a case-control study. *Eur J Gastroenterol Hepatol* 2012;24:42–7.
- 93 Fischbach W, Goebeler ME, Ruskone-Fourmestreaux A, *et al.* Most patients with minimal histological residuals of gastric MALT lymphoma after successful eradication of Helicobacter pylori can be managed safely by a watch and wait strategy: experience from a large international series. *Gut* 2007;56:1685–7.
- 94 Gisbert JP, Calvet X. Helicobacter pylori 'test-and-treat' strategy for management of dyspepsia: a comprehensive review. *Clin Transl Gastroenterol* 2013;4:e32.
- 95 Gisbert JP, Pajares JM. Review article: 13C-urea breath test in the diagnosis of Helicobacter pylori infection—a critical review. *Aliment Pharmacol Ther* 2004;20:1001–17.
- 96 Nocon M, Kuhlmann A, Leodolter A, *et al.* Efficacy and cost-effectiveness of the 13C-urea breath test as the primary diagnostic investigation for the detection of Helicobacter pylori infection compared to invasive and non-invasive diagnostic tests. *GMS Health Technol Assess* 2009;5:Doc14.
- 97 Ferwana M, Abdulmajeed I, Alhajahmed A, *et al.* Accuracy of urea breath test in Helicobacter pylori infection: meta-analysis. *World J Gastroenterol* 2015;21:1305–14.
- 98 Gisbert JP, de la Morena F, Abraira V. Accuracy of monoclonal stool antigen test for the diagnosis of H. pylori infection: a systematic review and meta-analysis. *Am J Gastroenterol* 2006;101:1921–30.
- 99 Feldman RA, Deeks JJ, Evans SJ. Multi-laboratory comparison of eight commercially available Helicobacter pylori serology kits. Helicobacter pylori Serology Study Group. *Eur J Clin Microbiol Infect Dis* 1995;14:428–33.
- 100 Buruoca C, Delchier JC, Courillon-Mallet A, *et al.* Comparative evaluation of 29 commercial Helicobacter pylori serological kits. *Helicobacter* 2013;18:169–79.
- 101 Duggan AE, Elliott C, Logan RF. Testing for Helicobacter pylori infection: validation and diagnostic yield of a near patient test in primary care. *BMJ* 1999;319:1236–9.
- 102 Gatta L, Vakili N, Ricci C, *et al.* Effect of proton pump inhibitors and antacid therapy on 13C urea breath tests and stool test for Helicobacter pylori infection. *Am J Gastroenterol* 2004;99:823–9.
- 103 Graham DY, Opekun AR, Hammoud F, *et al.* Studies regarding the mechanism of false negative urea breath tests with proton pump inhibitors. *Am J Gastroenterol* 2003;98:1005–9.
- 104 Malfertheiner P. Diagnostic methods for H. pylori infection: choices, opportunities and pitfalls. *United European Gastroenterol J* 2015;3:429–31.
- 105 Connor SJ, Ngu MC, Katelaris PH. The impact of short-term ranitidine use on the precision of the 13C-urea breath test in subjects infected with Helicobacter pylori. *Eur J Gastroenterol Hepatol* 1999;11:1135–8.
- 106 Savarino V, Tracci D, Dulbecco P, *et al.* Negative effect of ranitidine on the results of urea breath test for the diagnosis of Helicobacter pylori. *Am J Gastroenterol* 2001;96:348–52.
- 107 Dulbecco P, Gambaro C, Bilardi C, *et al.* Impact of long-term ranitidine and pantoprazole on accuracy of [¹³C]urea breath test. *Dig Dis Sci* 2003;48:315–21.
- 108 el-Zimaity HM, al-Assi MT, Genta RM, *et al.* Confirmation of successful therapy of Helicobacter pylori infection: number and site of biopsies or a rapid urease test. *Am J Gastroenterol* 1995;90:1962–4.
- 109 Woo JS, el-Zimaity HM, Genta RM, *et al.* The best gastric site for obtaining a positive rapid urease test. *Helicobacter* 1996;1:256–9.
- 110 Lan HC, Chen TS, Li AFY, *et al.* Additional corpus biopsy enhances the detection of Helicobacter pylori infection in a background of gastritis with atrophy. *BMC Gastroenterol* 2012;12:182.
- 111 Weston AP, Campbell DR, Hassanein RS, *et al.* Prospective, multivariate evaluation of CLOtest performance. *Am J Gastroenterol* 1997;92:1310–15.
- 112 Moon SW, Moon SW, Kim TH, *et al.* United rapid urease test is superior than separate test in detecting Helicobacter pylori at the gastric antrum and body specimens. *Clin Endosc* 2012;45:392–6.
- 113 Osaki T, Mabe K, Hanawa T, *et al.* Urease-positive bacteria in the stomach induce a false-positive reaction in a urea breath test for diagnosis of Helicobacter pylori infection. *J Med Microbiol* 2008;57(Pt 7):814–19.
- 114 Kimura K. Chronological transition of the fundic-pyloric border determined by stepwise biopsy of the lesser and greater curvatures of the stomach. *Gastroenterology* 1972;63:584–92.
- 115 Wyatt JL, Rathbone BJ, Heatley RV. Local immune response to gastric Campylobacter in non-ulcer dyspepsia. *J Clin Pathol* 1986;39:863–70.
- 116 Craanen ME, Dekker W, Blok P, *et al.* Intestinal metaplasia and Helicobacter pylori: an endoscopic biopsies study of the gastric antrum. *Gut* 1992;33:16–20.
- 117 Satoh K, Kimura K, Taniguchi Y, *et al.* Distribution of inflammation and atrophy in the stomach of Helicobacter pylori-positive and -negative patients with chronic gastritis. *Am J Gastroenterol* 1996;91:963–9.
- 118 Dixon MF, Genta RM, Yardley JH, *et al.* Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996;20:1161–81.
- 119 Hazell SL, Borody TJ, Gal A, *et al.* Campylobacter pyloridis gastritis I: detection of urease as a marker of bacterial colonization and gastritis. *Am J Gastroenterol* 1987;82:292–6.
- 120 Genta RM, Graham DY. Comparison of biopsy sites for the histopathologic diagnosis of Helicobacter pylori: a topographic study of H. pylori density and distribution. *Gastrointest Endosc* 1994;40:342–5.
- 121 Satoh K, Kimura K, Taniguchi Y, *et al.* Biopsy sites suitable for the diagnosis of Helicobacter pylori infection and the assessment of the extent of atrophic gastritis. *Am J Gastroenterol* 1998;93:569–73.
- 122 Bayerdörffer E, Lehn N, Hatz R, *et al.* Difference in expression of Helicobacter pylori gastritis in antrum and body. *Gastroenterology* 1992;102:1575–82.

- 123 Genta RM, Huberman RM, Graham DY. The gastric cardia in *Helicobacter pylori* infection. *Hum Pathol* 1994;25:915–19.
- 124 Louw JA, Falck V, van Rensburg C, et al. Distribution of *Helicobacter pylori* colonisation and associated gastric inflammatory changes: difference between patients with duodenal and gastric ulcers. *J Clin Pathol* 1993;46:754–6.
- 125 Khulusi S, Mendall MA, Patel P, et al. *Helicobacter pylori* infection density and gastric inflammation in duodenal ulcer and non-ulcer subjects. *Gut* 1995;37:319–24.
- 126 Shibata T, Imoto I, Taguchi Y, et al. High acid secretion may protect the gastric mucosa from injury caused by ammonia produced by *Helicobacter pylori* in duodenal ulcer patients. *J Gastroenterol Hepatol* 1996;11:674–80.
- 127 Carmack SW, Genta RM, Graham DY, et al. Management of gastric polyps: a pathology-based guide for gastroenterologists. *Nat Rev Gastroenterol Hepatol* 2009;6:331–41.
- 128 Stolte M. Clinical consequences of the endoscopic diagnosis of gastric polyps. *Endoscopy* 1995;27:32–7.
- 129 Tongtawee T, Dechsukhum C, Leeanansakiri W, et al. Improved detection of *Helicobacter pylori* infection and premalignant gastric mucosa using "site specific biopsy": a randomized control clinical trial. *Asian Pac J Cancer Prev* 2015;16:8487–90.
- 130 Hartman DJ, Owens SR. Are routine ancillary stains required to diagnose *Helicobacter* infection in gastric biopsy specimens? An institutional quality assurance review. *Am J Clin Pathol* 2012;137:255–60.
- 131 Wang XI, Zhang S, Abreo F, et al. The role of routine immunohistochemistry for *Helicobacter pylori* in gastric biopsy. *Ann Diagn Pathol* 2010;14:256–9.
- 132 Doglioni C, Turrin M, Macri E, et al. HpSS: a new silver staining method for *Helicobacter pylori*. *J Clin Pathol* 1997;50:461–4.
- 133 Smith SB, Snow AN, Perry RL, et al. *Helicobacter pylori*: to stain or not to stain? *Am J Clin Pathol* 2012;137:733–8.
- 134 Shukla S, Pujani M, Agarwal A, et al. Correlation of serology with morphological changes in gastric biopsy in *Helicobacter pylori* infection and evaluation of immunohistochemistry for *H. pylori* identification. *Saudi J Gastroenterol* 2012;18:369–74.
- 135 Tajalli R, Nobakht M, Mohammadi-Barzelighi H, et al. The immunohistochemistry and toluidine blue roles for *Helicobacter pylori* detection in patients with gastritis. *Iran Biomed J* 2013;17:36–41.
- 136 Toulaymat M, Marconi S, Garb J, et al. Endoscopic biopsy pathology of *Helicobacter pylori* gastritis. Comparison of bacterial detection by immunohistochemistry and Genta stain. *Arch Pathol Lab Med* 1999;123:778–81.
- 137 Anim JT, Al-Sobkie N, Prasad A, et al. Assessment of different methods for staining *Helicobacter pylori* in endoscopic gastric biopsies. *Acta Histochem* 2000;102:129–37.
- 138 Jonkers D, Stobberingh E, de Bruine A, et al. Evaluation of immunohistochemistry for the detection of *Helicobacter pylori* in gastric mucosal biopsies. *J Infect* 1997;35:149–54.
- 139 Wenzhen Y, Yumin L, Quanlin G, et al. Is antimicrobial susceptibility testing necessary before first-line treatment for *Helicobacter pylori* infection? Meta-analysis of randomized controlled trials. *Intern Med* 2010;49:1103–9.
- 140 Sugimoto M, Furuta T. Efficacy of tailored *Helicobacter pylori* eradication therapy based on antibiotic susceptibility and CYP2C19 genotype. *World J Gastroenterol* 2014;20:6400–11.
- 141 Gisbert JP, Calvet X. Review article: non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther* 2011;34:604–17.
- 142 Selgrad M, Meissle J, Bornschein J, et al. Antibiotic susceptibility of *Helicobacter pylori* in central Germany and its relationship with the number of eradication therapies. *Eur J Gastroenterol Hepatol* 2013;25:1257–60.
- 143 Malfertheiner P, Bazzoli F, Delchier JC, et al. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet* 2011;377:905–13.
- 144 Laheij RJ, Straatman H, Jansen JB, et al. Evaluation of commercially available *Helicobacter pylori* serology kits: a review. *J Clin Microbiol* 1998;36:2803–9.
- 145 Leal YA, Flores LL, García-Cortés LB, et al. Antibody-based detection tests for the diagnosis of *Helicobacter pylori* infection in children: a meta-analysis. *PLoS One* 2008;3:e3751.
- 146 Loy CT, Irwig LM, Katelaris PH, et al. Do commercial serological kits for *Helicobacter pylori* infection differ in accuracy? A meta-analysis. *Am J Gastroenterol* 1996;91:1138–44.
- 147 Correa P. Serum pepsinogens in gastric cancer screening. *Dig Dis Sci* 2010;55:2123–5.
- 148 Shiota A, Cen P, Graham DY. Eradication of gastric cancer is now both possible and practical. *Semin Cancer Biol* 2013;23(Pt B):492–501.
- 149 Dinis-Ribeiro M, Areia M, de Vries AC, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European *Helicobacter* Study Group (EHS), European Society of Pathology (ESP), and the Sociedade Portuguesa. *Endoscopy* 2012;44:74–94.
- 150 Leja M, Kupcinskas L, Funka K, et al. Value of gastrin-17 in detecting antral atrophy. *Adv Med Sci* 2011;56:145–50.
- 151 McNicholl AG, Forné M, Barrio J, et al. Accuracy of GastroPanel for the diagnosis of atrophic gastritis. *Eur J Gastroenterol Hepatol* 2014;26:941–8.
- 152 Leodolter A, Domínguez-Muñoz JE, von Arnim U, et al. Validity of a modified 13C-urea breath test for pre- and posttreatment diagnosis of *Helicobacter pylori* infection in the routine clinical setting. *Am J Gastroenterol* 1999;94:2100–4.
- 153 Vaira D, Vakil N, Menegatti M, et al. The stool antigen test for detection of *Helicobacter pylori* after eradication therapy. *Ann Intern Med* 2002;136:280–7.
- 154 Chey WD, Metz DC, Shaw S, et al. Appropriate timing of the 14C-urea breath test to establish eradication of *Helicobacter pylori* infection. *Am J Gastroenterol* 2000;95:1171–4.
- 155 Neil GA, Suchower LJ, Ronca PD, et al. Time of *Helicobacter pylori* eradication assessment following treatment. *Helicobacter* 1997;2:13–20.
- 156 Rokkas T, Pistiolas D, Sechopoulos P, et al. The long-term impact of *Helicobacter pylori* eradication on gastric histology: a systematic review and meta-analysis. *Helicobacter* 2007;12(Suppl 2):32–8.
- 157 Wang J, Xu L, Shi R, et al. Gastric atrophy and intestinal metaplasia before and after *Helicobacter pylori* eradication: a meta-analysis. *Digestion* 2011;83:253–60.
- 158 Chen HN, Wang Z, Li X, et al. *Helicobacter pylori* eradication cannot reduce the risk of gastric cancer in patients with intestinal metaplasia and dysplasia: evidence from a meta-analysis. *Gastric Cancer* 2016;19:166–75.
- 159 Thung I, Aramin H, Vavinskaya V, et al. Review article: the global emergence of *Helicobacter pylori* antibiotic resistance. *Aliment Pharmacol Ther* 2016;43:514–33.
- 160 Kobayashi I, Murakami K, Kato M, et al. Changing antimicrobial susceptibility epidemiology of *Helicobacter pylori* strains in Japan between 2002 and 2005. *J Clin Microbiol* 2007;45:4006–10.
- 161 Lee JW, Kim N, Kim JM, et al. Prevalence of primary and secondary antimicrobial resistance of *Helicobacter pylori* in Korea from 2003 through 2012. *Helicobacter* 2013;18:206–14.
- 162 Khademi F, Poursina F, Hosseini E, et al. *Helicobacter pylori* in Iran: a systematic review on the antibiotic resistance. *Iran J Basic Med Sci* 2015;18:2–7.
- 163 Karamanolis GP, Daikos GL, Xouris D, et al. The evolution of *Helicobacter pylori* antibiotic resistance over 10 years in Greece. *Digestion* 2014;90:229–31.
- 164 Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013;62:34–42.
- 165 Boyanova L, Gergova G, Evstatiev I, et al. *Helicobacter pylori* resistance to six antibiotics by two breakpoint systems and resistance evolution in Bulgaria. *Infect Dis (Lond)* 2016;48:56–62.
- 166 Liou JM, Chang CY, Chen MJ, et al. The primary resistance of *Helicobacter pylori* in Taiwan after The National Policy to Restrict Antibiotic Consumption and Its Relation to Virulence Factors-A Nationwide Study. *PLoS One* 2015;10:e0124199.
- 167 Nishizawa T, Maekawa T, Watanabe N, et al. Clarithromycin versus metronidazole as first-line *Helicobacter pylori* eradication: a multicenter, prospective, randomized controlled study in Japan. *J Clin Gastroenterol* 2015;49:468–71.
- 168 Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol* 2014;12:177–86.
- 169 Shiota S, Reddy R, Alsarraj A, et al. Antibiotic resistance of *Helicobacter pylori* among male United States veterans. *Clin Gastroenterol Hepatol* 2015;13:1616–24.
- 170 Molina-Infante J, Gisbert JP. Optimizing clarithromycin-containing therapy for *Helicobacter pylori* in the era of antibiotic resistance. *World J Gastroenterol* 2014;20:10338–47.
- 171 Cuadrado-Lavín A, Salcines-Caviedes JR, Diaz-Perez A, et al. First-line eradication rates comparing two shortened non-bismuth quadruple regimens against *Helicobacter pylori*: an open-label, randomized, multicentre clinical trial. *J Antimicrob Chemother* 2015;70:2376–81.
- 172 Molina-Infante J, Lucendo AJ, Angueira T, et al. Optimised empiric triple and concomitant therapy for *Helicobacter pylori* eradication in clinical practice: the OPRICON study. *Aliment Pharmacol Ther* 2015;41:581–9.
- 173 McNicholl AG, Marin AC, Molina-Infante J, et al. Randomised clinical trial comparing sequential and concomitant therapies for *Helicobacter pylori* eradication in routine clinical practice. *Gut* 2014;63:244–9.
- 174 Molina-Infante J, Romano M, Fernandez-Bermejo M, et al. Optimized nonbismuth quadruple therapies cure most patients with *Helicobacter pylori* infection in populations with high rates of antibiotic resistance. *Gastroenterology* 2013;145:121–128.e1.
- 175 Georgopoulos SD, Xirouchakis E, Zampeli E, et al. A randomised study comparing 10 days concomitant and sequential treatments for the eradication of *Helicobacter pylori*, in a high clarithromycin resistance area. *Helicobacter* 2014;19(Suppl 1):80.
- 176 Georgopoulos SD, Xirouchakis E, Martínez-González B, et al. Clinical evaluation of a ten-day regimen with esomeprazole, metronidazole, amoxicillin, and clarithromycin for the eradication of *Helicobacter pylori* in a high clarithromycin resistance area. *Helicobacter* 2013;18:459–67.

- 177 Zullo A, Scaccianoce G, De Francesco V, *et al.* Concomitant, sequential, and hybrid therapy for *H. pylori* eradication: a pilot study. *Clin Res Hepatol Gastroenterol* 2013;37:647–50.
- 178 Liu WZ, Xie Y, Cheng H, *et al.* Fourth Chinese National Consensus Report on the management of *Helicobacter pylori* infection. *J Dig Dis* 2013;14:211–21.
- 179 Liang X, Xu X, Zheng Q, *et al.* Efficacy of bismuth-containing quadruple therapies for clarithromycin-, metronidazole-, and fluoroquinolone-resistant *Helicobacter pylori* infections in a prospective study. *Clin Gastroenterol Hepatol* 2013;11:802–7. e1.
- 180 Federico A, Nardone G, Gravina AG, *et al.* Efficacy of 5-day levofloxacin-containing concomitant therapy in eradication of *Helicobacter pylori* infection. *Gastroenterology* 2012;143:55–61.e1; quiz e13–14.
- 181 Toracchio S, Capodicasa S, Soraja DB, *et al.* Rifabutin based triple therapy for eradication of *H. pylori* primary and secondary resistant to tinidazole and clarithromycin. *Dig Liver Dis* 2005;37:33–8.
- 182 Ince AT, Tozlu M, Baysal B, *et al.* Yields of dual therapy containing high-dose proton pump inhibitor in eradication of *H. pylori* positive dyspeptic patients. *Hepatogastroenterology* 2014;61:1454–8.
- 183 Hinostroza Morales D, Díaz Ferrer J. [Addition of bismuth subsalicylate to triple eradication therapy for *Helicobacter pylori* infection: efficiency and adverse events]. *Revista de gastroenterología del Perú: órgano oficial de la Sociedad de Gastroenterología del Perú* 2014;34:315–20.
- 184 Srinarong C, Siramolpiwat S, Wongcha-um A, *et al.* Improved eradication rate of standard triple therapy by adding bismuth and probiotic supplement for *Helicobacter pylori* treatment in Thailand. *Asian Pac J Cancer Prev* 2014;15:9909–13.
- 185 Ford AC, Malfertheiner P, Giguere M, *et al.* Adverse events with bismuth salts for *Helicobacter pylori* eradication: systematic review and meta-analysis. *World J Gastroenterol* 2008;14:7361–70.
- 186 Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. *Aliment Pharmacol Ther* 2007;26:343–57.
- 187 Yuan Y, Ford AC, Khan KJ, *et al.* *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd, 1996.
- 188 Dore MP, Farina V, Cuccu M, *et al.* Twice-a-day bismuth-containing quadruple therapy for *Helicobacter pylori* eradication: a randomized trial of 10 and 14 days. *Helicobacter* 2011;16:295–300.
- 189 Salazar CO, Cardenas VM, Reddy RK, *et al.* Greater than 95% success with 14-day bismuth quadruple anti-*Helicobacter pylori* therapy: a pilot study in US Hispanics. *Helicobacter* 2012;17:382–90.
- 190 Rimbara E, Fischbach LA, Graham DY. Optimal therapy for *Helicobacter pylori* infections. *Nat Rev Gastroenterol Hepatol* 2011;8:79–88.
- 191 Lu H, Zhang W, Graham DY. Bismuth-containing quadruple therapy for *Helicobacter pylori*: lessons from China. *Eur J Gastroenterol Hepatol* 2013;25:1134–40.
- 192 Laine L, Hunt R, El-Zimaity H, *et al.* Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of *Helicobacter pylori* in duodenal ulcer patients: a prospective, randomized, multicenter, North American trial. *Am J Gastroenterol* 2003;98:562–7.
- 193 Delchier JC, Malfertheiner P, Thieroff-Ekerdt R. Use of a combination formulation of bismuth, metronidazole and tetracycline with omeprazole as a rescue therapy for eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther* 2014;40:171–7.
- 194 Graham DY, Shiotani A. Which therapy for *Helicobacter pylori* infection? *Gastroenterology* 2012;143:10–12.
- 195 Filipec Kanizaj T, Katić M, Skurla B, *et al.* *Helicobacter pylori* eradication therapy success regarding different treatment period based on clarithromycin or metronidazole triple-therapy regimens. *Helicobacter* 2009;14:29–35.
- 196 Lee ST, Lee DH, Lim JH, *et al.* Efficacy of 7-day and 14-day bismuth-containing quadruple therapy and 7-day and 14-day moxifloxacin-based therapy as second-line eradication for *Helicobacter pylori* infection. *Gut Liver* 2015;9:478–85.
- 197 Choung RS, Lee SW, Jung SW, *et al.* [Comparison of the effectiveness of quadruple salvage regimen for *Helicobacter pylori* infection according to the duration of treatment]. *Korean J Gastroenterol* 2006;47:131–5.
- 198 Lee BH, Kim N, Hwang TJ, *et al.* Bismuth-containing quadruple therapy as second-line treatment for *Helicobacter pylori* infection: effect of treatment duration and antibiotic resistance on the eradication rate in Korea. *Helicobacter* 2010;15:38–45.
- 199 Park SC, Chun HJ, Jung SW, *et al.* [Efficacy of 14 day OBMT therapy as a second-line treatment for *Helicobacter pylori* infection]. *Korean J Gastroenterol* 2004;44:136–41.
- 200 Liou JM, Chen CC, Chen MJ, *et al.* Sequential versus triple therapy for the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomised trial. *Lancet* 2013;381:205–13.
- 201 Gatta L, Vakil N, Vaira D, *et al.* Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy. *BMJ* 2013;347:f4587.
- 202 Yoon H, Lee DH, Kim N, *et al.* Meta-analysis: is sequential therapy superior to standard triple therapy for *Helicobacter pylori* infection in Asian adults? *J Gastroenterol Hepatol* 2013;28:1801–9.
- 203 Zullo A, Hassan C, Ridola L, *et al.* Standard triple and sequential therapies for *Helicobacter pylori* eradication: an update. *Eur J Intern Med* 2013;24:16–19.
- 204 Feng L, Wen MY, Zhu YJ, *et al.* Sequential therapy or standard triple therapy for *Helicobacter pylori* infection: an updated systematic review. *Am J Ther* 2016;23:e880–93.
- 205 Wu JY, Hsu PI, Wu DC, *et al.* Feasibility of shortening 14-day hybrid therapy while maintaining an excellent *Helicobacter pylori* eradication rate. *Helicobacter* 2014;19:207–13.
- 206 He L, Deng T, Luo H. Meta-analysis of sequential, concomitant and hybrid therapy for *Helicobacter pylori* eradication. *Intern Med* 2015;54:703–10.
- 207 Kim JS, Park SM, Kim BW. Sequential or concomitant therapy for eradication of *Helicobacter pylori* infection: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2015;30:1338–45.
- 208 Wang B, Wang YH, Lv ZF, *et al.* Review: efficacy and safety of hybrid therapy for *Helicobacter pylori* infection: a systematic review and meta-analysis. *Helicobacter* 2015;20:79–88.
- 209 Greenberg ER, Anderson GL, Morgan DR, *et al.* 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial. *Lancet* 2011;378:507–14.
- 210 Essa AS, Kramer JR, Graham DY, *et al.* Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing ‘concomitant therapy’ versus triple therapy for *Helicobacter pylori* eradication. *Helicobacter* 2009;14:109–18.
- 211 Gisbert JP, Calvet X. Update on non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*. *Clin Exp Gastroenterol* 2012;5:23–34.
- 212 Sardarian H, Fakheri H, Hosseini V, *et al.* Comparison of hybrid and sequential therapies for *Helicobacter pylori* eradication in Iran: a prospective randomized trial. *Helicobacter* 2013;18:129–34.
- 213 Hsu PI, Wu DC, Wu JY, *et al.* Modified sequential *Helicobacter pylori* therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. *Helicobacter* 2011;16:139–45.
- 214 Oh DH, Lee DH, Kang KK, *et al.* Efficacy of hybrid therapy as first-line regimen for *Helicobacter pylori* infection compared with sequential therapy. *J Gastroenterol Hepatol* 2014;29:1171–6.
- 215 De Francesco V, Hassan C, Ridola L, *et al.* Sequential, concomitant and hybrid first-line therapies for *Helicobacter pylori* eradication: a prospective randomized study. *J Med Microbiol* 2014;63(Pt 5):748–52.
- 216 Heo J, Jeon SW, Jung JT, *et al.* Concomitant and hybrid therapy for *Helicobacter pylori* infection: a randomized clinical trial. *J Gastroenterol Hepatol* 2015;30:1361–6.
- 217 Vakil N. *H. pylori* treatment: new wine in old bottles? *Am J Gastroenterol* 2009;104:26–30.
- 218 Treiber G, Wittig J, Ammon S, *et al.* Clinical outcome and influencing factors of a new short-term quadruple therapy for *Helicobacter pylori* eradication: a randomized controlled trial (MACLOR study). *Arch Intern Med* 2002;162:153–60.
- 219 Kwon B, Park E, Lee D, *et al.* Effectiveness of 5-day and 7-day quadruple ‘concomitant’ therapy regimen for *Helicobacter pylori* infection in Korea. *Helicobacter* 2011;16(Suppl 1):135.
- 220 Kongchayanun C, Vilaichone RK, Pornthisarn B, *et al.* Pilot studies to identify the optimum duration of concomitant *Helicobacter pylori* eradication therapy in Thailand. *Helicobacter* 2012;17:282–5.
- 221 Kim SY, Lee SW, Hyun JJ, *et al.* Comparative study of *Helicobacter pylori* eradication rates with 5-day quadruple ‘concomitant’ therapy and 7-day standard triple therapy. *J Clin Gastroenterol* 2013;47:21–4.
- 222 Toros AB, Ince AT, Kesici B, *et al.* A new modified concomitant therapy for *Helicobacter pylori* eradication in Turkey. *Helicobacter* 2011;16:225–8.
- 223 Lim JH, Lee DH, Choi C, *et al.* Clinical outcomes of two-week sequential and concomitant therapies for *Helicobacter pylori* eradication: a randomized pilot study. *Helicobacter* 2013;18:180–6.
- 224 McNicholl A, Molina-Infante J, Bermejo F, *et al.* Non-bismuth quadruple concomitant therapies in the eradication of *Helicobacter pylori*: standard vs. optimized (14 days, high-dose PPI) regimens in clinical practice. *Helicobacter* 2014;19:11.
- 225 Labenz J. Current role of acid suppressants in *Helicobacter pylori* eradication therapy. *Best Pract Res Clin Gastroenterol* 2001;15:413–31.
- 226 Villoria A, Garcia P, Calvet X, *et al.* Meta-analysis: high-dose proton pump inhibitors vs. standard dose in triple therapy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2008;28:868–77.
- 227 Vallve M, Vergara M, Gisbert JP, *et al.* Single vs. double dose of a proton pump inhibitor in triple therapy for *Helicobacter pylori* eradication: a meta-analysis. *Aliment Pharmacol Ther* 2002;16:1149–56.
- 228 Huang J, Hunt RH. The importance of clarithromycin dose in the management of *Helicobacter pylori* infection: a meta-analysis of triple therapies with a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole. *Aliment Pharmacol Ther* 1999;13:719–29.

- 229 Furuta T, Ohashi K, Kamata T, *et al.* Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann Intern Med* 1998;129:1027–30.
- 230 Sharara AI. Rabeprazole: the role of proton pump inhibitors in *Helicobacter pylori* eradication. *Expert Rev Anti Infect Ther* 2005;3:863–70.
- 231 De Francesco V, Ierardi E, Hassan C, *et al.* *Helicobacter pylori* therapy: present and future. *World J Gastrointest Pharmacol Ther* 2012;3:68–73.
- 232 Miftahussurur M, Yamaoka Y. Appropriate first-line regimens to combat *Helicobacter pylori* antibiotic resistance: an Asian perspective. *Molecules* 2015;20:6068–92.
- 233 Choi HS, Park DII, Hwang SJ, *et al.* Double-dose, new-generation proton pump inhibitors do not improve *Helicobacter pylori* eradication rate. *Helicobacter* 2007;12:638–42.
- 234 Tang HL, Li Y, Hu YF, *et al.* Effects of CYP2C19 loss-of-function variants on the eradication of *H. pylori* infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. *PLoS One* 2013;8:e62162.
- 235 Padol S, Yuan Y, Thabane M, *et al.* The effect of CYP2C19 polymorphisms on *H. pylori* eradication rate in dual and triple first-line PPI therapies: a meta-analysis. *Am J Gastroenterol* 2006;101:1467–75.
- 236 Zhao F, Wang J, Yang Y, *et al.* Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication: a meta-analysis. *Helicobacter* 2008;13:532–41.
- 237 McNicholl AG, Linares PM, Nyssen OP, *et al.* Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2012;36:414–25.
- 238 Tokoro C, Inamori M, Koide T, *et al.* Does pretreatment with proton pump inhibitors influence the eradication rate of *Helicobacter pylori*? *Hepatogastroenterology* 2010;57:1645–9.
- 239 Yoon SB, Park JM, Lee JY, *et al.* Long-term pretreatment with proton pump inhibitor and *Helicobacter pylori* eradication rates. *World J Gastroenterol* 2014;20:1061–6.
- 240 Calvet X, García N, López T, *et al.* A meta-analysis of short versus long therapy with a proton pump inhibitor, clarithromycin and either metronidazole or amoxicillin for treating *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2000;14:603–9.
- 241 Ford A, Moayyedi P. How can the current strategies for *Helicobacter pylori* eradication therapy be improved? *Can J Gastroenterol* 2003;17(Suppl B): 36B–40B.
- 242 Flores HB, Salvana A, Ang ELR, *et al.* Duration of proton-pump inhibitor-based triple therapy for *Helicobacter pylori* eradication: a meta-analysis. *Gastroenterology* 2010;138:5–340.
- 243 Wong AYS, Root A, Douglas JJ, *et al.* Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ* 2016;352:h6926.
- 244 Graham DY. *Helicobacter pylori* update: gastric cancer, reliable therapy, and possible benefits. *Gastroenterology* 2015;148:719–31.e3.
- 245 Gatta L, Zullo A, Perna F, *et al.* A 10-day levofloxacin-based triple therapy in patients who have failed two eradication courses. *Aliment Pharmacol Ther* 2005;22:45–9.
- 246 Gisbert JP, Gisbert JL, Marcos S, *et al.* Third-line rescue therapy with levofloxacin is more effective than rifabutin rescue regimen after two *Helicobacter pylori* treatment failures. *Aliment Pharmacol Ther* 2006;24:1469–74.
- 247 Rokkas T, Sechopoulos P, Robotis I, *et al.* Cumulative *H. pylori* eradication rates in clinical practice by adopting first and second-line regimens proposed by the Maastricht III consensus and a third-line empirical regimen. *Am J Gastroenterol* 2009;104:21–5.
- 248 Gisbert JP. Letter: third-line rescue therapy with levofloxacin after failure of two treatments to eradicate *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2012;35:1484–5.
- 249 Kang KK, Lee DH, Oh DH, *et al.* *Helicobacter pylori* eradication with moxifloxacin-containing therapy following failed first-line therapies in South Korea. *World J Gastroenterol* 2014;20:6932–8.
- 250 Liu KSH, Hung IFN, Seto KWV, *et al.* Ten day sequential versus 10 day modified bismuth quadruple therapy as empirical firstline and secondline treatment for *Helicobacter pylori* in Chinese patients: an open label, randomised, crossover trial. *Gut* 2014;63:1410–15.
- 251 Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment Pharmacol Ther* 2006;23:35–44.
- 252 Saad RJ, Schoenfeld P, Kim HM, *et al.* Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: a meta-analysis. *Am J Gastroenterol* 2006;101:488–96.
- 253 Marin AC, McNicholl AG, Gisbert JP. A review of rescue regimens after clarithromycin-containing triple therapy failure (for *Helicobacter pylori* eradication). *Expert Opin Pharmacother* 2013;14:843–61.
- 254 Li Y, Huang X, Yao L, *et al.* Advantages of moxifloxacin and levofloxacin-based triple therapy for second-line treatments of persistent *Helicobacter pylori* infection: a meta analysis. *Wien Klin Wochenschr* 2010;122:413–22.
- 255 Di Caro S, Fini L, Daoud Y, *et al.* Levofloxacin/amoxicillin-based schemes vs quadruple therapy for *Helicobacter pylori* eradication in second-line. *World J Gastroenterol* 2012;18:5669–78.
- 256 Saracino IM, Zullo A, Holton J, *et al.* High prevalence of primary antibiotic resistance in *Helicobacter pylori* isolates in Italy. *J Gastrointest Liver Dis* 2012;21:363–5.
- 257 Chung JW, Lee JH, Jung HY, *et al.* Second-line *Helicobacter pylori* eradication: a randomized comparison of 1-week or 2-week bismuth-containing quadruple therapy. *Helicobacter* 2011;16:289–94.
- 258 Gisbert JP, Romano M, Gravina AG, *et al.* *Helicobacter pylori* second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments. *Aliment Pharmacol Ther* 2015;41:768–75.
- 259 Matsumoto Y, Miki I, Aoyama N, *et al.* Levofloxacin- versus metronidazole-based rescue therapy for *H. pylori* infection in Japan. *Dig Liver Dis* 2005;37: 821–5.
- 260 Hu TH, Chuah SK, Hsu PI, *et al.* Randomized comparison of two nonbismuth-containing rescue therapies for *Helicobacter pylori*. *Am J Med Sci* 2011;342:177–81.
- 261 Gisbert JP, Molina-Infante J, Marin AC, *et al.* Second-line rescue triple therapy with levofloxacin after failure of non-bismuth quadruple 'sequential' or 'concomitant' treatment to eradicate *H. pylori* infection. *Gastroenterology* 2014;146:5–394.
- 262 Manfredi M, Bizzarri B, de'Angelis GL. *Helicobacter pylori* infection: sequential therapy followed by levofloxacin-containing triple therapy provides a good cumulative eradication rate. *Helicobacter* 2012;17:246–53.
- 263 Perna F, Zullo A, Ricci C, *et al.* Levofloxacin-based triple therapy for *Helicobacter pylori* re-treatment: role of bacterial resistance. *Dig Liver Dis* 2007;39:1001–5.
- 264 Pontone S, Standoli M, Angelini R, *et al.* Efficacy of *H. pylori* eradication with a sequential regimen followed by rescue therapy in clinical practice. *Dig Liver Dis* 2010;42:541–3.
- 265 Chung KH, Lee DH, Jin E, *et al.* The efficacy of moxifloxacin-containing triple therapy after standard triple, sequential, or concomitant therapy failure for *Helicobacter pylori* eradication in Korea. *Gut Liver* 2014;8:605–11.
- 266 Gisbert JP, Romano M, Molina-Infante J, *et al.* Two-week, high-dose proton pump inhibitor, moxifloxacin triple *Helicobacter pylori* therapy after failure of standard triple or non-bismuth quadruple treatments. *Dig Liver Dis* 2015;47: 108–13.
- 267 Chuah SK, Tai WC, Hsu PI, *et al.* The efficacy of second-line anti-*Helicobacter pylori* therapy using an extended 14-day levofloxacin/amoxicillin/proton-pump inhibitor treatment—a pilot study. *Helicobacter* 2012;17:374–81.
- 268 Di Caro S, Franceschi F, Mariani A, *et al.* Second-line levofloxacin-based triple schemes for *Helicobacter pylori* eradication. *Dig Liver Dis* 2009;41:480–5.
- 269 Malfertheiner P. Infection: Bismuth improves PPI-based triple therapy for *H. pylori* eradication. *Nat Rev Gastroenterol Hepatol* 2010;7:538–9.
- 270 Liao J, Zheng Q, Liang X, *et al.* Effect of fluoroquinolone resistance on 14-day levofloxacin triple and triple plus bismuth quadruple therapy. *Helicobacter* 2013;18:373–7.
- 271 Bago P, Vcev A, Tomic M, *et al.* High eradication rate of *H. pylori* with moxifloxacin-based treatment: a randomized controlled trial. *Wien Klin Wochenschr* 2007;119:372–8.
- 272 Gao X-Z, Qiao X-L, Song W-C, *et al.* Standard triple, bismuth pectin quadruple and sequential therapies for *Helicobacter pylori* eradication. *World J Gastroenterol* 2010;16:4357–62.
- 273 Yee YK, Cheung TK, Chu KM, *et al.* Clinical trial: levofloxacin-based quadruple therapy was inferior to traditional quadruple therapy in the treatment of resistant *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2007;26:1063–7.
- 274 Hsu PI, Chen WC, Tsay FW, *et al.* Ten-day quadruple therapy comprising proton-pump inhibitor, bismuth, tetracycline, and levofloxacin achieves a high eradication rate for *Helicobacter pylori* infection after failure of sequential therapy. *Helicobacter* 2014;19:74–9.
- 275 Fakheri H, Bari Z, Sardarian H. A modified bismuth-containing quadruple therapy including a short course of furazolidone for *Helicobacter pylori* eradication after sequential therapy failure. *Helicobacter* 2012;17:264–8.
- 276 López-Góngora S, Puig I, Calvet X, *et al.* Systematic review and meta-analysis: susceptibility-guided versus empirical antibiotic treatment for *Helicobacter pylori* infection. *J Antimicrob Chemother* 2015;70:2447–55.
- 277 Liou JM, Chen CC, Chang CY, *et al.* Efficacy of genotypic resistance-guided sequential therapy in the third-line treatment of refractory *Helicobacter pylori* infection: a multicentre clinical trial. *J Antimicrob Chemother* 2013;68:450–6.
- 278 Cosme A, Lizasoan J, Montes M, *et al.* Antimicrobial susceptibility-guided therapy versus empirical concomitant therapy for eradication of *Helicobacter pylori* in a region with high rate of clarithromycin resistance. *Helicobacter* 2016;21: 29–34.
- 279 O'Morain C, Borody T, Farley A, *et al.* Efficacy and safety of single-triple capsules of bismuth biscaltrate, metronidazole and tetracycline, given with omeprazole, for the eradication of *Helicobacter pylori*: an international multicentre study. *Aliment Pharmacol Ther* 2003;17:415–20.

- 280 Wueppenhorst N, Stueger HP, Kist M, *et al.* High secondary resistance to quinolones in German *Helicobacter pylori* clinical isolates. *J Antimicrob Chemother* 2013;68:1562–6.
- 281 Gisbert JP, Calvet X. Review article: rifabutin in the treatment of refractory *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2012;35:209–21.
- 282 Uygun A, Ozel AM, Yildiz O, *et al.* Comparison of three different second-line quadruple therapies including bismuth subcitrate in Turkish patients with non-ulcer dyspepsia who failed to eradicate *Helicobacter pylori* with a 14-day standard first-line therapy. *J Gastroenterol Hepatol* 2008;23:42–5.
- 283 Gisbert JP, Perez-Aisa A, Rodrigo L, *et al.* Third-line rescue therapy with bismuth-containing quadruple regimen after failure of two treatments (with clarithromycin and levofloxacin) for *H. pylori* infection. *Dig Dis Sci* 2014;59:383–9.
- 284 Malfertheiner P, Link A, Selgrad M. *Helicobacter pylori*: perspectives and time trends. *Nat Rev Gastroenterol Hepatol* 2014;11:628–38.
- 285 Sagar PS, Katelaris CH. Utility of penicillin allergy testing in patients presenting with a history of penicillin allergy. *Asia Pacific allergy* 2013;3:115–9.
- 286 Gisbert JP, Calvet X, Bermejo F, *et al.* [III Spanish Consensus Conference on *Helicobacter pylori* infection]. *Gastroenterol Hepatol* 2013;36:340–74.
- 287 Gisbert JP, Gisbert JL, Marcos S, *et al.* *Helicobacter pylori* first-line treatment and rescue options in patients allergic to penicillin. *Aliment pharmacol ther* 2005;22:1041–6.
- 288 Gisbert JP, Barrio J, Modolell I, *et al.* *Helicobacter pylori* first-line and rescue treatments in the presence of penicillin allergy. *Dig Dis Sci* 2015;60:458–64.
- 289 Gisbert JP, María Pajares J. [*Helicobacter pylori* resistance to metronidazole and to clarithromycin in Spain. A systematic review]. *Medicina clinica*. 2001;116:111–6.
- 290 Molina-Infante J, Gisbert JP. [Update on the efficacy of triple therapy for *Helicobacter pylori* infection and clarithromycin resistance rates in Spain (2007–2012)]. *Gastroenterología y Hepatología* 2013;36:375–81.
- 291 Rodríguez-Torres M, Salgado-Mercado R, Ríos-Bedoya CF, *et al.* High eradication rates of *Helicobacter pylori* infection with first- and second-line combination of esomeprazole, tetracycline, and metronidazole in patients allergic to penicillin. *Dig Dis Sci*. 2005;50:634–39.
- 292 Matsushima M, Suzuki T, Kurumada T, *et al.* Tetracycline, metronidazole and amoxicillin-metronidazole combinations in proton pump inhibitor-based triple therapies are equally effective as alternative therapies against *Helicobacter pylori* infection. *Gastroenterología y Hepatología* 2006;21:232–6.
- 293 Gisbert JP, Gisbert JL, Marcos S, *et al.* *Helicobacter pylori* first-line treatment and rescue options in patients allergic to penicillin. *Aliment Pharmacol Ther* 2005;22:1041–6.
- 294 Gisbert JP. ‘Rescue’ regimens after *Helicobacter pylori* treatment failure. *World J Gastroenterol* 2008;14:5385–402.
- 295 Furuta T, Sugimoto M, Yamade M, *et al.* Eradication of *H. pylori* infection in patients allergic to penicillin using triple therapy with a PPI, metronidazole and sitafloxacin. *Intern Med* 2014;53:571–5.
- 296 Murakami K, Okimoto T, Kodama M, *et al.* Sitafloxacin activity against *Helicobacter pylori* isolates, including those with *gyrA* mutations. *Antimicrob Agents Chemother* 2009;53:3097–9.
- 297 IARC/WHO. *Helicobacter pylori* eradication as a strategy for preventing gastric cancer. International Agency for Research on Cancer/ World Health Organisation, 2014. “<http://www.iarc.fr/en/publications/pdfs-online/wrk8/>” www.iarc.fr/en/publications/pdfs-online/wrk8/ (accessed online Aug 2016).
- 298 Herrero R, Park JY, Forman D. The fight against gastric cancer—the IARC Working Group report. *Best Pract Res Clin Gastroenterol* 2014;28:1107–14.
- 299 Fock KM, Graham DY, Malfertheiner P. *Helicobacter pylori* research: historical insights and future directions. *Nat Rev Gastroenterol Hepatol* 2013;10:495–500.
- 300 Yu S, Yang M, Nam KT. Mouse models of gastric carcinogenesis. *J Gastric Cancer* 2014;14:67–86.
- 301 Ma JL, Zhang L, Brown LM, *et al.* Fifteen-year effects of *Helicobacter pylori*, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst* 2012;104:488–92.
- 302 Li W-Q, Ma J-L, Zhang L, *et al.* Effects of *Helicobacter pylori* treatment on gastric cancer incidence and mortality in subgroups. *J Natl Cancer Inst* 2014;106:dju116.
- 303 Hansson LE, Engstrand L, Nyrén O, *et al.* *Helicobacter pylori* infection: independent risk indicator of gastric adenocarcinoma. *Gastroenterology* 1993;105:1098–103.
- 304 Hansson LR, Engstrand L, Nyrén O, *et al.* Prevalence of *Helicobacter pylori* infection in subtypes of gastric cancer. *Gastroenterology* 1995;109:885–8.
- 305 Bornschein J, Selgrad M, Warnecke M, *et al.* *H. pylori* infection is a key risk factor for proximal gastric cancer. *Dig Dis Sci* 2010;55:3124–31.
- 306 Abrams JA, Gonsalves L, Neugut AI. Diverging trends in the incidence of reflux-related and *Helicobacter pylori*-related gastric cardia cancer. *J Clin Gastroenterol* 2013;47:322–7.
- 307 Kamada T, Kurose H, Yamanaka Y, *et al.* Relationship between gastroesophageal junction adenocarcinoma and *Helicobacter pylori* infection in Japan. *Digestion* 2012;85:256–60.
- 308 Wong BC-Y, Lam SK, Wong WM, *et al.* *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004;291:187–94.
- 309 Lee YC, Chiang TH, Chou CK, *et al.* Association between *Helicobacter pylori* eradication and gastric cancer incidence: a systematic review and meta-analysis. *Gastroenterology* 2016;150:1113–1124.e5.
- 310 Pan KF, Zhang L, Gerhard M, *et al.* A large randomised controlled intervention trial to prevent gastric cancer by eradication of *Helicobacter pylori* in Linqu County, China: baseline results and factors affecting the eradication. *Gut* 2016;65:9–18.
- 311 Saito D, Boku N, Fujioka T, *et al.* Impact of *H. pylori* eradication on gastric cancer prevention: endoscopic results of the Japanese intervention trial (JITHP-Study): a randomized multi-center trial. *Gastroenterology* 2005;128(Suppl 2):A4.
- 312 Bouvard V, Baan R, Straif K, *et al.* A review of human carcinogens—part B: biological agents. *Lancet Oncol* 2009;10:321–2.
- 313 Brenner H, Arndt V, Stegmaier C, *et al.* Is *Helicobacter pylori* infection a necessary condition for noncardia gastric cancer? *Am J Epidemiol* 2004;159:252–8.
- 314 Uemura N, Okamoto S, Yamamoto S, *et al.* *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001;345:784–9.
- 315 González CA, Megraud F, Buissonniere A, *et al.* *Helicobacter pylori* infection assessed by ELISA and by immunoblot and noncardia gastric cancer risk in a prospective study: the EurGast-EPIC project. *Ann Oncol* 2012;23:1320–4.
- 316 de Martel C, Ferlay J, Franceschi S, *et al.* Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol* 2012;13:607–15.
- 317 Zhou L, Sung JY, Lin S, *et al.* A five-year follow-up study on the pathological changes of gastric mucosa after *H. pylori* eradication. *Chin Med J* 2003;116:11–14.
- 318 Gatta L, Di Mario F, Vaira D, *et al.* Quantification of serum levels of pepsinogens and gastrin to assess eradication of *Helicobacter pylori*. *Clin Gastroenterol Hepatol* 2011;9:440–2.
- 319 Leja M, Lapina S, Polaka I, *et al.* Pepsinogen testing for evaluation of the success of *Helicobacter pylori* eradication at 4 weeks after completion of therapy. *Medicina (Kaunas)* 2014;50:8–13.
- 320 Okubo M, Tahara T, Shibata T, *et al.* Changes in gastric mucosal patterns seen by magnifying NBI during *H. pylori* eradication. *J Gastroenterol* 2011;46:175–82.
- 321 Lee YC, Chen THH, Chiu HM, *et al.* The benefit of mass eradication of *Helicobacter pylori* infection: a community-based study of gastric cancer prevention. *Gut* 2013;62:676–82.
- 322 Jung DH, Kim JH, Chung HS, *et al.* *Helicobacter pylori* eradication on the prevention of metachronous lesions after endoscopic resection of gastric neoplasm: a meta-analysis. *PLoS One* 2015;10:e0124725.
- 323 Arkkila PET, Seppälä K, Färkkilä M, *et al.* *Helicobacter pylori* eradication in the healing of atrophic gastritis: a one-year prospective study. *Scand J Gastroenterol* 2006;41:782–90.
- 324 Mera R, Fontham ETH, Bravo LE, *et al.* Long term follow up of patients treated for *Helicobacter pylori* infection. *Gut* 2005;54:1536–40.
- 325 Rokkas T, Pistoliadis D, Sechopoulos P *et al.* The long-term impact of *Helicobacter pylori* eradication on gastric histology: a systematic review and meta-analysis. *Helicobacter*, 2007;12(suppl 2):32–8.
- 326 Kong YJ, Yi HG, Dai JC, *et al.* Histological changes of gastric mucosa after *Helicobacter pylori* eradication: a systematic review and meta-analysis. *World J Gastroenterol* 2014;20:5903–11.
- 327 Ford AC, Forman D, Hunt RH, *et al.* *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014;348:g3174.
- 328 Harvey RF, Lane JA, Nair P, *et al.* Clinical trial: prolonged beneficial effect of *Helicobacter pylori* eradication on dyspepsia consultations—the Bristol *Helicobacter* Project. *Aliment Pharmacol Ther* 2010;32:394–400.
- 329 Lansdorp-Vogelaar I, Sharp L. Cost-effectiveness of screening and treating *Helicobacter pylori* for gastric cancer prevention. *Best Pract Res Clin Gastroenterol* 2013;27:933–47.
- 330 Roderick P, Davies R, Raftery J, *et al.* Cost-effectiveness of population screening for *Helicobacter pylori* in preventing gastric cancer and peptic ulcer disease, using simulation. *J Med Screen* 2003;10:148–56.
- 331 Fock KM, Katelaris P, Sugano K, *et al.* Second Asia-Pacific consensus guidelines for *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 2009;24:1587–600.
- 332 Herrero R, Parsonnet J, Greenberg ER. Prevention of gastric cancer. *JAMA* 2014;312:1197–8.
- 333 Huang YK, Yu JC, Kang WM, *et al.* Significance of serum pepsinogens as a biomarker for gastric cancer and atrophic gastritis screening: a systematic review and meta-analysis. *PLoS One* 2015;10:e0142080.
- 334 Kishikawa H, Kimura K, Takarabe S, *et al.* *Helicobacter pylori* antibody titer and gastric cancer screening. *Dis Markers* 2015;2015:156719.
- 335 Mocellin S, Verdi D, Pooley KA, *et al.* Genetic variation and gastric cancer risk: a field synopsis and meta-analysis. *Gut* 2015;64:1209–19.
- 336 Arnold M, Moore SP, Hassler S, *et al.* The burden of stomach cancer in indigenous populations: a systematic review and global assessment. *Gut* 2014;63:64–71.
- 337 De Vries AC, Van Driel HF, Richardus JH, *et al.* Migrant communities constitute a possible target population for primary prevention of *Helicobacter pylori*-related complications in low incidence countries. *Scand J Gastroenterol* 2008;43:403–9.

- 338 El-Omar EM, Oien K, Murray LS, *et al.* Increased prevalence of precancerous changes in relatives of gastric cancer patients: critical role of *H. pylori*. *Gastroenterology* 2000;118:22–30.
- 339 Oh S, Kim N, Yoon H, *et al.* Risk factors of atrophic gastritis and intestinal metaplasia in first-degree relatives of gastric cancer patients compared with age-sex matched controls. *J Cancer Prev* 2013;18:149–60.
- 340 Tanaka M, Ono H, Hasuike N, *et al.* Endoscopic submucosal dissection of early gastric cancer. *Digestion* 2008;77(Suppl 1):23–8.
- 341 GLOBOCAN Cancer Fact Sheets: stomach cancers.
- 342 Miki K, Morita M, Sasajima M, *et al.* Usefulness of gastric cancer screening using the serum pepsinogen test method. *Am J Gastroenterol* 2003;98:735–9.
- 343 Miki K. Gastric cancer screening using the serum pepsinogen test method. *Gastric Cancer* 2006;9:245–53.
- 344 Isajevs S, Liepniece-Karele I, Janciauskas D, *et al.* Gastritis staging: interobserver agreement by applying OLGA and OLGIM systems. *Virchows Arch* 2014;464:403–7.
- 345 den Hoed CM, Holster IL, Capelle LG, *et al.* Follow-up of premalignant lesions in patients at risk for progression to gastric cancer. *Endoscopy* 2013;45:249–56.
- 346 Capelle LG, de Vries AC, Haringsma J, *et al.* The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. *Gastrointest Endosc* 2010;71:1150–8.
- 347 Song H, Ekheden IG, Zheng Z, *et al.* Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. *BMJ* 2015;351:h3867.
- 348 Vannella L, Lahner E, Osborn J, *et al.* Risk factors for progression to gastric neoplastic lesions in patients with atrophic gastritis. *Aliment Pharmacol Ther* 2010;31:1042–50.
- 349 Bergman M, Huikko S, Huovinen P, *et al.* Macrolide and azithromycin use are linked to increased macrolide resistance in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 2006;50:3646–50.
- 350 Megraud F. Potential impact of bacterial resistance after population-based *Helicobacter pylori* treatment. In: *Helicobacter pylori eradication as a strategy for preventing gastric cancer*. Lyon: IARC, 2014:80–7.
- 351 Zeng M, Mao XH, Li JX, *et al.* Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;386:1457–64.
- 352 Andersson AF, Lindberg M, Jakobsson H, *et al.* Comparative analysis of human gut microbiota by barcoded pyrosequencing. *PLoS One* 2008;3:e2836.
- 353 Bik EM, Eckburg PB, Gill SR, *et al.* Molecular analysis of the bacterial microbiota in the human stomach. *Proc Natl Acad Sci USA* 2006;103:732–7.
- 354 Li XX, Wong GLH, To KF, *et al.* Bacterial microbiota profiling in gastritis without *Helicobacter pylori* infection or non-steroidal anti-inflammatory drug use. *PLoS One* 2009;4:e7985.
- 355 Yang I, Nell S, Suerbaum S. Survival in hostile territory: the microbiota of the stomach. *FEMS Microbiol Rev* 2013;37:736–61.
- 356 Yang I, Woltemate S, Piazuolo MB, *et al.* Different gastric microbiota compositions in two human populations with high and low gastric cancer risk in Colombia. *Sci Rep* 2016;6:18594.
- 357 Delgado S, Cabrera-Rubio R, Mira A, *et al.* Microbiological survey of the human gastric ecosystem using culturing and pyrosequencing methods. *Microb Ecol* 2013;65:763–72.
- 358 Ianiro G, Molina-Infante J, Gasbarrini A. Gastric microbiota. *Helicobacter* 2015;20(Suppl 1):68–71.
- 359 Yu G, Gail MH, Shi J, *et al.* Association between upper digestive tract microbiota and cancer-predisposing states in the esophagus and stomach. *Cancer Epidemiol Biomarkers Prev* 2014;23:735–41.
- 360 Engstrand L, Lindberg M. *Helicobacter pylori* and the gastric microbiota. *Best Pract Res Clin Gastroenterol* 2013;27:39–45.
- 361 Dicksved J, Lindberg M, Rosenquist M, *et al.* Molecular characterization of the stomach microbiota in patients with gastric cancer and in controls. *J Med Microbiol* 2009;58(Pt 4):509–16.
- 362 Aviles-Jimenez F, Vazquez-Jimenez F, Medrano-Guzman R, *et al.* Stomach microbiota composition varies between patients with non-atrophic gastritis and patients with intestinal type of gastric cancer. *Sci Rep* 2014;4:4202.
- 363 Eun CS, Kim BK, Han DS, *et al.* Differences in gastric mucosal microbiota profiling in patients with chronic gastritis, intestinal metaplasia, and gastric cancer using pyrosequencing methods. *Helicobacter* 2014;19:407–16.
- 364 Lofgren JL, Whary MT, Ge Z, *et al.* Lack of commensal flora in *Helicobacter pylori*-infected INS-GAS mice reduces gastritis and delays intraepithelial neoplasia. *Gastroenterology* 2011;140:210–20.
- 365 Hansen R, Thomson JM, Fox JG, *et al.* Could *Helicobacter* organisms cause inflammatory bowel disease? *FEMS Immunol Med Microbiol* 2011;61:1–14.
- 366 Xiao M, Gao Y, Wang Y. *Helicobacter* species infection may be associated with cholangiocarcinoma: a meta-analysis. *Int J Clin Pract* 2014;68:262–70.
- 367 Segura-López FK, Güitrón-Cantú A, Torres J. Association between *Helicobacter* spp. infections and hepatobiliary malignancies: a review. *World J Gastroenterol* 2015;21:1414–23.
- 368 Flahou B, Rimbara E, Mori S, *et al.* The other helicobacters. *Helicobacter* 2015;20(Suppl 1):62–7.
- 369 Debongnie JC, Donnay M, Mairesse J, *et al.* Gastric ulcers and *Helicobacter heilmannii*. *Eur J Gastroenterol Hepatol* 1998;10:251–4.
- 370 Matsumoto T, Kawakubo M, Akamatsu T, *et al.* *Helicobacter heilmannii* sensu stricto-related gastric ulcers: a case report. *World J Gastroenterol* 2014;20:3376–82.
- 371 Morgner A, Bayerdörffer E, Meining A, *et al.* *Helicobacter heilmannii* and gastric cancer. *Lancet* 1995;346:511–12.
- 372 Morgner A, Lehn N, Andersen LP, *et al.* *Helicobacter heilmannii*-associated primary gastric low-grade MALT lymphoma: complete remission after curing the infection. *Gastroenterology* 2000;118:821–8.
- 373 Haesebrouck F, Pasmans F, Flahou B, *et al.* Gastric helicobacters in domestic animals and nonhuman primates and their significance for human health. *Clin Microbiol Rev* 2009;22:202–23.
- 374 Stolte M, Kroher G, Meining A, *et al.* A comparison of *Helicobacter pylori* and *H. heilmannii* gastritis. A matched control study involving 404 patients. *Scand J Gastroenterol* 1997;32:28–33.
- 375 Andersen LP, Boye K, Blom J, *et al.* Characterization of a culturable ‘*Gastrospirillum hominis*’ (*Helicobacter heilmannii*) strain isolated from human gastric mucosa. *J Clin Microbiol* 1999;37:1069–76.
- 376 Haesebrouck F, Pasmans F, Flahou B, *et al.* Non-*Helicobacter pylori* *Helicobacter* species in the human gastric mucosa: a proposal to introduce the terms *H. heilmannii sensu lato* and *sensu stricto*. *Helicobacter* 2011;16:339–40.
- 377 Jalava K, On SL, Harrington CS, *et al.* A cultured strain of ‘*Helicobacter heilmannii*’, a human gastric pathogen, identified as *H. bizzozeronii*: evidence for zoonotic potential of *Helicobacter*. *Emerging Infect Dis* 2001;7:1036–8.
- 378 Mandai S, Kasagi Y, Kusaka K, *et al.* *Helicobacter cinaedi* kidney cyst infection and bacteremia in a patient with autosomal dominant polycystic kidney disease. *J Infect Chemother* 2014;20:732–4.
- 379 Liu J, He L, Haesebrouck F, *et al.* Prevalence of coinfection with gastric non-*Helicobacter pylori* *Helicobacter* (NHPH) species in *Helicobacter pylori*-infected patients suffering from gastric disease in Beijing, China. *Helicobacter* 2015;20:284–90.
- 380 Debongnie JC, Donnay M, Mairesse J. *Gastrospirillum hominis* (‘*Helicobacter heilmannii*’): a cause of gastritis, sometimes transient, better diagnosed by touch cytology? *Am J Gastroenterol* 1995;90:411–16.
- 381 Antonopoulos DA, Huse SM, Morrison HG, *et al.* Reproducible community dynamics of the gastrointestinal microbiota following antibiotic perturbation. *Infect Immun* 2009;77:2367–75.
- 382 Buffie CG, Jarchum I, Equinda M, *et al.* Profound alterations of intestinal microbiota following a single dose of clindamycin results in sustained susceptibility to *Clostridium difficile*-induced colitis. *Infect Immun* 2012;80:62–73.
- 383 Dethlefsen L, Huse S, Sogin ML, *et al.* The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol* 2008;6:e280.
- 384 Engelbrektson A, Korzenik JR, Pittler A, *et al.* Probiotics to minimize the disruption of faecal microbiota in healthy subjects undergoing antibiotic therapy. *J Med Microbiol* 2009;58(Pt 5):663–70.
- 385 Jernberg C, Löfmark S, Edlund C, *et al.* Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *ISME J* 2007;1:56–66.
- 386 Ladirat SE, Schols HA, Nauta A, *et al.* High-throughput analysis of the impact of antibiotics on the human intestinal microbiota composition. *J Microbiol Methods* 2013;92:387–97.
- 387 Marteau P, Rambaud JC. Potential of using lactic acid bacteria for therapy and immunomodulation in man. *FEMS Microbiol Rev* 1993;12:207–20.
- 388 Lessa FC, Mu Y, Bamberg WM, *et al.* Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015;372:825–34.
- 389 Cox LM, Yamanishi S, Sohn J, *et al.* Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* 2014;158:705–21.
- 390 Cox LM, Blaser MJ. Antibiotics in early life and obesity. *Nat Rev Endocrinol* 2015;11:182–90.
- 391 Ajslev TA, Andersen CS, Gamborg M, *et al.* Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *Int J Obes (Lond)* 2011;35:522–9.
- 392 Azad MB, Bridgman SL, Becker AB, *et al.* Infant antibiotic exposure and the development of childhood overweight and central adiposity. *Int J Obes (Lond)* 2014;38:1290–8.
- 393 Bailey LC, Forrest CB, Zhang P, *et al.* Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatr* 2014;168:1063–9.
- 394 Murphy R, Stewart AW, Braithwaite I, *et al.* Antibiotic treatment during infancy and increased body mass index in boys: an international cross-sectional study. *Int J Obes (Lond)* 2014;38:1115–19.
- 395 Trasande L, Blustein J, Liu M, *et al.* Infant antibiotic exposures and early-life body mass. *Int J Obes (Lond)* 2013;37:16–23.
- 396 Adamsson I, Edlund C, Nord CE. Impact of treatment of *Helicobacter pylori* on the normal gastrointestinal microflora. *Clin Microbiol Infect* 2000;6:175–7.

- 397 Jakobsson H, Wreiber K, Fall K, *et al.* Macrolide resistance in the normal microbiota after *Helicobacter pylori* treatment. *Scand J Infect Dis* 2007;39:757–63.
- 398 Sjölund M, Wreiber K, Andersson DI, *et al.* Long-term persistence of resistant *Enterococcus* species after antibiotics to eradicate *Helicobacter pylori*. *Ann Intern Med* 2003;139:483–7.
- 399 Sjölund M, Tano E, Blaser MJ, *et al.* Persistence of resistant *Staphylococcus epidermidis* after single course of clarithromycin. *Emerging Infect Dis* 2005;11:1389–93.
- 400 Tacconelli E, De Angelis G, Cataldo MA, *et al.* Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. *J Antimicrob Chemother* 2008;61:26–38.
- 401 Weber SG, Gold HS, Hooper DC, *et al.* Fluoroquinolones and the risk for methicillin-resistant *Staphylococcus aureus* in hospitalized patients. *Emerging Infect Dis* 2003;9:1415–22.
- 402 Rodríguez-Baño J, Navarro MD, Romero L, *et al.* Risk-factors for emerging bloodstream infections caused by extended-spectrum β -lactamase-producing *Escherichia coli*. *Clin Microbiol Infect* 2008;14:180–3.
- 403 Dang Y, Reinhardt JD, Zhou X, *et al.* The effect of probiotics supplementation on *Helicobacter pylori* eradication rates and side effects during eradication therapy: a meta-analysis. *PLoS One* 2014;9:e111030.
- 404 Lv Z, Wang B, Zhou X, *et al.* Efficacy and safety of probiotics as adjuvant agents for *Helicobacter pylori* infection: a meta-analysis. *Exp Ther Med* 2015;9:707–16.
- 405 Tong JL, Ran ZH, Shen J, *et al.* Meta-analysis: the effect of supplementation with probiotics on eradication rates and adverse events during *Helicobacter pylori* eradication therapy. *Aliment Pharmacol Ther* 2007;25:155–68.
- 406 Wang ZH, Gao QY, Fang JY. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in *Helicobacter pylori* eradication therapy. *J Clin Gastroenterol* 2013;47:25–32.
- 407 Zhang M-M, Qian W, Qin Y-Y, *et al.* Probiotics in *Helicobacter pylori* eradication therapy: a systematic review and meta-analysis. *World J Gastroenterol* 2015;21:4345–57.
- 408 Zheng X, Lyu L, Mei Z. Lactobacillus-containing probiotic supplementation increases *Helicobacter pylori* eradication rate: evidence from a meta-analysis. *Rev Esp Enferm Dig* 2013;105:445–53.
- 409 Zhu R, Chen K, Zheng Y-Y, *et al.* Meta-analysis of the efficacy of probiotics in *Helicobacter pylori* eradication therapy. *World J Gastroenterol* 2014;20:18013–21.
- 410 Zou J, Dong J, Yu X. Meta-analysis: lactobacillus containing quadruple therapy versus standard triple first-line therapy for *Helicobacter pylori* eradication. *Helicobacter* 2009;14:97–107.
- 411 Li S, Huang XL, Sui JZ, *et al.* Meta-analysis of randomized controlled trials on the efficacy of probiotics in *Helicobacter pylori* eradication therapy in children. *Eur J Pediatr* 2014;173:153–61.
- 412 Sachdeva A, Nagpal J. Effect of fermented milk-based probiotic preparations on *Helicobacter pylori* eradication: a systematic review and meta-analysis of randomized-controlled trials. *Eur J Gastroenterol Hepatol* 2009;21:45–53.
- 413 Szajewska H. Pooling data on different probiotics is not appropriate to assess the efficacy of probiotics. *Eur J Pediatr* 2014;173:975.
- 414 Szajewska H, Horvath A, Piwowarczyk A. Meta-analysis: the effects of *Saccharomyces boulardii* supplementation on *Helicobacter pylori* eradication rates and side effects during treatment. *Aliment Pharmacol Ther* 2010;32:1069–79.
- 415 Szajewska H, Horvath A, Kolodziej M. Systematic review with meta-analysis: *Saccharomyces boulardii* supplementation and eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2015;41:1237–45.
- 416 Nista EC, Candelli M, Cremonini F, *et al.* *Bacillus clausii* therapy to reduce side-effects of anti-*Helicobacter pylori* treatment: randomized, double-blind, placebo controlled trial. *Aliment Pharmacol Ther* 2004;20:1181–8.