








Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report

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ABSTRACT

Helicobacter pylori Infection is formally recognised as an infectious disease, an entity that is now included in the International Classification of Diseases 11th Revision. This in principle leads to the recommendation that all infected patients should receive treatment. In the context of the wide clinical spectrum associated with *Helicobacter pylori* gastritis, specific issues persist and require regular updates for optimised management. The identification of distinct clinical scenarios, proper testing and adoption of effective strategies for prevention of gastric cancer and other complications are addressed. *H. pylori* treatment is challenged by the continuously rising antibiotic resistance and demands for susceptibility testing with consideration of novel molecular technologies and careful selection of first line and rescue therapies. The role of *H. pylori* and antibiotic therapies and their impact on the gut microbiota are also considered.

Progress made in the management of *H. pylori* infection is covered in the present sixth edition of the Maastricht/Florence 2021 Consensus Report, key aspects related to the clinical role of *H. pylori* infection were re-evaluated and updated. Forty-one experts from 29 countries representing a global community, examined the new data related to *H. pylori* infection in five working groups: (1) indications/associations, (2) diagnosis, (3) treatment, (4) prevention/gastric cancer and (5) *H. pylori* and the gut microbiota. The results of the individual working groups were presented for 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 various clinical fields.

INTRODUCTION

The Maastricht V/Florence Consensus Report was published in 2017¹ and substantial developments have ensued to necessitate an update that captures the progress and addresses the challenging clinical issues in the field of *Helicobacter pylori*. The increasing *H. pylori* resistance to previously effective antibiotic treatments has become of great concern and requires careful selection of therapies and revision of therapeutic strategies. In this edition, a new focus is set on molecular testing for

H. pylori detection and antibiotic susceptibility with support for the role of antibiotic stewardship. The most effective empirical regimens are revised if individual antibiotic resistance is not available.

A recent important evolution has taken place as a consequence of the Kyoto consensus report on gastritis² with the designation of *H. pylori* gastritis as an infectious disease. *H. pylori* gastritis as an infectious disease is now included as a nosological entity in itself in the new International Classification of Disease 11th Revision (ICD 11), which implies treatment of all *H. pylori*-infected patients. This represents a paradigm shift, as the indication for treatment is no longer reserved for patients with clinical manifestations of infection. Nevertheless, the clinical scenarios of *H. pylori* gastritis-related diseases remain diverse with specific aspects that require critical re-examination.

New studies conducted to demonstrate feasibility and efficacy of primary and secondary gastric cancer prevention strategies are presented and discussed in their complexity at the individual and population level. Endoscopy-based enhanced imaging is taken note of for its contributions in early detection and treatment of small neoplastic foci and surveillance.

The role of *H. pylori* infection has also been assessed for potential interactions with other microbiota in the upper and lower digestive tract, as the gut microbiome emerges as a critical player in human health and disease.

The aim of this consensus report is to provide a state-of-the-art guide for the management of *H. pylori* infection and related clinical manifestations and as an inspiration for new clinical research in the area. In the current Maastricht VI/Florence Consensus Report, 41 experts from 29 countries convened for 2 days for a face-to-face meeting after having been actively involved in a previous Delphi process.

The working groups (WG) were set under the following topics: WG1: indications/associations, WG2: diagnosis, WG3: treatment, WG4: prevention/gastric cancer, WG5: *H. pylori* and the gut microbiota.

METHODS

Meeting logistics and coordination

The evidence-based Delphi process developed consensus statements following proposals by



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designated coordinators. The process allowed individual feedback and changes during the process guided by the coordinators and the consensus chair. The principal steps in the process were: (1) selection of the consensus group; (2) identification of areas of clinical importance; (3) systematic literature reviews to identify the latest and best evidence to support each statement, draft statements and discussions specific to each statement. Two rounds of voting were conducted. The groups were asked to choose one of the following ratings for each statement:

- ▶ Agree strongly.
- ▶ Agree with reservation.
- ▶ Undecided.
- ▶ Disagree.
- ▶ Disagree strongly.

When fewer than 80% of the votes were for 'agree strongly' or 'agree with reservation' 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 was required by 80% of respondents who (1) strongly agreed or (2) agreed with reservation. The level of evidence and strength of the recommendations were completed only after the individual WG meetings. Based on the type of studies, evidence levels and grade of recommendation were based on the Grades of Recommendations, Assessment, Development and Evaluation system,^{3–5} which takes into account the quality of evidence and strength of recommendations as follows.

Quality of evidence

A High quality

Further research is very unlikely to change our confidence in the estimate of effect.

B Moderate quality

Further research is very unlikely to have an important impact on our confidence in the estimate of effect and may change the estimate.

C Low quality

Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

D Very low quality

Any estimate of effect is very uncertain.

Strength of recommendation

1 Strong recommendation

Strong recommendation for using an intervention. Strong recommendation against using an intervention.

2 Weak recommendation

Weak recommendation for using an intervention. Weak recommendation against using an intervention.

The final meeting was held on 27 September 2021–28 September 2021 in a hybrid format, that is, a mixture of face-to-face meeting in Florence (24 delegates) and teleparticipation (17 delegates). The statements were reviewed and presented to all delegates for final voting.

An overview of all statements along, the level of evidence and strength of recommendation is shown in [table 1](#).

WG1: INDICATIONS/ASSOCIATIONS

Statement 1: *H. pylori* infection always causes gastritis, irrespective of symptoms or complications.

Agreement 100%

Grade A1

H. pylori infects more than half of the world's population and always causes chronic gastritis, that may progress to severe complications such as peptic ulcer disease, gastric adenocarcinoma and gastric MALT lymphoma. In a majority of patients in spite of structural and functional abnormalities due to chronic active inflammation of the gastric mucosa there are no apparent clinical symptoms.^{1 2} The Kyoto *H. pylori* consensus in 2015, based on these objective pathological criteria, defined *H. pylori*-induced gastritis as an infectious disease regardless of clinical symptoms and complications.²

The Kyoto consensus went on to propose an aetiology-based classification for gastritis and now *H. pylori* gastritis is included as a specific disease entity in ICD 11.

Eradication of *H. pylori* is the first-line treatment of *H. pylori*-infected patients with dyspeptic symptoms previously defined as functional dyspepsia (FD) as it can reduce symptoms in a substantial subset of them, minimise the risk of serious complications of the infection and reduce gastric cancer risk.^{1 2 6 7}

Statement 2: *H. pylori* is a gastric pathogen. *H. pylori* gastritis is an infectious disease.

Agreement 94%

Grade A1

In the absence of *H. pylori* the gastric mucosa does not demonstrate signs of chronic active inflammation, neutrophils are absent and infiltration with mononuclear cells is minor.^{8–10} Therefore, an agent causing such changes in the gastric mucosa cannot be considered part of the normal microbiota and the fact that *H. pylori* has coinhabited mankind for millennia does not preclude its pathogenicity of today.¹¹ Koch's postulate for pathogenicity has been documented since the early days of *H. pylori* discovery.¹² Eradication therapy restores normal gastric mucosa or halts progression to mucosal lesions¹³ and can reduce symptoms, minimise complications of the infection and reduce gastric cancer risk. Eradication of *H. pylori* is recommended even in the absence of symptoms.^{1 2 6} There is an entity of *H. pylori*-negative gastritis with characteristics similar to *H. pylori* gastritis but its pathological relevance remains unclear.¹⁴

Statement 3: Test-and-treat is an appropriate strategy for uninvestigated dyspepsia.

Agreement 94%

Grade A1

Test-and-treat is a well-defined strategy and refers to non-invasive testing for *H. pylori* in patients with dyspeptic symptoms and to eradication of the infection whenever detected. It is distinct from the scope-and-treat strategy (Upper GI-endoscopy followed by treatment) which is mandatory in defined clinical settings outlined below.

The test-and-treat strategy will cure most cases of underlying peptic ulcer disease and prevent serious consequences of gastroduodenal diseases associated with *H. pylori* gastritis. Eradication therapy will also benefit a subset of patients with *H. pylori* infection associated dyspepsia in the absence of gross mucosal lesions, (ie, FD).^{15 16}

Several prospective studies and decision analyses support the use of the test-and-treat strategy.^{17 18} These strategies are

Table 1 Statements, Level of evidence, Strength of recommendation

	Grading	Agreement	
WG1: Indications/Associations			
Statement 1	A1	100.00%	H. pylori infection always causes gastritis, irrespective of symptoms or complications.
Statement 2	A1	94.00%	H. pylori is a gastric pathogen. H. pylori gastritis is an infectious disease.
Statement 3	A1	94.00%	Test-and-treat is an appropriate strategy for uninvestigated dyspepsia.
Statement 4	A1	92.00%	Endoscopy is not necessary in the initial investigation of dyspepsia in low H. pylori prevalence areas.
Statement 5	A1	100.00%	H. pylori gastritis is associated with increased, decreased or no overall change in acid secretion in the stomach.
Statement 6	A1	100.00%	Overall, H. pylori eradication is superior to placebo or acid suppressive therapy for long-term relief of dyspepsia, but the magnitude of the benefit is small.
Statement 7	B1	100.00%	H. pylori gastritis has to be excluded before a reliable diagnosis of functional dyspepsia can be made.
Statement 8	A1	100.00%	The use of either aspirin or NSAIDs increases the risk of peptic ulcer disease and its complications in H. pylori infected subjects.
Statement 9	A1	100.00%	H. pylori testing and treatment are advisable for high-risk patients who are already on long-term aspirin. H. pylori testing and treatment are advisable for naïve patients starting long-term NSAID therapy. Those at high-risk may need additional PPI therapy.
Statement 10	A1	91.00%	There is no evidence to suggest that anticoagulants (coumarins, direct oral and vitamin K antagonists) increase the risk of bleeding in patients with H. pylori infection.
Statement 11	A1	94.00%	Long-term treatment with PPIs alters the topography of H. pylori gastritis.
Statement 12	A1	97.00%	H. pylori eradication improves gastritis in long-term PPI users.
Statement 13	A1	97.00%	H. pylori eradication is recommended for patients with unexplained iron deficiency anaemia (IDA), idiopathic thrombocytopenic purpura (ITP) and Vitamin B12 deficiency.
Statement 14	A1	100.00%	H. pylori eradication is the first-line treatment for localised low grade gastric MALT lymphoma. H. pylori eradication therapy is also recommended for cases without evidence of H. pylori infection and may provide benefit even for more advanced staged disease
Statement 15	D2	90.00%	H. pylori has been positively and negatively associated with some extra-gastrointestinal disorders. However, the causality of these associations has not been definitively proven.
Statement 16	A1	86.00%	The COVID-19 pandemic has negatively impacted the management of H. pylori-related diseases.
WG 2 Diagnostics			
Statement 1	A1	97.00%	In young dyspeptic patients (age below 50) with no specific risk and no alarm symptoms, non-invasive testing for H. pylori infection is recommended.
Statement 2	B1	94.00%	In dyspeptic patients older than 50 years, upper GI endoscopy is required. Functional serology may be considered as complementary diagnostic tool.
Statement 3	A2	100.00%	When endoscopy is indicated it should: i) apply the best available technologies; ii) include biopsy sampling. Biopsy samples, as obtained in accordance with validated protocols, should result in both aetiological diagnosis and gastritis staging. Any focal lesions should be additionally sampled.
Statement 4	A1	87.00%	UBT remains an important tool for H. pylori diagnosis before and after eradication therapy. Citric acid is an essential component of the protocol.
Statement 5	A1	96.00%	Monoclonal stool antigen test, if properly validated, is an appropriate test before and after H. pylori treatment
Statement 6	A1	98.00%	Gastric functional serology (pepsinogens I-II and gastrin levels), anti-H. pylori antibodies, anti-intrinsic factor and anti-parietal cell auto-antibodies may provide clinically valuable information on the likelihood of gastric mucosal atrophy, including its aetiology.
Statement 7	A1	100.00%	Molecular methods (in particular, real time-PCR, whole genome sequencing and digital PCR) allow detection of H. pylori mutations associated with resistance to clarithromycin, levofloxacin, tetracycline and rifampicin.
Statement 8	B2	100.00%	Gastric biopsies recovered from rapid urease tests (RUT) can be reused for molecular testing by PCR.
Statement 9	A1	91.00%	Clarithromycin susceptibility testing, if available through molecular techniques or culture, is recommended before prescribing any clarithromycin containing therapy.
Statement 10	A1	96.00%	In the short-term post-eradication (4–6 weeks) follow-up, no antibiotics or bismuth should be used to permit optimum testing for H. pylori. Proton pump inhibitors should be stopped 14 days before testing
Statement 11	A1	91.00%	Tests for serum IgG antibodies against H. pylori can serve as a screening test in specific clinical situations.
Statement 12	A1	100.00%	Gastric mucosal atrophy is defined as "loss of native glands." Atrophy is the major determinant of non-hereditary gastric cancer risk assessed by endoscopy and histology, and it may be complementarily assessed by gastric serology.
Statement 13	A1	97.00%	The histological assessment of atrophy should result in a conclusive gastritis staging (OLGA/OLGIM), which consistently ranks the patient-specific cancer risk. Histological staging makes IM subtyping clinically redundant.
Statement 14	B2	91.00%	In H. pylori-negative gastritis (primary or after eradication), clinically suspected autoimmune gastritis (AIG) requires testing for gastrin, pepsinogens ratio, and auto-antibodies to intrinsic factor and parietal cells. Clinical factors and functional serology may provide the rationale for any further need for endoscopy/biopsy assessment.
Statement 15	B2	97.00%	Currently, no large-scale trials have provided evidence that molecular biomarkers can reliably predict the risk of non-hereditary (ie, non-syndromic) gastric cancer.
Statement 16	B1	100.00%	In H. pylori-eradicated patients, low-stage gastritis as properly assessed by endoscopy/histology, only requires clinical follow-up.
Statement 17	B1	100.00%	After successful H. pylori eradication, patients with high-stage (III-IV) gastritis and/or extensive endoscopic atrophy are still at risk for gastric cancer. The timing of the endoscopic/biopsy surveillance is based on the gastritis stage as assessed at the last check-up.
Statement 18	A1	100.00%	Low- and high-grade intra-epithelial neoplasia requires: i) confirmatory histological assessment, ii) gastric mapping by high resolution endoscopy and iii) targeted EMR or SBD, particularly for high grade, in tertiary endoscopy centres. Ablation does not abolish metachronous cancer risk. H. pylori eradication and post-ablation surveillance are both mandatory.
WG3 Treatment			
Statement 1	D2	91.00%	It is reasonable to recommend that susceptibility tests (molecular or after culture) are routinely performed, even before prescribing first-line treatment, in respect to antibiotic stewardship. However, the generalised use of such a susceptibility-guided strategy in routine clinical practice remains to be established.
Statement 2	B1	92.00%	If individual susceptibility testing is not available, the first line recommended treatment in areas of high (>15%) or unknown clarithromycin resistance is bismuth quadruple therapy. If this is not available, non-bismuth concomitant quadruple therapy may be considered.
Statement 3	D2	85.00%	The treatment duration of bismuth quadruple therapy should be 14 days, unless 10- days effective therapies are available.

Continued

Table 1 Continued

	Grading	Agreement	
Statement 4	B1	94.00%	In choosing a non-bismuth quadruple therapy, concomitant therapy (PPI, amoxicillin, clarithromycin, and a nitroimidazole administered concurrently) should be the preferred choice given its proven reproducible effectiveness and less complexity compared with sequential and hybrid therapies.
Statement 5	D2	100.00%	The recommended treatment duration of non-bismuth quadruple therapy (concomitant) is 14 days.
Statement 6	B1	94.00%	In areas of low clarithromycin resistance, bismuth quadruple therapy or clarithromycin-containing triple therapy may be recommended as first-line empirical treatment, if proven effective locally.
Statement 7	B1	100.00%	The recommended treatment duration of PPI-clarithromycin-based triple therapy is 14 days.
Statement 8	C2	97.00%	The use of high dose PPI twice daily increases the efficacy of triple therapy. It remains unclear whether high dose PPI twice daily can improve the efficacy of quadruple therapies.
Statement 9	B2	100.00%	Potassium-Competitive Acid Blockers (P-CAB) - antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first- and second-line treatment, and superior in patients with evidence of antimicrobial resistant infections.
Statement 10	D2	94.00%	Empiric second line and rescue therapies should be guided by local resistance patterns assessed by susceptibility testing and eradication rates in order to optimise treatment success.
Statement 11	C2	83.00%	After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or the high-dose PPI-amoxicillin dual therapy may be recommended. In cases of high fluoroquinolone resistance, the combination of bismuth with other antibiotics, or rifabutin, may be an option.
Statement 12	C2	84.00%	After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy, or a PPI-amoxicillin high-dose dual therapy are recommended as a second-line treatment.
Statement 13	C2	87.00%	After failure of a non-bismuth quadruple therapy, either a bismuth quadruple therapy or a fluoroquinolone-containing quadruple (or triple) therapy is recommended. PPI-amoxicillin high-dose dual therapy might also be considered.
Statement 14	B2	86.00%	After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies and second line with bismuth quadruple therapy, it is recommended to use a fluoroquinolone-containing regimen. In regions with a known high fluoroquinolone resistance, a bismuth quadruple therapy with different antibiotics, rifabutin-containing rescue therapy, or a high dose PPI-amoxicillin dual therapy, should be considered.
Statement 15	B2	84.00%	After failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies, and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use the bismuth-based quadruple therapy. If bismuth is not available, high-dose PPI-amoxicillin dual or a rifabutin-containing regimen could be considered.
Statement 16	C2	90.00%	After failure of first-line treatment with bismuth quadruple and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use a clarithromycin-based triple or quadruple therapy only if from an area of low (<15%) clarithromycin resistance. Otherwise, a high-dose PPI-amoxicillin dual therapy, a rifabutin-containing regimen or a combination of bismuth with different antibiotics should be used.
Statement 17	C2	85.00%	In patients with proven penicillin allergy, for a first-line treatment, bismuth quadruple therapy (PPI-bismuth-tetracycline-metronidazole) should be recommended. As second line therapy, bismuth quadruple therapy (if not previously prescribed) and fluoroquinolone-containing regimen may represent empirical second-line rescue options.
WG 4 Gastric cancer & prevention			
Statement 1	A1	100.00%	<i>H. pylori</i> infection is the primary aetiological factor for gastric adenocarcinoma including proximal gastric cancer (PGC)
Statement 2	A1	94.00%	<i>H. pylori</i> infection plays an aetiological role in a subset of adenocarcinoma of the Gastro-oesophageal Junction zone.
Statement 3	A1	100.00%	The influence of environmental factors is subordinate to the effect of <i>H. pylori</i> infection.
Statement 4	D2	100.00%	Hereditary gastric cancer is a distinct entity. The role of <i>H. pylori</i> infection in the clinical course of the disease remains to be elucidated.
Statement 5	A1	100.00%	Severe atrophy (OLGA3/4) in the context of <i>H. pylori</i> gastritis carries a much higher risk for gastric cancer development as compared with atrophy in the context of autoimmune gastritis.
Statement 6	C2	97.00%	<i>H. pylori</i> infection and EBV are independent risk factors of gastric cancer. Whether coinfection of <i>H. pylori</i> and EBV is associated with higher risk of gastric cancer than either one alone remains uncertain.
Statement 7	A1	100.00%	<i>H. pylori</i> eradication eliminates a) the active inflammatory response in chronic active non-atrophic gastritis and b) prevents further progression to atrophy and intestinal metaplasia in chronic non-atrophic gastritis.
Statement 8	A1	97.00%	<i>H. pylori</i> eradication may reverse gastric atrophy and to some extent intestinal metaplasia and may halt the progression from chronic atrophic gastritis to neoplastic lesions in a subset of patients.
Statement 9	A1	100.00%	<i>H. pylori</i> eradication offers the chance for gastric cancer prevention at any age in adulthood. The magnitude of the benefit decreases with age.
Statement 10	A1	100.00%	<i>H. pylori</i> eradication is most effective for gastric cancer prevention before the development of severe chronic atrophic gastritis.
Statement 11	C2	89.00%	Diagnostic tests used to screen <i>H. pylori</i> infection for the purpose of gastric cancer prevention should preferably be non-invasive.
Statement 12	A2	91.00%	If a serological method is used for <i>H. pylori</i> detection a further test (UBT, SAT) confirming current infection is required before initiating therapy
Statement 13	C2	89.00%	Endoscopy with biopsies is recommended in asymptomatic individuals with a family history of gastric cancer (does not refer to hereditary gastric cancer) at age 45 and above.
Statement 14	A1	97.00%	Asymptomatic individuals at age above 50 years are considered vulnerable and at increased risk of gastric cancer compared with younger individuals.
Statement 15	B1	95.00%	Population-based <i>H. pylori</i> test-and-treat programmes for gastric cancer prevention require caution in the selection of antibiotics to minimise development of antimicrobial resistance.
Statement 16	B2	84.00%	Broad use of <i>H. pylori</i> eradication therapies for the purpose of gastric cancer prevention does not lead to an increase in other severe pathologies
Statement 17	A1	94.00%	Population-based <i>H. pylori</i> test-and-treat strategy provides additional benefits by preventing other gastroduodenal pathologies.
Statement 18	C2	81.00%	Screening modalities for gastric cancer prevention (noninvasive or endoscopic) combined with colorectal cancer screening is an opportunity
Statement 19	A1	97.00%	A population-based <i>H. pylori</i> test and treat programme is cost-effective in populations with intermediate or high incidence of gastric cancer.
Statement 20	B1	97.00%	Follow-up at regular intervals, and by use of endoscopic biopsy protocols, is mandatory in patients with severe atrophic gastritis (OLGA 3/4).

Continued

Table 1 Continued

	Grading	Agreement	
Statement 21	A1	100.00%	Eradication of <i>H. pylori</i> is mandatory to reduce the risk of metachronous gastric cancer after curative endoscopic resection or gastric subtotal resection of early gastric cancer.
Statement 22	C2	100.00%	Medical and special dietary chemoprevention cannot in general be recommended in patients with severe gastric atrophy or intestinal metaplasia (OLGA3/4) after <i>H. pylori</i> eradication.
Statement 23	D1	94.00%	Population-based <i>H. pylori</i> test-and-treat programmes should be targeted to special requirements at the regional level (ie, selection of screening tool, use of eradication regimen, surveillance)
Statement 24	B1	94.00%	Population-based <i>H. pylori</i> test-and-treat programmes should be integrated into healthcare priorities, especially in regions with intermediate to high gastric cancer incidence.
Statement 25	D2	100.00%	The use of genetic and epigenetic markers for gastric cancer risk assessment and gastric cancer progression in clinical management requires further validation.
Statement 26	A1	100.00%	Image-enhanced endoscopy (IEE) should be used in the endoscopy-based screening for dysplasia and early gastric cancer.
Statement 27	C1	100.00%	There is still demand for a prophylactic and/or therapeutic vaccine.
WG 5 Helicobacter pylori and the Gut Microbiota			
Statement 1	B2	100.00%	Early life antibiotic exposure has a long-lasting effect on the intestinal microbiota.
Statement 2	A1	94.00%	The human stomach is colonised by other bacteria beyond <i>H. pylori</i> , the so-called gastric microbiome.
Statement 3	B2	91.00%	Gastric bacteria other than <i>H. pylori</i> may also affect <i>H. pylori</i> related changes.
Statement 4	C2	91.00%	Non- <i>H. pylori</i> <i>Helicobacter</i> species can cause human gastric disease.
Statement 5	B2	89.00%	<i>H. pylori</i> eradication therapy has the potential to select resistant strains of gut microbiota.
Statement 6	A2	89.00%	Certain probiotics have been shown to be effective in reducing GI side effects caused by <i>H. pylori</i> eradication therapies.
Statement 7	B2	80.00%	Certain probiotics may have a beneficial effect on <i>H. pylori</i> eradication therapy through reduction of antibiotic related side effects.
Statement 8	B2	97.00%	Antibiotic treatment for other reasons might select resistant <i>H. pylori</i> strains.
Statement 9	A2	86.00%	The oral cavity may contribute to the gastric microbiota composition.

recommended only in 'young' patients, with no 'alarm' symptoms. For the initial management of dyspepsia, test-and-treat and empirical proton pump inhibitor (PPI) therapy perform equally well in terms of short-term symptom resolution. However, those with *H. pylori* infection can obtain a durable effect of cure following successful eradication.^{18–20} From previous meta-analyses, prompt endoscopy confers a small benefit in terms of cure of dyspepsia. Endoscopy is generally associated with testing for *H. pylori* and if positive, its treatment leads to benefits. However, the cost of endoscopy as a first-line approach for management of dyspepsia in patients without alarm symptoms argues against this in everyday practice.²¹ It is widely accepted that endoscopy should be reserved for patients with symptom onset after 50 (45–55) years of age, those who have alarm features and all patients who fail empirical antisecretory therapy or test-and-treat strategy fails^{17–20}

Statement 4: Endoscopy is not necessary in the initial investigation of dyspepsia in low *H. pylori* prevalence areas.

Agreement 92%

Grade A1

The prevalence of serious upper GI lesions in dyspepsia in the age groups below 50 (45–55), depending on geographical area, is very low. In a global meta-analysis, the prevalence of gastric cancer was only 0.4% and was even lower in those aged below 45. Consequently, it is expected that in a low *H. pylori* prevalence area, the rate of malignancy will be even lower. However, caution is advised with regard to the geographical region and age adjusted cut-offs taken into consideration with selection of diagnostic strategies. Additionally, it should be noted that in high gastric cancer incidence and high *H. pylori* prevalence regions, alarm symptoms for upper GI cancers may not be present.^{21–25}

Statement 5: *H. pylori* gastritis is associated with increased, decreased or no overall change in acid secretion in the stomach.

Agreement 100%

Grade A1

Gastric secretion is increased if the infection is predominantly confined to the antrum with relative sparing of the corpus. If the infection significantly affects the corpus or there is pangastritis with gastric atrophy, acid secretion is decreased.²⁶

H. pylori positive duodenal ulcer (DU) patients have increased acid secretion rates (driven by low somatostatin, high gastrin) that falls after eradication.^{27–29} Patients with severe body gastritis have low acid secretion rates that increase after *H. pylori* eradication. Patients without DU and severe body gastritis (most patients) have no change or a modest increase in acid secretion after *H. pylori* eradication.^{28–30} Patients with gastric ulcer, whose acid secretion is generally lower, show higher acid secretion after eradication.³¹

Statement 6: Overall, *H. pylori* eradication is superior to placebo or acid suppressive therapy for long-term relief of dyspepsia, but the magnitude of the benefit is small.

Agreement 100%

Grade A1

Since the last Maastricht consensus conference,¹ there has been very little additional information regarding the long-term effects of *H. pylori* eradication on dyspepsia symptoms. This is perhaps because the adoption of the test-and-treat strategy for dyspepsia by national guidelines since the early 2000s has meant that further dyspepsia trials without eradication of *H. pylori* are deemed unethical and unnecessary.³² In a Cochrane meta-analysis, the number needed to treat (NNT) to cure dyspepsia was initially estimated to be 15.³³ In further meta-analyses the significant improvement of symptoms in the *H. pylori* eradication group was confirmed.^{16,34} The most recent meta-analysis,³⁵ including 29 randomised controlled trials (RCTs) and 6781 *H. pylori*-positive patients with FD, confirmed that eradication therapy was superior to any other treatment option for symptom cure (relative risk, RR of symptoms not being cured=0.91; 95% CI 0.88 to 0.94, NNT=14; 95% CI 11 to 21) and improvement (RR of symptoms not improving=0.84; 95% CI 0.78 to 0.91, NNT=9; 95% CI 7 to 17). A network meta-analysis (NWM) of management strategies in uninvestigated dyspepsia,

reported a significant effect of eradication therapy on epigastric pain and burning (epigastric pain syndrome), but not on early satiety or postprandial fullness (postprandial distress syndrome).³⁶ Furthermore, based on the NWM the comparison of management strategies in uninvestigated dyspepsia, showed that the test-and-treat approach ranked first over acid suppression or prompt endoscopy for all or only *H. pylori* positive patients. A long-term follow-up population-based screening study reported no difference in reduction of dyspepsia symptoms in those screened (and treated) for *H. pylori* vs controls at 13 years³⁷ which is contrast with the only other study with more than 12 months follow-up.³⁸

Statement 7: *H. pylori* gastritis has to be excluded before a reliable diagnosis of functional dyspepsia (FD) can be made.

Agreement 100%

Grade B1

In *H. pylori*-infected patients with dyspepsia, and where other pathologies have been excluded endoscopically, symptoms can be attributed to *H. pylori* gastritis if successful eradication therapy is followed by sustained symptom remission. Patients with persisting dyspeptic symptoms despite successful eradication therapy may be considered as having 'FD'.² Therefore, *H. pylori* gastritis has to be excluded before a reliable diagnosis of FD can be made.^{33 39–42}

Statement 8: The use of either aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of peptic ulcer disease and its complications in *H. pylori*-infected subjects.

Agreement 100%

Grade A1

NSAIDs, aspirin and *H. pylori* infection are independent risk factors for peptic ulcer (gastric and duodenal) and their complications.^{43 44} Most, but not all, studies (observational studies, randomised clinical trials and meta-analyses) also show that *H. pylori*-infected patients have an increased risk of peptic ulcer disease and its complications when compared with non-*H. pylori*-infected patients when using NSAIDs, cyclo-oxygenase-2 inhibitors or aspirin. Some studies show a synergistic or at least an additional risk when both factors (*H. pylori* infection and NSAIDs or aspirin) are present compared with either factor alone.^{45–49}

Statement 9: *H. pylori* testing and treatment are advisable for high-risk patients who are already on long-term aspirin. *H. pylori* testing and treatment are advisable for naïve patients starting long-term NSAID therapy. Those at high-risk may need additional PPI therapy.

Agreement 100%

Grade A1

The effect of eradication on occurrence of peptic ulcer or peptic ulcer bleeding has been studied in clinical trials more often with NSAIDs than with aspirin. Overall, *H. pylori* eradication reduces the risk of peptic ulcer in patients taking long-term NSAID therapy. This benefit is well documented in naïve patients starting NSAIDs but does not apply in patients already on long-term NSAIDs. High-risk patients such as those with previous peptic ulcer will also need continuing PPI therapy to reduce further the risk of ulcer recurrence while on NSAID therapy. *H. pylori* increases the risk of peptic ulcer and peptic ulcer bleeding in patients taking low-dose aspirin, and eradication reduces the risk of peptic ulcer recurrence. However, the potential beneficial effect of systematic *H. pylori* eradication in all aspirin users is questionable due to the huge number of people taking low-dose aspirin worldwide, and the NNT being somewhere between

100 and more than 1000 patients to prevent one peptic ulcer bleeding event. It seems reasonable to advise *H. pylori* testing and treatment only in high-risk patients on low-dose aspirin and consider additional PPI treatment, especially in those with previous peptic ulcer history.^{45–49}

Statement 10: There is no evidence to suggest that anticoagulants (coumarins, direct oral and vitamin K antagonists) increase the risk of bleeding in patients with *H. pylori* infection.

Agreement 91%

Grade A1

The potential effect of *H. pylori* infection on the risk of GI bleeding in patients taking anticoagulants has been poorly investigated. Limited evidence from case control and cohort studies showed no increased risk of bleeding due to *H. pylori* infection in patients taking anticoagulants.⁵⁰ More studies are needed since the magnitude of bleeding risk with anticoagulants may mask the effect of *H. pylori* infection.

Statement 11: Long-term treatment with PPIs alters the topography of *H. pylori* gastritis.

Agreement 94%

Grade A1

PPI use suppresses gastric acid secretion with resultant persistent hypergastrinaemia in all. The gastrin levels are higher (about 1.5-fold) in patients colonised by *H. pylori* compared with uninfected patients. *H. pylori*-positive patients show more enterochromaffin-like (ECL) cell hyperplasia in the gastric corpus than uninfected PPI users (OR for prevalence ~2.5, *H. pylori* positive vs *H. pylori* negative).⁵¹ Long-term PPI treatment is associated with the spread of gastritis from antrum to corpus, and increased body atrophic gastritis (OR of 11.5 for RR of atrophy (95% CI 6.3 to 21.0) when comparing *H. pylori* positive vs *H. pylori* negative cases), and an approximately 2–3 fold increase in mean corpus atrophy score when comparing *H. pylori* positive versus *H. pylori* negative cases on PPIs.⁵¹ Caveats concerning these studies of the effects of PPIs on the topography of *H. pylori*-associated gastritis are that they were mostly conducted in Europe or the USA, and that there have been no significant advances published on this topic since the last Maastricht V in 2017.¹ Because atrophy is an early stage in the pathway to gastric cancer, the concern that PPI use increases gastric cancer risk in *H. pylori* positive patients was raised by early studies. This has been much debated in recent years, stimulated by several recent retrospective cohort and case-control studies identifying a possible association of PPI use with gastric cancer development.^{52 53} However, the literature is difficult to interpret, due to confounding by indication for PPI use and in most cases unknown *H. pylori* status. Adding further complexity, hypochlorhydria from PPIs or loss of parietal cell mass from other causes (including *H. pylori*-associated atrophy) has also been associated with changes in the non-*H. pylori* gastric microbiome.⁵⁴ The precise relationships between changes in the gastric microbiome, altered topography of gastritis and subsequent gastric mucosal atrophy and preneoplasia development (all of which correlate with persistent *H. pylori* infection) remain to be fully elucidated.

Statement 12: *H. pylori* eradication improves gastritis in long-term PPI users.

Agreement 97%

Grade A1

Long-term PPI use shifts gastritis from an antrum-predominant to corpus-predominant pattern and increases gastrin levels.

H. pylori eradication improves gastritis in long-term PPI users.^{51–53 55–58}

Statement 13: *H. pylori* eradication is recommended for patients with unexplained iron deficiency anaemia (IDA), idiopathic thrombocytopenic purpura (ITP) and vitamin B₁₂ deficiency.

Agreement 97%

Grade A1

There are recent meta-analyses representing the beneficial effects of eradicating *H. pylori* infection in improving IDA and ITP, although the results were heterogeneous. Concerning IDA, meta-analyses have shown that eradication improves anaemia and increases haemoglobin levels in those with moderate to severe anaemia. Recent guidelines on the management of IDA recommend eradication of *H. pylori*, where present, in patients with recurrent IDA with normal upper GI endoscopy and colonoscopy results. The main benefits for IDA are obtained in children in contrast to adults.^{59–61} On the contrary the main benefits for ITP are achieved in adults. Thus, recent studies have shown increased platelet counts in such patients treated for *H. pylori* and furthermore increased response rates in countries with a high prevalence of *H. pylori* infection in the background population. ITP patients with atrophic gastritis are more likely to respond to *H. pylori* eradication therapy. Finally, some 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. However, the data on *H. pylori* eradication, concerning B₁₂ deficiency, are less robust.^{62–64}

Statement 14: *H. pylori* eradication is the first-line treatment for localised low-grade gastric MALT lymphoma. *H. pylori* eradication therapy is also recommended for cases without evidence of *H. pylori* infection and may provide benefit even for more advanced staged disease

Agreement 100%

Grade A1

The success of *H. pylori* eradication as the initial therapy for MALT-lymphomas (marginal zone B-cell lymphoma) results in 70%–80% long-term remission and has since many years become well established as standard of care.^{65–67} Caveats about cases with the 11:18 translocation being unlikely to respond to *H. pylori* eradication therapy persist. Close endoscopic follow-up (3–6 months) to evaluate regression and surveillance for other premalignant lesions is advisable, given the increased risk also of gastric adenocarcinoma in these patients. Recent European Society for Medical Oncology (ESMO) guidelines emphasise that *H. pylori* should be thoroughly sought in cases of gastric lymphomas (if negative in tissue, should then investigate by serology, stool and breath tests). Post-treatment testing to ensure eradication is mandatory; second-line treatments should be used if infection persists. Endoscopic remission may take a year or more to achieve.⁶⁷ *H. pylori* negative cases deserve special attention. A meta-analysis reports a 30% complete response rate even in apparently *H. pylori*-negative cases treated with eradication therapy, supporting eradication therapy as initial treatment also in *H. pylori*-negative cases.⁶⁸ This is congruent with a recent US series published subsequently.⁶⁹ ESMO guidelines⁶⁷ support waiting 3–6 months after eradication to assess regression in *H. pylori*-negative patients before starting other treatment—usually radiation for localised disease, chemotherapy for more advanced cases. ESMO guidelines have now extended this recommendation for *H. pylori* eradication to all cases of gastric marginal

zone B-cell lymphoma (the preferred WHO term), regardless of stage⁶⁷ due to the occasional response even in some cases of disseminated disease.^{65 66 70–72} Unlike the association of Cag-carriage and VacAs1/m1/i1 type with gastric adenocarcinoma, no specific *H. pylori* gene products are linked to lymphoma development.⁷³

Statement 15: *H. pylori* has been positively and negatively associated with some extra-gastrointestinal disorders. However, the causality of these associations has not been definitively proven.

Agreement 90%

Grade D2

Apart from few well-defined clinical conditions associated with *H. pylori* infection reported in statement 13 there remains uncertainty and frequent contradictory findings about the role of *H. pylori* as potential trigger for extragastrointestinal diseases. Comprehensive reviews have extensively dealt with this intriguing issue reporting pros and cons.^{74–76} *H. pylori* infection has been positively associated with cardiovascular diseases (acute coronary syndrome, ischaemic stroke), metabolic disorders (metabolic syndrome, insulin resistance, diabetes mellitus), neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, multiple sclerosis), migraine, chronic urticaria and rosacea. References on these associations are provided in online supplemental table 5. Nonetheless, these associations are not sufficient to demonstrate a causal link which warrants *H. pylori* eradication. Inverse (negative) associations have also been described between *H. pylori* infection and a number of extra-gastrointestinal disorders. For instance, declining rates of *H. pylori* infection in some countries have been suggested to interfere with an increasing prevalence of asthma and other atopic conditions, obesity and IBD.^{75 77–79}

Statement 16: The COVID-19 pandemic has negatively impacted the management of *H. pylori*-related diseases.

Agreement 86%

Grade A1

COVID-19 has negatively influenced the prevention and management of multiple conditions including *H. pylori*-related diseases. Many cancer preventative and screening activities, including those for colorectal cancer, have been modified or even temporarily stopped, followed by more intensive catch-up testing in periods of improvement of the epidemiological situation. The number of planned outpatient consultations have been decreased during the pandemic, including the number of gastroenterology consultations.⁸⁰ Breath testing has been stopped in many units across Europe, expecting to result in decreased quality of *H. pylori* diagnosis as less accurate tests may have been used instead. There is a negative influence of COVID-19 reported on the cancer detection rates.⁸¹ It must be noted that by taking adequate care of hygienic and sterilisation techniques, the risk of COVID-19 transmission when performing endoscopy was low.⁸²

WG 2: DIAGNOSTICS

Statement 1: In young dyspeptic patients (age below 50) with no specific risk and no alarm symptoms, non-invasive testing for *H. pylori* infection is recommended.

Agreement 97%

Grade A1

Several non-invasive tests are available that can detect *H. pylori* infection with high sensitivity and specificity.⁸³ These

include ^{13}C urea breath test (UBT), stool antigen tests (SAT), and serological tests for IgG anti-*H. pylori* antibodies. IgG antibody tests do not differentiate between active and prior infections and are therefore not suitable to evaluate the success of eradication treatments. All tests have specific limitations in certain groups of patients. In regions/populations with low *H. pylori* prevalence, the probability of false-positive advises a confirmatory test. The age threshold of 50 years may vary between 45 and 55 years depending on different countries and regions in relation to the age risk for gastric cancer.

Statement 2: In dyspeptic patients older than 50 years, upper GI endoscopy is required. Functional serology may be considered as complementary diagnostic tool.

Agreement 94%

Grade B1

The risk of gastric cancer increases with age.^{84 85} In dyspeptic patients older than 50 (45–55) years, particularly with coexisting risk factors, upper GI endoscopy is recommended. Gastric functional serology (ie, pepsinogen I–II, and gastrin 17) may provide complementary diagnostic information, potentially useful in patients' follow-up. In the non-invasive assessment of corpus atrophy, functional serology has shown high level accuracy (96%) and very high negative predictive value (98%).⁸⁶

Statement 3: When endoscopy is indicated it should: (1) apply the best available technologies; (2) include biopsy sampling. Biopsy samples, as obtained in accordance with validated protocols, should result in both aetiological diagnosis and gastritis staging. Any focal lesions should be additionally sampled.

Agreement 100%

Grade A2

Gastric endoscopic inspection combined with biopsy sampling is the most reliable, sensitive and specific diagnostic procedure in the assessment of patients with alarm gastro-oesophageal symptoms.^{87–89} Regardless of clinical indication(s),^{87–91} upper GI endoscopy should accomplish specific quality requirements⁹²: (1) washing of the mucosa (performed regardless of local constraints); (2) adequate time of inspection; (3) endoscopic assessment of all the different gastric mucosa compartments (oxyntic vs antral); (4) photographic recording. After proper training, high-resolution endoscopy (implemented by virtual chromoendoscopy) improves the diagnostic performance and provides a reliable assessment of both inflammatory lesions, mucosal atrophy and focal abnormalities. Endoscopy enables obtaining biopsy specimens for either gastritis phenotyping/staging, and microscopic profiling of any focal lesion.^{90–95} At least two biopsies should be obtained from both functional compartments, antrum and fundus, and the samples should be submitted in different containers.^{89–91} An additional biopsy obtained from the incisura results in a biopsy-set adapted to gastritis histological staging, that is, OLGa (Operative Link on Gastric Atrophy) and OLGIM (Operative Link on Gastric Intestinal Metaplasia).^{95 96} Additional tissue specimen(s) should be taken to assess the *H. pylori* status.⁹³ Focal lesions, potentially harbouring dysplasia, must be separately identified and submitted for microscopic phenotyping and possible endoscopic submucosal dissection (ESD).⁹⁷

Statement 4: UBT remains an important tool for *H. pylori* diagnosis before and after eradication therapy. Citric acid (CA) is an essential component of the protocol.

Agreement 87%

Grade A1

The ^{13}C -UBT is widely employed for the diagnosis of *H. pylori* infection as well as to verify successful eradication after

treatment. In order to overcome some of the challenges associated with the test, and to improve accuracy and sensitivity, CA has been suggested to be more favourable than other test meals, such as the standard semi liquid meal, semi-fatty acid meal and orange or apple juice.^{16–18 98 99} CA helps slow gastric emptying, enhances gastric distribution of the substrate and increases its contact time with *H. pylori* urease.^{99 100} The test meal may also inhibit antral motility and relax the gastric fundus. In addition, CA is cheaper than other test meals and is more palatable when sweeteners are added.^{98 100} One report found an increase in urease hydrolysis with CA which was not attributable to delayed gastric emptying.¹⁰¹ Studies performed in Asian populations have reported a limited difference in the performances of UBT with or without CA.¹⁰² However other studies found particularly in conditions of atrophy that the use of CA test meal improves ^{13}C -UBT sensitivity.^{103 104}

Statement 5: Monoclonal SAT, if properly validated, is an appropriate test before and after *H. pylori* treatment

Agreement 96%

Grade A1

Active *H. pylori* infection of the stomach results in shedding of bacterial antigens in the patient's stool. Multiple tests can detect *H. pylori*-specific antigens (eg, catalase) in stool, providing a convenient non-invasive diagnostic tool¹⁰² that is suitable for patients before and after eradication.^{103 104} Early tests relied on antigen detection with polyclonal antisera, but more recent tests that use monoclonal antibodies are superior in comparative studies.¹⁰² Available SATs for *H. pylori* include both enzyme immuno assay (EIA) test kits for use in laboratories, as well as rapid immunochromatography tests for near patient testing by the gastroenterologist or general practitioner.^{102 105} In most comparative studies, laboratory-based EIA tests performed better than rapid tests,^{103 106 107} but the best rapid tests do have acceptable performance for clinical diagnostic use.^{108 109} Results vary substantially between the different available rapid tests. For most tests, sensitivity was more problematic than specificity, and users should be aware of the limitations of the specific test used.^{105 106}

Statement 6: Gastric functional serology (pepsinogens I–II and gastrin levels), anti-*H. pylori* antibodies, anti-intrinsic factor and antiparietal cell auto-antibodies (APCA) may provide clinically valuable information on the likelihood of gastric mucosal atrophy, including its aetiology.

Agreement 98%

Grade A1

Gastric mucosal atrophy, due to long-standing, non-self-limiting mucosal inflammation, recognises two main aetiologies: *H. pylori* and autoimmunity.² The two conditions are distinguished by the topography of the inflammatory/atrophic lesions. Inflammation/atrophy due to *H. pylori* infection first involves the distal stomach (antrum) and later spreads to proximal (fundic) mucosa whereas by definition, autoimmune gastritis (AIG) is 'restricted' to the oxyntic (fundus/corpus) mucosa. Gastric functional serology (pepsinogens I–II, and their ratio), gastrin 17 (primarily increased in autoimmune atrophy), and APCA may reliably distinguish the two aetiological forms.¹¹⁰ Pepsinogen serology and APCA are also useful in the follow-up of AIG.¹¹¹ Pepsinogen serology may differentiate autoimmune from *H. pylori* gastritis, also providing useful information on the clinical profiling of the most advanced atrophic stages.¹¹² Serum pepsinogens are useful for detecting AIG in patients affected by

autoimmune thyroiditis.¹¹³ The clinical importance of intrinsic factor antibodies is limited due to possible occurrence of late-stage seroconversion.¹¹⁴ APCA positivity levels do not correlate with severity of atrophy,¹¹⁵ while they do fit with pepsinogen levels.^{110 111}

Statement 7: Molecular methods (in particular, real time-PCR, whole-genome sequencing and digital PCR) allow detection of *H. pylori* mutations associated with resistance to clarithromycin, levofloxacin, tetracycline and rifampicin.

Agreement 100%

Grade A1

The prevalence of antibiotic resistance in *H. pylori* has steadily increased over the last four decades.¹¹⁶

The gold standard for antibiotic susceptibility testing are phenotypical methods, that is, agar dilution testing, which requires culture of the organisms and are time-consuming and labour-intensive. There is a substantial need for culture-independent methods to predict antibiotic resistance. *H. pylori*'s mechanisms of resistance against antibiotics are now largely known.¹¹⁷

Detection of resistance against several antibiotics can now be achieved by detection of different mutations or other genetic changes, such that the correlation between genotypes and phenotypes can be either relatively straightforward (eg, for clarithromycin and fluoroquinolones), or highly complex (eg, for metronidazole). As a result, the accuracy of the molecular detection methods for predicting antibiotic resistance varies widely between different antibiotics.¹¹⁸

Resistance against clarithromycin is, with very few exceptions, due to mutations in the 23S rRNA gene. Relatively few mutations (most importantly, A2143G, A2142G and A2142C) are responsible for almost all clinical resistance.¹¹⁷ Similarly, resistance to levofloxacin is mostly due to point mutations in the gyrase gene *gyrA*, so that PCR or sequencing-based tests can also predict quinolone resistance with good accuracy.^{118 119}

Resistance to tetracycline is mostly due to mutations in 16S rRNA genes, and to rifampicin due to mutations in the RNA polymerase gene *rpoB*.¹¹⁷ Fewer data are available for these two antibiotics, but molecular methods can also predict resistance against these in most cases. Importantly, resistance to metronidazole is highly complex. While some mutations (in particular in the *rdxA* gene) are highly predictive of metronidazole resistance, many other genes can also have an impact on metronidazole susceptibility, such that the sensitivity of assays for specific genetic changes is low with respect to the metronidazole resistance phenotype. The situation is comparable for the rare cases of amoxicillin resistance. Whole genome or focused next generation sequencing bears promise to permit more precise prediction of antibiotic resistance phenotypes, including those with many contributing mutations, such as metronidazole or amoxicillin resistance. First studies have been reported with promising results.^{120–124}

Statement 8: Gastric biopsies recovered from rapid urease tests (RUT) can be used for molecular testing by PCR.

Agreement 100%

Grade B2

Rapid urease testing is widely used for the diagnosis of *H. pylori* infection. Most often, test tubes are discarded after reading of results, and molecular tests are performed using further biopsies. PCR-based methods are widely used to confirm diagnosis of *H. pylori* and so, instead of taking

additional biopsies for PCR or other tests, those taken from RUT can be reused^{125–128} for detection of *H. pylori* and of the mutations associated with clarithromycin resistance. The correlation observed between the reuse of gastric biopsies from RUT for molecular tests after storage at room temperature for 30 days was 93%.¹²⁵ In patients with RUT negative samples, reuse of RUT gastric biopsies for PCR testing will be particularly helpful to confirm *H. pylori* infection. In addition, it reduces cost and burden to both the physician and the patient. Gastric biopsies reuse for PCR testing is also particularly useful in areas where *H. pylori* infections are prevalent and facilities for culture and susceptibility testing.¹²⁵

Statement 9: Clarithromycin susceptibility testing, if available through molecular techniques or culture, is recommended before prescribing any clarithromycin containing therapy.

Agreement 91%

Grade A1

The WHO and the European Union Council both advocate prudent use of antibiotics to avoid development of bacterial resistance, one of the biggest threats to global health.¹²⁹

Clarithromycin is currently a key antibiotic to eradicate *H. pylori*, but when resistance is present, the probability of treatment success is very low,¹³⁰ that is, this antibiotic becomes useless but continues to induce resistance in other bacteria. One option is to avoid this antibiotic but that leads to the need for quadruple therapies, which are effective treatments.¹³¹ However, this creates adverse effects especially on the gut microbiota and resistance of other bacteria,¹³² because quadruple therapies include three antimicrobial drugs, consequences which were not considered in the review mentioned before.¹³¹ To avoid this dilemma, a simple method is to test for clarithromycin susceptibility. Indeed, antimicrobial susceptibility testing is performed for any infectious disease when there is a risk of resistance. Furthermore, besides the standard method including culture and antibiogram, we now have access to molecular tests, especially real-time PCR kits which are commercially available and provide excellent sensitivity and specificity to detect both *H. pylori* and its clarithromycin susceptibility.¹³³ Such tests are also performed rapidly (in a few hours) and do not necessitate special transport conditions, in contrast to culture. The previous objection of non-availability is no longer true given that, following the COVID-19 pandemic, millions of real-time PCRs have been performed in virtually all laboratories. A recent systematic review and meta-analysis pointed out that the pooled RR of eradication in patients with susceptible vs resistant strains to clarithromycin was 0.682 (95% CI 0.636 to 0.731)¹³⁴ and in another study the OR for failure of clarithromycin-containing regimens was 6.97 (95% CI 5.23 to 9.28).¹³⁵ A clarithromycin resistance threshold of 15% was proposed in the past¹ but now this threshold has been exceeded in most WHO regions¹³⁵ which is a plea for systematic testing. A limit could be the need to perform an endoscopy which is considered unnecessary in young patients, with an age limit depending on the regional risk of gastric cancer. Progress has been made in DNA extraction and, consequently, PCR on stool is possible. A recent meta-analysis found a sensitivity of 91% and specificity of 97%.¹³⁶ Applying a systematic detection of clarithromycin resistance would allow the use of the optimised triple therapy for 60%–90% of patients, and therefore, limit the consequences of quadruple therapies.

Statement 10: In the short-term posteradication (4–6 weeks) follow-up, no antibiotics or bismuth should be used to permit optimum testing for *H. pylori*. PPIs should be stopped 14 days before testing

Agreement 96%

Grade A1

H. pylori treatment suppresses the infection in many cases even if eradication fails due to different factors, mostly related to antibiotic resistance. For this reason, absence of the bacteria at the end of treatment was named ‘clearance’ while absence after a period of 4–6 weeks following treatment is defined as ‘eradication’.¹³⁷ Such a drug-free period is necessary to exclude recrudescence of the bacteria which may occur with such time delay and potentially leads to false negative test results. Consequently, any drug having a negative impact on *H. pylori* growth, for example, antibiotics, bismuth (for at least 4 weeks) and PPI (for 14 days) must be avoided within the defined time frame. If pain relief is necessary, drugs that do not impact on *H. pylori*, for example, H₂ Receptor Antagonist (H₂ RA),¹³⁸ gastric mucosal protective or antacid medications can be prescribed. Serology cannot be used for testing the eradication success.

Statement 11: Tests for serum IgG antibodies against *H. pylori* can serve as a screening test in specific clinical situations.

Agreement 91%

Grade A1

Clinical conditions where serological tests can be of particular value include bleeding peptic ulcers, gastric MALT lymphoma, gastric cancer, atrophy, recent use of antibiotics or PPI.^{83 139–141} Importantly, serology does not indicate an active infection, because the antibodies decrease slowly after eradication of the bacteria and a positive test can still be observed after several months. Therefore, serology is not suitable for posteradication confirmation.

Other limits are that *H. pylori* strains are diverse, and it is necessary to use locally validated tests. Indeed, it has been shown that the tests using antigens from Western countries may lead to poor results in Asian countries. It is also important to have a well-validated cut-off level for positivity. Despite that, equivocal results may still be obtained requiring a further follow-up.

Several antigen combinations have been used to look for markers of evolution to gastric cancer but none can be recommended for current use.

Statement 12: Gastric mucosal atrophy is defined as ‘loss of native glands’. Atrophy is the major determinant of non-hereditary gastric cancer risk assessed by endoscopy and histology, and it may be complementarily assessed by gastric functional serology.

Agreement 100%

Grade A1

Longstanding *H. pylori* gastritis and AIG can both result in loss of native gastric glands, that is, mucosal atrophy. Atrophy is the cancerisation field of non-hereditary/non-syndromic gastric adenocarcinoma. Glandular loss includes two main histological variants: (1) disappearance (ie, shrinking) of glandular units, replaced by fibrosis of the lamina propria, (2) metaplastic replacement of the native glands (2a) Intestinal metaplasia (IM)¹⁴²; (2b) pseudopyloric metaplasia (spasmolytic polypeptide-expressing metaplasia (SPEM)).^{142–144} Interobserver histological reproducibility of the atrophy assessment, as supported by morphometric studies, prompts the prioritisation of appropriate training.^{143 144} The histological score of atrophy includes all atrophy microscopic subtypes, which should be scored as overall percentage occurring in the available biopsy specimens (distinguishing

oxyntic vs the mucous secreting compartment, which should be submitted in separate containers).^{145–147} Atrophy score(s) establish the histological gastritis stage (OLGA or OLGIM). Histological gastritis staging is consistently recognised as a reliable predictor of the gastric cancer risk.^{148 149} Serum pepsinogens have a strong correlation with OLGA/OLGIM III/IV gastritis stage and provide reliable information concerning the presence of severe atrophy. Their use in screening for severe atrophy or for improving accuracy of the histological assessment if atrophic changes have a patchy distribution is worth considering.^{150–152}

Statement 13: The histological assessment of atrophy should result in a conclusive gastritis staging (OLGA/OLGIM), which consistently ranks the patient-specific cancer risk. Histological staging makes IM subtyping clinically redundant.

Agreement 97%

Grade A1

Gastritis staging is based on the average of the atrophy score values as separately obtained from the mucosa of the gastric antrum (distal mucus-secreting stomach, including the angularis incisura) and the corpus/fundus (proximal oxyntic stomach). OLGA staging includes the histological assessment of all atrophy subtypes (ie, metaplastic and non-metaplastic)¹⁵³ while OLGIM staging only considers IM.¹⁴⁹ Both staging systems do not require IM subtyping.¹⁵⁴ A meta-analysis of prospective case–control studies has consistently demonstrated the significant association between the OLGA/OLGIM stages III/IV (ie, high-risk stages) and gastric cancer risk.¹⁵⁵ OLGIM has been considered more reproducible than OLGA; the OLGIM-score, however, does not include the assessment of pseudo-pyloric atrophy (synonym: SPem), that has been claimed to be a precancerous lesion.¹⁵⁶ In two cohort studies (218 patients), the RR of gastric epithelial neoplasia associated with OLGA III–IV was 27.70 (95% CI 3.75 to 204.87); in another cohort study (125 patients) the RR of high-grade dysplasia associated with the high-risk OLGIM-stage was 16.67 (95% CI 0.80 to 327.53).¹⁵⁵

Statement 14: In *H. pylori*-negative gastritis (primary or after eradication), clinically suspected AIG requires testing for gastrin, pepsinogens ratio and auto-antibodies to intrinsic factor and parietal cells. Clinical factors and functional serology may provide the rationale for any further need for endoscopy/histological assessment.

Agreement 91%

Grade B2

The prevalence of autoimmune gastritis (AIG) ranges between 0.5% and 4.5% with significant variations according to geographical regions.¹⁵⁷ AIG is mostly associated with autoimmune comorbidities, prevails in females and increases with age.¹⁵⁷ By definition, ‘primary’ AIG, is topographically restricted to oxyntic mucosa where it features either non-atrophic or atrophic phenotypes. ‘Secondary’ immune-mediated gastritis may be triggered by *H. pylori* infection.¹⁵⁸ The clinical suspicion of AIG requires testing for anaemia and serology (pepsinogens, gastrin 17, autoantibodies against intrinsic factor and parietal cell).¹⁵⁹ In primary AIG, the risk of adenocarcinoma is controversial, but it is consistently believed to be lower than in multifocal atrophy (involving antral and corpus mucosa) that results from longstanding *H. pylori* infection.¹⁶⁰ Solid evidence associates AIG to the increased risk of neuroendocrine tumours, mostly Type I so-called ‘carcinoids’.¹⁵⁹ The initial assessment of gastric autoimmunity is based on symptoms which may include anaemia and comorbidities.¹⁵⁷ Endoscopy includes biopsy sampling from both antral and oxyntic mucosa (according to Sydney or Kimura protocols), which strictly require submission in two separate

containers.^{8 161} Histological diagnosis is based on the features of oxyntic-restricted gastritis, with or without concurrent atrophy,¹⁵⁷ and should include immunohistochemical assessment of the ECL cells. The endoscopy follow-up schedule of primary (corpus-restricted) AIG is usually recommended every 2–4 years.

Serological follow-up (gastrin 17, pepsinogens I/II) can be useful for monitoring the gastric oxyntic-restricted atrophy.⁹ The follow-up schedule of ‘secondary’ autoimmune atrophic gastritis (involving both antral and oxyntic mucosa in *H. pylori* eradicated subjects) is plausibly consistent with that recommended for atrophic gastritis primarily due to *H. pylori*.^{94 115 162}

Statement 15: Currently, no large-scale trials have provided evidence that molecular biomarkers can reliably predict the risk of non-hereditary (ie, non-syndromic) gastric cancer.

Agreement 97%

Grade B2

While some observational studies^{163–167} as well as systematic reviews^{168–170} have shown an increased risk for gastric cancer associated with some molecular polymorphisms/dysregulations, no consistent evidence is available to suggest that genetic testing will predict individual risk for gastric cancer. Molecular testing for hereditary gastric cancer is a notable exception.

Statement 16: In *H. pylori*-eradicated patients, low-stage gastritis as properly assessed by endoscopy/histology, only requires clinical follow-up.

Agreement 100%

Grade B1

In the absence of risk-factors for surveillance (high scores of endoscopic assessment for IM/atrophy, AIG or family history of cancer) low-stage gastritis patients (OLGA 0-I) as assessed by proper work-up (ie, high-quality endoscopic/histological assessment)^{89 171} are at very low risk of developing gastric cancer and they should not undergo prescheduled endoscopy surveillance.^{163 172} Stage II gastritis in dyspeptic patients, and/or inadequate baseline work-up calls for reconsideration of the diagnostic work-up. While functional gastric serology (pepsinogen I–II, gastrin) should never be applied as a cancer-screening test, it can be considered for support of the clinical follow-up.¹⁷³

Statement 17: After successful *H. pylori* eradication, patients with high-stage (OLGA/ OLGIM III–IV) gastritis and/or extensive endoscopic atrophy are still at risk for gastric cancer. The timing of the endoscopic/histological surveillance is based on the gastritis stage as assessed at the last check-up.

Agreement 100%

Grade B1

H. pylori infection is consistently recognised as the most important risk factor for sporadic gastric cancer.^{1 2} However, even after successful eradication patients found to have OLGA/ OLGIM stage III/IV^{174–177} and/or showing extensive endoscopic atrophy,^{148 178–180} remain at increased risk of cancer progression.

OLGA or OLGIM are corresponding histological staging systems to assess the grade of atrophy severity. While IM is a component of atrophy and thus comprised also inside the OLGA staging system in the OLGIM staging IM is the only parameter. OLGA therefore is the comprehensive definition of atrophy (includes SPEM an IM) and may become apparent earlier. Both systems allow to identify patients at increased risk for gastric cancer and thus require surveillance. The timing of the follow-up schedule should apart from specific personal conditions (eg, familial gastric cancer risk) be 3 years as detailed in the European MAPS II guidelines.^{89 179 180}

Statement 18: Low-grade and high-grade intra-epithelial neoplasia requires: (1) confirmatory histological assessment, (2) gastric mapping by high resolution endoscopy and (3) targeted Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection (ESD), particularly for high grade, in tertiary endoscopy centres. Ablation does not abolish metachronous cancer risk. *H. pylori* eradication and postablation surveillance are both mandatory.

Agreement 100%

Grade A1

Even after successful *H. pylori* eradication, intra-epithelial neoplasia (synonym: dysplasia), poses a significant risk for progression to invasive cancer. *H. pylori* eradication always has to be confirmed and a confirmatory endoscopic/histological assessment is advisable. In high-grade dysplasia, the risk of cancer (either synchronous and/or metachronous) is very high, and the endoscopic/histological follow-up should be scheduled accordingly.^{181–183} Endoscopic mapping is mandatory (high-magnification endoscopy in tertiary endoscopy centres), and each biopsy specimen must be topographically identified.

Dysplasia (presence and grading) requires a confirmatory second opinion. EMR or submucosal dissection is the first therapeutic option (depending on the endoscopic characteristics of the lesion). Most dysplastic lesions occur against a background of high-stage gastritis (OLGA/OLGIM stage III/IV). After successful ablation, the risk of metachronous cancer requires endoscopic surveillance.^{183–186} The timing of endoscopic surveillance is based on the gastritis stage (endoscopy and/or histology).

WG3: TREATMENT

Preamble

The goal of any antimicrobial therapy is to cure reliably *H. pylori* infection in the majority (eg, $\geq 90\%$) of patients. This requires the use of antimicrobials to which local infections are susceptible. The physician gains knowledge about population antimicrobial resistance by several methods. Antimicrobial susceptibility testing can be performed on *H. pylori* strains from infected patients by molecular testing, most relevant for clarithromycin or by culture followed by antibiogram which concerns all of the antibiotics. A number of commercial kits are available that allow testing for clarithromycin (and possibly quinolone) susceptibility using PCR. PCR is now available in almost all hospitals making this a simple procedure.

Another possibility, much less accurate, is to look at the prevalence of clarithromycin (and quinolone) resistance in other organisms in the community such as respiratory pathogens. The third, widely available to all, is to look at the results of the eradication therapy which is routinely performed for all patients, and share the data. Treatment failure with an otherwise optimised therapy provides a strong indication of the presence of resistance and that therapy should no longer be recommended and used unless local susceptibility is proven by culture or molecular testing.¹⁸⁷

Statement 1: It is reasonable to recommend that susceptibility tests (molecular or after culture) are routinely performed, even before prescribing first-line treatment, in respect to antibiotic stewardship. However, the generalised use of such a susceptibility-guided strategy in routine clinical practice remains to be established.

Agreement 91%

Grade D2

Resistance of *H. pylori* to antibiotics has reached alarming levels worldwide.¹³⁵ Local surveillance networks are required to select appropriate eradication regimens for each region. Tailoring treatment of *H. pylori* infection based on systematic antimicrobial susceptibility testing is useful to limit the increase

of global antibiotic resistance by avoiding the use of unnecessary antibiotics. However, whether patients should systematically undergo an upper endoscopy for bacterial culture (or molecular techniques such as PCR) before administering *H. pylori* eradication treatment in clinical practice remains a contentious debate.¹⁸⁸ The advantages and limitations of the susceptibility-guided and the empirical strategies are summarised in online supplemental table 2¹³¹ On one hand, local resistance patterns and the efficacy rates in the context of a specific environment are essential for establishing a correct treatment of the infection in real-world settings. Susceptibility testing has been proposed, especially for clarithromycin, by using molecular testing which provides a result at the same time as *H. pylori* detection. Clarithromycin resistance is all or none, such that if clarithromycin resistance is present, clarithromycin will not have any role for eradication. On the other hand, unfortunately, susceptibility to clarithromycin in vitro does not necessarily lead to eradication in vivo because of a few other causes of eradication failure. Furthermore, endoscopy has several disadvantages: it is expensive and uncomfortable. In addition, it frequently involves prolonged waiting times. Furthermore, since most endoscopy findings are normal, they do not contribute to management. In summary, although performing an endoscopic evaluation of the upper GI tract in all dyspeptic patients is a theoretical option, it is not always possible in practice.

Several diagnostic strategies have been proposed for selecting patients with dyspeptic symptoms who are expected to benefit most from endoscopy. The “test-and-treat” strategy is based on searching for *H. pylori* and its subsequent eradication when detected. Several decision analyses and prospective studies support the use of the test-and-treat strategy for dyspeptic patients, and it has been recommended by all international consensus conferences.²¹ Considering that dyspepsia is the main indication for *H. pylori* eradication, a contradiction exists in recommending a susceptibility-based strategy and the test-and-treat strategy, as culture (or PCR) if susceptibility testing requires endoscopic evaluation to obtain biopsies. However, more recently, non-invasive methods to evaluate antibiotic susceptibility, such as stool samples, have recently been developed.¹⁸⁸

Several meta-analyses have compared cure rates for susceptibility-guided versus empirical therapy for *H. pylori* first-line treatment, but all suffer significant limitations. The first meta-analysis focused specifically on first-line treatment.¹⁸⁹ Only five RCTs were included, and the authors concluded that culture-guided triple therapy was more effective than standard triple therapy for first-line treatment. The second meta-analysis selected RCTs and analysed separately for first- and second-line treatments. In first-line treatment (nine studies), susceptibility-guided therapy was more efficacious than empirical 7–10 days triple therapy (which was the regimen prescribed in most studies). The third meta-analysis included both RCT and non-RCTs (nine studies in total).⁸ First-line tailored therapy achieved higher eradication rates than empirical regimens. Finally, another meta-analysis, only assessed first-line treatments and better overall efficacy was seen with the susceptibility-guided strategy (although the results were borderline statistically significant).¹⁹⁰ However, when prescribing only empirical first-line quadruple regimens (both with and without bismuth, excluding the suboptimal triple therapies) not based on CYP2C19 gene polymorphism, no differences in efficacy were found vs the susceptibility-guided group (online supplemental figure 1); this lack of difference was confirmed when only RCTs were included. Therefore, these authors concluded that susceptibility-guided treatment was not better than empirical treatment of *H. pylori*

infection in first-line if the most updated quadruple regimens are empirically chosen.¹⁹⁰

These different studies, which have evaluated the cost-effectiveness of *H. pylori* susceptibility-guided treatment in the era prior to the availability of non-invasive next generation sequencing of stools have shown contradictory results.¹³¹ An eradication strategy based on culture or molecular susceptibility testing consists of several parts, each of which has a precise cost, including procedures and regimens.¹⁹¹ Also, *H. pylori* antibiotic resistance varies geographically, which may limit the applicability of the results of the cost-effective analyses in other populations. Furthermore, savings of a strategy are linked with the characteristics of the specific practice setting; for example, performing pretreatment susceptibility testing in patients with previous, independent indication of upper endoscopy would be obviously more cost-effective.¹⁹¹ Finally, the cost-effectiveness may vary according to the cost of care in a given country, and therefore the same conclusion may not be applied to other settings.

In summary, it is appropriate to recommend that susceptibility tests (culture or PCR) are routinely performed, even before prescribing first-line treatment, in respect to antibiotic stewardship. This provides opportunity to evaluate the prevalence of antibiotic resistance in naïve patients and influence of any such resistance on the effectiveness of up-to-date first-line eradication treatments. Successful integration of susceptibility guided strategy will depend on the rapidity of the spread and acceptability of these methods. Practical, economical and logistical issues will need to be evaluated and addressed according to the target population and the clinical situations to allow prescription of the most effective first-line *H. pylori* eradication treatments—that is, those regimens that have been shown to achieve cure rates $\geq 90\%$ in the local setting (figure 1) treatment algorithm. This also necessitates monitoring *H. pylori* cure rates of our clinical practice, should be continuously audited to confirm that we always maintain a high success rate.

Statement 2: If individual susceptibility testing is not available, the first-line recommended treatment in areas of high (>15%) or unknown clarithromycin resistance is bismuth quadruple therapy (BQT). If this is not available, non-bismuth concomitant quadruple therapy may be considered.

Agreement 92%

Grade B1

If susceptibility testing is not yet available, the clinician has to rely on the prevalence of antibiotic resistance in the population being treated and current local cure rates of specific regimens. If this is unknown, a high prevalence of clarithromycin resistance should be assumed. A high prevalence of clarithromycin resistance would result in a high rate of eradication failure if using clarithromycin-containing regimens. This is certainly the case with clarithromycin-containing triple therapy or sequential therapy, where success was only 43% and 75%, respectively, against clarithromycin resistant strains.¹⁹²

Non-bismuth quadruple concomitant therapy has superior outcomes when compared with sequential therapy in head-to-head trials against clarithromycin resistant strains (92% vs 62%, respectively).¹⁹³ It also works well in metronidazole resistant, clarithromycin susceptible cases because of its PPI-amoxicillin-clarithromycin component. Indeed, concomitant therapy was the only therapy other than BQT that consistently achieved eradication success in >90% in all the regions of Europe in the European Registry on *Helicobacter pylori* Management (Hp-EuReg).^{194 195} However, with this regimen, all patients are exposed to at least one unnecessary antibiotic, be it clarithromycin in clarithromycin-resistant cases or metronidazole in

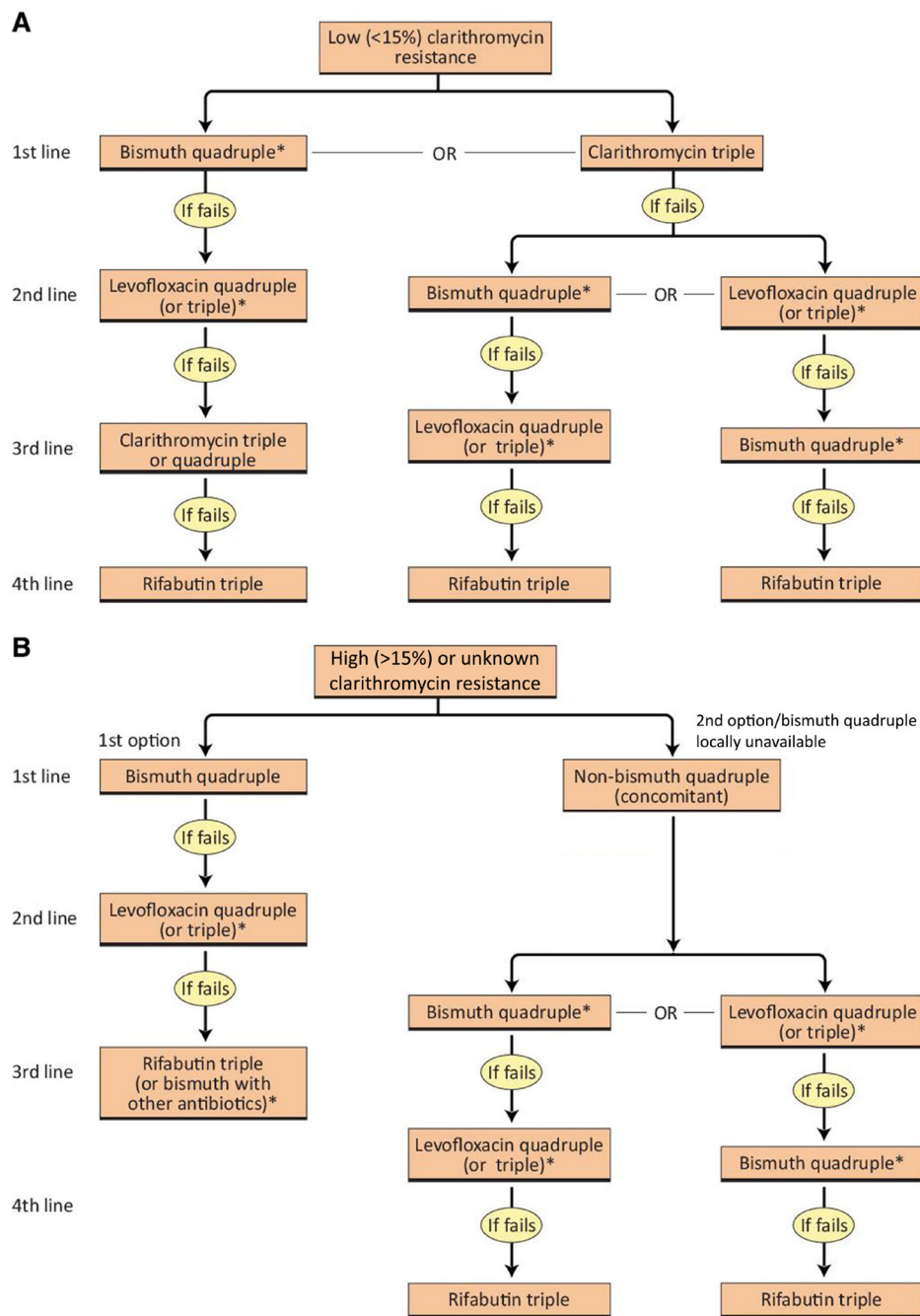


Figure 1 Algorithm for empirical *Helicobacter pylori* eradication if individual antibiotic susceptibility testing is not available. Bismuth quadruple: proton pump inhibitor (PPI), bismuth, tetracycline and metronidazole. Clarithromycin triple: PPI, clarithromycin and amoxicillin; only use if proven effective locally or if clarithromycin sensitivity is known. Non-bismuth quadruple (concomitant): PPI, clarithromycin, amoxicillin and metronidazole. Levofloxacin quadruple: PPI, levofloxacin, amoxicillin and bismuth. Levofloxacin triple: the same but without bismuth. In cases of high fluoroquinolone resistance (>15%), the combination of bismuth with other antibiotics, high-dose PPI-amoxicillin dual or rifabutin, may be an option. *High-dose PPI or P-CAB (vonoprazan where available) plus amoxicillin may be another option. P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

metronidazole-resistant cases, which may contribute to global antimicrobial resistance.¹⁹⁶

BQT functions very well with consistent >90% eradication rates,^{194 195} as it avoids clarithromycin resistance and usually overcomes metronidazole in vitro resistance, as demonstrated by its high efficacy in spite of significant metronidazole resistance in Europe. Although there are no unnecessary antibiotics administered with this regimen, there is a larger pill burden which can sometimes discourage patients. Pylera is a three-in-one capsule formulation of this combination aimed at

reducing pill burden with a >90% success rate in over 5000 patients in clinical practice.¹⁹⁵ The widespread use of BQT is limited however because bismuth, tetracycline or Pylera are not universally available.

If individual susceptibility testing is not yet available, the first line recommended treatment for areas of high (>15%) or unknown clarithromycin resistance is BQT. If this is not available, non-bismuth concomitant quadruple therapy may be considered. Local success rates should be monitored to confirm that these were the correct choices.

The prevalence of *H. pylori* resistance to both clarithromycin and metronidazole (dual resistance) is also an important consideration. Concomitant therapy is ineffective against dual resistant strains. A recent review found a success rate of only 79%, leading to a suggestion that this combination should not be used if the prevalence of dual resistance is >15%.¹⁹³ BQT was considered the first line treatment for areas of high dual resistance in the last European consensus report.¹ Other regimens potentially useful in this situation would be high-dose PPI-amoxicillin dual therapy or rifabutin triple therapy as these avoid the issue of clarithromycin and metronidazole resistance all together. Resistance to rifabutin or amoxicillin are very low.

However, the success rates of these regimens have not been consistently above 90% (8). Although rifabutin-based regimens appear effective, bone marrow suppression, although not common and seemingly always reversible, can occur with this drug.^{197–199} Further studies are required before a strong recommendation can be made for their use in first-line therapy, but in areas of high dual resistance (>15%), high-dose dual therapy can be considered as an alternative to BQT especially where bismuth, tetracycline or Pylera are not available. Because of potential adverse events with rifabutin-based regimens, further study is required before advocating them as a first-line alternative even in the setting of highly prevalent dual resistance. Fluoroquinolone-containing regimens should be reserved for rescue treatment given the already high or rapidly rising prevalence of quinolone resistance in the community and the possible adverse events observed.

Statement 3: The treatment duration of BQT should be 14 days, unless 10-day equally effective therapies are available.

Agreement 85%

Grade D2

Bismuth salts act locally and their bactericidal effects on *H. pylori* work through unclear complex mechanisms involving the bacterial wall and periplasmic space, and inhibition by several enzymes of ATP synthesis, gastric mucosa bacterial adherence, etc. No *H. pylori* resistance to bismuth has yet been reported.²⁰⁰ Bismuth subcitrate and bismuth subsalicylate are the two formulations commercially available and there are no head-to-head comparisons regarding their efficacy. Bismuth subcitrate salts, available as monodrug or associated in a single (three-in-one) capsule, are the main available presentations available and two meta-analyses have shown them safe and well tolerated for *H. pylori* eradication therapy.^{201 202}

Several studies have evaluated the optimum duration of BQT as well as the role of PPIs and metronidazole resistance in therapeutic efficacy, considering that bacterial resistance observed against tetracycline and bismuth remains negligible.^{203–205} A meta-analysis evaluating the efficacy, adverse events, and adherence related to first-line *H. pylori* quadruple eradication therapies found that BQT for 1–3 days, 4 days or 7 days was less effective than when given for 10–14 days.²⁰³ 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. Considering that metronidazole resistance is common, and the susceptibility testing is rare and sometimes showing controversial results, 14-day therapy is usually recommended.^{1 187 204 205}

Recently, a meta-analysis involving 30 studies (6482 patients) evaluated the efficacy and safety of 10-day BQT with a three-in-one single capsule (Pylera) plus PPI to eradicate *H. pylori*.²⁰² The intention-to-treat efficacy observed was 90% (95% CI 87%

to 92%, 21 studies) in first-line therapy, 89% (95% CI 86% to 93%, 12 studies) in second-line therapy and 82% (95% CI 78% to 87%, nine studies) in third-line therapy, with no differences between the type or dosage of PPI used. In 8/30 studies, the proportion of patients with metronidazole resistance was provided, and the therapeutic regimen showed a significant cure rate of *H. pylori* infection despite metronidazole resistance.²⁰² The clarithromycin resistance rate did not have any impact.

The Hp-EuReg has recently analysed the effectiveness and safety of 10-day single-capsule BQT in real-world use in European countries (mostly Spain, Italy and Portugal), where 2100 cases were studied: 64% in naive patients, 22% as second line and 14% as subsequent attempts.¹⁹⁵ The modified intention-to-treat efficacy achieved was 94.6% (95% CI 93.2% to 95.8%) in first-line therapy, 89.3% (95% CI 86.2% to 92.3%) in second-line therapy and 91.9% (95% CI 79.5% to 88.4%) as rescue treatments from third to sixth line.

Although culture to evaluate antibiotic resistance was performed in only 48/2100 cases, single-capsule BQT was effective (>90%) to eradicate the infection in those patients with bacterial resistance to either metronidazole or clarithromycin (or both). Compliance was considered excellent in 97% of cases.¹⁹⁵ A recent update of the Hp-EuReg reviewed 5068 patients treated with single-capsule bismuth-quadruple therapy.²⁰⁶ Overall, it achieved 92% modified intention-to-treat eradication rate, 94% as first-line treatment, 90% as second-line treatment and 86% as rescue treatments, with a favourable safety profile.

There are no direct comparisons between classical BQT and three-in-one bismuth-containing single capsule regimens lasting 10–14 days, and more studies should be done in populations to better define the optimum duration of BQT where the pattern of resistance is known.

In summary, the treatment duration of BQT should be 14 days. However, 10-day therapies have increasingly achieved very good and consistent results in different geographic areas.

Statement 4: In choosing a non-BQT, concomitant therapy (PPI, amoxicillin, clarithromycin and a nitroimidazole administered concurrently) should be the preferred choice given its proven reproducible effectiveness and less complexity compared with sequential and hybrid therapies.

Agreement 94%

Grade B1

Non-BQTs include sequential, concomitant and hybrid therapies. The disadvantage of these regimens is that they all include an unnecessary antibiotic, which would not be necessary if the susceptibility profile of the bacterium was known. Such treatment should be considered if antimicrobial susceptibility testing is not available and BQT is also not available.

The non-BQTs all work well against susceptible *H. pylori* strains as do conventional triple therapies. Their advantage over triple therapy therefore lies in the treatment of infections with unknown susceptibility profiles, or from regions with relatively high rates (>15%) of clarithromycin resistance. Non-BQTs have acceptable eradication success in these settings.^{192 193 207 208} They would not be ideal choices, for regions with high (>15%) dual resistance, where concomitant quadruple therapy was only successful in 68%–79% of cases.^{193 209}

When comparing the different non-BQTs, one must consider patient compliance, adverse events and eradication success. Sequential and hybrid therapies are more complex than concomitant in that they require a change in medication halfway through the treatment course. This can risk errors in prescribing or dispensing of the medication as well as reduce patient compliance, as shown in a meta-analysis comparing sequential to concomitant therapy.²¹⁰

A slightly higher occurrence of adverse events with concomitant therapy over hybrid or sequential therapies might be expected given the longer treatment duration of some individual antibiotics. There was no difference in comparison to sequential therapy (risk difference=0.03; 95% CI=0.00 to 0.06; 15 studies), but there was a higher rate of adverse events in comparison to hybrid therapy (risk difference=0.09; 95% CI=0.02 to 0.16; 5 studies).²⁰⁹ These differences seem minor and within acceptable clinical standards^{208 211–213} As for antibiotic stewardship, there is no difference in the antibiotics to which the patient is exposed with these three therapeutic regimens.

With regard to efficacy, interpretation of results requires care, as several studies compared different treatments using different durations (eg, 10 days of treatment A vs 7 days of treatment B), and longer duration is clearly a predictor of success. A meta-analysis, that considered this variable, included 12 studies (7 conducted in Asia and 5 in Europe) with over 1200 patients treated with sequential and over 1200 with concomitant, clearly demonstrating superiority of concomitant over sequential therapy achieving an OR of 1.49 (95% CI=1.21 to 1.85).¹⁹³ There was also a tendency towards increased differences with shorter treatment durations. An update on this meta-analysis, including 19 studies of same treatment duration, also demonstrated superiority of concomitant versus sequential therapy (risk difference=0.04; 95% CI=0.01 to 0.06).²⁰⁹ Concomitant therapy for 14 days was also the only therapy other than bismuth quadruple to consistently have an eradication rate of >90% in the Hp-EuReg.¹⁹⁴ This superiority may be related to an increase duration of exposure to all the antibiotics during concomitant therapy. Although less studied, hybrid or reverse hybrid non-BQT seem to provide similar eradication success as concomitant therapy.^{209 211 212 214}

Given the superiority of concomitant therapy in eradication success over sequential therapy, the identical exposure to number of antibiotics, similar side effect profile, and the reduced complexity compared with sequential or hybrid therapies, concomitant therapy should be the preferred non-BQT.

Statement 5: The recommended treatment duration of non-BQT (concomitant) is 14 days.

Agreement 100%

Grade D2

Among non-BQTs, concomitant therapy (PPI, amoxicillin, clarithromycin and metronidazole prescribed as the same time) is generally recommended. The last Maastricht consensus recommended 14 days treatment, unless 10-day therapies were proven locally effective.¹ The optimum duration of concomitant therapy is still under debate. A recent prospective randomised study from Greece compared, head-to-head, 10-day and 14-day concomitant therapy in 364 patients with newly diagnosed *H. pylori* infection. The intention-to-treat eradication rates were similar: 87.9% vs 87.4% for 10-day and 14-day treatment group, respectively, with similar compliance.²¹⁵ An Italian real-life study compared 10-day and 14-day concomitant treatment in 203 patients without previous exposure to clarithromycin. Intention-to-treat eradication rates were higher with the 14-day (96.1%) than the 10-day regimen (80%) ($p=0.001$).²¹⁶ The Hp-EuReg analysed 21213 first-line empirical *H. pylori* treatments in real clinical practice from 27 European countries during a 5-year audit.¹⁹⁴ Concomitant therapy was prescribed to 4164 patients. Modified intention-to-treat eradication rates observed in 10-day and 14-day treatment regimens were 88.3% and 92.1%, respectively.

In summary, it may be concluded that the recommended treatment duration of non-BQT (concomitant) is 14 days, unless 10-day therapies are proven effective locally.

Statement 6: In areas of low clarithromycin resistance, BQT or clarithromycin-containing triple therapy may be recommended as first-line empirical treatment, if proven effective locally.

Agreement 94%

Grade B1

Lacking susceptibility testing or in areas of limited healthcare resources, the physician must rely on evidence of local results (ie, test of cure data). There are very few areas remaining with low clarithromycin resistance. With few exceptions, worldwide the presence of resistance prohibits empiric use of triple therapies containing clarithromycin, metronidazole, or a fluoroquinolone. However, if locally one of these therapies proves effective (ie, evidence that it reliably achieves $\geq 90\%$ cure rates locally) it can be used. Thus, in areas of low clarithromycin resistance and locally confirmed evidence of effectiveness ($\geq 90\%$), the standard PPI-clarithromycin-containing regimen may still be recommended as the first-line treatment. Bismuth-based quadruple regimens are also valid first-line alternatives. Dual therapy with high dose PPI and amoxicillin (\pm rifabutin, where available) may be another option if it is confirmed effective locally.^{187 217–219} Vonoprazan dual therapy may be chosen as well where available.

Statement 7: The recommended treatment duration of PPI-clarithromycin-based triple therapy is 14 days.

Agreement 100%

Grade B1

Previous studies and meta-analyses have justified the recommendation of at least 14 days for triple therapy including PPI, amoxicillin and clarithromycin (PAC) or metronidazole (PAM) by different consensus conferences.^{1 60} The Hp-EuReg have analysed 21213 first-line empirical *H. pylori* treatments on real clinical practice from 27 European countries during a 5-year audit.¹⁹⁴ PAC was the most commonly prescribed regime (8337 patients, 39%), having its use declined over time from >50% in 2013–2015 to 32% in 2017–2018. Overall, 81.5% modified intention-to-treat cure rate was observed (7 days: 82.7%; 10 days: 84.2%; 14 days: 86.2%). A recent update of this audit analysed 29634 first-line empirical *H. pylori* treatment.²²⁰ Seven-day PAC, 10-day PAC and 14-day PAC achieved 82%, 83% and 87% modified intention-to-treat eradication rate, respectively.²²⁰ 14-day PAC therapy remains effective until clarithromycin resistance exceeds approximately 15%, whereas 7-day therapy is compromised by clarithromycin resistance exceeding 5%.²²¹

PAM is used in countries, such as Japan, where metronidazole-resistant rates are relatively low. To evaluate the efficacy of PAM as first-line *H. pylori* therapy, a large meta-analysis involving 94 studies (8061 patients) was performed in areas with moderate-to-high resistance to clarithromycin.²²¹ Primary metronidazole resistance was reported in 26/94 studies and was present in 32% of patients tested. Overall, it showed a mean intention-to-treat eradication rate of 75% (95% CI 73% to 78%). Significantly higher PAM efficacy was observed according to metronidazole susceptibility: 59% (55%–63%) eradication in patients harbouring metronidazole-resistant strains vs 89% (87%–91%) in metronidazole-susceptible strains, the risk difference being 30%. However, in 14-day schedules, this difference decreased to 20%. Although this regimen is, overall, 30% less effective in metronidazole-resistant strains, high-dose 14-day schedules can partially overcome the resistance effect.²⁰⁴ The Hp-EuReg

analysed the duration of PAM *H. pylori* treatment in 463 patients.¹⁹⁴ Seven-day, 10-day and 14-day PAM treatment achieved 80.8%, 85.7% and 80% modified intention-to-treat eradication rate, respectively, remaining unable to achieve cure rates $\geq 90\%$.

The length of other less effective first-line PPI-based triple therapies has also been studied by Hp-EuReg audit.¹⁹⁴ The association of PPI, clarithromycin, and metronidazole for 7 day, 10-day and 14-day treatment achieved 84.4%, 66.7% and 67.9% modified intention-to-treat eradication rates, respectively, in 903 patients.

In summary, it may be concluded that the recommended treatment duration of PPI-clarithromycin-based triple therapy is 14 days unless shorter therapies are proven effective locally.

Statement 8: The use of high-dose PPI twice daily increases the efficacy of triple therapy. It remains unclear whether high dose PPI twice daily can improve the efficacy of quadruple therapies.

Agreement 97%

Grade C2

PPIs have an in vitro bactericidal effect with minimum inhibitory concentrations in the bismuth salts' order of magnitude. Moreover, antisecretory drugs influence antibiotics efficacy against *H. pylori* in vivo by raising intragastric pH, which in turn affects antibiotics delivery to the gastric mucosa and to the mucus layer, their stability and their antibacterial activity. *H. pylori* is more difficult to eradicate when gastric pH is low; by raising pH, bacteria enter the replicative state and become susceptible to antibiotics. Response to PPI is strongly determined by the capacity of the patient to metabolise the drug, which is dependent of the cytochrome 2C19 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 compared with Asian.²²² Different PPIs can be used interchangeably based on their omeprazole equivalency.²²³

The role of PPIs is supported by many reports, where significantly higher eradication rates were found with clarithromycin and amoxicillin or metronidazole containing triple-therapy regimens with high-dose PPI twice daily.^{194 204 224} High-dose PPI means 40 mg of omeprazole (that is, double dose), or equivalent (if other PPI is prescribed). Up to now, it remains unclear whether higher doses PPI can increase the efficacy of quadruple therapies. For BQT, there is no significant difference in the eradication efficacy among low-dose, standard-dose and high-dose PPI groups.¹⁹⁴ Compared with low-dose PPI group, higher doses of PPI may improve the eradication efficacy of non-BQT (concomitant therapy and sequential therapy) and triple therapy plus bismuth,^{194 204} but there are few relevant studies, and they lack consistency.²²⁵ When lansoprazole, rabeprazole (10 mg) or esomeprazole (20 mg) are administered four times daily, a stable and sufficient gastric acid suppression effect (percentage of time with median intragastric pH above 6 or all-day intragastric pH of ≥ 4 above 90%) could be obtained, regardless of cytochrome 2C19 polymorphism.^{226 227} Under this condition, amoxicillin alone can achieve a good eradication efficacy provided the doses, dosing and treatment duration are appropriate.^{228 229}

Statement 9: Potassium-competitive acid blockers (P-CAB)—antimicrobial combination treatments are superior, or not inferior, to conventional PPI-based triple therapies for first-line and second-line treatment, and superior in patients with evidence of antimicrobial resistant infections.

Agreement 100%

Grade B2

Optimal eradication of *H. pylori* infection requires predictable and long-lasting inhibition of gastric acid secretion, especially throughout the night-time hours. The target to be achieved is pH between 6 and 7, when the organism is in growth phase and especially susceptible to clarithromycin and amoxicillin.²³⁰ Currently available PPIs do not typically achieve this degree or duration of acid suppression required over the full 24 hours period to meet this target. However, the introduction of the P-CABs with their unique pharmacological profile are better suited to combination treatment with one or more antimicrobial agents.^{231 232} P-CABs are characterised by a rapid onset of action, a predictable antisecretory profile which is not dependent on the CYP2C19 genotype or activation of parietal cells. This profile provides the opportunity to improve the management of *H. pylori* eradication treatments, particularly by simplifying complex eradication regimens and potentially developing very effective dual therapy.^{232 233}

Vonoprazan is the P-CAB class leader and tegoprazan, fexuprazan and linaprazan are in clinical development. A recent review includes a section on the use of P-CABs for *H. pylori* eradication in combination regimens.²³³ An early meta-analysis of 10 studies found that vonoprazan based triple therapy was superior to PPI based triple therapy in first-line treatment with similar safety and patient tolerance.²³⁴ A more recent systematic review of 16 studies found superiority in both first line and second line treatments. A particular benefit was the high rates of eradication in patients harbouring clarithromycin resistant strains.²³⁵

Four exploratory trials have evaluated vonoprazan dual therapy with 40 mg daily with amoxicillin 1.5 or 2.0 g/day as dual therapy in a total 261 patients.²³³ Eradication rates ranged from 63% to 100% and the pooled eradication rate was 85.6% with significant heterogeneity ($I^2=65\%$) The eradication rate in patients with clarithromycin resistance was 95.4% confirming that clarithromycin was not needed in PCAB- triple therapy. Overall minor adverse events were reported in 26% of the patients.²³³ Furthermore, one retrospective trial explored the use of vonoprazan based triple therapy in a susceptibility-guided management strategy and reported it as non-inferior compared with PPI-based triple therapy.²³⁶ The initial development and clinical experience with vonoprazan based eradication regimen has been largely limited to East Asian countries but equivalent rates of eradication to PPI based treatments have been reported in North American and European studies. But these have failed to achieve a threshold of 90% at the doses studied.²³⁷ Dose ranging studies and prospective comparative trials in western countries offer important new directions and the prospect of simpler, dual therapies at a time when global resistance rates are a serious challenge to the successful management of *H. pylori* infection.^{238–240}

Statement 10: Empiric second-line and rescue therapies should be guided by local resistance patterns assessed by susceptibility testing and eradication rates in order to optimise treatment success.

Agreement 94%

Grade D2

Antimicrobial susceptibility testing provides the opportunity to tailor therapy and enables more rational use of antibiotics, thereby minimising the emergence of future antibiotic resistance. However, until recently susceptibility tests requires endoscopy to obtain samples for microbiology examination. Endoscopy is invasive, expensive and not readily available in all health systems. Moreover, culturing of *H. pylori* is challenging. Several studies have shown that culture success falls

below 80% in those who have already failed at least one *H. pylori* eradication therapy,¹³¹ further limiting the number of patients for which tailored therapy was possible. Molecular tests overcome the challenges of *H. pylori* culture. Commercially available kits have been approved for clinical use for the detection of clarithromycin and levofloxacin resistance.²⁴¹ Evidence in support of tailored therapy over empirical therapy in those who have failed *H. pylori* treatment is limited. Meta-analyses of studies to date have shown no significant difference between susceptibility-guided versus empirical therapies.^{209 242 243} Also those who have failed two or more *H. pylori* therapies have shown similar eradication rates between tailored and empirical therapies.^{244 245} A meta-analysis that included four observational studies on the eradication rate of tailored third line therapy reported a mean eradication rate of only 72%.²⁴⁶ Finally, in an updated meta-analysis conducted in 2020, when all rescue-therapies were included (13 studies, most as second-line), similar results were demonstrated with both strategies—empirical and tailored—both when including all studies (RR: 1.09; 95% CI: 0.97 to 1.22) and also when only RCTs were considered (RR: 1.15; 95% CI: 0.97 to 1.36).²⁰⁹

Given the current absence of strong data on tailoring second line and rescue therapies and still limited access to *H. pylori* culture or molecular testing, it will be some time before routine testing can become the expected approach for routine clinical use. With regards to empirical second line therapy, recent data from the Hp-EuReg reports eradication rates of >90% using different regimens.²⁴⁷ Regularly monitoring eradication rates and local resistance patterns is key to guide the most appropriate empirical therapies. This information should be communicated to the Gastroenterology, Family practice and Public Health communities. Currently, the evidence to support the routine use of susceptibility-guided therapy after *H. pylori* eradication failure is limited and therefore further studies are required to evaluate the benefits of tailored therapy over empirical therapy.

Statement 11: After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy or the high-dose PPI-amoxicillin dual therapy may be recommended. In cases of high fluoroquinolone resistance, the combination of bismuth with other antibiotics or rifabutin, may be an option.

Agreement 83%

Grade C2

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. A systematic review and NWM including 54 RCTs found that quinolone-based triple (ie, PPI, levofloxacin and amoxicillin) or quadruple therapy (ie, PPI, levofloxacin, bismuth and amoxicillin or tetracycline) administered for at least 10 days, was more effective than bismuth-containing quadruple therapy as a second-line treatment.²⁴⁸ Recent warnings about serious adverse effects of fluoroquinolones have been issued, restricting their use to infections in which the therapeutic benefit outweighs the risks, and this should be the case. Using a clarithromycin-containing treatment after failure of a BQT might not be practical since bismuth-based therapies are usually proposed as first-line treatments for areas of high clarithromycin resistance. A PPI-amoxicillin high-dose dual therapy might be an option, as it overcomes the issue of clarithromycin and metronidazole resistance. A meta-analysis including 4 RCTs administering PPI-amoxicillin dual therapy in patients with at least

one prior failed therapeutic attempt found an eradication rate of 81%, being comparable to other recommended therapies.²⁴⁹ Dosing frequency is essential for the efficacy of PPI-amoxicillin dual therapy, as amoxicillin has a time-dependent bactericidal effect. A meta-analysis including 15 RCTs found that administering PPI-amoxicillin four times daily achieved a significantly higher eradication rate than lower dosages (ie, 87% vs 73%).²⁵⁰ In case of high quinolone resistance, rifabutin might be an option.^{198 199}

Statement 12: After failure of PPI-clarithromycin-amoxicillin triple therapy, a bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy or a PPI-amoxicillin high-dose dual therapy are recommended as a second-line treatment.

Agreement 84%

Grade C2

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.²⁵¹ Several meta-analyses have shown that, after failure of a first-line eradication treatment with PPI-clarithromycin-amoxicillin triple therapy, a levofloxacin-containing rescue regimen is at least equally effective, and better tolerated, than the bismuth quadruple regimen.²⁵² Higher cure rates have been reported with longer treatments (>10 to 14 days), and 500 mg levofloxacin daily is the recommended dose.²⁵²

However, an increased prevalence of primary levofloxacin resistance has been reported, affecting the efficacy of levofloxacin-based regimens.²⁵² Some authors have evaluated a combination of a triple therapy with a PPI-amoxicillin-levofloxacin but adding bismuth and thus converting this triple regimen into a quadruple one, with encouraging results (online supplemental table 3), generally better than those obtained by previously published studies with levofloxacin triple therapies.²⁵² One of these levofloxacin-bismuth studies was focused specifically on patients with one previous.

H. pylori eradication failure (the most common scenario for the use of quinolones in clinical practice), achieving an eradication rate of 90% which may be considered encouraging, especially considering that this rescue regimen was prescribed empirically.²⁵³ In this respect, the levofloxacin-containing quadruple therapy (ie, PPI, levofloxacin, amoxicillin and bismuth) administered for at least 10 days proved to be the most effective treatment in a NWM including 26 RCTs on second-line therapies.^{253 254}

Warnings about serious adverse effects of fluoroquinolones have been issued thus their use should be restricted to infections in which the therapeutic benefit outweighs the risks. Indeed, the Hp-EuReg found that after failure of first-line clarithromycin-containing treatment, optimal eradication (ie, ≥90%) was obtained with bismuth-containing quadruple therapy, with or without levofloxacin, but not with levofloxacin-based triple therapy.¹⁹⁴ Therefore, bismuth-containing quadruple therapy is a pivotal second-line option for *H. pylori* eradication, especially in areas with high quinolone resistance. In this respect, a recent meta-analysis showed that BQT achieved a pooled eradication rate of 76%, further increased to 82% for 10-day or 14-day therapy.²⁵⁵ The PPI-amoxicillin high-dose dual therapy might be another option, given the 81% eradication rate achieved as second-line or further-line treatment, being comparable to other recommended therapies.²⁵⁶ High efficacy is also documented with vonoprazan-amoxicillin therapy.^{239 240}

Statement 13: After failure of a non-BQT, either a BQT or a fluoroquinolone-containing quadruple (or triple) therapy is recommended. PPI-amoxicillin high-dose dual therapy might also be considered.

Agreement 87%

Grade C2

Non-bismuth quadruple regimens, including a PPI, amoxicillin, clarithromycin and a nitroimidazole (either sequentially or concomitantly), are frequently used as first-line treatments. However, following eradication failure with these regimens, the best empirical rescue therapy remains a challenge. These patients have limited options for further therapy because they already have received three different relevant antibiotics such as clarithromycin, amoxicillin and metronidazole.

BQT (eg, PPI, bismuth, tetracycline and metronidazole) can be regarded as an effective second-line treatment for *H. pylori* infection. A systematic review and meta-analysis including 30 comparative trials, 12 of which included patients with a previous failed therapeutic attempt, found that BQT achieved an 89% eradication rate as second-line treatment.²⁰² Of note, among 11 studies in patients who had been previously treated with clarithromycin-containing therapy, the efficacy of BQT was 90%.²⁰²

As an alternative, a quinolone-containing triple or quadruple therapy proved effective.²⁵⁷⁻²⁶⁰ A systematic review and meta-analysis including 16 comparative studies found that 10-day levofloxacin, amoxicillin and PPI triple therapy achieved a pooled eradication rate of 80%, similar to the 14-day moxifloxacin, amoxicillin and PPI triple therapy.²⁶⁷ The same analysis found eradication rates over 90% for two studies investigating a levofloxacin, bismuth-containing quadruple therapy.²⁶⁷

An important caveat of levofloxacin-containing therapy is that it is markedly less effective in the presence of fluoroquinolone resistance. The efficacy of levofloxacin-containing therapy is decreasing, most likely due to increased primary quinolone resistance. Bismuth has a synergistic effect with antibiotics and overcomes clarithromycin and levofloxacin resistance.²⁵² A quadruple regimen adding bismuth to levofloxacin (PPI, amoxicillin, levofloxacin and bismuth) showed encouraging results.²⁵² 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.²⁶⁴ 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 (90%).²⁵³ Therefore, the levofloxacin plus 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.

Finally, PPI-amoxicillin high-dose dual therapy might be another option, given the 81% eradication rate achieved as second- or further-line treatment, being comparable to other recommended therapies.²⁵⁶

Statement 14: After failure of the first-line treatment with clarithromycin-containing triple or non-BQTs and second line with BQT, it is recommended to use a fluoroquinolone-containing regimen. In regions with a known high fluoroquinolone resistance, a BQT with different antibiotics, rifabutin-containing rescue therapy, or a high dose PPI-amoxicillin dual therapy, should be considered.

Agreement 86%

Grade B2

Several studies have confirmed the efficacy of a third-line combination of a PPI, amoxicillin and third generation quinolone, such as levofloxacin and moxifloxacin, for eradication of *H. pylori* infection as proposed by the Maastricht V Consensus conference.^{252 268-270} Several studies have evaluated the efficacy of a third-line combination of a PPI, amoxicillin, and levofloxacin after two eradication failures (first-line with a PPI-clarithromycin-amoxicillin-metronidazole, and second-line with a bismuth quadruple regimen), which are summarised in online supplemental table 4. The addition of bismuth to this levofloxacin-containing triple regimen may increase the effectiveness, mainly in the presence of levofloxacin resistance. However, the increasing antibiotic resistance to quinolones has affected quinolone-containing therapies in recent years. Specific patterns of *gyrA* mutation are the most sensitive markers for predicting successful eradication.²⁷¹ Therefore, there is a need to enhance the effectiveness of quinolone-containing therapies.^{271 272 275} Sitafloxacin, a fourth-generation quinolone, and vonoprazan, a novel P-CAB, are now available as more effective treatment options.²⁷³ A BQT with different antibiotics (not previously used) or a rifabutin-containing rescue therapy should also be considered.^{198 199 274}

Statement 15: After failure of the first-line treatment with clarithromycin-containing triple or non-BQTs, and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use the bismuth-based quadruple therapy. If bismuth is not available, high-dose PPI-amoxicillin dual or a rifabutin-containing regimen could be considered.

Agreement 84%

Grade B2

BQT is not influenced by clarithromycin and fluoroquinolone resistance and may serve as successful third-line eradication therapy.²⁸² A regimen of bismuth, metronidazole and tetracycline (as combination therapy or 3-in-1 single capsule: Pylera) with PPI offers an effective option of rescue therapy after failure of clarithromycin-containing (first line) and levofloxacin-containing (second line) therapies.^{195 202 283-288}

Statement 16: After failure of first-line treatment with bismuth quadruple and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use a clarithromycin-based triple or quadruple therapy only if from an area of low (<15%) clarithromycin resistance. Otherwise, a high-dose PPI-amoxicillin dual therapy, a rifabutin-containing regimen or a combination of bismuth with different antibiotics should be used.

Agreement 90%

Grade C2

Since no clarithromycin has been used previously, a clarithromycin-based triple therapy (in areas of low clarithromycin resistance), a combination of bismuth with different antibiotics not previously used²⁷⁴ or a rifabutin-containing rescue therapy (in areas of high clarithromycin resistance)^{198 199 280 289} are valid options. Rifabutin has low rates of resistance, and optimised treatment duration and dose of amoxicillin achieves acceptable *H. pylori* cure rates.^{198 199} Cumulative effectiveness after several consecutive rescue therapies (including rifabutin as a third-line regimen) was 99.8% in 1200 patients and 18 years of follow-up.²⁸⁰ Thus, eradication can be achieved virtually in all cases by the administration of several consecutive empirical therapies.

Statement 17: In patients with proven penicillin allergy, for a first-line treatment, BQT (PPI-bismuth-tetracycline-metronidazole) should be recommended. As second-line therapy, BQT (if not previously prescribed) and fluoroquinolone-containing regimen may represent empirical second-line rescue options.

Agreement 85%

Grade C2

The eradication of *H. pylori* in patients with penicillin allergy (reported in about 5%–10% of individuals) represents a significant challenge. 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 so that these patients are not excluded from the best therapy.²⁹⁰

The substitution of amoxicillin with metronidazole in the standard clarithromycin-triple therapy is not an effective option for the first-line treatment regimen in areas of high clarithromycin and/or metronidazole resistance.²⁸⁸ Although eradication with PPI-tetracycline-metronidazole was effective,²⁹¹ this triple combination was better with the addition of bismuth (resulting in BQT), and should be preferred as the first-line regimen in patients with penicillin allergy (especially in areas with high clarithromycin and/or metronidazole resistance)^{288 292} PPI-clarithromycin-metronidazole combinations can be used if bismuth is not available in areas with low clarithromycin and/or metronidazole resistance.

For the second-line treatment in patients allergic to penicillin, after failure of PPI-clarithromycin-metronidazole triple therapy, BQT may represent an empirical rescue option.²⁸⁸ Fluoroquinolone-containing regimens in various combinations (for example with clarithromycin) are also effective,^{288 293} however, resistance to quinolones is acquired easily, and in countries with a high consumption of these drugs the resistance rate is relatively high.

The possible strategies to increase eradication include adding bismuth to PPI-clarithromycin-metronidazole,²⁹⁴ increasing antisecretory potency with a P-CAB (eg, vonoprazan),²⁹⁵ substituting amoxicillin with cefuroxime²⁹⁶ and using regimens containing sitafloxacin or semisynthetic tetracycline (doxycycline or minocycline).^{288 297 298}

WG 4: GASTRIC CANCER AND PREVENTION

Statement 1: *H. pylori* infection is the primary aetiological factor for gastric adenocarcinoma including proximal gastric cancer (PGC).

Agreement 100%

Grade A1

Based on a large number of epidemiological, experimental studies and meta-analyses of the outcomes of *H. pylori* eradication therapies in humans,^{299–301} it is now firmly established that *H. pylori* infection is the most important aetiological factor for gastric adenocarcinoma. According to the IARC WG reports, nearly 90% of gastric cancers are attributed to *H. pylori* infection world-wide.³⁰² In some high-risk countries such as Japan, even a higher rate, estimated to be more than 95%, was reported.³⁰³ Although there are some discrepancies between the prevalence of

H. pylori infection and gastric cancer mortality, the so-called African Enigma and Indian Enigma,^{304 305} *H. pylori* infection remains the most important aetiological factor for distal gastric adenocarcinoma irrespective of major histological types (both diffuse and intestinal type).³⁰²

PGC, which should be separated from oesophagogastric junctional cancer as defined by IARC,³⁰⁶ is also strongly associated with proximal extension of gastric atrophy caused by *H. pylori* infection.^{307 308} However, in Mongolia, where gastric cancer incidence is among the highest in the world, PGC without *H. pylori* infection is predominant,³⁰⁹ indicating that other aetiological factors such as diet and gastric dysbiosis may also contribute to the PGC in this region.

Statement 2: *H. pylori* infection plays an aetiological role in a subset of adenocarcinoma of the Gastro-oesophageal Junction (GOJ) zone (GOJZ).

Agreement 94%

Grade A1

GOJ cancer, which was classified as a separate entity in the IARC classification,³¹⁰ is included into oesophageal cancer in the new edition.³⁰⁶ It should be noted that neither ‘gastric cancer in the cardia’ nor ‘cardia gastric cancer (CGC)’ is recommended as a categorical naming in this classification, because the presence of genuine cardiac mucosa has been questioned or, if present, is limited to a very narrow area mostly within 5 mm from the GOJ. Thus, conventional CGC is now either classified as GOJ cancer or PGC depending on the location of the tumour in relation to GOJ, namely those classified as Siewert type II as GOJ cancer and those of type III as PGC. *H. pylori* is the key risk factor also in PGC.³⁰⁸ This fits in the new concept of GOJZ cancer which addresses the adenocarcinoma occurring 1 cm proximal to and 1 cm distal to GOJ which clarifies the pathogenetic mechanisms for cancer occurring at the GOJZ.³¹¹

A number of studies have strongly indicated that there are at least two major aetiological factors for GOJ adenocarcinoma, one from inflammation caused by gastroduodenal reflux and the other from inflammation of junctional gastric mucosa including cardiac-type mucosa mainly by *H. pylori* infection.^{307 312–314}

Statement 3: The influence of environmental factors is subordinate to the effect of *H. pylori* infection.

Agreement 100%

Grade A1

H. pylori is the most important infectious cause of cancer worldwide. In case-control and cohort studies the attributable risk fraction of *H. pylori* to gastric cancer worldwide is 89% (79%–94%).^{315–317} Several studies show a detrimental effect of cigarette smoking on gastric cancer risk in *H. pylori* infected^{318–320} and a higher risk of gastric cancer is also reported in association with ethnic minorities in the USA.³²⁰ Less robust associations were found for salt and meat consumption. The EurGast-EPIC cohort found that factors such as excessive salt intake and cigarette smoking had only a low ‘add-on effect’ in the presence of *H. pylori* infection.³¹⁵ It must be noted that these associations occur only among individuals that are simultaneously seropositive for *H. pylori*. No significant interaction is reported with alcohol consumption.³²⁰

Therefore, it can be concluded that *H. pylori* infection is a necessary environmental factor in the aetiology of non-cardiac gastric cancer in the vast majority of cases.³²¹ Exceptions include gastric cancers that arise in the setting of hereditary conditions or AIG. The role of infection with Epstein-Barr virus (EBV) deserves specific consideration presented in statement 6.

Statement 4: Hereditary gastric cancer is a distinct entity. The role of *H. pylori* infection in the clinical course of the disease remains to be elucidated.

Agreement 100%

Grade D2

While the great majority of gastric cancers are sporadic, familial aggregation occurs in about 10% of the cases and, of these, only 1%–3% constitute hereditary forms. Hereditary diffuse gastric cancers (HDGC) include syndromes such as HDGC, gastric adenocarcinoma and proximal polyposis of the stomach, and familial intestinal gastric cancer. Gastric cancer has also been identified as part of other hereditary cancer syndromes such as hereditary non-polyposis colorectal cancer, Li-Fraumeni syndrome, familial adenomatous polyposis and Peutz-Jeghers

syndrome. Recently, a comprehensive review was carried out searching for total gastrectomies performed in asymptomatic HDGC patients. In 174 CDH1 carriers, microscopic cancer foci were detected in 95.3% of the cases. In this same series, *H. pylori* infection was reported in 23.4% of the cases, showing that at least in about 75% of the cases, cancer onset and development occurred irrespective of *H. pylori* infection.³²² Other reports on the clinicopathological characteristics of hereditary gastric carcinoma show that *H. pylori*-positive and -negative patients coexist in these families. This contrasts with data showing that the vast majority of patients with sporadic gastric carcinoma are *H. pylori* positive. Data corroborating that hereditary gastric cancer is independent from *H. pylori* stems from genetically modified animals with high prevalence of gastric cancer in the absence of *H. pylori* infection.³²³ However, while there is compelling evidence that triggering of hereditary gastric cancer is independent from *H. pylori* infection, at least in HDGC, little is known regarding the role of *H. pylori* in those cases where the bacterium is present.^{324–326} One cannot ignore that *H. pylori* infection is associated with epigenetic alterations and genomic instability in gastric epithelial cells, which have oncogenic potential.

In conclusion, hereditary gastric cancer develops in pathogenic mutation carriers independently of *H. pylori* infection. However, there is no evidence to claim that *H. pylori* does not influence the pathogenesis of hereditary gastric cancer and its clinical phenotype. It is also recommended that *H. pylori* is eradicated if present.

Statement 5: Severe atrophy (OLGA III/IV) in the context of *H. pylori* gastritis carries a much higher risk for gastric cancer development as compared with atrophy in the context of autoimmune gastritis (AIG).

Agreement 100%

Grade A1

Gastric atrophy results either from *H. pylori* gastritis or from AIG but considering the low prevalence of AIG as compared with *H. pylori* in the general population the magnitude of gastric cancer incidence differs accordingly. The estimate of the frequency of AIG varies between 2%–5% of all gastritis forms.¹⁵⁷ However gastric cancer in *H. pylori* gastritis with atrophy is often not stratified according to the degree of severity and not appropriately distinguished from atrophy in AIG. This leads to a difficult interpretation of existing data concerning the RR of gastric cancer related to the two aetiologies. Studies with well-defined AIG estimate the incidence rate of gastric adenocarcinoma among this group as 14.2 cases per 1000 person-years, compared with 0.073 per 1000 person-years in the general population.³²⁷ An overlap with *H. pylori* is not adequately excluded. The estimated risk varies among populations and is related to the incidence of *H. pylori* infection.³²⁸ In Europe, a study from Sweden reports the risk of gastric cancer in AIG of 7.4 vs 1.4 cases per 1000 patient years in the general population,³²⁹ and a study from Finland reports a similar magnitude of risk with a standardised incidence ratio of 5.0.³³⁰ The prevalence of AIG in patients with gastric cancer is low in study from Germany.³³¹ Furthermore prognosis in patients with AIG is much better compared with those with severe atrophy in *H. pylori* gastritis OLGA stage III–IV.³³¹ Earlier gastroscopy performed in patients with AIG due to an earlier onset of symptoms (ie, pernicious anaemia) may leads to earlier detection of gastric cancer. Ultimately the increased gastric cancer risk in atrophic *H. pylori* gastritis is related to the extent of atrophy that involves both the antrum and corpus while atrophy is limited to the corpus mucosa in AIG.¹⁵⁷

In long-term follow-up studies, a significant risk of gastric cancer development was only documented in *H. pylori* gastritis with severe gastric atrophy but not observed in patients with AIG.^{148 160}

The impact of these findings is reflected in the clinical management by endoscopic/histological follow-up of preneoplastic gastric changes.⁹¹ In populations with low *H. pylori* prevalence the risk of AIG for the development of gastric cancer, particularly in young females, has recently received much attention and AIG in this context is gaining great importance.³³² For now, it needs to be noted that cases with mild focal atrophy are often grouped together with cases with severe atrophy. OLGA was the first attempt to overcome this problem and showed that stages III and IV in *H. pylori* infection bear a higher risk for gastric carcinoma than AIG.

Statement 6: *H. pylori* infection and EBV are independent risk factors of gastric cancer. Whether coinfection of *H. pylori* and EBV is associated with higher risk of gastric cancer than either one alone remains uncertain.

Agreement 97%

Grade C2

EBV is associated with gastric lymphoepithelioma-like carcinomas, which have a relatively higher frequency in proximal location and diffuse histological subtype.³³³ A comprehensive molecular characterisation further showed that EBV-associated gastric adenocarcinoma displayed recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, PD-L1 and PD-L2.³³⁴ A recent systematic review and meta-analysis of case–control studies showed that the pooled prevalence of EBV was 8.8% in 20 361 patients with gastric cancer.³³⁵ Of the 20 studies with matched pairs design from 4116 gastric cancer patients, EBV was associated with 18-fold increased risk of gastric cancer.³³⁵ Some case–control studies showed that coinfection of *H. pylori* and EBV was associated with more severe gastric inflammation and increased risk of gastric cancer^{336–338} However, evidence from cohort studies or nested case–control studies is lacking on this issue.

Statement 7: *H. pylori* eradication eliminates (1) the active inflammatory response in chronic active non-atrophic gastritis and (2) prevents further progression to atrophy and IM in chronic non-atrophic gastritis.

Agreement 100%

Grade A1

Successful *H. pylori* eradication eliminates the active inflammation, that is, neutrophil infiltrates, in the antrum and corpus. Mild chronic inflammatory infiltrates (ie, lymphocytes) often persist for at least up to 1 year.^{13 339 340}

The gastric mucosal inflammatory activity (ie, neutrophil infiltration) in non-atrophic gastritis is completely reversed as early as 2 weeks after starting eradication therapy.³⁴¹ The disappearance of neutrophils and the normalisation of the surface epithelium closely goes along with disappearance of *H. pylori*.³⁴² These data meet with all the empirical evidence accumulated over decades that in most patients with non-atrophic gastritis the gastric mucosa is restored to normal following *H. pylori* eradication and further progression is therefore prevented.

The best evidence for *H. pylori* eradication therapy to prevent an entire community from progression to gastric atrophy was from the pioneering work performed on Matsu Islands with a 77.2% prevention of atrophy.^{343 344}

Statement 8: *H. pylori* eradication may reverse gastric atrophy and to some extent IM and may halt the progression from chronic atrophic gastritis to neoplastic lesions in a subset of patients.

Agreement 97%

Grade A1

Several meta-analyses have been consistent in reporting the effect of eradication therapy on the reduction of gastric atrophy but not of IM.^{345–347} The reversibility of atrophic changes in the gastric mucosa after *H. pylori* therapy was also confirmed in patients who underwent endoscopic resection (ER) of early gastric cancer.^{348–349} In a large single-centre study, gastric mucosal atrophy was shown to be significantly reduced half a year to 6 years after eradication. IM reversal was gradual and limited to the lesser curvature of the corpus 6 years after eradication.³⁵⁰ Similar findings were reported in a large population followed for 10 years after eradication³⁵¹ and in a population where mass *H. pylori* eradication had been conducted with a decrease in presence and severity of atrophic gastritis as well as of IM over time.^{343–344} A series of other studies have shown the partial regression of IM after a long period of observation.³⁵²

Contrary to early reports in which gastric atrophy and IM were considered as points of no return, a 53% gastric cancer risk reduction was found in the population in which *H. pylori* mass eradication had been performed and where also patients with atrophic gastritis had been included. The effect of halting the progression of advanced atrophic gastritis to gastric cancer becomes even more apparent with a 50% and 52% gastric cancer risk reduction from trials in patients who received ER of early-stage gastric cancer^{349–353} and in patients with premalignant lesions, respectively.³⁵⁴

Statement 9: *H. pylori* eradication offers the chance for gastric cancer prevention at any age in adulthood. The magnitude of the benefit decreases with age.

Agreement 100%

Grade A1

The natural history of *H. pylori* gastritis is characterised by a persistent active inflammation that may progress over decades via a cascade of preneoplastic lesions to gastric cancer in a subset of patients. Therefore, it is self-evident that eradication of *H. pylori* at a younger age is most cost-effective in gastric cancer prevention.^{355–356} There are additional benefits with the reduction of other *H. pylori*-related disease manifestations and complications that may increase during the prolonged course of disease (ie, dyspepsia and peptic ulcer disease). Furthermore curing the infection in young adults, especially in young females before their motherhood, can contribute to reducing the major risk of intra-familial *H. pylori* transmission to children.³⁵⁷ Taking these aspects into account, it is never too late to eradicate *H. pylori* for the purpose of gastric cancer prevention and older age is not a limiting factor.^{358–359}

Statement 10: *H. pylori* eradication is most effective for gastric cancer prevention before the development of severe chronic atrophic gastritis.

Agreement 100%

Grade A1

In an early randomised controlled therapeutic trial only patients without precancerous lesions (gastric atrophy, IM or gastric dysplasia) on study entry did not develop gastric cancer during a 7.5 years observation period following *H. pylori* eradication.³⁶⁰ This observation led to the notion of ‘the point of no return’, beyond which *H. pylori* eradication may no longer reliably prevent gastric cancer. In a recent article with the

application of machine learning models, patient’s age (usually the group with more advanced lesions of *H. pylori* gastritis) and presence of IM were confirmed as most relevant risk factors for the progression to gastric cancer after *H. pylori* eradication.³⁶¹ Beyond histological characteristics of severe gastritis, endoscopic criteria of severe atrophy also provided evidence for the increased risk of gastric cancer development after *H. pylori* eradication.³⁶² Several studies have reported on the reversibility of preneoplastic changes following *H. pylori* eradication.^{363–364} This consideration, and the fact and only a minority (approximately 5%) of patients with severe atrophic gastritis may progress to gastric cancer, justifies *H. pylori* eradication even at the advanced stage of severe chronic atrophic gastritis.³⁶⁵ At present endoscopic surveillance is required to follow up patients with severe atrophic gastritis following *H. pylori* eradication but in the near future the molecular characterisation of gastritis will provide a more reliable assessment of patients who are cured or protected from progression to gastric cancer.^{366–367}

Statement 11: Diagnostic tests used to screen *H. pylori* infection for the purpose of gastric cancer prevention should preferably be non-invasive.

Agreement 89%

Grade C2

The accuracy of non-invasive diagnostic tests for *H. pylori* infection is similar to that of invasive tests that require endoscopy.^{83–368} However, invasive tests are more expensive and carry small but potential risks associated with endoscopy and biopsy.³⁶⁸ Therefore, non-invasive tests, such as UBT, are the tests of choices in average risk subjects receiving mass screening programmes of *H. pylori* for gastric cancer prevention.³⁶⁹ However, subjects who have a high risk of gastric cancer, such as those with positive family history of gastric cancer in first-degree relatives, should undergo endoscopy to exclude the presence of gastric cancer or precancerous lesions.^{7–369}

Statement 12: If a serological method is used for *H. pylori* detection a further test (UBT, SAT) confirming current infection is required before initiating therapy

Agreement 91%

Grade A2

UBT is the most accurate non-invasive test for screening of *H. pylori* infection. A recent systematic review and meta-analysis showed that the sensitivity of UBT was 94% (95% CI 89% to 97%) estimated at a fixed specificity of 90%, whereas the sensitivity of serology was 84% (95% CI 74% to 91%).⁸³ Considering that a serology test is more convenient and less expensive than UBT, it can be an alternative test in mass screening of *H. pylori* for gastric cancer prevention.^{368–369} To serve the purpose of screening rapid serology/blood tests with a high diagnostic sensitivity that can be performed at the physician’s office would be optimal; these tests are currently awaiting further validation.³⁷⁰ However, serology tests may remain positive years after successful eradication of *H. pylori*. Therefore, providing a confirmatory test, such as UBT or SAT, in subjects with positive serology may avoid unnecessary exposure to antibiotics in those with past *H. pylori* infection.³⁶⁹

Statement 13: Endoscopy with biopsies is recommended in asymptomatic individuals with a family history of gastric cancer (does not refer to hereditary gastric cancer) at age 45 and above.

Agreement 89%

Grade 2C

Family history of gastric cancer encompasses both hereditary and non-hereditary cases.^{371 372} It is important to make this distinction as hereditary cases need a different type of surveillance, including endoscopic surveillance.^{41 91} It is well established that individuals with family history of gastric cancer, that is at least one first-degree relative with a history of gastric cancer diagnosed at any age, are at increased risk of developing gastric cancer.^{371 372} It is also known that endoscopy has the highest rate of detecting gastric cancer compared with other gastric cancer screening methods. Therefore endoscopy with the opportunity of early gastric cancer detection combined with *H. pylori* eradication is the most effective prevention strategy.³⁷³ However, there is no data in support of any specific age to start endoscopic screening.

Statement 14: Asymptomatic individuals at age above 50 years are considered vulnerable and at increased risk of gastric cancer compared with younger individuals.

Agreement 97%

Grade 1A

The incidence of gastric cancer starts to rise substantially after the age of 50 years in the majority of countries, especially in high incidence countries.³⁷⁴ The incidence of gastric cancer was higher than 20/100 000 at the age of 40 years in high incidence countries, such as Korea, Japan and China.³⁷⁴ Therefore, asymptomatic individuals aged 50 years or greater are at higher risk of gastric cancer and should be listed as higher priority for gastric cancer screening and prevention.

Statement 15: Population-based *H. pylori* test-and-treat programmes for gastric cancer prevention require caution in the selection of antibiotics to minimise development of antimicrobial resistance.

Agreement 95%

Grade 1B

Globally, there is a trend of increasing prevalence of *H. pylori* resistance.^{116 375–377} Clarithromycin-resistant *H. pylori* is a high priority for research and development of effective drugs according to the recommendation of WHO.³⁷⁸ There is an alarming level of more than 15% of both primary and secondary resistance of *H. pylori* to clarithromycin, metronidazole and levofloxacin in most of the WHO regions.¹³⁵ The latest European survey including 18 countries reported that the rate of primary clarithromycin resistance has doubled in the past 20 years, suggesting limited treatment options for *H. pylori* infection unless novel treatment strategies are developed.¹¹⁶

For successful implementation of the population-based *H. pylori* search-and-treat programmes, selection of the optimal first-line eradication regimen that is highly efficacious and affordable and that can at the same time minimise the potential antibiotic resistance development is a prerequisite. Considering that the global application of the *H. pylori* test and treat strategy will unequivocally lead to increased consumption of antibiotics, as estimated in Latvia,³⁷⁹ it is important that the treatment programmes are adapted relative to country/region-specific resistance patterns wherever possible. For example, the choice of antibiotic combinations should avoid, if possible, products that are essential for the treatment of life-threatening infections in the population (eg, clarithromycin)³⁸⁰ especially in areas of high (>15%) clarithromycin resistance. In such regions, consideration should be given to alternative regimens such as Bismuth, Tetracycline with combination of Metronidazole and PPI. In this context, community-based studies with a long-term follow-up such as the cohort study on Matsu Islands are greatly needed.

These studies can be used to generate data on local *H. pylori* antibiotic resistance patterns and quantitate any changes in the resistance rates during the implementation of the strategy³⁴⁴ while simultaneously monitoring the incidence of serious infections and mortality in the community.

Statement 16: Broad use of *H. pylori* eradication therapies for the purpose of gastric cancer prevention does not lead to an increase in other severe pathologies

Agreement 84%

Grade B2

At the origin of still ongoing debates related to a protective effect of *H. pylori* from a variety of diseases that was observed was an increase of mild reflux oesophagitis following *H. pylori* eradication observed in patients with DU disease.³⁸¹ Early on, several other studies based on sub-analysis from therapeutic trials of *H. pylori* eradication reported discordant results. The claim that *H. pylori* eradication leads to clinically relevant damage to the oesophagus was not based on consistent findings.^{382 383} In particular, the concern of an increased incidence of oesophageal adenocarcinoma in the absence of or following cure of *H. pylori* infection has not been substantiated.^{384 385}

A most recent meta-analysis in line with previous meta-analyses reported a weak association of *H. pylori* infection with decreased gastro-oesophageal reflux symptoms and a weak negative association with mild oesophagitis; a negative association of *H. pylori* with Barrett's oesophagus was not confirmed.³⁸⁶ Furthermore, in a nationwide population-based study in Sweden *H. pylori* eradication did not increase the risk for the development of oesophageal adenocarcinoma.³⁸⁷

In a recent meta-analysis, a negative association between *H. pylori* exposure and Eosinophilic Oesophagitis was reported.³⁸⁸ However no convincing mechanisms for a beneficial interaction between *H. pylori* and Eosinophilic Oesophagitis and no evidence of *H. pylori* eradication on this condition have been provided so far.

There continues to be controversy around the effect of *H. pylori* eradication on body weight and metabolic syndrome. The best documented and clinically most relevant evidence to date shows a rather beneficial long-term effect of *H. pylori* with improvement in metabolic parameters.¹³²

In an analysis of data from the National Health Insurance Research Database in Taiwan, treatment for *H. pylori* infection was associated with a significant increase in the risk for autoimmune disease, including IBD.³⁸⁹ Other reports did not provide evidence for *H. pylori* eradication therapy related to the onset of IBD.³⁹⁰ At present the published data on the effect of *H. pylori* eradication on immune-mediated diseases are not conclusive. There are currently no concerns to justify withholding *H. pylori* eradication therapy for gastric cancer prevention. A recent study from Japan reports on a significant association of *H. pylori* with allergic diseases and in fact previous guidelines on *H. pylori* management from Japan had included the advice to consider eradication in this patient group (Sugano K personal communication).

Statement 17: Population-based *H. pylori* test-and-treat strategy provides additional benefits by preventing other gastroduodenal pathologies.

Agreement 94%

Grade A1

H. pylori eradication benefits patients with gastric and duodenal peptic ulcer, dyspepsia, gastric mucosa-associated lymphoid tissue lymphoma and a series of defined extragastric diseases.^{1 36 43 44 391 392}

Low-dose aspirin intake and NSAID use are independent risk factors for the development of peptic ulcer bleeding. While the risk of bleeding is 4.8-fold increased with NSAIDs it rises to 6.13-fold in presence of *H. pylori*.³⁹³ Patients with both risk factors have a fourfold increased risk for peptic ulcer bleeding.⁵⁰ *H. pylori* eradication is current standard in these clinical conditions for prevention of peptic ulcer disease and bleeding complications (see WG 1 Statements 8 and 9).

H. pylori-positive patients on combined antiplatelet therapy carry the highest risk for peptic ulcer bleeding, and *H. pylori* eradication is a suitable option in this frequent clinical scenario. This is currently being tested in a large Scandinavian trial in patients with myocardial infarction.^{394 395} In the absence of *H. pylori* infection, non-aspirin antiplatelet agents do not increase the risk of peptic ulcer bleeding. The demographic evolution with the increase in the elderly population with comorbidities requiring multiple drugs with gastrototoxic potential also needs to be considered in the context.

All these aspects should be taken into account when analysing cost-effectiveness in the adoption of *H. pylori* eradication for the prevention of gastric cancer.

Statement 18: Screening modalities for gastric cancer prevention (noninvasive or endoscopic) combined with colorectal cancer screening is an opportunity

Agreement 81%

Grade C2

In several Western countries colorectal cancer programmes start at the age of 50. At that time, approximately 10% *H. pylori*-infected patients may already have gastric preneoplastic lesions (atrophy, IM). The prevalence of advanced preneoplastic lesions in Europe in the older age group is up to 19%.^{396–399} To reduce costs and to increase the compliance, a screen and treat approach for *H. pylori* infection could be combined with colorectal cancer screening in countries with intermediate and high gastric cancer risk. The best option for non-invasive assessment of preneoplastic changes in gastric mucosa is serological screening with the determination of serum pepsinogen I and II (sPG-I and sPG-II), including the calculation of the sPG-I/II ratio, in combination with the analysis of anti-*H. pylori* antibodies. A systematic review that enrolled 20 studies calculated a pooled sensitivity of 74.7% and specificity of 95.6%, respectively, to detect atrophic gastritis by these means.⁴⁰⁰ Eradication therapy should be offered to all *H. pylori* positive patients² combined with upper GI endoscopy for all patients with positive serologic biopsy (pepsinogen I/II < 3 and/or pepsinogen I < 30 µg/L). Regular endoscopic surveillance should be offered to those with OLGA/OLGIM II-IV stage as recommended by MAPPS II guidelines.⁸⁹

Statement 19: A population-based *H. pylori* test and treat programme is cost-effective in populations with intermediate or high incidence of gastric cancer.

Agreement 97%

Grade A1

The cost-effectiveness of test-and-treat strategies for gastric cancer prevention is affected by the incidence of gastric cancer, the estimated proportion of gastric cancer reduced by *H. pylori* eradication, the age at screening, the prevalence of *H. pylori* infection, and the costs of testing and for the treatment of gastric cancer.^{401–403} As an example, an earlier performed analysis reported the incremental cost-effectiveness ratio would be <US\$50 000 per life-years saved if the cancer reduction rate is 15%.⁴⁰¹ In an analysis modelled for conditions in Spain,

the test-and-treat strategy appears to be the most cost-effective (524€/gastric cancer avoided/year) compared with upper GI endoscopy and a 'symptomatic treatment' strategy (respectively, €716 and €696/gastric cancer avoided/year).²¹ The strategy in general is cost-effective in populations with incidence of gastric cancer higher than 15–20 per 100 000.⁷ Such a strategy is still effective in populations with low incidence of gastric cancer but is associated with higher cost.⁷ It is noteworthy that the incidence of gastric cancer is higher than 20 per 100 000 in subjects aged greater than 50 years even in western countries where the overall incidence of gastric cancer is low. In high incidence countries, this strategy is more cost-effective when the starting age of screening is at 20–30 years than at older age.⁴⁰⁴

Statement 20: Follow-up at regular intervals, and by use of endoscopic biopsy protocols, is mandatory in patients with severe atrophic gastritis (OLGA III/IV or OLGIM III/IV).

Agreement 97%

Grade B1

Gastritis staging ranks the atrophy-associated risk for gastric cancer into different degrees of severity and serves the intention in designing patient-tailored endoscopy follow-up protocols aimed at the secondary prevention of gastric cancer.^{89 91 148} *H. pylori* eradication prevents gastric cancer and leads in some extent to regression of atrophic gastritis and IM.^{163 351} The long-term follow-up study of an epidemiologically stable cohort of 7436 patients demonstrated that OLGA staging is a reliable predictor of the risk for gastric neoplastic lesions, including gastric cancer.¹⁴⁸ Among *H. pylori*-positive patients, even those with a low-risk OLGA stage, the persistence of the infection may promote neoplastic progression, further supporting the need for both eradication and the non-invasive assessment of its success.^{155 405} Among patients with OLGA stage III/IV, the eradication of the *H. pylori* infection does not necessarily reverse the cancer risk. In these patients, high-resolution endoscopy with image enhanced modalities is recommended to reduce the risk of missing small neoplastic foci.^{89 91 406} (Details on enhanced endoscopic imaging are reported in statement 26). Patients with advanced stages of atrophic gastritis (severe atrophic changes or IM in both antrum and corpus, OLGA/OLGIM III/IV) should be followed up with a high-quality endoscopy every 3 years according to the European MAPS II guidelines.^{89 406}

Statement 21: Eradication of *H. pylori* is mandatory to reduce the risk of metachronous gastric cancer after curative endoscopic resection (ER) or gastric subtotal resection of early gastric cancer.

Agreement 100%

Grade A1

Eradication of *H. pylori* can reduce the risk of gastric cancer after ESD or EMR of early gastric cancer.³⁵³ A meta-analysis of five studies confirmed the initial report that *H. pylori* eradication significantly lowers the risk of metachronous malignancies after ER of gastric neoplasms (five studies, OR=0.392, 95% CI 0.259 to 0.593, $p < 0.001$).³⁴⁸

The conclusive evidence was obtained from a recent RCT from Korea, with 396 patients included in the modified intention-to-treat analysis (194 in the treatment group and 202 in placebo group).³⁴⁹ During a median follow-up of 5.9 years, metachronous gastric cancer developed in 14 patients (7.2%) in the treatment group and in 27 patients (13.4%) in the placebo group (HR in the treatment group, 0.50; 95% CI, 0.26 to 0.94; $p = 0.03$; 3). In the most recent meta-analysis of 11 retrospective cohort studies and 3 RCTs, robust evidence shows that

an important risk reduction of metachronous gastric cancer is obtained in the *H. pylori* eradication group when compared with the non-eradication group (HRs: 0.65, 95% CI: 0.50 to 0.86, $p=0.002$). Furthermore the occurrence of metachronous gastric cancer in the *H. pylori* eradication group was not significantly different from that in *H. pylori* negative group.⁴⁰⁷ Although *H. pylori* eradication halts progression to metachronous neoplasia, eradication is unable to reset the biological clock to zero. Therefore, patients with atrophic gastritis and IM are still at risk of gastric cancer and need endoscopic surveillance at regular intervals.^{89 358}

Statement 22: Medical and special dietary chemoprevention cannot in general be recommended in patients with severe gastric atrophy or IM (OLGAIII/IV or OLGIM III/IV) after *H. pylori* eradication.

Agreement 100%

Grade C2

There is no equally effective alternative to *H. pylori* eradication for primary prevention of gastric cancer. Studies with supplementation of dietary antioxidants had some minor effects in the reduction of gastric cancer incidence in a long-term follow-up trial.^{408 409} Vitamin supplements (beta-carotene and/or ascorbic acid) were significantly associated with regression of precancerous lesions but this effect was lost at 12 years of follow-up.⁴¹⁰ At present we do not know whether vitamins and other antioxidant supplements would be beneficial in preventing the progression of preneoplastic changes (atrophy and IM). The case with medications is slightly different. Aspirin, Cox-2 inhibitors, metformin and statins are all potential candidates to reduce the potential malignant progression of preneoplastic changes via well documented anti-proliferative mechanisms; however the ultimate evidence from clinical trials is lacking.⁴¹¹ Non-aspirin NSAID use was not found to reduce the risk of gastric cancer among patients who underwent *H. pylori* eradication in a territory wide study.⁴¹⁰ On a case-by-case scenario the risk-benefit profile looks best for aspirin in gastric cancer prevention as its combined benefits include cardiovascular system protection as well as colorectal cancer prevention.⁴¹² An increase in gastric cancer risk in patients on long-term PPI after *H. pylori* eradication is controversial, but if real appears to be confined to those with baseline preneoplastic lesions.^{411 413} No recommendation for any putative chemopreventive natural substances and drugs can be made following *H. pylori* eradication. Surveillance at regular intervals for those at risk after *H. pylori* eradication is the strategy of choice. Caution is required for those who need ongoing PPI therapy as more data have been published on the risk of long-term PPI use on gastric cancer.⁴¹⁴⁻⁴¹⁶ Although an increased risk of gastric cancer with PPI is not confirmed in all studies⁴¹⁷ this remains an intriguing issue necessitating future research.

Statement 23: Population-based *H. pylori* test-and-treat programmes should be targeted to special requirements at the regional level (ie, selection of screening tool, use of eradication regimen, surveillance)

Agreement 94%

Grade D1

The latest summary of evidence supports *H. pylori* eradication for both healthy individuals and patients with gastric cancer patients to reduce gastric cancer development.³⁰¹ The IARC/WHO WG emphasised the importance of introducing the population-based *H. pylori* search-and-treat programmes with a scientific assessment of programme processes, feasibility, effectiveness, and possible adverse consequences, while cautioned

that how to implement the strategy must hinge on local considerations,³⁰² incorporating regional specific requirements. Accurate *H. pylori* detection, high efficacy of the eradication regimen and monitoring of the eradication success are among the key requirements to determine successful implementation of the programmes, however each choice requires the incorporation of local considerations. For example, various testing methods have different advantages and disadvantages⁴¹⁸ and the availability of accurate and affordable diagnostic tests may vary according to different settings.⁴¹⁹ The choice of the regimen would require local data on the efficacy, adverse effects and costs to optimise the performance of the programme. Follow-up of the treatment to confirm eradication success should be incorporated and needs to be evaluated based on feasibility and cost-effectiveness at the regional level. Results from ongoing large randomised clinical trials in China,⁴²⁰ the Republic of Korea⁴²¹ and Latvia⁴²² are eagerly awaited as they are expected to provide important insights into the many details required for the population-based programme implementation. Additional demonstration projects in various community settings are encouraged.

Statement 24: Population-based *H. pylori* test-and-treat programmes should be integrated into healthcare priorities, especially in regions with intermediate to high gastric cancer incidence.

Agreement 94%

Grade B1

In the latest meta-analysis³⁰¹ of seven RCTs with 8323 asymptomatic healthy participants found that *H. pylori* eradication therapy reduced incidence of gastric cancer (RR=0.54, 95% CI 0.40 to 0.72, NNT=72) and mortality from gastric cancer (RR=0.61, 95% CI 0.40 to 0.92, NNT=135). More importantly, the study suggested that 8743 815 disability-adjusted life-years would be gained if population-based test-and-treat programmes were implemented globally.³⁰¹ As the best evidence-based intervention that is currently available for gastric cancer prevention, population-based *H. pylori* test-and-treat programmes have been recommended for gastric cancer prevention especially in high incidence areas^{17 302 418} and decision models consistently find the strategy cost-effective in those regions.^{423 424} However very few public health intervention programmes have been established to implement this strategy. Currently, evidence from a real-life setting comes from Matsu Island, Taiwan, where six rounds of population-based *H. pylori* test-and-treat programmes were introduced from 2004 and continued until 2018 for a high-risk population aged 30 years or older infected with *H. pylori*.³⁴⁴ The programmes resulted in a significant reduction in *H. pylori* prevalence in the population (64.2%–15.0%) accompanied by reductions in the presence and severity of atrophic gastritis and IM as well as gastric cancer incidence and mortality during the chemoprevention period, without significant changes in the rates of antibiotic resistance and other digestive tract cancers. Eradication of *H. pylori* infection has additional health benefits beyond the prevention of gastric cancer such as reduction in ulcers, dyspepsia, iron deficiency, ITP. Based on the current evidence, population-based *H. pylori* test-and-treat programmes should be immediately integrated into healthcare priorities, especially in regions with high gastric cancer burden (ASR greater than 20/100 000). Similar efforts need to be made to prioritise and implement the programme in regions with intermediate gastric cancer incidence (ASR 10-20/100 000), especially in the context of demonstration projects to be later scaled up to be integrated into national healthcare systems.

The *H. pylori* test-and-treat programmes should ideally target a younger adult population, for example, 20–40 years of age, before developing preneoplastic changes in gastric mucosa. This also reduces infection transmission to their children.⁷ Locally validated *H. pylori* serology with high sensitivity could be used for detecting *H. pylori* and the infection then requires confirmation by ¹³C-UBT. One month after the treatment, confirmatory UBT should be provided to ensure treatment success. For the older age group, for example, 40 years or older, the programmes would benefit from additional inclusion of serum pepsinogen testing, based on which individuals requiring endoscopic surveillance can be identified. The programme is likely beneficial in reducing gastric cancer burden for subpopulations such as immigrants or indigenous populations who are at higher risk of developing gastric cancer in the regions with low gastric cancer risk (ASR 6-10/100 000). For example, immigrants from regions with a high incidence of gastric cancer living in regions of lower incidence maintain a higher risk of gastric cancer and related mortality⁴²⁵ and could therefore be candidates for the programme. Implementation of the population-based *H. pylori* test-and-treat programmes in high gastric cancer incidence regions would allow evaluation of its application to high-risk groups in lower risk areas.

Statement 25: The use of genetic and epigenetic markers for gastric cancer risk assessment and gastric cancer progression in clinical management requires further validation.

Agreement 100%

Grade D2

Gastric cancer is a heterogeneous disease and the end point of a long and multistep process, which results from the stepwise accumulation of numerous genetic and epigenetic alterations, leading to dysregulation of oncogenic and tumour suppressor pathways. Although several of the molecular mechanisms underlying gastric cancer pathogenesis have been identified, there are currently no clinically validated biomarkers of gastric cancer risk or progression, except for those related with the diagnosis of the different forms of hereditary gastric cancer.⁴²⁶ The use of molecular biomarkers is limited to predictive biomarkers for selection of patients with advanced gastric cancer to therapy selection. These include HER2 amplification for anti-HER2 therapy, and MSI status determination for immunotherapy. In the foreseeable future, screening for genetic and epigenetic alteration in blood liquid biopsies for early diagnosis of gastric cancer is likely to occur.^{427–429}

Statement 26: Image-enhanced endoscopy (IEE) should be used in the endoscopy-based screening for dysplasia and early gastric cancer.

Agreement 100%

Grade A1

In endoscopic examination, a systematic examination procedure to cover entire mucosal areas should be adopted with photo- documentation. Recently, higher diagnostic yields have been described with new modalities of IEE, such as blue-laser imaging, linked-colour imaging (LCI), as compared with conventional white light imaging (WLI).^{430–434} The main reason for this high diagnostic yield may be due to enhanced colour difference obtained with LCI that facilitates detection of neoplastic lesions in the background of IM.^{430 435} At present, however, excellent results have been reported only from Japan and China, and therefore, the high diagnostic capability of LCI reported from these countries should be validated in other countries. Of note, another IEE modality, narrow band imaging even with

the second-generation system, failed to be superior to conventional WLI in detecting early gastric cancer, suggesting further improvements are needed.^{436 437}

Statement 27: There is still demand for a prophylactic and/or therapeutic vaccine.

Agreement 100%

Grade C1

A vaccine against *H. pylori* would constitute the most powerful tool to prevent gastric malignancies and other severe *H. pylori*-related complications. However an effective protective human vaccine has still not been developed despite of the high efficacy that was reported already some 30 years ago in animal experiments followed also by a series of encouraging results from studies conducted in humans.^{438 439}

The use of recombinant *H. pylori* antigens that were shown to induce a high specific humoral and cellular immune response in healthy volunteers failed to confirm sufficient protection from *H. pylori* infection when tested in a human challenge model.⁴⁴⁰

In contrast to the negative *H. pylori* challenge study in adults a large field trial conducted in Chinese children with the oral administration of a recombinant (urease-subunit :ure-B) oral vaccine provided strong evidence of protection,⁴⁴¹ but the study unfortunately had no follow-up. Given the epidemiological relevance of *H. pylori* infection, the burden of gastric cancer on the individual person's life and on health economics, an *H. pylori* vaccine may still merit consideration.⁴³⁹ Finally, in times of emerging antibiotic resistance development of a therapeutic *H. pylori* vaccine could provide an especially important contribution.

WG 5: *HELICOBACTER PYLORI* AND THE GUT MICROBIOTA

Statement 1: Early life antibiotic exposure has a long-lasting effect on the intestinal microbiota.

Agreement 100%

Grade B2

Antibiotics have a major impact on gut microbiota.^{442–444} Life-long prospective studies of the antibiotic impact on gut microbiota are lacking. However, data obtained from animal models, in infants and children suggest that antibiotics induce changes in microbiota composition and function that persist over many years. In infants, antibiotic exposure is associated with the initial depletion of microbiota diversity and has an effect on the abundance of several bacterial species. This effect could be measured during the entire duration of the study (up to 2 years).⁴⁴² Antibiotics, birth mode, and diet shape microbiome maturation during early life. The impact of antibiotic use on the microbiota of healthy Finish preschool children (age 2–7 years) could be shown even 24 months after antibiotic application, and the impact of the change was more pronounced for macrolide than for penicillin(β -lactam) type antibiotic.⁴⁴⁵ Microbiota change induced by macrolides was associated with increased risk of asthma and antibiotic-associated weight gain.⁴⁴⁵ Another study from the same group showed that when given to infants both penicillin and macrolide antibiotics have a significant impact on the course of microbiota development.⁴⁴⁶ It could be shown that multiple antibiotic treatments of children (followed until the age of 3) have a dramatic impact on gut microbiota composition. In addition to the compositional shifts the microbiota of antibiotic-treated children had significantly more species dominated by a single strain. On the functional level, antibiotic treatment significantly enriched antibiotic resistance genes.⁴⁴⁷ Of note, at age of

3, the total abundance of species belonging to Ruminococcaceae and Lachnospiraceae as inducers of T regulatory immune cells was significantly reduced in antibiotics treated children.⁴⁴⁷ A study on premature hospitalised infants treated with antibiotics showed that antibiotics had a dramatic and rapid impact on microbial diversity and composition.⁴⁴⁸ With increasing age, microbiota of preterm infants despite the strong effect of hospitalisation and antibiotic treatment develops towards microbiota of full-term infants. The difference between antibiotic-naïve and treated children decreases with age.⁴⁴⁸ Given that changes of microbiota following antibiotic course in children are evident months after antibiotic application, a complete 'reset' of the microbiota composition towards 'naïve' composition is a highly unlikely event, even if the developmental trends are similar in the affected and naïve ecosystems. Early exposure to macrolide-type antibiotics in animals induced long-lasting changes of microbiota and increased susceptibility to *Citrobacter rodentium*-induced colitis.⁴⁴⁹ Although low dose penicillin exposure did not induce a long-lasting change in gut microbiota composition in mice, the treatment had long-lasting metabolic consequences.⁴⁵⁰ Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. This suggests that even if compositional changes cannot be pinpointed, on a functional level, microbiota communities are permanently changed. A meta-analysis of different cohort studies showed that exposure to different antibiotic classes was associated with different risks for IBD development. Use of antibiotics is an important risk factor for Crohn's disease in children <18 years.⁴⁵¹

Statement 2: The human stomach is colonised by other bacteria beyond *H. pylori*, the so-called gastric microbiome.

Agreement 94%

Grade A1

The human stomach harbours its own specific microbial community.⁴⁵² Its composition depends on physiological conditions in this unique ecological niche. *H. pylori* is the only resident component that has been thoroughly characterised, but other transient bacteria were characterised using culture-independent molecular approaches (eg, 16S rRNA gene and transcripts sequencing). Current data are based on 16S rRNA-based next-generation sequencing approaches under healthy conditions and along malignant transformation of the gastric mucosa.^{453–455} Several studies on the gastric bacteria indicate a distinct gastric microbial pattern with Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria and Proteobacteria as the dominating phyla, and Streptococcus as the most dominant genus.^{456 457}

The composition of the mucosal gastric microbiota differs significantly from the luminal composition which resembles the oral cavity.⁴⁵⁸ This suggests the oral cavity as the main source of gastric bacteria. *H. pylori* significantly impacts on the composition of gastric microbiota and represents the most abundant species in infected subjects.^{457–459}

H. pylori uninfected subjects have a significantly higher bacterial enrichment of Firmicutes, Fusobacteria, Bacteroidetes, and Actinobacteria at phylum level compared with *H. pylori*-infected subjects.⁴⁶⁰ Changes in physiological conditions as acidity and the appearance of gastric cancer lead to distinct changes of bacterial communities.⁴⁵² A decreased microbial diversity and a decreased abundance of *H. pylori* was depicted in biopsies along the Correa cascade with increasing trends of Firmicutes and Proteobacteria, whereas Bacteroidetes significantly decrease.^{461–464} These findings indicate that the human stomach harbours a complex microbial community which is composed of resident and transient bacteria.

Thus far, only *H. pylori* has been demonstrated to be able to infect, adhere and persist in the human stomach.

Statement 3: Gastric bacteria other than *H. pylori* may also affect *H. pylori*-related changes.

Agreement 91%

Grade B2

Over the past few years, several studies have reported altered gastric microbiome profiles that develop as a complication of *H. pylori*-related gastritis. Reduced acid secretion in the atrophic stomach creates favourable conditions for the growth of a number of microorganisms that would otherwise not survive in low gastric pH of healthy individuals. Although the concept of true gastric microbiome is still evolving,⁴⁶⁵ deregulation of bacterial communities has been identified both in premalignant *H. pylori* associated gastric conditions and gastric cancer.⁴⁶⁴ Gastric cancer microbiome profiling studies show that the most enriched microbiota species are *Lactobacillus* spp.^{461 466 467}; Streptococcaceae,^{467–469} *Staphylococcus* spp.,^{466 470} *Clostridium* spp.^{461 466} and *Fusobacterium* spp.^{466 467 471} Several species from the oral cavity are also frequently enriched in gastric cancer including *Prevotella*, *Veillonella*,^{466 471} *Citrobacter* and *Rhodococcus*.⁴⁶¹ It is also worth pointing out that results from different gastric microbiome profiling studies remain partly conflicting.⁴⁶⁴ Furthermore, the clinical relevance of these findings remains unclear, but a recent study showed that *Fusobacterium nucleatum* is associated with worse prognosis in diffuse type gastric cancer.⁴⁷² The turning point of microbiome deregulation in the stomach due to *H. pylori* infection remains to be defined. Interestingly, no differences in overall microbial profiles were found in patients with non-atrophic and atrophic *H. pylori* gastritis.^{461 473 474} Meanwhile, decreased microbiome diversity in IM was found in comparison with chronic gastritis.⁴⁶⁷ Furthermore, a recent comprehensive study aimed to explore the possible microbial mechanisms in gastric carcinogenesis and potential dysbiosis arising from *H. pylori* infection.⁴⁷¹ This study showed strong complex interactions in gastric microbiota between *H. pylori* and Fusobacteria, *Neisseria*, *Prevotella*, *Veillonella* and *Rothia* species that were found only in patients with advanced gastric lesions and were absent in the normal/superficial gastritis group. In particular, this study emphasised the detected complex interactions of *Neisseria* and *Prevotella* species with *H. pylori* in gastric advanced preneoplastic lesions. Overall, *H. pylori* remains the major bacterial trigger of gastric diseases but an increasing number of studies suggest that other non-*Helicobacter* micro-organisms may contribute to *H. pylori* induced changes in the stomach. However, the mechanisms and pathways of these interactions remain poorly understood.

Statement 4: Non-*H. pylori* *Helicobacter* species can cause human gastric disease.

Agreement 91%

Grade C2

Many novel *Helicobacter* species other than *H. pylori* have been identified.⁴⁷⁵ Most of the reported new *Helicobacter* species have been identified in animals. Furthermore, some of these new species were also detected in humans including *H. bilis*, *H. cinaedi*, *H. fennelliae*, *H. caesarodunensis*, *H. burdigaliensis* and *H. labetoulli*. Despite emerging data on non-*H. pylori* *Helicobacter* species and their role in human diseases, most of the reported associations are based on limited quality of evidence. Data on association between non-*H. pylori* *Helicobacter* species and extraintestinal diseases come from studies on extrahepatic cholangiocarcinoma,^{476 477} Parkinson's

disease,⁴⁷⁸ colorectal cancer⁴⁷⁹ and many other clinical entities, but solid associative evidence is lacking. Few case reports showed that *H. cinaedi* infections occur more often in immunocompromised patients.^{480–482} In addition, cases of bacteraemia of non-*H. pylori* *Helicobacter* species have been reported.^{483 484} Multiple non-*H. pylori* *Helicobacter* species have been linked with various gastric conditions in patient cohorts, case series or case reports including dyspepsia,⁴⁸⁵ gastritis,^{486 487} peptic ulcer disease,^{488 489} gastric cancer⁴⁹⁰ and gastric mucosa-associated lymphoid tissue lymphoma.^{491 492} In addition, numerous case reports have been published revealing associations with gastroenteritis.^{493 494} One of the remaining challenges is the correct identification of specific non-*H. pylori* *Helicobacter* species that are sometimes still misclassified as '*H. heilmannii*'⁴⁹⁵ and difficulties in identification due to uneven colonisation of the stomach.⁴⁹⁶ Overall, despite several reported associations, the role of non-*H. pylori* *Helicobacter* species in human gastric diseases requires further research and novel technologies including metagenomic sequencing, which might bring the required progress in the field.^{497 498}

Statement 5: *H. pylori* eradication therapy has the potential to select resistant strains of gut microbiota.

Agreement 89%

Grade B2

Antibiotics used for *H. pylori* eradication therapy might lead to the evolution of resistant strains in the gut microbiota. So far only a very few studies have investigated this association. Jakobsson and colleagues reported persistent macrolide resistance in the host's microbiota (eg, *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Bacteroides* spp.) after triple eradication therapy using omeprazole, clarithromycin and metronidazole.⁴⁹⁹ A quadruple *H. pylori* eradication therapy decreased alpha-diversity of the gut microbiome and *Bifidobacterium adolescentis* abundance, whereas abundance of *Enterococcus faecium* increased.⁵⁰⁰ Furthermore, certain microbial resistome profiles such as *ermB* conferring resistance to macrolides and *tetQ* genes to tetracycline were enhanced.⁵⁰⁰ Ampicillin and amoxicillin both lead to an increase in carbapenem-resistant Enterobacteriaceae via promoting transmission of the multidrug-resistant (MDR)-encoding plasmid bla New Delhi Metallo-beta-lactamase-1 in the gut microbiome.⁵⁰¹ Diet may have an additive effect on antibiotic-induced antimicrobial resistance. Experimental data suggest that a high fat diet alone leads to loss of Bacteroidetes and the promotion of MDR pathobionts including CR extended-spectrum beta-lactamase-producing *Serratia marescens*, an effect which was further enhanced by antibiotic usage.⁵⁰² Widespread use of antibiotics in food production has led to emergence of commensal antibiotic resistant bacteria in the human gut and these strains may act as a reservoir of antibiotic resistance genes and a source of spreading antibiotic resistance. Human studies comparing omnivores, ovo-lacto vegetarians and vegans have shown that omnivores tended to have higher rates of antibiotic resistance compared the latter two groups.⁵⁰³ In summary, more information is needed on how various *H. pylori* eradication strategies affect the promotion of resistant strains and resistome profiles of commensals and especially regarding the additional effects of cofounders such as diet.

Statement 6: Certain probiotics have been shown to be effective in reducing GI side effects caused by *H. pylori* eradication therapies.

Agreement 89%

Grade A2

A growing number of systematic reviews and meta-analyses of RCTs have evaluated the efficacy of probiotics in decreasing side effects caused by *H. pylori* eradication therapies, with

overall positive findings. Some showed conflicting results.^{504–511} However, several meta-analyses have pooled together data from studies differing by probiotic species/strain, length of therapy, dosages, risk, also incorporating assessments of bias.⁵¹² More recently, some meta-analyses have focused on specific probiotics. Meta-analyses on Lactobacilli have overall shown that this genus can be effective in decreasing side effects associated with *H. pylori* antibiotic therapy^{504 505 507 508} especially if the probiotic therapy is given for more than 2 weeks.⁵⁰⁵ Beyond Lactobacilli, *Saccharomyces boulardii* has also been investigated in several meta-analyses, with a risk reduction of overall adverse events ranging from 0.44 to 0.47.^{509 512 513} In conclusion, certain probiotics (some Lactobacilli and *S. boulardii*) have been shown to be effective in alleviating adverse events associated with *H. pylori* eradication therapy

A fermented milk containing *L. paracasei* CNCM I-1518 and I-3689 and *L. rhamnosus* CNCM I-3690 did not improve antibiotic associated diarrhoea and GI symptoms in a selected population of young adults who underwent *H. pylori* eradication treatment for 14 days in a randomised trial.⁵¹⁴ It may well depend which cohort of patients is included as side effects due to antibiotics intake are more likely to occur in fragile populations. Non-viable *L. reuteri* DSM17648 could not improve *H. pylori* eradication rates but reduced abdominal complaints. Both study medications seem to have the potential to induce a significant faster recovery of GI microbiota.^{511 514 515}

Statement 7: Certain probiotics may have a beneficial effect on *H. pylori* eradication therapy through reduction of antibiotic-related side effects

Agreement 80%

Grade B2

Probiotics are known to inhibit *H. pylori* by multiple pathways, including the production of antimicrobial substances, or the competition with *H. pylori* for colonisation and survival. Different meta-analyses of RCTs have assessed the efficacy of probiotics in increasing the efficacy of *H. pylori* eradication therapies, showing overall positive findings,^{504–510} but subgroup analysis, has shown that this benefit only applies to specific strains, including different strains of *Lactobacillus* spp.^{504 505 508} *Bifidobacterium* spp.,^{504 505} and *S. boulardii*.⁵⁰⁵ These data confirm the bias that can arise from pooling together studies investigating different probiotics.⁵¹¹ Finally, in three meta-analyses, *S. boulardii* was shown to increase the *H. pylori* eradication rate, with respectively, an RR of 1.13 (95% CI 1.05 to 1.21),⁵¹² 1.11 (95% CI 1.06 to 1.17),⁵¹³ 1.09.⁵⁰⁹ Despite these promising data, probiotics appear to increase *H. pylori* eradication rate by reducing side effects related to eradication therapy, rather than through direct effects on *H. pylori*. Consequently, more data are still necessary to assess the direct efficacy of probiotics against *H. pylori*.

Statement 8: Antibiotic treatment for other reasons might select resistant *H. pylori* strains

Agreement 97%

Grade B2

Antibiotic treatments for other reasons may have the potential to select resistant *H. pylori* strains. The absence of significant amoxicillin resistance among *H. pylori* strains after decades of treatment indicates the inability of the pathogen to adapt to penicillin exposure. Despite the unknown cumulative doses of antibiotics for different reasons and also the timepoint of *H. pylori* infection, associations between increased macrolide and quinolone consumption and the proportion of *H. pylori* resistance to

these drugs were shown in European studies.^{116 117 516} A possible analogy can be seen in the development of increasing resistance rates after prior unsuccessful *H. pylori* eradication therapies with quinolones, macrolides and metronidazole in different cohorts.^{194 517–519} Prospective trials capturing cumulative doses of antibiotics on *H. pylori* resistance are lacking.

Statement 9: The oral cavity may contribute to the gastric microbiota composition

Agreement 86%

Grade A2

Studies on bacterial communities in gastric fluid demonstrated significant concordance with microbial networks from the oral cavity. Distinct differences between mucosal and luminal microbiota profiles were shown in the human stomach.^{458 459} Neighbouring ecological niches have been shown to harbour overlapping bacterial communities based on permanent transport of substances such as saliva and sputum.⁵²⁰ Approximately 600 swallowing acts per day lead to a transfer of oral bacteria into the stomach.^{521 522} Disseminated bacteria from the oral cavity are associated with different GI disorders. Since gastric acid is a bottleneck for swallowed bacteria, several metabolically active bacteria from the saliva were detected in the stomach and duodenum suggesting incomplete denaturation of transient bacteria.^{458 523}

Looking forward

It has become usual for the quinquennial Maastricht *H. pylori* Guidelines Initiative to summarise the latest advances and provide a consensus guidance for those in clinical practice to implement the most effective and practical approach into their everyday patient care and thus achieve optimal outcomes.

These are often challenging objectives and we are aware that not all that is feasible for clinical practice in the academic setting can be translated so readily to practice elsewhere, for reasons of logistics, health economics or differences in national healthcare systems.

In the next 5 years, we face critical issues which we need to address including, first, the mission of global prevention of gastric cancer. This we could achieve by providing a healthy stomach for all. This would be a *Helicobacter pylori* free stomach achieved by adopting population based test-and-treat strategies which are designed to consider local prevalence, circumstances and needs.

The second is better to understand and control antibiotic resistance, which continues a dramatic increase. We are making considerable advances and it is clear that the selection of treatments will require the systematic use of molecular resistance testing which is now increasingly available in some centres. These molecular tests are proving increasingly dependable in gastric mucosal biopsies and stool samples both for accurate diagnosis and also to detect resistance to various antibiotics but particularly clarithromycin.

Third will be the improvements in potential treatments/combinations, including achievement of optimal acid suppression, where progress with the P-CAB class of antisecretory drugs needs the exploration of drug dose and timing and the prospects of a dual therapy. Future studies are needed to optimise these possibilities, especially in non-Asian populations, where the predominance of the data exist.

Finally, there is hope for novel antibiotics and as we better understand the role of the gastric microbiome, the administration of selective probiotics may find a role.

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general comment: please separate the collaborators from their institutions in bolt letters

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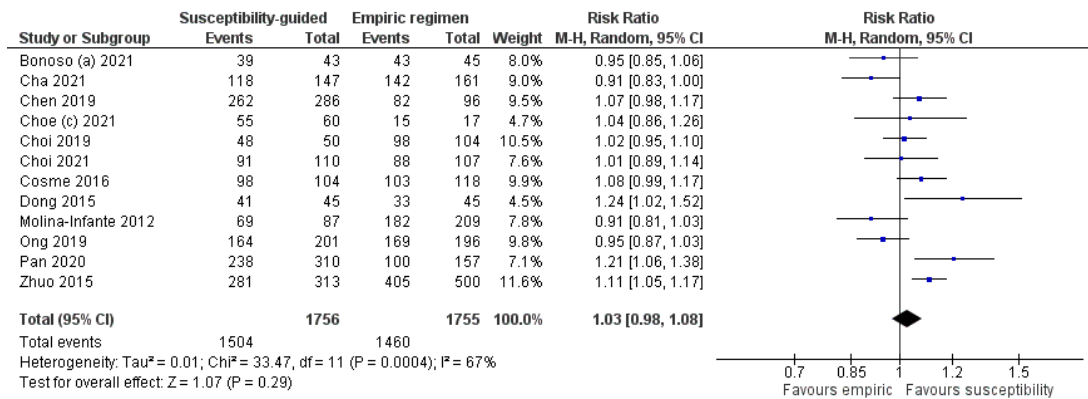
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Susceptibility-guided treatment	Empirical treatment
<p>Advantages:</p> <ul style="list-style-type: none"> • Provide personalized treatment • Reduce unnecessary antibiotic prescription • Limit the emergence of antibiotic resistance worldwide • Allow performing resistance surveys over time • Might allow prescribing the optimized clarithromycin-based triple therapy to patients with clarithromycin-susceptible strains in areas with high overall clarithromycin resistance • Molecular testing on gastric biopsies is a highly accurate diagnostic method. <p>Limitations:</p> <p>While molecular tests based on gastric biopsies benefit from a long experience, it is not the same with stool samples. However novel commercial molecular kits have recently become available.</p> <ul style="list-style-type: none"> • An endoscopy is required to obtain gastric biopsies which is expensive and uncomfortable • Low rate of acceptance of endoscopy by patients • Since most endoscopy findings are normal this procedure does not contribute to management in young patients (age below 50 years) • Culture is time-consuming and requires expertise • Culture is not always available on a routine basis • Culture provides information for all antibiotics but it is useful only for clarithromycin and quinolones • Metronidazole testing is not reproducible and has an imperfect correlation between <i>in vitro</i> and <i>in vivo</i> results • Expensive (mainly because of endoscopy) 	<p>Advantages:</p> <ul style="list-style-type: none"> • “Test-and-treat” strategy for dyspepsia is recommended by all consensus conferences (for young patients without alarm symptoms) • Resistance to amoxicillin , tetracycline and rifabutin is extremely rare, so they can be empirically prescribed • No <i>in vitro</i> resistance to bismuth has been described, so it can be also empirically prescribed • <i>in vitro</i> metronidazole resistance has a limited impact on the efficacy of treatments when sufficiently long treatments and high metronidazole doses are used • The position in the case of failure is clear: not to re-administer any of the antibiotics against which <i>H. pylori</i> has probably become resistant • Rifabutin and furazolidone are good alternatives for empirical treatment after several eradication failures • Cumulative <i>H. pylori</i> eradication rate with several successive rescue therapies empirically prescribed reaches almost 100% <p>Limitations:</p> <ul style="list-style-type: none"> • Resistance of <i>H. pylori</i> to antibiotics has reached alarming levels worldwide • Empirical treatment may increase the emergence of antibiotic resistance worldwide • In some cases, it will imply prescribing an antibiotic that will lack efficacy • Increase unnecessary antibiotic prescription • Does not allow performing resistance surveys • Does not provide personalized treatment • May induce transient increase of antibiotic resistance to certain other bacteria • May induce short-term perturbation of gut microbiota after <i>H. pylori</i> eradication

Author	Year	Country	Treatment order	Duration (days)	Eradication n/N (intention-to-treat, %)
Bago [257]	2007	Croatia	First	7	57/66 (86%)
Cao [258]	2015	China	First	14	117/141 (83%)
Fu [259]	2017	China	First	14	167/200 (84%)
Gan (a) [260]	2018	China	First	14	155/200 (78%)
Gan (b) [260]	2018	China	First	14	155/187 (83%)
Gao [261]	2010	China	First	10	60/72 (83%)
Gisbert [253]	2015	Spain	Second	14	180/200 (90%)
Hsu [262]	2008	Taiwan	Third	10	31/37 (84%)
Aksoy [263]	2017	Turkey	First	14	93/111 (84%)
Liao [264]	2013	China	First	14	70/80 (88%)
Song [265]	2016	China	Second	14	97/132 (74%)
Yee [266]	2007	China	≥ Second	7	37/51 (73%)

Gan (a): levofloxacin 500 mg/24h; Gan (b): levofloxacin 200 mg/12h.

Author and Reference	Year of publication	Number of patients	Previous (failed) treatments	Duration (days)	Eradication (%)
<i>Gatta et al. [275]</i>	2005	151	1 st : PPI+C+A or M 2 nd : PPI+C+A or M;	7-14	76
<i>Gisbert et al [276]</i>	2006	100	1 st : PPI+C+A 2 nd : Q	10	60
<i>Gisbert et al [277]</i>	2006	20	1 st : PPI+C+A 2 nd : Q	10	85
<i>Hsu et al [262]</i>	2008	37	1 st : PPI+C+A 2 nd : Q	10	84
<i>Rokkas et al [278]</i>	2009	30	1 st : PPI+C+A 2 nd : Q	10	70
<i>Gisbert et al [279]</i>	2012	200	1 st : PPI+C+A 2 nd : Q	10	68
<i>Burgos-Santamaría [280]</i>	2019	65	1 st : PPI+C+A 2 nd : Q	7-14	75
<i>Burgos-Santamaría [280]</i>	2019	19	1 st : PPI+C+A 2 nd : Q	14	84
<i>Burgos-Santamaría [281]</i>	2021	39	1 st : PPI+C+A±M 2 nd : Q	10-14	74
<i>Burgos-Santamaría [281]</i>	2021	28	1 st : PPI+C+A±M 2 nd : Q	14	75

PPI: proton pump inhibitor; C: clarithromycin; M: metronidazole; A: amoxicillin; Q: bismuth-containing quadruple therapy (PPI, bismuth, tetracycline and M).

[†]Bismuth was added to the triple regimen with a proton pump inhibitor, amoxicillin, and levofloxacin.

METABOLISM
<ul style="list-style-type: none"> • Metabolic syndrome and diabetes mellitus (DM) <p><i>For:</i> Chen <i>et al.</i>[524], Yang <i>et al.</i> [525] <i>Against:</i> Naja <i>et al.</i>[526], Wada <i>et al.</i> [527]</p>
LIVER DISEASE
<ul style="list-style-type: none"> • Non-alcoholic fatty liver disease (NAFLD) <p><i>For:</i> Kim <i>et al.</i>[528], Ning <i>et al.</i>[529] <i>Against:</i> Okushin <i>et al.</i>[530]</p>
CARDIOVASCULAR DISEASES
<ul style="list-style-type: none"> • Coronary artery disease (CAD) <p><i>For:</i> Yu <i>et al.</i>[531]. <i>Against:</i> Schottker <i>et al.</i>[532]</p>
NEUROLOGIC DISEASES
<ul style="list-style-type: none"> • Stroke <p><i>For:</i> Wang <i>et al.</i> [533], Alvarez-Arellano <i>et al.</i> [534] <i>Against:</i> Chen <i>et al.</i> [535]</p> <ul style="list-style-type: none"> • Alzheimer's disease <p><i>For:</i> Huang <i>et al.</i>[536], Roubaud Baudron <i>et al.</i>[537], Beydoun <i>et al.</i>[538], Kountouras <i>et al.</i>[539], Kountouras <i>et al.</i>[540], Kountouras <i>et al.</i>[541], Santos <i>et al.</i> [542], Kountouras <i>et al.</i> [543], Zelaya <i>et al.</i> [544], Attems J <i>et al.</i> [545], Thomann <i>et al.</i> [546], Forster <i>et al.</i> [547], Chang <i>et al.</i>[548] <i>Against:</i> Shiota <i>et al.</i> [549]</p> <ul style="list-style-type: none"> • Multiple sclerosis <p><i>Against:</i> Mohebi <i>et al.</i>[550], Cook <i>et al.</i>[551]</p> <ul style="list-style-type: none"> • Parkinson's disease <p><i>For:</i> Shen X <i>et al.</i>[552], Huang HK <i>et al.</i> [553], Fasano <i>et al.</i> [554], Tan <i>et al.</i> [555], Mridula <i>et al.</i> [556], Candelario-Jalil <i>et al.</i> [557], Lo <i>et al.</i> [558], Dobbs <i>et al.</i> [559]</p> <ul style="list-style-type: none"> • Guillain-Barré syndrome <p><i>For:</i> Kountouras <i>et al.</i> [560], Moran <i>et al.</i> [561], Chiba <i>et al.</i>[562]</p>
DERMATOLOGICAL DISEASES
<ul style="list-style-type: none"> • Rosacea <p><i>For:</i> Gravina <i>et al</i> [563], Argenziano <i>et al</i> [564], El-Khalawany <i>et al</i> [565]</p> <ul style="list-style-type: none"> • Psoriasis <p><i>For:</i> Qayoom <i>et al</i> [566], Mesquita <i>et al</i>[567], Ribaldone <i>et al</i> [568], Onsun <i>et al</i> [569] <i>Against:</i> Campanati <i>et al</i> [570], Azizzadeh <i>et al</i> [571]</p> <ul style="list-style-type: none"> • Chronic urticaria <p><i>For:</i> Hizal <i>et al</i> [572], Galadari <i>et al</i> [573], Yoshimasu <i>et al</i> [574] <i>Against:</i> Campanati <i>et al</i> [575]</p> <ul style="list-style-type: none"> • Alopecia areata <p><i>For:</i> Behrangi <i>et al</i> [576] <i>Against:</i> Rigopoulos <i>et al</i> [577]</p> <ul style="list-style-type: none"> • Autoimmune bullous diseases <p><i>For:</i> Sagi <i>et al</i>[578], Mortazavi <i>et al</i>[579]</p> <ul style="list-style-type: none"> • Schöenlein-Henoch purpura <p><i>For:</i> Novák <i>et al</i>[580], Grivceva-Panovska <i>et al</i> [581], Hoshino <i>et al</i> [582]</p>
OCULAR DISEASES
<ul style="list-style-type: none"> • Open-angle glaucoma <p><i>For:</i> Zeng J <i>et al</i> [583], Testerman <i>et al</i>[77] <i>Against:</i> Galloway <i>et al</i> [584], Kurtz <i>et al</i> [585]</p> <ul style="list-style-type: none"> • Central serous chorioretinitis <p><i>For:</i> Casella <i>et al</i> [586], Liu <i>et al</i> [587], Cotticelli <i>et al</i> [588], Rahbani-Nobar <i>et al</i> [589], Dang <i>et al</i> [590] Zavoloka <i>et al</i> [591]</p> <ul style="list-style-type: none"> • Blepharitis <p><i>For:</i> Saccà <i>et al</i>[592] <i>Against:</i> Saccà <i>et al</i> [593]</p>