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BELGIAN CONSENSUS FOR HELICOBACTER PYLORI MANAGEMENT 2023

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection causes chronic gastritis, peptic ulcers and gastric cancer. Although *H. pylori* prevalence is decreasing worldwide, regional variations exist in Europe, with the lowest infection prevalence in Northern Europe, and the highest in Eastern and Southern Europe. (1) Changes in the treatment recommendations and the increasing available evidence have justified the implementation of new recommendations since last Belgian consensus in 1998 (2). Several non-*H*. *pylori Helicobacter* species (N*H.PYLORI-H*), colonizing the stomach of domestic animals, also have the ability to cause gastric disease in humans, although to a lesser extent. These zoonotic N*H. PYLORI*H are not the subject of the current recommendations.

METHODS

The Belgian Helicobacter pylori and Microbiota Study Group (BHMSG) commissioned these recommendations and appointed a coordinator (RG-D) who invited the listed authors to the project development. The key questions were prepared by the coordinator and then approved by the other members. The coordinator formed task force subgroups, each with its own leaders, who were assigned key questions. Each task force performed a systematic review of the scientific evidence and developed a series of recommendations that were subjected to a process of iterative voting. All members of the BHMSG were invited to participate, including gastroenterologists, microbiologists, pathologists, and paediatricians. The team members were instructed to scrutinize the literature for relevant articles pertaining to their fields of expertise. For bibliographic research, priority was given to identifying systematic reviews and other critical synthesis documents of the scientific literature. In a second phase, a search for individual studies, randomized clinical trials and observational studies was carried out, as well as a review of the bibliographic references of the included papers up to August 2022.

The team leaders initially developed the recommendations and various web meetings were held to discuss and resolve issues. The recommendations resulting from the online voting were discussed and approved during a face-to-face meeting, which took place in Brussels in May 2022. After each vote, the coordinator reviewed the recommendations according to the comments and votes received, integrating the suggestions to maximize the agreement. They were then subjected to anonymous voting interaction process using the Delphi method. For each recommendation, participants rated their level of agreement on a 6-point Likert scale (1: strongly disagree; 2: disagree; 3: somewhat disagree; 4: somewhat agree; 5: agree; 6: strongly agree). Any rating lower than 6 obliged the coordinators to review each of the sections of the recommendation (wording, degree of evidence, strength of the recommendation and justification) and make suggestions for improvement. A recommendation was endorsed if more than 80% of the participants agreed (score 4-6 on

the Likert scale). The Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) system was used to classify the scientific evidence and the strength of the recommendations. (3) The GRADE system is a structured and explicit grading process that is being widely adopted at the inter- national level, with the advantage of overcoming the limitations of previous systems and homogenizing the recommendation formulation system for all institutions. (4) Each recommendation is accompanied by the grade of recommendation (GR; strong or weak), the quality of evidence (QE; high, moderate, low or very low) and a discussion of the corresponding evidence. In August 2022, a final draft was sent to all group members for review. After agreement of the final version, the manuscript was submitted to Acta Gastroenterologica for publication. This Consensus document has been endorsed by the BHMSG, which has adhered to and supports the consensus recommendations. No funding was provided by any pharmaceutical company.
These recommendations were issued in 2023 and will be considered for review and update in 2028 or sooner if new and relevant evidence becomes available.

Keywords: *Helicobacter pylori*, Recommendations, Diagnosis, Treatment, Belgium

ABBREVIATIONS

A	**Amoxicillin**
AST	**Antimicrobial susceptibility testing**
C	**Clarithromycin**
CR	**Clarithromycin Resistance**
CS	**Clarithromycin Sensitive**
IDA	**Iron deficiency Anaemia**
H. pylori	***Helicobacter pylori***
LS	**Levofloxacin Sensitive**
LR	**Levofloxacin Resistance**
M	**Metronidazole**
MALToma	**Mucosa-associated lymphoid tissue lymphoma**
NSAIDS	**Non-Steroidal Anti-inflammatory Drugs**
PAC	**PPI-Amoxicillin-Clarithromycin**
PAM	**PPI-Amoxicillin-Metronidazole**
PAMC	**PPI-Amoxicillin-Metronidazole-Clarithromycin**
PBMT	**PPI-Bismuth-Metronidazole-Tetracycline**
PCR	**Polymerase chain reaction**
PMC	**PPI-Metronidazole-Clarithromycin**
PPI	**Proton pump inhibitors**
RAC	**Regular arrangement of collecting venules**
RUT	**Rapid Urease Testing**
UBT	**Urea Breath Test**

KEY QUESTIONS

1: Epidemiology.

- *1.1. What is known about the epidemiology of H. pylori infection in Belgium?*
- *1.2. Which are the high-risk groups?*
- *1.3. Is there a risk of reinfection and how is it transmitted?*

2: Indications.

- *2.1. What are the main indications to test and treat H. pylori infection?*
- *2.2. When H. pylori eradication can be considered?*
- *2.3. Does H. pylori eradication prevent gastric cancer?*
- *2.4. Screening and treating everyone?*

3: Diagnosis.

- *3.1. When to use invasive and non-invasive tests?*
- *3.2. Do we need to stop PPIs?*
- *3.3 When to use immunohistochemical testing?*
- *3.4. Are there endoscopic findings of H. pylori infection and how to biopsy?*

4: Resistance.

- *4.1. What do we know about H. pylori antimicrobial resistance in Belgium?*
- *4.2. How to manage metronidazole resistance?*
- *4.3. What methods can be used to evaluate H. pylori antibiotic resistance and when should AST be performed?*

5. First line treatment.

- *5.1. What are the first-line treatment strategies in Belgium?*
- *5.2. What to do in case of penicillin allergy?*
- *5.3. What PPI to choose?*
- *5.4. Should we test for treatment success after H. pylori eradication therapy?*

6. Refractory management.

- *6.1. When is H. pylori considered refractory?*
- *6.2. When primary therapy fails, what are the options for salvage therapy? When to use rifampicin?*
- *6.3. What about adjuvant therapies?*
- *6.4. Which patients need long-term follow-up after eradication?*

7. Special populations.

- *7. 1. What to do in HIV patients?*
- *7.2. What to do in children and teenagers?*

RECOMMENDATIONS

1.1. The prevalence of *H. pylori* infection is decreasing, especially in children. .....
Strong recommendation, high quality evidence.
1.2. Factors influencing the risk for infection with *H. pylori* are ethnicity, socio-economic background, education level, living in an urban or rural area and family history of previous *H. pylori* infection. .....
Strong recommendation, high quality evidence.
1.3. Transmission occurs mainly through mother-to-child contact in childhood. Risk of *H. pylori* reinfection remains low.....
Strong recommendation, moderate quality evidence.

2.1 Testing for *H. pylori* is strongly recommended in patients with active or history of peptic ulcer disease, active or family history of (early) gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma (MALToma). .....
Strong recommendation, high quality evidence.
2.2 Testing is recommended in adults with dyspepsia, before chronic use of proton-pump inhibitors (PPIs) or non-steroid anti-inflammatory drugs (NSAIDs), immune thrombocytopenic purpura (ITP), unexplained iron deficiency anemia (IDA) and prior to bariatric surgery…..
Strong recommendation, moderate quality evidence.
2.3. Eradication of *H. pylori* prevents gastric cancer. However, the incidence of gastric cancer in patients with premalignant lesions at baseline will not be affected by eradication.....
Strong recommendation, high quality evidence.
2.4. Every person with an indication for testing who has a positive test result should be treated. There is currently no evidence in favor of a population wide screening strategy in the prevention of gastric cancer. .....
Strong recommendation, moderate quality evidence.

3.1. *H. pylori* infection can be diagnosed using invasive (endoscopy with biopsies for rapid urease testing (RUT), histology, culture or molecular diagnosis) and non-invasive methods (serology, urea breath test (UBT) and stool antigen test). Clinical factors and performances of diagnostic tests need to be considered when choosing the appropriate test. .....
Strong recommendation, high quality evidence.
3.2. PPIs should be discontinued at least 2 weeks before testing for *H. pylori* infection. Antibiotics and bismuth compounds should be discontinued at least 4 to 6 weeks before the test.....
Strong recommendation, high quality evidence.
3.3 *H. pylori* detection by immunohistochemistry (IHC) should be used routinely.....
Strong recommendation, moderate quality evidence.
3.4 A minimum of 4 gastric biopsies needs to be taken from the antrum and the body of the stomach for the assessment of *H. pylori*-induced gastritis. Consider additional biopsies for AST and from incisura for the detection of precancerous lesions. Regular arrangement of collecting venules (RAC) has a high sensitivity for *H. pylori*-negative patients, avoiding supplementary biopsies for AST in these patients……..
Strong recommendation, moderate quality evidence.

4.1. Resistance to clarithromycin in Belgium demonstrates regional variations and is between 13.5% and 19.8 %. Resistance to nitro-imidazoles varies from 29.7% to 51.6%, as well as resistance to fluoroquinolones from 22.2% to 31.7%. Resistance to amoxicillin and tetracycline remains very low. .....

Strong recommendation, high quality evidence.

4.2. Resistance to nitro-imidazoles is relative and can be overcome by increasing the frequency, doses or duration of therapy. .....

Strong recommendation, moderate quality evidence.

4.3. AST can be performed either by a standard method after culture or by a molecular test on the gastric biopsy specimen. In case of both empirical *H. pylori* treatment failures, AST is recommended to guide the rescue treatment. If an endoscopy is carried out, it is recommended to perform AST in RAC negative patients from populations or regions with well-documented high clarithromycin resistance > 15%.....

Strong recommendation, moderate quality evidence.

5.1. The empirical first-line treatment in adults would be either a concomitant non-bismuth quadruple therapy (PPI, clarithromycin, amoxicillin and metronidazole) for 14 days or a quadruple combination with bismuth (PPI, bismuth, tetracycline and metronidazole) for 10 days.

If clarithromycin resistance has been excluded by AST, a classical clarithromycin based triple therapy can still be used for 14 days.

Fluoroquinolones are not recommended without prior AST.....

Strong recommendation, moderate quality evidence.

5.2. Classic bismuth-containing quadruple therapy is the best choice in first-line treatment in case of penicillin allergy in adults. .....

Strong recommendation, high quality evidence.

5.3. Esomeprazole 2 x 40 mg and rabeprazole 2 x 20 mg are more powerful than other PPIs and less sensitive to variations in CYP2C19; therefore, they are the best choice for *H. pylori* eradication. .....

Strong recommendation, moderate quality evidence.

5.4. We recommend confirmation of successful eradication testing, especially prior to bypass bariatric surgery. .....

Strong recommendation, high quality evidence.

6.1. In the clinical setting, *H. pylori* infection is considered refractory when failing two eradication attempts. .....

Strong recommendation, low quality evidence.

6.2. In case of failure of 2 prior therapies, we recommend a 14-days AST based therapy. Consider increasing dosage of PPIs, amoxicillin or metronidazole. Consider rifampicin if all options have been used and eradication is mandatory.....

Strong recommendation, moderate quality of evidence.

6.3. Probiotics and N-acetylcysteine are not recommended as an adjuvant therapy for *H. pylori* infection. .....

Strong recommendation, moderate quality of evidence.

6.4. We recommend long-term follow-up in patients with intestinal metaplasia and family history of gastric cancer, incomplete intestinal metaplasia, advanced atrophic gastritis or persistent *H. pylori* infection. .....

Strong recommendation, moderate quality of evidence.

7.1. AST should be used to tailor *H. pylori* treatment in any HIV patient. If not available, bismuth-containing therapy is the best option. .....

Strong recommendation, high quality of evidence.

7.2. Eradication of *H. pylori* in children is indicated only in case of peptic ulcer disease, refractory IDA and chronic ITP. Biopsies for histology and AST are mandatory for diagnosis and treatment of *H. pylori* in children. AST-based treatment in children should last 14 days. .....

Strong recommendation, moderate quality of evidence.

FIGURES

Figure 1. Global prevalence of *H. pylori* .....
Figure 2. Primary antimicrobial resistance rates of *H. pylori* in Wallonia and Brussels between 2016 and 2020. .....
Figure 3. Antibiotic resistance of *H. pylori* in first line testing in 37 patients in West Flanders in 2020. .....
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Table 1. Comparison of non-invasive diagnostic methods for *H. pylori* detection. Reference value with respect to histological diagnosis by biopsy (gold standard).....
Table 2. Comparison of invasive diagnostic methods for *H. pylori* before eradication.....
Table 3. Algorithm adapted and proposed for the treatment of *H. pylori* infection.....
Table 4. Proposed schemes for *H. pylori* eradication in children and adolescents. .....
Table 5. Proposed doses for first line *H. pylori* eradication treatment in children and adolescents. .....

KEY QUESTION 1: EPIDEMIOLOGY.

What is known about the epidemiology of H. pylori infection in Belgium?

1.1. The prevalence of *H. pylori* infection is decreasing, especially in children.
Strong recommendation (100% of agreement), high quality evidence.

In Belgium, no studies on prevalence are available in adults since the 1990s, when it was around 32%. (5) The overall prevalence in Europe is estimated to be around 20 to 40%. Although recent studies are lacking, the current prevalence of *H. pylori* in Belgium is estimated to be above 20%. (1,5) In contrast, a prospective study from 2010 showed a very low prevalence in children of Belgian origin (3.2%), but still high prevalence in children with a personal or familial migration background (30 - 60 %) (**Figure 1**). (5,6) The rapid decline in *H. pylori* prevalence has been attributed to successful treatment regimens and improved personal and community hygiene. A decrease has been described in numerous studies worldwide in both adults and children, with the most prominent decline seen among children, although large differences are observed depending on different factors such as ethnicity and economic background. (7)

Which are the high-risk groups?

1.2. Factors influencing the risk for infection with *H. pylori* are ethnicity, socio-economic background, education level, living in an urban or rural area and family history of previous *H. pylori* infection.
Strong recommendation (100% of agreement), high quality evidence.

The risk factors for infection remain the same over the years: prevalence rates are lower in certain isolated ethnical groups, in individuals with a higher education level, in children whose parents have a higher level of education, in families with a better socioeconomic status, and in individuals living in cities with better sanitation and housing conditions. (8–10) The presence of domestic animals or contact with animals such as dogs and sheep is also mentioned. This, among other things, is based on a study in which identical strains were found in two dogs and their owner. (11,12) No prospective data on this subject are available for the Belgian population.

Is there a risk of reinfection and how is it transmitted?

1.3. Transmission occurs mainly through mother-to-child contact in childhood. Risk of *H. pylori* reinfection remains low.
Strong recommendation (93% of agreement), moderate quality evidence.

Although *H. pylori* infection has been recognized and studied for more than 30 years, its transmission mode remains partly unknown. Retrospective sero-epidemiological studies have shown a cohort effect consistent with the hypothesis that infection is mainly acquired

in early childhood. The intrafamilial route of transmission is common and probably primary from mother to child, rather than from father to child, between siblings or outside the family. (13,14) Other routes of transmission studied include possible transmission through infected food and water or domestic animals. (15–17) Infection is mainly acquired in childhood and the risk of reinfection is low, probably around 1-2 % per year, especially in industrialized countries. However, in low socio-economic situations, reinfection can be as high as 23 %. Genetic factors may also play a role and susceptible individuals in whom *H. pylori* has been eradicated may be prone to reinfection when they are exposed to *H. pylori*-positive people. (16,18) Recurrence during the first 3 - 12 months after cure is mostly due to failed eradication attempts. (19) A recent meta-analysis suggested that there is an increase in relapse rates in Europe, however this review did not distinguish between relapse and failed eradication. (20)

KEY QUESTION 2: INDICATIONS.

What are the main indications to test and treat H. pylori infection?

2.1 Testing for *H. pylori* is strongly recommended in patients with active or history of peptic ulcer disease, active or family history of (early) gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma (MALToma).
Strong recommendation (100% of agreement), high quality evidence.

In different global guidelines, there is no doubt about the necessity to test for *H. pylori* infection in strong indications such as peptic ulcer disease (21), (early) gastric cancer and MALToma with the recommendation to confirm eradication success. (22–24) Moreover, if the test is negative but the clinical suspicion is high (for example in duodenal ulcer or active treatment by PPI), a new *H. pylori* diagnostic method should be repeated. (25)

When H. pylori eradication can be considered?

2.2 Testing is recommended in adults with dyspepsia, before chronic use of proton-pump inhibitors (PPIs) or non-steroid anti-inflammatory drugs (NSAIDs), immune thrombocytopenic purpura (ITP), unexplained iron deficiency anaemia (IDA) and prior to bariatric surgery.
Strong recommendation (100% of agreement), moderate quality evidence.

However, testing for *H. pylori* infection in case of non-investigated dyspepsia without any alarm symptoms depends on cost-benefit considerations. Based on economic evaluations, some guidelines advocate initial empiric treatment with a PPI if the *H. pylori* prevalence in a population is below 20% due to the low chance of a positive test as well as *H. pylori*-related disease. More debatable is the indication for testing before the chronic use of PPIs. This indication is based on observational studies that have shown an increased risk of atrophic gastritis, a precursor of gastric cancer, in association with long-term use of PPIs. (26) The

recommendation to test for *H. pylori* before the intake of NSAIDs is based on the fact that NSAIDs and *H. pylori* are independent risk factors for peptic ulcer disease and the associated complications. A few clinical trials conducted in these high-risk patients of Chinese origin, have shown that *H. pylori* eradication reduces but does not eliminate the risks, and that PPIs co-therapy seems still necessary to further reduce the risk of upper GI bleeding. It can be considered to test for *H. pylori* infection in IDA with normal gastroscopy and colonoscopy results, because the association of *H. pylori* with unexplained IDA has been conclusively proven in adult and paediatric populations in the past. Moreover, meta-analyses have shown that *H. pylori* eradication improves anaemia and increases haemoglobin levels, in particular in those with moderate to severe anaemia. (27–29) Similar results are known for adults with ITP. Studies have shown increased platelet counts in some patients after successful treatment of *H. pylori* infection. (23,30–32) According to the last European surgical guidelines, no recommendation can be formulated for either routine *H. pylori* eradication or no eradication prior to bariatric surgery on the basis of available evidence for surgical complications. (33) Nevertheless, there are preventive reasons to attempt eradication of *H. pylori*, particularly in those patients undergoing bariatric bypass in which a large part of the stomach will remain inaccessible to upper gastrointestinal endoscopy. (34)

Does H. pylori eradication prevent gastric cancer?

2.3. Eradication of *H. pylori* prevents gastric cancer. However, the incidence of gastric cancer in patients with premalignant lesions at baseline will not be affected by eradication.
Strong recommendation (100% of agreement), high quality evidence.

Chronic *H. pylori* infection further increases the risk of gastric cancer. Bacterial virulence factors, such as HomB and BabA2, seem to be implicated at least in the Asian population. (35,36) Therefore successful eradication of *H. pylori* is expected to reduce the incidence of gastric cancer, especially in populations with high incidence of infection. Multiple meta-analyses, including a Cochrane meta-analysis, support the importance of *H. pylori* eradication in the prevention of gastric cancer (13,37–41), although one meta-analysis did not confirm this. (42) This reduced incidence was also apparent in healthy individuals without history of gastric ulcer disease or dyspepsia. (41) Other studies analysed the role of *H. pylori* eradication on the incidence of metachronous gastric cancer and preneoplastic lesions such as atrophic gastritis and intestinal metaplasia after treatment of early gastric cancer. (41,43,44) *H. pylori* eradication appeared to be associated with reduced gastric cancer incidence in these patients as well as with an improvement in atrophic gastritis and intestinal metaplasia. However, the incidence of gastric cancer in patients with premalignant lesions at baseline was not affected by eradication. Some caution is warranted when extrapolating the above mentioned evidence to the worldwide population. Most studies were performed in Eastern populations, with a higher incidence of gastric cancer. Other confounders might come into play, such as dietary habits and genetic predisposition among others.

Screening and treating everyone?

2.4. Every person with an indication for testing who has a positive test result should be treated. There is currently no evidence in favour of a population wide screening strategy in the prevention of gastric cancer.
Strong recommendation (100% of agreement), moderate quality evidence.

As *H. pylori* is classified as a human carcinogen by the International Agency for Research on Cancer (IARC), screening everyone in the population has been considered in Asian countries with a high incidence of gastric cancer. A recent systematic review and meta-analysis provides moderate quality evidence that *H. pylori* eradication therapy reduces the incidence of gastric cancer in healthy individuals in East Asian countries, and it was estimated that the number needed to treat (NNT) to prevent one gastric cancer in East Asian countries is 72. (41) In Northern European countries where the incidence of gastric cancer is generally much lower, the cost-benefit of a population-wide screen-and-treat strategy would be less favourable. Therefore, screening everyone in our population is currently not justified. On the other hand, it is accepted that all patients with an active *H. pylori* infection should be treated. (24) In *H. pylori* positive patients, it is recommended to test the related family members for *H. pylori* either by serological, stool antigen or urease breath tests, or both; this includes parents, spouses, children, or other members living in the same household. (45)

KEY QUESTION 3: DIAGNOSIS.

When to use invasive and non-invasive tests?

3.1. *H. pylori* infection can be diagnosed using invasive (endoscopy with biopsies for rapid urease testing (RUT), histology, culture, or molecular diagnosis) and non-invasive methods (serology, urea breath test (UBT) and stool antigen test). Clinical factors and performances of diagnostic tests need to be considered when choosing the appropriate test.
Strong recommendation (100% of agreement), high quality evidence.

The C13-UBT harbours the highest sensitivity for the non-invasive diagnosis of *H. pylori* infection, before as well as after eradication. UBT is the most investigated and best-recommended non-invasive test in the context of a 'test-and-treat strategy'. (24,46) Faecal *H. pylori* antigen assays using monoclonal antibodies are easy to perform and are useful for eradication assessment as well. Nevertheless, local validation is important because accuracy depends on the target antigen used and the prevalence of diseases associated with *H. pylori* infection. (46) Total price of stool *H. pylori* antigen in Belgium is around 30€, the personal share of the patients is approximately 8€. Serology is able to detect past infection of *H. pylori* but it plays no role in the diagnosis of active infection or the monitoring of the effectiveness of eradication. (23) **Table 1** shows the differences and advantages of each of the non-invasive tests.

In case of endoscopy, histology, and antimicrobial susceptibility testing (AST) are essential for a better management of patients. Histology is the gold standard for the assessment of *H. pylori*-associated gastritis. To detect *H. pylori* it is desirable to combine a routine hematoxylin-eosine (H-E) stain with conventional stains such as Giemsa stain. Compared to the Giemsa stain, the H-E stain has a lower sensitivity (85.7 % vs. 57.1%) and specificity (82.1% vs.78.6%). (47) Sensitivity of both stains however decreases significantly when the eradication of *H. pylori* needs to be confirmed after therapy. (48) RUT can be useful in the rapid diagnosis of *H. pylori* in case of gastrointestinal bleeding of peptic origin. (49) The choice of culture or molecular diagnosis for AST will depend on transport conditions and accessibility at each centre. **Table 2** shows the differences and advantages of the invasive tests.

Do we need to stop PPIs?

3.2. PPIs should be discontinued at least 2 weeks before testing for *H. pylori* infection. Antibiotics and bismuth compounds should be discontinued at least 4 to 6 weeks before the test.
Strong recommendation (100% of agreement), high quality evidence.

PPIs have an anti-*H. pylori* activity by decreasing the load of *H. pylori,* thus leading to false-negative results. They should be stopped at least 2 weeks before testing. The antibacterial activity of antibiotics and bismuth compounds lasts longer. These medications must be stopped at least for 4 weeks to allow an increase of a detectable bacterial load.(23,46)

When to use immunohistochemical testing?

3.3 *H. pylori* detection by immunohistochemistry (IHC) should be used routinely.
Strong recommendation (100% of agreement), moderate quality evidence.

Immunostaining is useful when the bacterial count is small and when the bacteria are in the coccoid form - which is seen with PPIs intake among others – negatively affecting interpretation with a non-specific stain. Furthermore, during PPIs treatment *H. pylori* migrates from the surface to the depth of the glands and from the antrum to the corpus. (50) PPIs also slow the growth of these microorganisms and may give a false negative result on staining. Studies have demonstrated that routine IHC has a significantly higher detection rate than H-E or histochemical stains, (51) it is highly sensitive and specific for *H. pylori* with the lowest rate of inter-observer variation when compared to histochemical stains and it may shorten the time required for the search of the bacteria, especially in cases with a low level of organisms. (52) However, the IHC staining procedure is more expensive than histochemical stains and it is not available in all laboratories. Use of IHC is recommended in cases with chronic gastritis, atrophic gastritis, extensive intestinal metaplasia, in patients treated with PPIs in follow-up biopsies after eradication treatment or when *H. pylori* is not

identified using histochemical stains. [4] In practice, it is performed in nearly all-gastric biopsies in Belgium, because the clinical information on the treatment of patients is sparse or even unavailable to the pathologist and because *H. pylori* can be detected even in the absence of gastritis. [45] The study of Lash and Genta has shown that this way of practice, in which the pathologist receives the H-E stain and immunohistochemical stain simultaneously, is associated with a significant improvement in detection of *H. pylori* ($p < 0.0001$) and recommends the application of this test on all gastric biopsies. (53)

Are there endoscopic findings of H. pylori infection and how to biopsy?

3.4 A minimum of 4 gastric biopsies needs to be taken from the antrum and the body of the stomach for the assessment of *H. pylori*-induced gastritis. Consider additional biopsies for AST and from incisura for the detection of precancerous lesions. Regular arrangement of collecting venules (RAC) has a high sensitivity for *H. pylori*-negative patients, avoiding supplementary biopsies for AST in these patients.
Strong recommendation (93% of agreement), moderate quality evidence.

Endoscopy should include visualization of the whole upper gastrointestinal tract in order to evaluate the mucosa and take biopsies according to standardised protocols. (23) When endoscopy-based strategy is considered, the Kyoto classification score for gastritis predicts the risk of *H. pylori* infection and gastric cancer. Endoscopic findings predict the risk of *H. pylori* infection and preneoplastic lesions. Enlarged folds had a relatively good positive predictive value (56.2–86.0%), nodularity had a low sensitivity (6.4%–32.1%) but excellent specificity for a current infection (95.8%–98.8%), diffuse redness had a good positive predictive value (65.6%–91.5%) and regular arrangement of collecting venules (RAC) had a very high sensitivity for *H. pylori*-negative patients (86.7%–100%), mostly in younger patients. (54,55) The Kyoto classification score for gastritis is based on the sum of scores of five endoscopic findings: atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. A high score is believed to reflect increased risk of *H. pylori* infection and gastric cancer; a score of 0 excludes the risk of *H. pylori* infection. Identification of RAC pattern in the lesser curvature is a reliable sign to exclude *H. pylori* infection on the spot, avoiding biopsies for supplementary AST in these patients. (55)

On the other hand, for the assessment of *H. pylori*-induced gastritis, a minimum standard biopsy setting includes two biopsies from the antrum (greater and lesser curvature 3 cm proximal to the pyloric region) and two biopsies from the middle of the body. Consider additional biopsy form the incisura for the detection of precancerous lesions. (23,56) Besides the detection of *H. pylori*, pathological examination of the gastric mucosa also provides information on the degree and pattern of inflammation and the presence/absence of preneoplastic lesions. Additional biopsies are considered from the antrum and the body for culture-based AST of *H. pylori* in those patients with high epidemiologic risk factors for *H. pylori* infection and negative RAC pattern. (57,58)

Rapid urease test (RUT) can be performed as a first-line diagnostic test but is less available in Belgian endoscopy units nowadays. RUT is not recommended for control after eradication because it requires high density of *H. pylori.* One biopsy should be taken from the corpus and one from the antrum. The main interest for performing RUT is to obtain a quick result, which is practical as it allows an eradication treatment to be prescribed immediately. (23) In patients with non-variceal upper gastrointestinal haemorrhage secondary to peptic ulcer, investigation for the presence of *H. pylori* in the acute setting (at index endoscopy) is recommended with initiation of appropriate antibiotic therapy when *H. pylori* is detected. (49) However, the test itself cannot be preserved as evidence and histological evaluation of gastritis or preneoplastic lesions is not possible. (46) Furthermore, RUT is less sensitive than other diagnostic methods in the setting of active bleeding. (59)

KEY QUESTION 4: RESISTANCE.

What do we know about H. pylori antimicrobial resistance in Belgium?

4.1. Resistance to clarithromycin in Belgium demonstrates regional variations and is between 13.5% and 19.8 %. Resistance to nitro-imidazoles varies from 29.7% to 51.6%, as well as resistance to fluoroquinolones from 22.2% to 31.7%. Resistance to amoxicillin and tetracycline remains very low.
Strong recommendation (100% of agreement), high quality evidence.

Owing to the increasing *H. pylori* resistance rate to antimicrobials coupled with the declining eradication rates in most part of the world, the Maastricht VI/Florence consensus report recommends to choose a local therapeutic strategy based on the rates of resistance to antibiotics and particularly clarithromycin. (23) The latest European survey, conducted in 2018, and including several Belgium centres, revealed high levels of primary *H. pylori* resistance to clarithromycin, metronidazole, and levofloxacin, respectively 21.4%, 38.9% and 15.8%. Resistance to amoxicillin and tetracycline remained limited. (60) The last national survey conducted in 2020 by the Belgian *H. pylori* Reference group included 6 centres among which one in Brussels and 5 in Wallonia. It also showed high levels of primary resistance to clarithromycin (19.8%), metronidazole (34.5%) and levofloxacin (31.7 %). Resistance to amoxicillin and tetracycline resistance remained rare. (61) (**Figure 2**). A recently published study performed in West Flanders from October 2017 to February 2019, showed primary resistance rates of 13.5% for clarithromycin, 29.7% for metronidazole, 29.7% for levofloxacin, 11.4% for rifampicin, 2.7% for amoxicillin and 0% for tetracycline. (**Figure 3**) (62) In the Brussels area, we observed increasing rates of primary resistance to macrolides (10.5% to 18%), nitro-imidazoles (28% to 51.6%) and fluoroquinolones (12.4% to 24%), respectively, from 2008/2009 to 2021. Resistance to amoxicillin and tetracycline were also rare. (63,64) This shows one more time the large regional difference and temporal variations in resistance patterns in Belgium (**Figure 4**).

How to manage metronidazole resistance?

4.2. Resistance to nitro-imidazoles is relative and can be overcome by increasing the frequency, doses or duration of therapy.
Strong recommendation (100% of agreement), moderate quality evidence.

It is not mandatory to test metronidazole resistance. Nevertheless, if available (**Figure 2**), the susceptibility result should be considered to adapt the dose of metronidazole in case of resistance up to 500 mg four times per day. (65) The latest European consensus considers local prevalence of *H. pylori* resistance to metronidazole to recommend the empiric treatment regimen. (23) Nitro-imidazoles were the first antibiotics used to treat *H. pylori* infection and their activity is enhanced with the use of tetracycline and bismuth salts. It has been proven that the clinical relevance of nitro-imidazole resistant strains is low (72.6% of eradication success compared to 97% if the strains are susceptible to metronidazole). (66)

What methods can be used to evaluate H. pylori antibiotic resistance and when should AST be performed?

4.3. AST can be performed either by a standard method after culture or by a molecular test on the gastric biopsy specimen. In case of both empirical *H. pylori* treatment failures, AST is recommended to guide the rescue treatment. If an endoscopy is carried out, it is recommended to perform AST in RAC negative patients from populations or regions with well-documented high clarithromycin resistance > 15%.
Strong recommendation (87% of agreement), moderate quality evidence.

Culture is excellent regarding specificity and allows AST on bacterial strains. (46) It is the only diagnostic method allowing susceptibility testing to all the antibiotics useful in treating *H. pylori* infection (clarithromycin, metronidazole, levofloxacin, tetracycline, amoxicillin, and rifampicin). (63,64) However, it is time consuming and depends on transport and processing conditions. The result is available only within one to two weeks after sampling and its accuracy depends on transport and processing conditions. Caution should be taken in the pre-analytical phase, which is a key step in the isolation of *H. pylori*. It is mandatory to use specific transport media to avoid oxygen and to keep frozen samples until the day of treatment (67): -18°C the first 24 hours and -80°C after 24 hours. Compared to culture, molecular methods are less affected by storage or transport constraints and could easily detect heteroresistance. (60,68) They are more frequently used nowadays to evaluate susceptibility to a limited number of antibiotics (one to maximum 2 antibiotics at the same time). Both homemade and commercially available methods are used. (67) According to our experience, the HELICO^{DR} is a suitable method to detect the presence of *H. pylori* in gastric biopsies and simultaneously test its susceptibility to macrolides and fluoroquinolones by detecting the most relevant mutations responsible for resistance. (68) Next generation sequencing could be used to predict *H. pylori* resistance to antibiotics in the future. (69) In Belgium, the National Reference Centre (Mont-Godinne) routinely proposes molecular

detection of clarithromycin resistance in *H. pylori* strains on gastric biopsies samples. In recent years, several molecular methods allowing detection of clarithromycin and levofloxacin resistance in stool have been proposed. (70–72) This could represent an alternative as a non-invasive AST but it is not yet available in Belgium. Considering antibiotic resistance rates in Belgium, biopsies for AST should be considered in those patients undergoing upper gastrointestinal endoscopy with endoscopic signs of *H. pylori* infection (RAC negative, diffuse redness) from regions or populations with high clarithromycin resistance rate over 15%.

KEY QUESTION 5. FIRST LINE TREATMENT.

What are the first-line treatment strategies in Belgium?

5.1. The empirical first-line treatment in adults would be either a concomitant non-bismuth quadruple therapy (PPI, clarithromycin, amoxicillin, and metronidazole) for 14 days or a quadruple combination with bismuth (PPI, bismuth, tetracycline and metronidazole) for 10 days.

If clarithromycin resistance has been excluded by AST, a classical clarithromycin based triple therapy can still be used for 14 days.

Fluoroquinolones are not recommended without prior AST.
Strong recommendation (94% of agreement), moderate quality evidence.

The management of *H. pylori* infection by some European gastroenterologists is heterogeneous, frequently suboptimal, and discrepant with current recommendations. Clinical practice is constantly adapting to updated recommendations, although the shift is delayed and slow. (73) Currently, an eradication therapy is considered effective when it is able to eradicate *H. pylori* infection in close to, or preferably more than, 90% of patients. (74) In 2016, The Maastricht/ Florence consensus report recommended to extend the duration of non-bismuth therapy of clarithromycin-based triple therapy to 14 days, unless shorter therapies are proven effective locally. The report substantiates these statements by studies where higher eradication rates were attained by a longer course of therapy. Overall, the eradication rates achieved by an eradication regimen of 7 days or less are inferior and should be avoided. (67)

In the last European consensus of 2022, the experts recommended bismuth quadruple therapy as the first-line recommended treatment in areas of high (>15%) or unknown clarithromycin resistance when individual AST is not available. On the other side, in areas of low clarithromycin resistance, the empirical first-line treatment in adults would be either a concomitant non-bismuth quadruple therapy (PPI, clarithromycin, amoxicillin and metronidazole) for 14 days or a quadruple combination with bismuth (PPI, bismuth, tetracycline and metronidazole) for 10 days. (23) (51,62) Nevertheless, a recent Belgian

study showed that triple therapy (PPI, amoxicillin and clarithromycin or PPI, amoxicillin and metronidazole) for 14 days could be used empirically in areas where the rate of resistance to clarithromycin is <15% as in West Flanders. (75)

In Belgium, the most available and used form of bismuth is the single three-in-one capsule containing bismuth, tetracycline, and metronidazole (Tryplera) for 10 days. (75) In recent years, bismuth-containing quadruple therapy has played an increasingly important role in first-line therapy because the resistance to clarithromycin, metronidazole, and levofloxacin does not affect its efficacy. (76) Metronidazole resistance is almost constantly high but its clinical impact is limited. Adverse events are more frequently observed in quadruple therapy, but these are usually rated as mild, with no impact in compliance in most included studies. (67) The alternative to empirical treatment is a treatment guided by an antibiogram in first line therapy. *H. pylori* eradication is important, but never an urgent matter. (75) This attitude is gaining ground in some areas where eradication of the infection is not considered an emergency. However, the number of centres culturing *H. pylori* for AST remains limited, so it would be difficult to generalize this option.

What to do in case of penicillin allergy?

5.2. Classic bismuth-containing quadruple therapy is the best choice in first-line treatment in case of penicillin allergy in adults.
Strong recommendation (100% of agreement), high quality evidence.

As first-line therapy in patients with penicillin allergy in areas of low clarithromycin resistance <15%, a PPI-clarithromycin-metronidazole combination may be prescribed for 14 days, whereas in areas of high clarithromycin resistance >15%, bismuth-containing quadruple therapy should be preferred. (23) However, a European study involving 1048 patients showed that classic bismuth-containing quadruple therapy seemed to be the better choice in first-line treatment (91% versus 69%; $p < 0.001$). (76)

What PPI to choose?

5.3. Esomeprazole 2 x 40 mg and rabeprazole 2 x 20 mg are more powerful than other PPIs and less sensitive to variations in CYP2C19; therefore, they are the best choice for *H. pylori* eradication.
Strong recommendation (100% of agreement), moderate quality evidence.

Genetic variations in CYP2C19 can contribute to treatment success through impacting PPI metabolism. Esomeprazole and rabeprazole are less influenced by extensive or ultra-rapid metabolism and are more potent than other PPIs; therefore, they may be the best choice in difficult cases, including regions with high rates of antibiotic resistance. Esomeprazole and rabeprazole show better overall *H. pylori* eradication rates than first-generation PPIs. (77) The concept that more acid suppression results in better eradication rates is supported by the promising results obtained with vonoprazan, a potassium-competitive acid secretion

inhibitor that provides more profound acid suppression than traditional PPIs. Although currently not available in European countries, studies of vonoprazan in first line *H. pylori* eradication were recently completed in the United States and Europe. Further studies of vonoprazan (and potentially other drugs in this class) are needed to determine whether or not they are superior to PPIs in refractory cases specifically. (75)

Should we test for treatment success after H. pylori eradication therapy?

5.4. We recommend confirmation of successful eradication testing, especially prior to bypass bariatric surgery.
Strong recommendation (100% of agreement), high quality evidence.

The increasing worldwide clarithromycin and metronidazole resistance of *H. pylori* has led the WHO to consider research and development on new treatments as a high priority. (78) With increasing resistance, the eradication rates drop below acceptable levels. Moreover, eradication failure exposes an individual to the increased risk associated with chronic *H. pylori* infection (gastric ulcer, gastric atrophy with intestinal metaplasia and eventually gastric cancer). As a result, confirmation of eradication success is largely recommended by guidelines. (23) The main determinants of successful *H. pylori* eradication are the choice of regimen, the patient's adherence to a multi-drug regimen with frequent side effects, and the sensitivity of the *H. pylori* strain to the combination of administered antibiotics. With declining success rates for *H. pylori* eradication therapy, many patients will remain persistently infected despite treatment and will therefore remain at risk for the complications of *H. pylori*-related disease, such as peptic ulceration and gastric malignancy. (24) Unfortunately, eradication confirmation remains infrequent in clinical practice, with only 1 in 4 patients being ever retested. (75) A recent observational study showed that only 35% of patients who had been treated for *H. pylori* infection underwent follow-up testing to confirm eradication and that many patients who had treatment failure were retreated with the same regimen. (79) We especially recommend confirming *H. pylori* eradication prior to by-pass bariatric surgery since exclusion of the gastric cavity precludes endoscopic control or subsequent urea breath testing.

Key question 6. Refractory management.

6.1. In the clinical setting, *H. pylori* infection is considered refractory when failing two eradication attempts.
Strong recommendation (100% of agreement), low quality evidence.

A well-accepted consensus on the definition of refractory *H. pylori* infection is lacking. According to the recent American Gastrointestinal Association (AGA) Clinical Practice Update refractory *H. pylori* infection is defined by a persistently positive non-serologic *H. pylori* test at least 4 weeks after 1 or more completed course(s) of a current guideline-recommended

first-line *H. pylori* eradication therapy, and off of any medications, such as PPIs, that might impact the test sensitivity. (80) This contrasts with the review by Liou et al. where refractoriness refers to an eradication failure after a second-line regimen. (81) Similarly, clinical trials consider *H. pylori* infection as refractory when failing 2 or 3 prior treatment attempts.(82–84) The definition in clinical research is attributable to the difficulties in establishing the adequateness of prior treatment courses in terms of patient compliance, optimal dosing and duration. These confounding factors all have an impact on the effectiveness of therapy despite absent antimicrobial resistance. In contrast, the second part of the definition from the AGA Practice Update refers to the reduced performance of *H. pylori* eradication testing when the patient takes certain interfering medication, which could cause a false negative test result. Upon retesting this individual, a positive result would incorrectly be interpreted as reinfection. Therefore, from a clinical point of view where compliance is lower than in the setting of clinical trials, we favour the pragmatic definition from clinical research, and consider *H. pylori* refractoriness when a patient has failed at least two prior eradication attempts. Of course, correct testing conditions remain mandatory to confirm eradication.

When primary therapy fails, what are the options for salvage therapy? When to use rifampicin?

6.2. In case of failure of 2 prior therapies, we recommend a 14-days AST based therapy. Consider increasing dosage of PPIs, amoxicillin, or metronidazole. Consider rifampicin if all options have been used and eradication is mandatory.
Strong recommendation (100% of agreement), moderate quality evidence.

For refractory cases, it may seem obvious that sensitivity testing should be considered after two failed attempts of treatment. However, in practice, the situation is complicated for the logistical challenges to obtain resistance profiles for *H. pylori* and the lack of convincing data demonstrating superiority of treatment based on AST compared to empirical treatment based on prior antibiotic exposure. (85) After multiple failed attempts at *H. pylori* eradication, a discussion about the necessity of eradication should be discussed. In case of complicated ulcer disease, lifelong PPIs and avoidance of NSAIDs and aspirin can be discussed. In case of high cancer risk, eradication is mandatory but an endoscopic follow-up for surveillance of premalignant gastric lesions may be suggested. The use of Rifampicin 2 x 150 mg remains anecdotal in our country. Although effective, this drug causes reversible myelotoxicity and an increased prevalence of mycobacteria resistance. Furthermore, it is expensive (+/- 236 euro in Belgium) and not reimbursed in this setting. It should be reserved for the treatment of special cases in the expert hospital setting. (74) In **Table 3** we propose different schemes of therapies depending on the different situations. (24,75,80,86)
Finally, a good briefing with oral and written instructions is a crucial item for compliance and treatment success. Compliance with therapy involves partnership between physician and

patient with a plan for eradication. As such, the importance of structured aftercare and follow up of patients is of critical significance. (87,88)

What about adjuvant therapies?

6.3. Probiotics and N-acetylcysteine are not recommended as an adjuvant therapy for *H. pylori* infection.
Strong recommendation (100% of agreement), moderate quality evidence.

The efficacy of probiotics as an adjuvant therapy for *H. pylori* eradication has been widely investigated in many clinical trials. Several randomized controlled trials (RCTs) concluded that supplementation of probiotic single strains, such as *Lactobacillus acidophilus, L. casei, L. gasseri, L. reuteri*, *Bifidobacterium infantis*, *Bacillus clausii*, *Clostridium butyricum*, *Saccharomyces boulardii* or *Enterococcus faecium*, during treatment for *H. pylori* infection may have beneficial effects on eradication rate, incidence of total side effects, patient's compliance or gut microbiota composition. (89,90,99–102,91–98) However, most of these trials assessed the impact of probiotic supplementation when added to triple rather than quadruple or sequential therapy. Other studies investigated the efficacy of a multi-strain probiotic compound as adjuvant agent of anti-*H. pylori* standard triple therapy. They also reported an improvement of the eradication rates, a decrease of therapy-related side effects or a restoral of depleted beneficial bacteria. (103–110) When added to a bismuth quadruple regimen or sequential therapy, a beneficial effect on eradication and compliance, respectively, was shown as well. (111–114).

On the contrary, several other RCTs rather reported no improvement in eradication rates with the addition of probiotics (based on single or multiple strains) to standard triple or quadruple therapy in adults compared with placebo. (115–121) In one study, however, there was a significant reduction in diarrhoea and nausea. (121) Although some studies highlight possible beneficial effects of probiotics on anti-*H. pylori* therapy, there are still inconsistencies among the results across studies. More specifically, compounds are not standardised, contain one or multiple bacterial strains in different combinations and different concentrations and different treatment regimens were used. Therefore, additional studies are needed to determine which, if any, specific formulations may actually have beneficial effects for a specific anti-*H. pylori* treatment regimen.
Using mucolytic agents, such as N-acetylcystin (NAC) that decrease viscosity of the gastric mucous and therefore increase the permeability of antibiotics through the gastric membrane, has been investigated with positive results. An open label randomized controlled trial has been published in 2010, involving 40 subjects with a history of at least four *H. pylori* eradication failures. Subjects were randomly assigned to receive (group A) or not (group B) 1 week N-acetylcysteine before a culture-guided antibiotic regimen. *H. pylori* was eradicated in 13/20 (both per-protocol and ITT analyses, 65%) group A participants and 4/20 (both per-protocol and ITT analyses, 20%;) group B participants ($p<0.01$). The authors concluded that

N-acetylcysteine pre-treatment before a culture-guided antibiotic regimen is effective in overcoming *H. pylori* antibiotic resistance. (122) However, a more recent meta-analysis failed to confirm the value of N-acetylcysteine. (123)

Which patients need long-term follow-up after eradication?

6.4. We recommend long-term follow-up in patients with intestinal metaplasia and family history of gastric cancer, incomplete intestinal metaplasia, advanced atrophic gastritis, or persistent *H. pylori* infection.
Strong recommendation (100% of agreement), moderate quality of evidence.

The selection of patients for follow-up should be based on histological classification criteria (OLGA/OLGIM: operative link for gastritis assessment for gastric atrophy / intestinal metaplasia assessment). (23) We recommend long-term follow-up in patients with intestinal metaplasia at a single location but with a family history of gastric cancer, with incomplete intestinal metaplasia, with advanced stages of atrophic gastritis, or with persistent *H. pylori* gastritis by high-quality endoscopy every 3 years. (124)

KEY QUESTION 7. SPECIAL POPULATIONS.

What to do in HIV patients?

7.1. AST should be used to tailor H. pylori treatment in any HIV patient. If not available, bismuth-containing therapy is the best option.
Strong recommendation (100% of agreement), high quality of evidence.

HIV infection is associated with immune function impairment; therefore, people living with HIV are more exposed to antibiotics than the general population. Subsequently, those who are H. pylori co-infected commonly carry H. pylori strains with single primary resistance (clarithromycin, 15.5%, levofloxacin, 29%, metronidazole, 55%), and multiple primary resistance (22%) compared with controls. This tendency of more resistant strains of H. pylori isolated in people living with HIV seems to be persistent over time. (125,126) Antimicrobial susceptibility testing should be used to tailor *H. pylori* infection treatment in any *H. pylori*/HIV co-infected individual as these patients have a greater proportion of single and multiple antibiotic resistances. If the antimicrobial susceptibility test is not available, bismuth-containing therapy is the best option. Since drug interactions are common between antiretroviral and non-antiretroviral drugs, they should be ruled out before prescribing any eradication regimen for *H. pylori* infection. (127)

The treatment duration can be like the one for the general population: 14 days for guided triple therapy and at least 10 days for bismuth-containing therapy. We also suggest a dedicated appointment to explain the pill schedule. These suggestions are based on our experience at the HIV/AIDS reference centre in Belgium.

What to do in children and teenagers?

7.2. Eradication of *H. pylori* in children is indicated only in case of peptic ulcer disease, refractory IDA and chronic ITP. Biopsies for histology and AST are mandatory for diagnosis and treatment of *H. pylori* in children. AST-based treatment in children should last 14 days.
Strong recommendation, moderate quality of evidence.

As previously discussed, *H. pylori* infection is most frequently acquired in childhood. However, in comparison with adults, children and adolescents less frequently develop serious complications and gastric adenocarcinoma that occurs later in the natural history of this infection. Accordingly, the last published ESPGHAN/NASPGHAN guidelines for the management of *H. pylori* in children and adolescents (128), only recommend eradication of *H. pylori* in children in the case of peptic ulcer disease, refractory IDA and chronic ITP. Concerning the situation of incidental finding during endoscopic evaluation of non-ulcer dyspepsia, there is no conclusive evidence that eradicating the infection will improve dyspepsia symptoms. Proposing a treatment should then carefully be discussed with the patient and the parents, considering the adverse events of antimicrobial treatment (diarrhoea, abdominal pain, dysbiosis) with the perceived advantage of eradication. There is no evidence to support a ‘‘test and treat’’ strategy for *H. pylori* infection in children. Therefore, the latest recommendation is against non-invasive testing and certainly treating in case of positive results. The primary goal of clinical investigation of gastrointestinal symptoms should be to determine the underlying cause of the symptoms and not solely the presence of *H. pylori* infection. The diagnosis of *H. pylori* infection should be based on either a) positive culture or b) histopathology (*H. pylori*-induced gastritis) plus at least one other positive biopsy-based test. For the diagnosis of *H. pylori* infection at upper gastrointestinal endoscopy, at least 6 gastric biopsies should be obtained. Two factors identified as affecting treatment success in children are adherence to treatment and antibiotics resistance. According to the last update of the joint ESPGHAN/NASPGHAN guidelines, treatment must be based on the result of antimicrobial susceptibility testing. Sufficiently high doses of PPIs and antibiotics should be used, and treatment should last 14 days. If antibiotic sensitivity is unknown, then a 14-days high-dose triple therapy is recommended or a bismuth-based therapy in countries where it is licensed for paediatric use. Studies from Korea, China but also in Belgium (129,130) show that use of bismuth-based therapies is safe in children and of particular interest in previously treated patients and in case of double antibiotics resistance. These data should be validated by larger multicentre studies. The physician should explain to the patient/ family the importance of adherence to the anti-*H. pylori* therapy to enhance treatment success as a concordance between prescribed and ingested treatment must be

higher than 90%. In **Tables 4 and 5,** schemes and doses are proposed for first line *H. pylori* eradication treatment in children and adolescents in Belgium for 14-day triple therapy tailored to AST according to ESPGHAN/NASPGHAN guidelines. (131)

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