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IVth Brazilian Consensus Conference on *Helicobacter pylori* infection

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ABSTRACT – Significant progress has been obtained since the III Brazilian Consensus Conference on *H. pylori* infection held in 2012, in Bento Gonçalves, Brazil, and justify a fourth meeting to establish updated guidelines on the current management of *H. pylori* infection. Therefore, the *Núcleo Brasileiro para Estudo do Helicobacter pylori e Microbiota* (NBEHPM), association linked to Brazilian Federation of Gastroenterology (FBG) held its fourth meeting again in Bento Gonçalves, RS, Brazil, on August 25–27, 2017. Twenty-six delegates, including gastroenterologists, endoscopists, and pathologists from the five regions of Brazil as well as one international guest from the United States, participated in the meeting. The participants were invited based on their knowledge and contribution to the study of *H. pylori* infection. The meeting sought to review different aspects of treatment for infection; establish a correlation between infection, dyspepsia, intestinal microbiota changes, and other disorders with a special emphasis on gastric cancer; and reassess the epidemiological and diagnostic aspects of *H. pylori* infection. Participants were allocated into four groups as follows: 1) Epidemiology and Diagnosis, 2) Dyspepsia, intestinal microbiota and other afections, 3) Gastric Cancer, and, 4) Treatment. Before the consensus meeting, participants received a topic to be discussed and prepared a document containing a recent literature review and statements that should be discussed and eventually modified during the face-to-face meeting. All statements were evaluated in two rounds of voting. Initially, each participant discussed the document and statements with his group for possible modifications and voting. Subsequently, during a second voting in a plenary session in the presence of all participants, the statements were voted upon and eventually modified. The participants could vote using five alternatives: 1) strongly agree; 2) partially agree; 3) undecided; 4) disagree; and 5) strongly disagree. The adopted consensus index was that 80% of the participants responded that they strongly or partially agreed with each statement. The recommendations reported are intended to provide the most current and relevant evidences to management of *H. pylori* infection in adult population in Brazil.

HEADINGS – *Helicobacter pylori*. *Helicobacter pylori* infection. *Helicobacter pylori* treatment. *Helicobacter pylori* diagnosis.

INTRODUCTION

Infection with *Helicobacter pylori* (HP) is one of the most common chronic bacterial infections in humans and causes several digestive problems, including chronic gastritis, peptic ulcer, and gastric cancer (GC). As a strategy to optimize the management of this infection in Brazil, three consensus meetings organized by the Brazilian Nucleus for the Study of *Helicobacter pylori*, recently renamed to Brazilian Nucleus for the Study of *Helicobacter pylori* and Microbiota (*Núcleo Brasileiro para Estudo de Helicobacter pylori e Microbiota*–NBEHPM), were held in 1995[1], 2004[2], and 2012[3]. Recent advances in knowledge of resistance to commonly used antimicrobials with a significant impact on patient therapy, the recognition that chronic gastritis secondary to *Helicobacter pylori* infection is an infectious disease with an indication for antimicrobial therapy regardless of the presence of symptoms[4], and progress in the study of the gut microbiota and its potential interactions with HP demonstrate the need for another consensus meeting on the subject. Therefore, the NBEHPM held its fourth meeting in Bento Gonçalves, Rio Grande do Sul, Brazil, on August 25–27, 2017. Twenty-six delegates, including gastroenterologists, endoscopists, and pathologists from the five regions of Brazil as well as one international guest from

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the United States, participated in the meeting. The participants were invited based on their knowledge and contribution to the study of HP infection. The meeting sought to review different aspects of treatment for infection; establish a correlation between infection, dyspepsia, gut microbiota changes, and other disorders with a special emphasis on GC; and reassess the epidemiological and diagnostic aspects of HP infection.

METHODS

Participants were allocated into four groups according to the main area of interest/practice as follows: Epidemiology and Diagnosis; Dyspepsia, Gut Microbiota Changes and other Disorders; Gastric Cancer; and Treatment. A rapporteur was assigned to each group. Before the consensus meeting, all participants received a topic to be discussed and prepared a document containing a recent literature review and statements that should be discussed and eventually modified during the face-to-face meeting. All statements were evaluated in two rounds of voting. Initially, each participant discussed the document and statements with his group for possible modifications and voting. Subsequently, during a second voting in a plenary session in the presence of all participants, the statements were voted upon and eventually modified. The participants could vote using five alternatives: 1) strongly agree; 2) partially agree; 3) undecided; 4) disagree; and 5) strongly disagree. The adopted consensus index was that 80% of the participants responded that they strongly or partially agreed with each statement. The levels of evidence and the strength of the recommendation were defined according to the Guidelines of the Brazilian Medical Association/Federal Council of Medicine (Associação Médica Brasileira/Conselho Federal de Medicina – AMB/CFM)[5]. The recommendations are reported below.

GROUP 1 – EPIDEMIOLOGY AND DIAGNOSIS

Statement 1
In Brazil, the risk factors for acquiring HP infection are inadequate living conditions, sanitary status, and socioeconomic status. There is no well-established evidence on the dynamics of the prevalence of HP infection in Brazil.
Level of evidence: 3B **Grade of recommendation: B**

Humans are the only reservoir and primary source of transmission of HP[6-9]. Childhood is considered the period of highest risk for acquiring this pathogen because of the higher interpersonal contact at this life stage[10-15]. The most important risk factors for transmitting HP are a large number of people living in the home, bed-sharing between children and adults, unhealthy environments, and precarious conditions in the domicile and peridomicile. Other contributing factors include the absence of basic sanitary facilities (drinking water supply, adequate disposal of household waste and sewage or septic tanks), inappropriate personal and family hygienic practices, lack of adequate food preservation systems, and parents low educacional level or of other adults living in the house[16-24]. The mode of interpersonal transmission of HP is unknown, but it may occur by the fecal-oral, oral-oral, and gastro-oral routes[6,9]. The fecal-oral route predominates in countries with low socioeconomic conditions, households with large families, and population groups with poor hygiene and sanitary conditions; in these cases, transmission occurs directly from person to person[19,25]. In developed countries, transmission occurs mainly via the oral-oral route, and the gastro-oral route may predominate among institutionalized individuals and children in day-care centers[17,26].

Epidemiological studies in Brazil have shown that the prevalence rates of HP infection are high in urban and rural areas and that infection starts in childhood[27-29]. The prevalence of infection is high in the first 2 years of life among individuals residing in urban or rural areas as well as areas with poor living conditions, low income, and limited health resources. In these regions, HP infection affects up to 50% of children aged 2 to 5 years. In children aged ≤10 years, the prevalence rate can reach 70%–90%, and this percentage is similar in adults[27,30]. In contrast, studies involving individuals with a higher education, children whose parents were more educated, families with a better socioeconomic status, and individuals living in cities with better sanitation and housing conditions demonstrated that the prevalence rates of HP infection were lower than those in populations with worse living conditions[27-30].

Statement 2
The 13C-urea breath test is the gold standard method for non-invasive diagnosis of HP infection. The stool antigen test using monoclonal antibodies is a good alternative. However, the availability of these two methods in Brazil is limited.
Level of evidence: 1A **Grade of recommendation: A**

The 13C-urea breath test (13C-UBT) is the gold standard test for non-invasive diagnosis of HP infection, with excellent accuracy, low cost, and easy execution[31-35]. In addition, this test has been validated in Brazil for adults and children aged >6 years[36-38]. It is considered the first-choice for eradication control of HP and implementation of the test-and-treat strategy[32,39,40]. Despite its excellent accuracy, use of the 13C-UBT has not been incorporated into daily practice in Brazil to date due to national authorities restrictions to acquire the substrate. The recent development of the 13C-urea isotope in Brazil may facilitate the dissemination of this test[41].

The need to determine the fasting period before undergoing 13C-UBT is controversial because of the possibility of false negative results[32,42,43]. Although the dose of labeled urea described in the pioneering study by Graham et al.[31] was 5 mg/kg body weight, the current dose of 75 mg for adults is the most recommended and adopted in clinical trials and commercial kits[43-45]. Ascorbic acid (e.g., orange juice) or citric acid is used as a vehicle for 13C-urea to accelerate the hydrolysis of urea and delay gastric emptying, favoring the distribution of the substrate in the stomach[32]. Despite small variations in the methodologies used by different research groups, the sensitivity and specificity of 13C-UBT are >95%[35].

Considering that the absolute values for 13C-UBT depend on urease activity in the stomach, its importance as a semiquantitative or quantitative measurement of gastric colonization has been speculated[46,47]. A large study in Brazil confirmed the results of previous population studies[48-50], demonstrating that 13C-UBT values in women were mildly but significantly higher than those in men, suggesting a higher density of infection in women[51]. More studies are needed to confirm these findings.

The stool antigen test (SAT) by enzyme-linked immunosorbent assay (ELISA) is another good option when 13C-UBT is not available[52], provided that monoclonal antigen is used as the reagent[53-56]. Although less accepted in some countries, the SAT has been validated for the initial diagnosis of infection and eradication therapy (ET) in adults, and its sensitivity and specificity are >92%[54,57-59]. Brazilian studies have also shown the effectiveness of SAT in the adult and pediatric populations[60-62].

Statement 3
For the study of HP using the rapid urease test (RUT), is recommended a collection of one biopsy from antrum and one from corpus. For histological examinations, collection of two biopsies from the antrum and two from the corpus is recommended because it allows morphological analysis of the mucosa. RUT alone is not recommended for eradication therapy control.
Level of evidence: 1A **Grade of recommendation: A**

For patients with an indication for upper gastrointestinal endoscopy, the RUT is an inexpensive, rapid, easy to perform, and highly accurate invasive test for initial diagnosis of HP infection[63]. In most cases, the specificity and sensitivity are approximately 95% and 87%–95%, respectively[64]. The number of analyzed stomach biopsies can increase the sensitivity of the test, and previous studies have demonstrated that collection of biopsies from the antrum and corpus increases the accuracy of the test, reduces false negative results due to the low density and segmental location of HP in the gastric mucosa, and increases the reaction time of the test[65,66].

Histology is considered the gold standard method for detecting HP infection and allows evaluation of morphological changes in the gastric mucosa[65]. Its accuracy is affected by several factors, including location and number of biopsies, staining technique, use of proton pump inhibitors (PPIs) and antibiotics, and level of experience of the pathologist. Antrum and corpus biopsies are usually recommended in clinical practice, although the most sensitive strategy consists of obtaining two antrum biopsies and two corpus biopsies from the small and greater curvature of the stomach[67]. Corpus biopsies are important for diagnosing HP in cases of atrophic gastritis[66]. With respect to the staining technique used in histology, immunohistochemistry is the most sensitive and specific method for detecting HP, but it is time-consuming and expensive. Thus, hematoxylin-eosin (HE) staining is the most commonly used technique in clinical practice. Among the additional staining techniques used to facilitate bacterial identification, Giemsa is the preferred method because it is simple, sensitive, and inexpensive[63,68].

Recently, with the technological advancement of endoscopic imaging, there has been increasing interest in the real-time identification of HP infection during the endoscopic procedure without biopsies, resulting in cost reduction and early diagnosis of infection[69]. The Japanese school divides the status of the gastric mucosa into three categories based on endoscopic findings: normal gastric mucosa without HP infection (absence of gastritis), active HP infection (active gastritis), and previous HP infection (inactive gastritis). The endoscopic classification of Kyoto for endoscopic gastritis lists 19 endoscopic findings to characterize gastric mucosa inflammation and the presence of HP infection with high accuracy, depending on the methods used[70-75].

Statement 4
The screening of HP after eradication therapy should be performed at least 4 weeks after the end of treatment. The 13C-UBT test and SAT with monoclonal antibody are the methods of choice. Histology is an alternative invasive method.
Level of evidence: 1A **Grade of recommendation: A**

The screening of HP after ET requires special attention because of the possible loss of sensitivity in some cases. For instance, use of the RUT is not recommended after eradication because the sensitivity is significantly decreased. Nishikawa et al.[76] compared the sensitivity of two RUTs (Helicocheck™ and PyloriTek™) before and after ET and found that the sensitivity of both tests was 91% and 92% before ET and 60.5% and 60.5% after therapy, respectively. The sensitivity of the tests increased when biopsies of the corpus and antrum were combined compared with the use of biopsies from each region separately. In contrast, sensitivity and specificity of histological diagnosis are maintained before and after ET, as confirmed by Yoshimura et al.[77], wherein the sensitivity of histology after ET in children was 100%. Therefore, histology is used as a control for determining the sensitivity of other tests. During ET testing, special care should be taken about the maintenance of the use of PPIs after administering antimicrobials because they may affect the sensitivity of the tests. Graham et al.[78] demonstrated that PPIs affected the sensitivity of 13C-UBT, which presented a false negative rate of 33% when performed 3 days after treatment suspension. Moreover, the sensitivity of the test began to increase after 4 days of discontinuation of PPIs and was highest 14 days after treatment suspension. Similar results were observed by Gatta et al.[79], wherein the sensitivity of 13C-UBT and SAT were decreased during PPI use. However, antacids did not affect the sensitivity of the tests. Yoshimura et al.[77] reported, with respect to the above recommendations, a high sensitivity of 13C-UBT for confirmation of ET. Similarly, Kuloglu et al.[80] found that the sensitivity of 14C-UBT one month after ET, with suspension of PPIs, bismuth, and antibiotics during this period, was 100%. Shirim et al.[81] performed 13C-UBT to confirm eradication control 7 and 14 days after ET and observed that the sensitivity was 76% and 83.9%, respectively. The attempt to anticipate the confirmation of eradication to 7 days after completing ET yielded a false negative rate of 7.3%. Therefore, eradication should be confirmed 4 to 6 weeks after completing ET[6]. Systematic reviews and meta-analyses indicated that 13C-UBT had good accuracy in all age groups[35,38].

The SAT is also a robust test for diagnosing HP infection and eradication control. The sensitivity of the SAT is maintained by storing stool samples at room temperature for a maximum of 24 hours or at 4 °C for up to 72 hours. This storage procedure and suspended use of antibiotics and bismuth for 30 days and PPIs for 14 days before the test yielded good sensitivity. The sensitivity with monoclonal antibodies was significantly higher than with polyclonal antibodies[82]. The sensitivity of 13C-UBT was higher than that of SAT. Perri et al.[83] compared the sensitivity of 13C-UBT and SAT using monoclonal antibodies and obtained similar results. Gisbert and Pajares[84] conducted a systematic review to determine SAT sensitivity and concluded that this test had good accuracy for confirming HP eradication after 4 weeks

of treatment, and the results were slightly better when performed after 8 weeks of treatment.

The choice of HP eradication test should be based on low invasiveness and high accuracy. The non-invasive 13C-UBT and SAT are good alternatives for eradication control with a slight advantage for 13C-UBT.

Statement 5
Molecular tests may be used to assess HP antimicrobials resistance after second or third treatment failure. However, the lack of availability of bacterial cultures and antibiograms limits the use of these tests.
Level of evidence: 4 **Grade of recommendation: C**

One the most important causes of eradication failure is the increasing resistance to clarithromycin and levofloxacin[85]. Resistance to nitroimidazoles is considered the most common type of resistance[86]. Resistance rate to amoxicillin and tetracycline is considered low and stable[87].

Resistance to clarithromycin is caused by mutations in the *rrl* gene encoding two nucleotides of rRNA 23S: 2142 and 2143. A2142G and A2143G are the most common mutations, whereas the A2142C mutation is less common. Other mutations have been described, but their clinical importance is unknown. Quinolones resistance involves genes encoding DNA gyrase (gyrA and gyrB) at gyrA positions 86, 87, 88, 91, or 97. The most common mutations are in positions 87 and 91[86]. A rate of resistance to clarithromycin <15% was adopted by the European Consensus for therapies without previous assessment of resistance[40].

Several methods for evaluating resistance based on phenotype (culture and antibiogram) and genotype (molecular biology) are available. Phenotypic methods, including bacterial culture and antibiogram, allow determination of the minimum inhibitory concentration (MIC) of antibiotics and are considered the gold standard. In addition to discrepancies in terms of the methodology and use of different MICs for some compounds, the small number of laboratories that perform these test limits the use of such methods in clinical practice. Molecular biology-based genotypic tests are fast, reproducible, easy to standardize, and do not depend on the presence of live bacteria. These tests can assess resistance to clarithromycin, levofloxacin, and tetracycline and are commercially available for levofloxacin and clarithromycin; however, they are not yet available for amoxicillin and metronidazole because of the lack of knowledge of the mechanisms of resistance to these antimicrobials[86,87].

Two meta-analyses and two studies evaluating ETs in geographical areas with high resistance to antibiotics reported that therapies based on antimicrobial susceptibility tests were superior to empirical therapy[88-91].

Statement 6
Locally validated serological tests are the methods of choice for population-based screening studies. Serology may be used as the initial test for diagnosing HP infection, especially in the presence of gastrointestinal bleeding, atrophic gastritis, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.
Level of evidence: 2A **Grade of recommendation: B**

Serological tests are based on the detection of anti-HP IgG antibodies and are non-invasive, widely available, inexpensive, easy to perform, and widely accepted by patients[92,93]. The most used serological tests are enzyme immunoassays (ELISAs), immunochromatographic assays (rapid tests), and immunoblot assays. ELISA is the most commonly used assay because of its higher accuracy compared with rapid tests[63,94]. Immunoblotting, despite its higher specificity than ELISA without the loss of sensitivity, is more expensive, requires greater expertise for interpretation, and is not widely available in clinical laboratories[95].

The accuracy of the serological tests depends on the antigen used in the commercial kit and prevalence rate of the HP-specific strain used as the antigen source. The heterogeneity of HP strains is well known, and the prevalence of specific strains varies significantly in different regions. Therefore, the success of these test depends on the use of antigens from HP strains found in the population in question[96,97]. A previous study compared the accuracy of 29 commercially available kits and indicated that the variability was high (66.7% to 91.3%). In turn, the accuracy of rapid tests was lower (66.7% to 91.3%) than that of ELISA (73.9% to 97.8%). Four ELISA kits presented excellent results and sensitivity, specificity, positive and negative predictive values (PPV and NPV) >90%[94]. Similarly, the sensitivity, specificity, PPV, and NPV of serological tests using high-molecular-weight antigens, recombinant antigens, and higher immunogenicity antigens were >90%[98-100]. Ideally, locally validated tests with an accuracy >90% are recommended[40]. Studies performed in Brazil evaluating serological tests by ELISA and immunoblot found a sensitivity of 93.9%–97.4% and specificity of 88.9%–100%[101-103].

Serology is primarily indicated for screening HP infection in epidemiological studies. Its main limitation is the inability to distinguish between active and past infections because the serum levels of anti-HP IgG antibodies may remain high for long periods, even after HP eradication. Thus, serology cannot be used for eradication control after treatment[63,92]. Serological tests, particularly highly accurate and locally validated tests, may be used as initial non-invasive tests for screening HP infection and should be especially considered in clinical situations involving a low gastric bacterial load, such as gastrointestinal bleeding, atrophic gastritis, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer (GC), because the sensitivity is not altered, and false negatives are not produced in these situations[40,93,104-106].

Statement 7
The use of PPIs should be discontinued up to 2 weeks before performing diagnostic tests for HP infection, except serology. The use of antibiotics and bismuth salts should be discontinued up to 4 weeks before using the diagnostic tests.
Level of evidence: 2B **Grade of recommendation: B**

PPIs may yield false negative results in the RUT, 13C-UBT, SAT, and histological diagnosis because these drugs have moderate anti-HP activity, leading to a reduced bacterial load and inhibition of urease activity[78,79,107-113]. A few discordant studies found that 13C-UBT accuracy was not significantly affected by a short-term PPI pantoprazole use[110] and that PPIs did not significantly affect SAT using monoclonal antibodies[111]. Molec-

ular studies with more sophisticated techniques can detect the presence of HP in patients treated with PPIs[114,115].

Considering this evidence, the adequate interval between PPI use suspension and diagnostic tests performance is 14 days, except when serological tests are requested, which are not affected by PPIs[63,111,116-120]. Antibiotics and bismuth salts use should be discontinued 4 weeks before performing diagnostic tests[63,117,119]. H2 blockers have minimal effects on the results of breath tests, and antacid drugs do not affect the sensitivity of breath tests or the detection of stool antigens[79,121,122].

Statement 8
Endoscopy indication for upper gastrointestinal bleeding patients turns histology the recommended test in patients with an indication for HP screening. Breath tests are an alternative. A new diagnostic screening of HP should be conducted in patients with negative results in the first test.
Level of evidence: 4 **Grade of recommendation: C**

The diagnosis of HP infection in patients with upper gastrointestinal bleeding (UGIB) has specific characteristics that should be considered. The occurrence of bleeding in the gastric cavity decreases the accuracy of endoscopic tests (RUT, histological diagnosis, culture, and PCR), and the bactericidal effect of human plasma on HP may explain the decrease in the sensitivity of these tests[123]. Different studies have shown a significant sensitivity decrease of the RUT and culture in patients with UGIB[124-128], and a few studies have presented discordant results[129]. A prospective case-control study demonstrated that RUT sensitivity was decreased in UGIB history patients with or without gastric cavity bleeding[127]. Lee et al.[130] suggested that increasing the number of biopsies might increase the sensitivity of the RUT, although the sensitivity remained low. The use of molecular tests (PCR) using gastric mucosa biopsies presented conflicting results[131,132] and increased costs. These results suggest that the use of invasive tests for HP diagnosis in UGIB patients is not the ideal choice and non-invasive tests are recommended in these cases. The sensitivity and specificity of SAT are decreased in UGIB patients[133-135]. In contrast, 13C-UBT consistently presents good sensitivity and specificity for HP diagnosis in UGIB patients[136-138]. A systematic review and a meta-analysis compared invasive and non-invasive tests and concluded that invasive tests (RUT, histology, and culture) had lower sensitivity in patients with UGIB[139]. Among the non-invasive tests, SATs have lower sensitivity while 13C-UBTs have higher accuracy in these patients.

Therefore, the best test for HP screening in patients with UGIB is 13C-UBT. Nonetheless, this test is not widely available in Brazil to date. It is also evident that endoscopic examination should be performed for diagnosing and/or treating UGIB cause. Therefore, in this context, histological examination is recommended and/or RUT and 13C-UBT in cases in which the results of the first two tests are negative. If the 13-UBT test is unavailable, HP screening should be repeated at least 1 month after bleeding is resolved to confirm the results. Güell et al.[140] conducted a retrospective study to evaluate the results of HP retesting in patients with gastric or duodenal ulcer who presented with UGIB but were negative in the RUT and histology performed in urgent care, and they observed that the second test was positive in 79% of the participants.

GROUP 2 – DYSPEPSIA, MICROBIOTA, AND OTHER DISORDERS

Statement 9
The test-and-treat strategy is recommended for patients aged <40 years with dyspepsia not yet diagnosed with HP and without alarming signs. The test of choice for diagnosis and treatment control is the 13C-UBT.
Level of evidence: 1B **Grade of recommendation: A**

The test-and-treat strategy using a non-invasive test should be considered for adult patients aged <40 years with dyspepsia but without alarming signs, including unintentional weight loss, dysphagia, persistent vomiting, palpable mass in the abdomen, jaundice, gastrointestinal bleeding, and absence of history of gastric cancer in first-degree relatives. As previously recommended in the last Brazilian Consensus[3], 13C-UBT and SAT are recommended as non-invasive tests for diagnosis and eradication control, with a preference for the former. Several prospective studies support the use of this strategy, particularly in regions with a high rate of infection like Brazil[40].

Statement 10
Dyspepsia is very common and is classified as investigated and uninvestigated. After investigation, dyspepsia is now classified as organic, HP-associated, or functional.
Level of evidence: 1C **Grade of recommendation: A**

Dyspepsia is defined as persistent or recurrent pain and/or discomfort in the central and upper abdomen (epigastrium) [141]. The prevalence of this condition is high worldwide, with an estimated rate of 10% to 30%[142], and most patients do not present organic changes that justify the symptoms[143]. A study conducted in Pelotas, Rio Grande do Sul, Brazil, reported that the prevalence of complaints compatible with dyspepsia was 44.4% in the study population[144].

Dyspepsia is classified as investigated or uninvestigated. After screening, dyspepsia is classified as organic, HP-associated, or functional[4,145]. Upper gastrointestinal endoscopy with HP screening should be performed in patients aged >40 years with uninvestigated dyspepsia; patients who do not respond to empirical treatment with H2 blockers, PPIs, or prokinetics, among others; and patients of any age with alarm signs[145]. Three classifications are possible after endoscopic examination and HP screening: 1) patients with dyspepsia who present endoscopic changes that justify the symptoms are considered as having organic dyspepsia (e.g., peptic ulcer and GC); 2) patients with dyspepsia with normal endoscopy and without HP infection are considered as having functional dyspepsia; and 3) patients with dyspepsia with normal endoscopy and HP infection. In the latter situation, patients should be treated for bacterial eradication. The diagnosis when symptoms improve steadily after treatment (6 to 12 months) is HP-associated dyspepsia. Patients with continued complaints of dyspepsia, despite confirmed eradication, are considered to have functional dyspepsia.

According to the Rome Consensus IV, functional dyspepsia is a clinical syndrome that impacts activities of daily living and is characterized by the presence of recurrent and chronic dyspepsia in the absence of underlying structural or metabolic lesions detected in clinical routine (including endoscopy) capable of justifying the clinical picture. Functional dyspepsia is confirmed by meeting the following diagnostic criteria[145]: 1) recurrent complaints of dyspepsia in the past 3 months that began at least 6 months prior; 2) the presence of one or more of the following symptoms: a) postprandial indigestion, b) early satiety, c) epigastric pain, and d) epigastric burning; and 3) the absence of structural lesions on digestive endoscopy that justify the symptoms.

For better therapeutic orientation, patients with functional dyspepsia should be classified into two syndromes according to the main symptom: a) postprandial discomfort syndrome (meal-related symptoms), especially postprandial indigestion and/or early satiety at least 3 times a week in the past 3 months; and/or b) epigastric pain syndrome (symptoms not necessarily related to meals), predominating moderate to intense intermittent pain and/or epigastric burning at least once a week in the past 3 months. Of note, the two syndromes may be present in the same patient[145].

Some regions of Brazil present a high rate of intestinal parasitic infections, particularly those caused by *Ascaris lumbricoides*, *Strongiloides stercoralis*, and *Giardia lamblia*. Parasitological examinations of stool should be requested serially (in at least three samples), and the execution of larval concentration methods (Baermann method modified by Moraes and its variations) and direct stool examination are essential, especially for the detection of giardiasis and strongyloidiasis. The World Health Organization (WHO) recommends the use of antiparasitic drugs at regular intervals for populations at high risk of developing intestinal parasitic diseases[146]. This consensus maintains the recommendation of the previous Brazilian Consensus related to the execution of parasitological stool examination or empirical use of antiparasitic drugs together with the criteria established by the Rome Consensus IV for diagnosing functional dyspepsia[3].

Statement 11
Patients with dyspepsia and HP should be subjected to eradication treatment.
Level of evidence: 3A **Grade of recommendation: B**

Standard ET is indicated after confirming the presence of HP either by endoscopy or non-invasive tests[145]. The diagnosis in cases with sustained improvement of symptoms (6 to 12 months) is HP-associated dyspepsia[4,145]. This new guideline of the Kyoto Consensus[4] confirmed by the Rome Consensus IV[145] and Maastricht V[40] has been consolidated by several studies and meta-analyses demonstrating that HP eradication is better than placebo in relieving the symptoms of dyspepsia and results in a therapeutic gain of 4%–14%[147,148]. The main justification for eradicating HP in patients with dyspepsia is symptom relief in a subset of patients, lower risk of late development of clinical sequelae (e.g., peptic ulcer and GC), and interruption of HP transmission.

Statement 12
HP and the drugs used in ET affect the physiology of the gastric and intestinal microbiota and may modify the microbiota with severe consequences to overall health.
Level of evidence: 5 **Grade of recommendation: D**

HP is part of the stomach microbiota and can modify the gastric physiology and vice versa. HP initially infects the antrum and increases gastrin production in this region. Gastrin stimulates the secretion of pepsin by enterochromaffin-like (ECL) cells and promotes hyperplasia and hypertrophy in oxyntic cells. The increased secretion of pepsin prevents bacterial overgrowth in the stomach and intestine and directly stimulates the release of secretin, which in turn increases the release of pancreatic enzymes. A low pH also triggers the release of cholecystokinin (CCK), which regulates biliary flow and gallbladder contraction[149]. Bile salts and pancreatic enzymes help maintain the balance of the intestinal microbiota[150,151]. Intestinal motility may be indirectly regulated by the effects of HP on ghrelin, GLP-1, GLP-2, PYY, and melatonin[152-155]. Gastric and intestinal chemoreceptors are also affected by pH changes, directly affecting the gut-brain axis and ultimately the whole organism[156].

HP eradication may affect all these factors, causing changes in the stomach, intestine, pancreas, biliary system, and other systems.

The existing eradication strategies use drugs that decrease gastric secretion (usually PPIs) and antimicrobials, which are administered together in most cases. The impact of many antibiotics on the microbiota is evident. First, these drugs have broad-spectrum activity and therefore affect microorganisms other than HP, including commensal bacteria. This problem may be aggravated with repeated antimicrobial treatments, and the modified microbiota may require months to years to recover. Some arqueas are unable to recolonize the digestive system. During the initial stages, dysbiosis may be due to mild or severe changes in bowel habits (post-antibiotic diarrhea) and conditions such as pseudomembranous enterocolitis, which are fatal in some cases. The gut microbiota is known to modulate different body systems, and the potentially definitive microbiota imbalance may be transmitted to future generations and may have a significant impact on our descendants[157-161].

Some strategies may be used to minimize this problem, including reviewing HP treatment indications, using HP-specific antibiotics, optimizing initial treatment as much as possible by avoiding retreatments, and supplementing with probiotics. Therefore, probiotics may play an important role by increasing eradication rates and minimizing intestinal adverse effects (post-antibiotic diarrhea, pseudomembranous enterocolitis, and inflammation of the gastric mucosa). Moreover, probiotics may have positive effects via bactericidal activity (competition for nutrients and receptors, production of bacteriocins, and modulation of urease function of HP strains), immunomodulatory activity through pattern recognition receptors, and anti-inflammatory activity by modulating the production and scavenging of free radicals in the stomach. As previously reported, HP and ET may strongly affect gastric physiology, and changes in the gastric region affect different body systems in various ways.

Statement 13
Probiotics use associated with ET is an attempt to optimize HP eradication and minimize adverse events, rebalancing the microbiota. Further studies are needed to better define the strain, amount, time, and period of supplementation.
Level of evidence: 4 **Grade of recommendation: C**

In theory, prebiotics, probiotics, and symbiotics can reestablish the gut microbiota, competing for nutrients with pathogenic bacteria, inhibiting the activity of toxins, and performing immunomodulatory functions[162]. Experimental animal studies have shown that surface proteins in probiotic strains limit the colonization of the stomach by HP[163]. Strains of *Lactobacillus salivarius* and *L. casei* may inhibit HP urease activity (by producing lactic acid) and synthesize cytokines, which are involved in inflammatory processes[164]. Therefore, these species of *Lactobacilli* may reduce the HP load, mucosal inflammation (by inhibiting IL-8 production), and gastric hyperacidity[165].

Some probiotics containing *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii* exert anti-HP activity in vitro and reduce antibiotics associated side effects (particularly diarrhea and nausea) administered during ET with PPIs and antibiotics[166].

Although some authors found promising results using pre- and probiotics as adjuvant therapy in anti-HP regimens, most clinical trials found that this association did not improve eradication rates, bacterial colonization, gastric inflammation scores, and side effects[165-167]. A prospective, randomized, double-blind, placebo-controlled study in Brazil evaluated the role of an anti-HP regimen combined with probiotics (*Lactobacillus acidophilus*, *L. rhamnosus*, *Bifidobacterium bifidum*, and *Streptococcus faecium*) in eradicating HP and decreasing the number of adverse events. The eradication rate and adverse effects in the group treated with the antibiotic regimen and probiotics were not significantly different from those in the placebo group[168].

Recently, three important consensus meetings on the use of probiotics for the treatment of HP considered that, despite some encouraging results, probiotics appeared to increase bacterial eradication rates by reducing the adverse effects associated with antimicrobial treatment and not by a possible direct effect on the bacterial strains[40,169,170]. Additional randomized, double-blind, and controlled trials are necessary to define the strain, concentration, optimal time, and period of probiotic use. In addition, routine use of probiotics in ET is not recommended.

Statement 14
There is evidence of an association between HP infection, iron deficiency anemia of unknown etiology, immune thrombocytopenic purpura (ITP), and vitamin B12 deficiency. In other extra-gastroduodenal conditions, there may be negative and positive associations with no proven causality.
Level of evidence: 3A **Grade of recommendation: B**

The role of HP in iron deficiency anemia, ITP, and vitamin B12 deficiency is well established, and baseline disease is improved with bacterial eradication in both adults and children[171-176]. Three recent meta-analyses evaluated iron deficiency anemia of obscure etiology and found that the levels of hemoglobin and ferritin were increased after HP eradication in adults and children[174,177,178], and these findings have motivated international guideline to recommend ET to treat iron deficiency anemia of obscure etiology[179].

With respect to ITP, some nonrandomized studies, and randomized studies with small sample sizes, have suggested that platelet counts are increased in adults after HP eradication[180-1820]; however, the evidence in the pediatric population was weaker[183]. A systematic review involving 25 studies suggests that bacterial eradication tends to cause an increase in platelet counts[184]. The response is usually stronger in patients with a mild degree of thrombocytopenia and patients from regions with high infection rates[173,174,176,184,185]. The mechanisms underlying HP infection and ITP have not been fully elucidated. One of the most studied mechanisms is molecular mimicry involving HP CagA protein and platelet glycoproteins, particularly GPI and GPII[186].

Some studies have observed that HP infection decreases the absorption of vitamins, especially vitamin B12, leading to the accumulation of serum homocysteine[185,187]. Pangastritis induced by HP infection with strong involvement of the oxyntic mucosa may promote achlorhydria or hypochlorhydria and decrease pepsinogen levels, compromising the absorption of cobalamin. A study demonstrated that HP eradication might increase cobalamin levels and decrease serum homocysteine levels in elderly patients with vitamin B12 deficiency in Brazil[188].

Other studies have evaluated a possible association between HP infection and cardiovascular events. Ultrasound images of the intima-media thickness of the carotid wall, which is considered an indirect marker of clinical or subclinical atherosclerosis, showed an increase in thickness in patients with HP infection, particularly those infected with positive CagA strains[189]. A recent meta-analysis of prospective studies published from 1992 to 2014 analyzing the association between HP infection and the risk of coronary disease found that HP infection increased the risk of coronary disease by 11% (RR: 1.11; 95% CI: 1.01–1.22)[190]. Other studies found promising associations—but without sufficient evidence of causality—for other diseases, including Parkinson's disease and Alzheimer's disease[191,192]. In contrast, other studies reported negative associations between HP infection and diseases such as asthma and other atopic conditions, including eosinophilic esophagitis[193,194].

Statement 15
There is no evidence for an association between HP infection and gastroesophageal reflux disease (GERD). Bacterial eradication usually does not lead to the onset of GERD symptoms. Epidemiological evidence indicates a negative correlation between HP infection, Barrett's esophagus, and adenocarcinoma of the distal esophagus.
Level of evidence: 3A **Grade of recommendation: B**

The relationship of HP infection, gastroesophageal reflux disease (GERD), and Barrett's esophagus (BE) has been controversial. However, for adequate distinction of the associations within the context of GERD, it needs to be subclassified into non-erosive reflux disease, erosive reflux

disease, BE, and adenocarcinoma of the distal esophagus (ADE). Therefore, the collective odds ratio of a meta-analysis for the association between HP infection and GERD in Europe was 0.97 (0.75–1.27), not statistically significant[195]. This analysis included only studies in which GERD was defined by erosive esophagitis or abnormal esophageal pH-metry results. A case-control study involving 65,363 patients in Europe revealed that HP infection alone was not associated with a lower risk of developing GERD-related symptoms. Moreover, there was a negative association of GERD symptoms in patients with reduced pepsinogen levels and atrophic gastritis (OR: 0.2; 95% CI: 0.8–1.5)[196]. Similar results were found in a study in the United States, in which GERD symptoms were not associated with HP infection regardless of the virulence of the strains (CagA status)[197]. A case-control study involving more than 5,000 patients in Korea found a negative correlation between HP seroprevalence and the risk and severity of erosive esophagitis (OR: 0.44 [0.39–0.49])[198].

The studies that sought to evaluate the association between HP, BE, and ADE found a high variability in the methods, selection bias, and characterization of the study population[199,200]. A meta-analysis reported that the relative risk of BE in patients with HP infection was 0.46 (0.35–0.60); i.e., there was a strong negative association between HP and BE[201]. Another prospective case-control study confirmed the negative association between HP and BE, particularly for CagA-positive strains (OR: 0.36 [0.14–0.90])[197]. Anderson et al.[202] prospectively analyzed the effect of gastric atrophy and suggested a negative association between HP infection, BE, and ADE in cases of oxyntic mucosal atrophy. These findings indicate that BE and ADE primarily occurred in patients with non-atrophic gastric mucosa. Wang et al.[203] demonstrated that there was no difference in HP infection in patients with BE and control individuals from a blood donor population and individuals with normal endoscopic findings. The comparison between patients with BE and individuals with normal endoscopy revealed that BE was associated with a lower rate of HP infection.

A large number of prospective studies and meta-analyses evaluated the relationship between HP eradication and GERD. Most of these studies found that ET was not associated with the rate of reflux or reflux esophagitis. In addition, ET did not aggravate symptoms in patients with pre-existing GERD[40,204-207].

Statement 16
In patients infected with HP, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetyl salicylic acid (ASA), even at low doses, increases the risk of ulcer and its complications. Anticoagulants (coumarin, clopidogrel, and new oral anticoagulants) may increase the risk of ulcer/bleeding in HP-infected patients.
In patients at high risk of developing ulcers, before the initiation of long-term treatment with NSAIDs or ASA, even at low doses, HP should be screened and eradicated. However, eradication alone does not prevent the recurrence of ulcer/bleeding.
Level of evidence: 1B **Grade of recommendation: A**

NSAIDs are one the most commonly used drugs worldwide. These drugs are effective, but they have many adverse effects. The most common adverse events affect the digestive tract and include dyspepsia, heartburn, abdominal discomfort, and duodenal ulcer and its complications, especially life-threatening bleeding[208]. By contrast, HP infection is the most important etiologic factor of gastroduodenal ulcer[209]. Huang et al.[210] analyzed 16 studies involving 1,625 NSAID users and observed that uncomplicated ulcer was more common in HP-positive patients (341/817, 41.7%) than in HP-negative patients (209/808, 25.9%) (OR=2.12). In five controlled studies, ulcer was significantly more common in NSAID users (138/385, 35.8%) than in controls (23/276, 8.3%), but it was not significantly correlated with HP infection. A comparison between HP-negative individuals not using NSAIDs and HP-positive individuals using NSAIDs indicated that the risk of ulcer was 61.1 times higher in the latter. The use of NSAIDs alone (OR=19.4) and HP infection (OR=18.1) increased the risk of ulcer. In NSAID users, HP infection increased the risk of ulcer by 3.53-fold. The risk of bleeding complications was increased 1.79-fold in HP-infected patients and 4.85-fold in NSAID users. The risk was increased 6.13-fold in HP-positive patients treated with NSAIDs. This meta-analysis indicated that HP infection and NSAIDs were independent risk factors for ulcer and its complications. However, this association significantly increased the risk of uncomplicated ulcer and ulcer bleeding. Lanas et al.[211] observed that in patients using low doses of ASA, HP was an independent risk factor for ulcer bleeding (OR=4.7). Uemura et al.[212] evaluated 1,454 Japanese individuals with high-risk cardiovascular disease receiving ASA (75–325 mg/day) and found that the rate of gastroduodenal ulcer was 6.5%. Moreover, HP infection was an important risk factor for gastroduodenal ulcer (OR=1.83; P<0.0082). In addition to HP, an age >65 years (P=0.0246) and current smoking (P<0.0321) increased the risk of gastroduodenal ulcer. Kono et al.[213] analyzed 245 patients who were chronically using NSAIDs and observed that an age >75 years and HP infection were important risk factors for severe gastric mucosal damage. Iijima et al.[214] used the levels of pepsinogen I and pepsinogen I/II ratio to estimate hyperchlorhydria and observed that hyperchlorhydria was an important risk factor for severe gastric mucosal damage (OR=34.0) and gastric ulcer (OR=10.2) and recommended that these patients should be treated in advance to prevent mucosal damage.

The effect of HP on the risk of ulcer and/or bleeding in patients using low doses of ASA has been controversial. Sostres et al.[215] found no additive or potentiating effect of HP and ASA on the risk of ulcer or ulcer bleeding, although both conditions were independent risk factors.

Antiplatelets other than aspirin and anticoagulants[216], including recently developed drugs[217,218], increase the risk of ulcer bleeding. The Maastricht V/Florence Consensus concluded that the use of ASA or NSAIDs increased the risk of ulcer bleeding in HP infected patients[40].

Other risk factors for gastroduodenal ulcer in users of NSAIDs/ASA included an age ≥65 years, smoking, previous history of ulcer/UGIB, current smoking, combination of NSAIDs, and concomitant use of antiplatelet or anticoagulant agents. Gabriel et al.[219] analyzed 16 studies (9 controlled studies and 7 cohort studies) and concluded that the risk of a

severe gastrointestinal event in NSAID users was 3-fold higher than that in non-users (OR=2.74). In addition, the following risk factors were identified: age >60 years; concomitant use of corticosteroids; and period of exposure to NSAIDs <1 month (OR=8.00), 1–3 months (OR=3.31), and >3 months (OR=1.92), without significant differences between sexes. Laine et al.[220] evaluated 8,076 rheumatoid arthritis patients aged >45 years who were randomized to treatment with either rofecoxib or naproxen, and they found that patients at higher risk of severe events (ulcer bleeding, perforation, obstruction, symptomatic ulcer) in the naproxen group were aged ≥75 years and/or had a history of gastrointestinal complications.

The use of low-dose NSAIDs or aspirin in HP-infected patients has become increasingly common. The interactions between these associations may have a significant impact on the digestive tract. The symptoms caused by NSAIDs/ASA usually appear during the first days of treatment, although some studies suggest that the risk of complications is higher in the first 2 months. Current evidence indicates that the risk of complications is the same during treatment in patients treated with NSAIDs for either short or long periods[221].

Chan et al.[222] conducted a prospective study to assess the effect of HP infection on the risk of ulcer bleeding in three different groups, of which two groups had a history of ulcer bleeding. The first group included patients with ulcer bleeding (n=249) who resumed aspirin use after HP eradication. The second group consisted of patients who were not infected with HP who presented ulcer bleeding due to low-dose ASA (n=118). The third group included patients who started to use ASA without a previous history of ulcer (n=537). None of the patients from the analyzed groups received antisecretory drugs, and the study was terminated in cases of occurrence of ulcer bleeding. In the patients with eradicated HP, the rate of recurrence of ulcer bleeding with the use of ASA was low, whereas the risk of recurrence of ulcer bleeding was high in patients treated with aspirin without past or current HP infection. The authors concluded that it was useful to evaluate the presence of HP to identify patients at high risk of ulcer bleeding among ASA users.

The guidelines of the Italian Consensus advised eradicating HP to decrease the risk of complicated or uncomplicated ulcerative disease, emphasizing that eradication was more effective in prevention when performed before initiating treatment with NSAIDs[223].

Scarpignatto et al.[221] indicated that although the role of HP and the benefit of HP eradication in the potential risk of gastrointestinal complications are controversial, eradication is beneficial in patients with risk factors (age ≥65 years, previous history of ulcer and/or ulcer bleeding, concomitant use of anticoagulants or antiplatelet agents) provided that eradication is performed at the beginning of treatment with low-dose NSAIDs or ASA. HP eradication in patients who initiate treatment with low-dose ASA or NSAIDs reduced the risk of ulcer to an extent similarly to that of treatment with PPIs. However, eradication alone was not sufficient to prevent the relapse of ulcer and/or ulcer bleeding[224].

The use of PPIs is necessary to decrease the risk of ulcers and ulcer bleeding in high-risk patients, even in those using coxibs, which are known to be less gastrotoxic than standard NSAIDs[40,219-221,225-227].

In conclusion, in patients at high risk of ulcer and ulcer bleeding, including those who intend to start treatment with COX-1 and/or COX-2 inhibitors, HP infection should be screened and eradicated. However, eradication alone does not prevent recurrence of the ulcer and its complications, and therefore, the use of PPIs is mandatory.

GROUP 3: GASTRIC CANCER

Statement 17
Gastric cancer has an intermediate incidence in Brazil and is one of the five main causes of cancer mortality in the country, and its incidence exhibits regional differences.
Level of evidence: 2C **Grade of recommendation: B**

GC is the most common epithelial gastric neoplasm, representing 95% of the malignant tumors that affect the human stomach. Although the incidence of GC has decreased in recent decades, it is the second leading cause of cancer death worldwide, with more than 900,000 new cases per year[228]. The rate of GC is usually 2 to 3 times higher in developing countries than that in developed countries and is higher in men than in women. The National Cancer Institute of the Ministry of Health of Brazil[229] estimated that there were 20,520 new cases of GC in 2016, including 12,920 cases in men and 7,600 cases in women. These rates correspond to an estimated risk of 13.04 new cases per 100,000 men and 7.37 cases per 100,000 women. There are regional differences in Brazil: without considering non-melanoma skin cancer, GC in men is the second most common cancer in the north (11.62/100,000) and northeast (10.67/100,000) and occupies the fifth place in the southeast region (13.79/100,000). The mortality due to GC has been decreasing worldwide, including in Latin America[230,231]. In Brazil, despite a mild decrease, mortality is high, and the survival rate during the first year of disease is estimated at 32% and decreases to 9% at the end of 5 years[232-234].

Statement 18
HP eradication is associated with a decrease in the rate of GC.
Level of evidence: 1A **Grade of recommendation: A**

Epidemiological and experimental evidence have demonstrated that HP infection plays a role in GC[235], leading the World Health Organization (WHO) to recognize HP as the only carcinogen for this type of cancer in group I[236]. Recent studies have validated previous evidence demonstrating that HP eradication interrupts the sequence of events known as Correa's cascade[237] in cases in which the intervention occurs before the establishment of pre-neoplastic lesions such as metaplasia or dysplasia[238]. There are controversies concerning the efficacy of HP eradication in preventing GC in the presence of gastric atrophy[238-240].

The role of HP eradication for preventing a second primary tumor is controversial. Studies examining this potential benefit after endoscopic or surgical resection indicate moderate efficacy, insufficient follow-up periods, and conflicting results[238-240].

Although it is impossible to demonstrate, with high levels of evidence, the benefit of HP eradication in the presence of pre-neoplastic lesions or after a gastric tumor, some consider-

ations are necessary to form a decision matrix: i) pre-neoplastic lesions affect only part of the mucosa, and extensive areas of the mucosa exposed to HP may benefit from HP eradication; ii) the field cancerization theory states that carcinogenic effects act in areas that are more extensive than those restricted to the tumor, justifying the occurrence of a second primary tumor in the same organ or region; iii) HP should be eradicated in relatives of GC patients because of their possible exposure to the same bacterial strains and presence of similar genetic backgrounds, indicating that the potential benefits of eradication to the gastric mucosa of the relatives are similar to those of individuals who have or had gastric tumors or pre-neoplastic lesions; and iv) most metaplasias do not evolve to GC[241]. Therefore, HP eradication is recommended in individuals with pre-neoplastic lesions, endoscopy-treated gastric tumors, or partial gastrectomy.

Despite the number of indications for HP eradication by different institutions, including this consensus, critical reflections and analyses are important: (i) experimental evidence for the role of HP in GC was obtained using a cancer model that is applicable only to intestinal cancer, including Correa's cascade of events, which do not occur in diffuse cancer; (see also statement 20) (ii) despite the lower exposure to HP due to improved sanitary conditions and higher rate of eradication, the expected decrease in the GC rate is restricted to the intestinal histological type according to Lauren's classification[242-244]; and iii) the role of the stomach microbiota, the effects of the antibiotic therapy used to eradicate HP[245], and prolonged use of drugs that modify the gastric pH are gaps in knowledge that need to be filled.

Statement 19
Serological analysis of gastric atrophy using pepsinogen I (PGI) and pepsinogen II (PGII), combined with antibodies against HP and gastrin 17, can be used to identify populations at risk of GC. However, further studies are necessary to validate this instrument in Brazil.
Level of evidence: 3A **Grade of recommendation: B**

Pepsinogens, which are pro-enzymes of pepsin, are classified into two types according to their biochemical and immunological properties: PGI and PGII. Both types are produced by the gastric mucosa, but in different regions. PGI is produced exclusively by chief and mucosal cells of the gastric body, whereas PGII is produced by these cells and by mucous cells of the cardiac region, pyloric glands, and Brunner glands in the duodenal mucosa. Both types are excreted primarily into the gastric lumen, but approximately 1% diffuse into the bloodstream and can be measured[246-247].

The levels of PGI and PGII increase according to the degree of chronic gastritis associated with HP infection. However, when atrophic changes in the gastric body are accompanied by the loss of cells in the oxyntic mucosa, including cells that secrete PGI, serum levels of PGI are decreased while serum levels of PGII remain high or stable. However, in some cases, mucosal inflammation associated with HP infection may increase PGI and PGII levels, leading to normal PGI levels even in the presence of atrophy[248]. To overcome this limitation, the PGI/PGII ratio, which is currently considered the best serological marker of gastric atrophy, is used for gastric cancer screening in Japan and less often in other countries[249-255]. It is important to emphasize that the predictive value of measuring pepsinogens can be low in cases in which atrophy is restricted to the gastric antrum[256]. In addition to infection with HP and its various phenotypes, other factors may affect the serum levels of pepsinogens, including geographical region, race, age, gender, height, body weight, BMI, smoking, and use of alcohol[257-258]. Therefore, the efficacy of pepsinogen and PGI/PGII ratio (PGR) measurement remain controversial, particularly for determining the best cut-off point of the PGR for the diagnosis of gastric atrophy. PGI levels ≤70 ng/mL and PGR ≤3 are the most acceptable values for detecting gastric atrophy, and the sensitivity and specificity of these markers were found to be 66.7%–84.6% and 73.5%–87.1%, respectively[250,259,260]. Studies have shown that the main commercial tests available for measuring serum levels of pepsinogens have good agreement with each other[261].

The accuracy of the non-invasive diagnosis of gastric atrophy may be improved by including biomarkers other than pepsinogens. A study in Asia demonstrated that the association of the serological quantification of anti-HP antibodies with the level of pepsinogens (ABCD method) might help identify healthy adults at higher risk of developing GC[262]. Another combination of biomarkers (GastroPanel®) using a single blood sample allows the measurement of pepsinogens and gastrin 17 (for diagnosing antral atrophy) and quantifying anti-HP antibodies by serology. Two recent meta-analyses evaluated this panel. Syrienen[263] analyzed the results of 8,654 patients from different countries and found that the sensitivity and specificity for diagnosing atrophic gastritis were 70.2% and 93.9% in the gastric body and 53.8% and 84.1% in the gastric antrum. Zagari et al.[264] analyzed 20 studies involving 4,241 participants and found that the sensitivity for diagnosing atrophic gastritis in the gastric body and antrum was 70.4% and 65.4%, respectively. However, few studies to date have measured the levels of pepsinogens for diagnosing gastric atrophy in Latin America[265] and Brazil[266]. Therefore, well-designed studies with a large sample size are necessary to define the performance of this panel in this region.

Statement 20
Epidemiological, experimental, molecular, and clinical studies have confirmed the role of HP as a risk factor for gastric cancer.
Level of evidence: 1A **Grade of recommendation: A**

Epidemiological, laboratory, molecular, and bacterial eradication studies in humans have confirmed that HP is considered the major etiological factor for GC[267]. It is estimated that approximately 80% of malignant gastric tumors are associated with HP infection[268]. The risk of GC due to HP is similar in the diffuse and intestinal subtypes[267]. HP eradication may decrease the risk of GC[269]. Clinical trials demonstrated that the incidence of GC might be decreased by 30%–40% in the eradicated bacteria patients group. The groups at risk of developing GC, including first-degree relatives of GC patients and immigrants from regions with a high rate of GC, should be screened and treated[270-273]. Treatments at the population level (screening and treatment) are recommended in regions with a high rate of GC[269]. Asian countries are implementing this strategy with promising results[274,275].

Role of HP in proximal GC: HP infection was believed to be associated only with distal GC. However, detailed studies taking into account the differentiation between proximal GC, esophageal cancer, and junctional cancer found that the prevalence of HP in proximal GC was similar to that of distal GC[276-278], and thus, HP was also associated with proximal GC. As a result, HP is now considered a risk factor for both types of GC.

Statement 21
The diagnosis of mucosa-associated lymphoid tissue lymphoma is based on the histopathological and immunohistochemical evaluation of gastric biopsies together with HP screening.
Level of evidence: 1A **Grade of recommendation: A**

MALT lymphoma of the stomach is characterized by the clonal expansion of lymphocytes from the extra-nodal marginal zone of lymphoid follicles, in which morphological, immunophenotypic, and MALT behavioral characteristics are reproduced[279]. Therefore, diagnosis is based on the identification of these characteristics for determining the nature and staging of the lesion when assessing the natural history of the tissue.

Diagnosis

Gastric MALT lymphoma affects primarily middle-aged and elderly patients of both sexes[280]. These lymphomas are slow-growing, primarily superficial—located in the mucosa and submucosa—with a low incidence of mesenteric lymph node involvement and extra-nodal dissemination[281]. The most common presentation symptoms are nonspecific complaints of dyspepsia, which usually lead to endoscopy[281]. Endoscopic changes are nonspecific in most cases and present as flat, irregular, granular, or nodular mucosa with minimal ulceration. Mass formation is rare and favors the suspicion of high-grade lymphoma[282]. The diagnosis is based on the histopathological evaluation of gastric biopsies[283-285]. Samples should be collected from abnormal and normal areas and fixed in separate flasks. Histological analysis reveals a dense lymphoid infiltrate composed of small, morphologically heterogeneous B lymphocytes, which infiltrate the marginal zone of lymphoid follicles, extend into the interfollicular region, invade the germinal centers of the follicles, and infiltrate the epithelium in most cases, forming lymphoepithelial lesions[279,282]. Although no immunophenotypic marker specific for MALT lymphoma is available to date, immunohistochemical evaluation (using a marker panel including CD20, CD10, CD5, and cyclin D1) is essential for disease diagnosis and classification and allows characterization of the cell population in the lymphoid tissue[282,285]. Diagnosis should be based on the current WHO classification and confirmed by review by an expert in hematopathology[279,285]. HP infection is considered the main risk factor for MALT lymphoma, and disease regression occurs in most patients after HP eradication[286]. Therefore, the diagnosis of HP is mandatory. The analysis should be complemented by immunohistochemistry, RUT, the breath test, or serological tests in cases in which HP is not evidenced by HE staining[284,285]. In addition to routine histology and immunohistochemistry, fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) may be used to identify the *t*(11; 18) (p21; p21) chromosomal translocation in patients who are unlikely to respond to therapy with antibiotics[284-287].

Cancer staging

During its natural history, MALT lymphoma can evolve with infiltration of the deep layers of the gastric wall and dissemination to lymph nodes, other regions of the body with MALT, regions favorable for the development of MALT lymphoma, and bone marrow. Disease staging evaluates the natural history of the disease, classifies disease spread and is positively correlated with the prognosis and prediction of the response to therapy. Disease spread can be staged using different classification systems. The most common staging systems are Ann Arbor and Lugan[288,289]. The recently developed Paris system accurately assesses the depth of gastric wall infiltration[290]. The initial staging of MALT lymphoma is based on the clinical history and physical examination (including peripheral lymph nodes and Waldeyer ring), laboratory tests (standard biochemical analysis, complete blood count, lactic dehydrogenase, beta2-microglobulin, protein electrophoresis, in addition to serology for HIV, HBV, and HCV), and computed tomography of the chest, abdomen, and pelvis. Endoscopic ultrasound should be performed during the initial staging to assess the depth of gastric wall infiltration and regional lymph node infiltration. Bone marrow biopsy is recommended in cases in which the lymphoma does not regress after HP eradication and before initiating cancer treatment. Colonoscopy can be considered[284,285].

Statement 22
The follow-up of patients with MALT lymphoma after HP eradication requires periodic histopathological evaluations. The GELA system is an adequate morphological method for follow-up.
Level of evidence: 4 **Grade of recommendation: C**

Since a clear majority of primary gastric marginal zone B cell lymphomas (MALT) arise in *Helicobacter* (*H. pylori* or *H. heilmannii*) infected stomachs, it is widely accepted that the elimination of *Helicobacter* would likely prevent most, if not all, these lymphomas. Likewise, the eradication of *Helicobacter* results in the complete remission of at least 70% of MALT lymphomas diagnosed in infected stomachs[291], and also in a sizable percentage of patients in whom *Helicobacter* could not be demonstrated[292,293].

Once the MALT lymphoma is diagnosed and *Helicobacter pylori infection* is eradicated, it is crucial to follow up the patient and evaluate how the lymphoid proliferation responds to treatment. No clear guidelines for the frequency of the follow up endoscopies have been issued, but a sensible approach would suggest that the first follow-up endoscopy be performed 3-6 months after eradication, and then, in patients with a complete response, every 12 months since an elevated risk for gastric carcinoma has been reported in patients with MALT lymphoma, especially when intestinal metaplasia or dysplasia are found[285]. The biopsy protocol should be extensive, since lymphomas are patchy and may be easily missed, particularly when in partial remission. The evaluation of monoclonality, particularly during the first year after eradication, is discouraged because it tends to yield many false positive results[294].

Pathologists should familiarize themselves with the GELA classification for the histopathologic evaluation of the follow up biopsies[295]. A simplified version of the classification is depicted in TABLE 1. A more recent set of guidelines for the diagnosis, treatment, and follow up of gastric marginal zone B cell lymphomas (MALT) of the gastrointestinal tract has been recently published[296].

Statement 23
Staging of pre-neoplastic lesions should be based on at least four endoscopic biopsies (two antrum biopsies and two corpus biopsies) using the OLGA system for histological staging of gastritis. Patients staged as OLGA III or IV should undergo endoscopic follow-up every 2 years.
Level of evidence: 2C **Grade of recommendation: B**

HP colonizes the gastric mucosa and induces the secretion of cytokines and free radicals during active inflammation, leading to the development of mucosal lesions and possible mutations in target cells[297,298]. These factors, which are directly or indirectly related to the presence of the bacterium, may act as the initial trigger in the carcinogenic process[299]. At some point in this process, the carcinogenic changes may continue regardless of the presence of the bacterium. This possibility reinforces the need for follow-up in patients with these lesions, even in the absence of HP. These lesions can be categorized into (a) gastric atrophy, usually subdivided into mild, moderate, or severe; (b) intestinal metaplasia, usually subdivided into complete and incomplete; and (c) gastric dysplasia, subdivided into low-grade and high-grade[300-302].

Gastric atrophy during its evolution is associated with intestinal metaplasia (IM) in most cases, and both lesion types usually present a multifocal distribution[303]. The histological diagnosis of IM is relatively common in endoscopic biopsies. The prevalence of IM varies from 10% to 60% in non-selected patients infected with HP[304]. It is believed that the location of IM foci, especially in the *incisura angularis*, are more closely related to gastric carcinogenesis[305]. Of note, the glandular atrophy when restricted to the gastric body may not adequately fit the evolutionary aspects of GC[306-308]. Complete and incomplete IM are described based on the histological pattern and secretion of mucins. Incomplete IM has been more closely correlated with gastric carcinogenesis, particularly in cases in which sulfomucins characteristic of the colon are secreted[241,309,310]. In practice, the identification of sulfomucins in histological sections is impractical. However, relevance as pre-neoplastic lesions has been attributed to the extent of the areas of gastric atrophy and IM[311]. The practical effects of using different IM types in prognosis are limited and controversial[312,313].

The same phenomenon occurs with the classification of the different degrees of gastric atrophy. The diagnosis of mild and moderate atrophy is inconsistent among different observers, limiting the diagnosis of possible regression in patients with eradicated HP[314,315]. Similar difficulties are also evidenced in the histological diagnosis of low-grade dysplasia. This diagnosis should be confirmed by at least two experts in pathology.

New histological classifications such as OLGA and OLGIM attempt to solve the problem of precancerous lesions[316-318]. Although the histological diagnosis of IM (OLGIM) is more reliable than that of gastric atrophy (OLGA), the two systems seem to complement each other in the staging of chronic gastritis[319]. These classifications attempt to categorize patients across the spectrum of risk of GC, and different follow-up schemes are proposed depending on the classification of patients in this spectrum[320].

The natural history of gastritis, with its progression to metaplastic atrophy and the establishment of fields of cancerization prone to further molecular and phenotypic changes, possibly resulting in the development of cancer, provides the clinicopathologic rationale for primary and secondary cancer prevention strategies. *Helicobacter pylori* infection is, by far, the most common etiologic agent of this inflammatory changes and, consequently, the most common cause of non-syndromic gastric cancer, often referred to as environmental cancer. The primary prevention of *H. pylori* infection and its timely eradication (before extensive atrophic changes develop) are currently considered as the most effective cancer preventing strategies[321]. Secondary prevention is founded on the early detection and management of its precursor. Most gastric adenocarcinomas (typically the intestinal-type variant most commonly arising in the distal stomach) are the ultimate step of a cascade of phenotypic changes occurring in the gastric mucosa, triggered by non-self-limiting inflammation. This approach requires the complementary competences of gastroenterologists, oncologists, and pathologists be amalgamated into a common strategy of health policy, which must be tailored to country-specific gastric cancer incidence, socioeconomic, and cultural factors.

Since both extension and topographic distribution of gastric atrophy parallel the risk for gastric cancer, histological staging-systems to rank the risk for gastric cancer have been proposed and have become widely used. The OLGA system[322] ranks patients in progressive stages (0 to IV) based on extension and topography of the atrophic metaplastic changes. Patients with stages III and IV have been designated as high-risk and dedicated follow-up has been recommended. The OLGIM system, based on similar principles, has restricted the assessment to intestinal metaplasia[318]. The prognostic value of both

TABLE 1. A simplified histologic classification of the different levels of remission following the treatment of MALT lymphomas. Modified from Copie-Bergman et al. (2003)[295]

Score	Infiltrate	LEL	Mucosa
Complete remission	None	No	Normal or atrophic
Minimal residual Disease	Lymphoid aggregates or nodules	No	Normal or atrophic
Responding with residual disease	Scattered aggregates or nodules	Yes	Focally atrophic
Not responding	Diffuse or nodular	Yes	Unchanged

MALT: mucosa-associated lymphoid tissue; LEL: lymphoepithelial lesion.

these gastritis staging systems has been documented in several studies involving series of patients in diverse populations.

Several international guidelines suggest that patients with extensive atrophic gastritis be entered in endoscopic surveillance protocols[4,223,320]. These guidelines recommend that patients with antrum-to-corpus spreading gastric atrophy have a surveillance endoscopy with biopsies at 3-year intervals. However, recent evidence gathered from a 5-year follow-up of 1,755 patients in an area of moderate to high incidence of gastric cancer indicates that the majority of neoplastic lesions were detected between 1 and 3 years from the initial OLGA staging evaluation[323]. This finding supports the recommendation that the 3-year endoscopy-interval for patients with antrum-to-corpus spreading gastric atrophy recommended by some international guidelines is too long. Therefore, based on this evidence and on expert opinion, this Brazilian Consensus recommends that these patients be followed at 2-year intervals.

GROUP 4: TREATMENT

Statement 24
Despite the increasing rates of resistance to clarithromycin and fluoroquinolones in Brazil, their use is still recommended for treating HP. Despite the high in vitro resistance of HP to nitroimidazoles, these drugs may be prescribed in specific situations, doses, and periods.
Level of evidence: 2C **Grade of recommendation: B**

The rate of bacterial eradication using the standard triple regimen has progressively decreased[324,325]. The factors responsible for the decrease in therapeutic efficacy include life habits, baseline disease, poor adherence to treatment, smoking, CYP2C19 genetic polymorphism, high gastric acidity, previous use of antimicrobials, and especially resistance of HP to antimicrobials, including clarithromycin, fluoroquinolone, and metronidazole[326-331]. Antibiotic resistance can be investigated in the laboratory using phenotypic or genotypic methods. Bacterial culture and measurement of the minimum inhibitory concentration (MIC) of antibiotics (phenotypic method) is infrequently used in clinical practice because of the difficulty associated with collecting and transporting samples, fastidious bacterial growth, and need for appropriate growth media for culturing[52]. More recently, molecular techniques (genotypic method), particularly PCR, have been progressively used to detect bacteria and identify point mutations, which is the main mechanism of antimicrobial resistance[332]. These methods are faster and allow the analysis of mixed strains, which is not always possible with culturing; furthermore, these methods can be performed directly in endoscopic gastric biopsies, thus precluding previous bacterial culture[332,333]. Commercial kits used for determining genotypic resistance to clarithromycin and fluoroquinolones are widely available, and studies comparing genotypic and phenotypic methods have shown a good correlation[332-335].

However, few studies to date have evaluated the resistance of HP to antimicrobials in Brazil. From 2010 to 2016, six national studies were conducted, of which only one multicenter study evaluated the resistance of HP to clarithromycin. The results indicated that the rate of primary resistance was 16.5% in Recife (2010)[336], 8% in São Paulo, state of São Paulo[337], 2.5% in Marília, state of São Paulo (2013)[338], 13% in Porto Alegre, state of Rio Grande do Sul (2014)[339], 12.5% in Belo Horizonte, state of Minas Gerais (2016)[240], and 16.9% in a national multicenter study (2016)[341]. For fluoroquinolones, the observed rates were 23% in São Paulo[337], 5% in Porto Alegre[339], 11.1% in Belo Horizonte[340], and 13.4% at the national level[341]. With regard to resistance to metronidazole, an analysis of seven national studies confirmed the previous results, indicating consistently high rates (approximately 54%)[342]. The analysis of double resistance to clarithromycin and metronidazole at the national level suggested that the rates varied from 7.5% to 10%. A previous study reported that the rates of resistance to amoxicillin, tetracycline, and furazolidone were usually lower than 5%[342].

Statement 25
The duration of HP eradication therapies should be 14 days, especially for the standard triple therapy, to achieve high rates of eradication.
Level of evidence: 2A **Grade of recommendation: B**

The rates of HP eradication with first-line regimens have been decreasing in the past few years, especially with the use of triple therapy for 7 days[343]. Meta-analyses have consistently demonstrated higher eradication rates in 14-day triple therapies containing clarithromycin than 7-day therapies[344-348]. These studies also showed a higher eradication rate using a 10-day therapeutic regimen than a 7-day regimen by approximately 4%; the 14-day regimen had an increased rate by approximately 5%–6% compared with the 7-day regimen. Other studies have confirmed these results[349-352], and a recent Cochrane review showed that irrespective of the type and dose of antibiotics, increasing the duration of triple therapy with PPIs from 7 to 14 days significantly increased the rate of eradication of HP (45 studies, 72.9% vs. 81.9%)[348]. Considering this evidence, extension of the duration of triple therapies containing clarithromycin for 14 days was incorporated into the main guidelines on anti-HP therapy[40,353-355]. However, it should be noted that resistance to clarithromycin remains the main cause of failure of triple therapies, and the duration of treatment does not affect the high rates of resistance to clarithromycin in the general population (see below).

Quadruple therapy containing bismuth is used for treating and retreating HP infection. The duration of the bismuth-containing therapies remains controversial, but a study reported that eradication rates using a 7-day regimen were low[356]. Most studies suggest a duration of 10 to 14 days[357-361], and a 14-day regimen is recommended in areas with high rates of resistance to metronidazole (including Brazil), where 14-day therapies can overcome resistance[85]. It is of interest that randomized studies using capsules containing a combination of bismuth, metronidazole, and tetracycline combined with omeprazole for 10 days found eradication rates during the initial treatment and retreatment of infection >90%[362-364].

Some studies showed that the rate of eradication using a 14-day concomitant therapy without bismuth was higher than that using shorter regimens, particularly those using second-generation PPIs[365,366]. Park et al. conducted a prospective randomized study comparing sequential and concomitant

therapy for 10 and 14 days and observed that the eradication rates with the concomitant regimen were 94.2% and 98.5% in these periods, respectively[367].

Studies evaluating the efficacy of 10- and 14-day sequential therapies reported different results depending on the geographic region and types of medications used. The eradication rates using the 10-day schedule were 94.2% in Slovenia[368], 91.7% in Korea[369], and 80.0% in India[370]. Two systematic reviews and meta-analyses compared 10-day and 14-day sequential therapies with other therapies for HP and concluded that the 14-day therapy was the most effective[371,372].

Statement 26
Using PPIs after HP eradication for healing duodenal peptic ulcer is unnecessary. In cases of gastric ulcer or complicated gastroduodenal ulcers, treatment with PPI for 4 to 8 weeks after eradication treatment is recommended.
Level of evidence: 2C **Grade of recommendation: B**

Patients with gastric ulcer (GU) or duodenal ulcer (DU) and HP as the only lesion-triggering factor usually receive ET with antimicrobials associated with a PPI for 7–14 days, and then a 2–4-week course with an antisecretory drug such as PPI to promote ulcer healing. Claessens et al.[373] reported that 75% of the evaluated ulcer patients continued to receive PPIs after ET. In 2005, Gisbert and Pajares[374] conducted a systematic review and meta-analysis on this subject and found high rates of ulcer healing using ET without additional use of PPIs after antimicrobial withdrawal. A total of 24 studies and 2,342 patients were analyzed, and the rate of healing with 1-week ET was 86%. The healing rate was increased to 95% when considering only the patients who achieved HP eradication. The authors concluded that in patients with DU caused by HP, the healing rate of triple therapy without extending the use of PPIs to heal ulcers was 91%, compared with 92% in those who prolonged the use of PPI for variable periods. The authors concluded that further use of PPIs was recommended only in patients who presented symptoms. Of note, Higuchi et al.[375] randomly allocated 120 GU patients infected with HP to receive either ET or PPI for 8 weeks and concluded that ET complemented with PPI for a specific period might be necessary in patients with GU >10 mm.

Gisbert et al. (2012)[376] conducted an observational study and followed-up 1,000 patients who presented UGIB secondary to peptic ulcer and observed that ulcerations and new complications did not occur in patients with eradicated HP, indicating that maintenance of antisecretory therapy after eradication was not necessary. In 2016, the Cochrane group published a systematic review conducted by Ford et al.[377] on this subject and concluded that ET for 1–2 weeks was effective for healing DU. However, the quality of the studies on GU was poor, and thus, there is little scientific evidence to date demonstrating that ET alone is sufficient for healing GU.

Considering this evidence, isolated therapy with ET in patients with GU or DU and infected with HP should use the regimen with higher local eradication capacity. The inclusion of antisecretory drugs may be beneficial to patients with large GUs (>10 mm) or persistent symptoms after ET. In cases of UGIB, the same therapeutic strategy can be used, reinforcing the importance of HP screening and initiation of treatment during hospitalization.

Statement 27
Triple therapy consisting of the combination of PPIs, amoxicillin, and clarithromycin for 14 days is recommended as the first-line treatment. Alternatives include quadruple therapy with bismuth for 10–14 days and concomitant therapy for 14 days.
Level of evidence: 2A **Grade of recommendation: B**

Among the factors that may affect the success of anti-HP therapy (adherence to treatment, smoking, altered immunity, hypersecretory states, high bacterial load, and associated diseases, among others), antimicrobial resistance is considered the primary contributor to therapeutic failure. Polymorphisms associated with cytochrome CYP2C19 and previous use of macrolides may also affect bacterial eradication when classic triple therapy is used[326,378]. During the past 20 years, triple therapy with PPI + clarithromycin + amoxicillin administered for 7 days was the most widely used regimen. However, there has been a marked decrease in efficacy in several countries in recent years, with success rates lower than 80% due to a significant increase in the rates of resistance to antibiotics, particularly clarithromycin 325). In Brazil, the higher resistance of HP to antimicrobials has become an increasing problem. From 2010 to 2016, six national studies were conducted, of which one multicenter study evaluated the resistance of HP to different antimicrobials and reported a rate of primary resistance to clarithromycin ranging from 2.5%–16.9% (see statement 24). These observed values, in some studies, reached the suggested threshold of resistance to clarithromycin of 15%, where the rates higher than this threshold would preclude the use of this antimicrobial as first-line empirical therapy for HP[40].

Recent studies have been conducted to optimize triple therapy. The results of a meta-analysis indicated that increasing the duration of triple therapy for 14 days slightly but consistently increased the rate of HP eradication (see statement 25). Similarly, the recommended use of high doses of PPIs, preferably rabeprazole or esomeprazole, in classical triple therapy in Europe and North America [where the prevalence of extensive or rapid metabolizers of PPIs is high (56%–81%)] increased bacterial eradication rates[379-381]. In Brazil, a few regional studies also found a high prevalence of extensive and rapid metabolizers in the general population[382-384]; further studies are needed to clarify this finding. Considering these results and despite the absence of controlled studies, the consensus recommends the maintenance of standard triple therapy for 14 days as the first treatment option, preferably using high doses of PPI formulations that are effective in patients who are extensive or rapid metabolizers of PPIs (TABLE 2). Further randomized controlled studies are needed to validate these therapies in Brazil.

The recommended alternatives to 14-day standard triple therapy include quadruple bismuth regimens (PPIs, bismuth, tetracycline, and metronidazole) for 10–14 days or concomitant therapy (PPI, amoxicillin, clarithromycin, and metronidazole or tinidazole) for 14 days[385] (TABLE 2). The use of metronidazole in both regimens may be problematic because of the high levels of resistance of HP to this medication. However, the increase in treatment duration and increase in imidazole dosage may overcome the resistance detected in vitro[85].

TABLE 2. Drugs, dosage, and duration of first-line treatments of infection with *Helicobacter pylori*

Recommended	Drug	Drug	Length of treatment
Standard triple therapy	PPI*	Full dose at 12/12 h	14 days
	Clarithromycin	500 mg at 12/12 h	
	Amoxicillin	1.0 g at 12/12 h	
Alternatives			
Quadruple therapy with bismuth	PPI	Full dose at 12/12 h	10–14 days
	Colloidal bismuth subcitrate	120 mg at 6/6 h or 240 mg at 12/12 h	
	Tetracycline hydrochloride**	500 mg at 6/6 h	
	Metronidazole	400 mg at 8/8 h	
Concomitant therapy without bismuth	PPI	Full dose at 12/12 h	14 days
	Amoxicillin	1.0 g at 12/12 h	
	Clarithromycin	500 mg at 12/12 h	
	Metronidazole or tinidazole	500 mg at 12/12 h	

*PPIs: proton pump inhibitors. Studies indicated that the use of second-generation PPIs (rabeprazole and esomeprazole) in this situation might increase eradication rates[379-381]. Full dose: omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg, dexlansoprazole 60 mg, vonoprazan 20 mg, or esomeprazole 40 mg. **Tetracycline hydrochloride, if not available, may be replaced with doxycycline 100 mg at 12/12 h[3].

Recommended as an alternative to the standard triple therapy in areas of high resistance to clarithromycin (>15%), the efficacy of the concomitant regimen is determined by the rates of double resistance of HP to clarithromycin and nitroimidazoles, and it is accepted that the rates of cure can reach approximately 90% in cases in which the double resistance rate does not exceed 15%[40,386-388]. In Brazil, considering a rate of resistance to metronidazole and clarithromycin of approximately 54%[342] and 16.9%[341], respectively, the estimated rate of double resistance to both antimicrobials ranges from 7.5%–10.0%[40]. However, no controlled studies to date have evaluated these therapeutic options in Brazil. Quadruple regimens containing bismuth and employing furazolidone in place of metronidazole have shown good results in Brazil[3]. However, suspension of the commercialization of furazolidone and the recent unavailability of bismuth salts in Brazil has limited the use of this therapeutic option. From a practical stance, it is important to note that, in quadruple bismuth therapy, tetracycline can be replaced by amoxicillin with similar results[389]. This finding is especially relevant because of the irregular availability of tetracycline in Brazil. Sequential therapy with PPI and amoxicillin for the first 5 days followed by maintenance of PPI associated with clarithromycin and tinidazole for another 5 days is no longer considered a first-line option. This therapy is complex, highly variable in different regions, and the results are similar to those of concomitant therapy and 14-day triple therapy[390]. In Brazil, a study comparing sequential therapy showed that the rate of eradication of HP (86%) was similar to that of standard triple therapy for 10 days[391]. Furthermore, data on the outcomes of hybrid therapy (PPI associated with amoxicillin for 5–7 days followed by PPI, amoxicillin, clarithromycin, and metronidazole for another 5–7 days) as the first-line option are limited and inconsistent[40].

Statement 28
In cases of failure of triple therapy with clarithromycin or concomitant quadruple therapy, the recommended strategies are triple therapy with levofloxacin or quadruple therapy with bismuth, both for 10–14 days. In cases of failure of one of the two recommended second-line regimens, the other regimen should be used as third-line therapy.
Level of evidence: 2A **Grade of recommendation: B**

Bacterial resistance is considered the main factor associated with therapeutic failure, particularly resistance to clarithromycin. Therefore, simple repetition of the standard triple scheme is not recommended because the cure rates achieved in this situation are less than 50%[392].

The anti-HP regimen with PPI, amoxicillin, and levofloxacin is one of the most commonly used regimens worldwide for retreating HP infections after failure of the first-line regimen using clarithromycin, and a meta-analysis found that the eradication rates were close to 80%[392]. The anti-HP regimen with PPI, amoxicillin, and levofloxacin is well tolerated and may cause mild gastrointestinal adverse events. This regimen is cheap and is available in kits, optimizing adherence to treatment. As a limitation, recent studies have called attention to the increasing rate of resistance of HP to quinolones[324]. A recent multicenter study in Brazil found that the rate of resistance of HP strains to fluoroquinolones was 13.4%[341], which is similar to the rate found in 18 European countries (14%)[327]. Although the duration of treatment was 10 days in most studies, a comparative study reported higher rates of eradication using 14-day compared with 10-day regimens[393]. The dose of 500 mg daily (or 250 mg twice daily) of levofloxacin was better tolerated, the efficacy was similar to that of higher doses, and the dose increase could not overcome drug resistance[394-397]. To increase the success rates of quinolone triple therapies, some

studies have added bismuth salt to the regimen, which provided good results for eradication[398,399].

Quadruple bismuth therapy (PPI, bismuth, tetracycline, and metronidazole) is usually recommended during retreatment, with eradication rates approaching 80%[392]. Although it constitutes the oldest anti-HP regimen, there is variability in the optimal doses of the constituents suggested by different consensuses[40,353]. A meta-analysis subanalysis compared retreatment with PPI, levofloxacin, and amoxicillin for 10 days with quadruple therapy with bismuth and demonstrated that triple therapy with levofloxacin was more effective (89% vs 66%; OR=4.22; 95% CI=2.84–6.26)[392]. The limiting factors of quadruple therapy with bismuth include its complexity, large number of tablets to be ingested, and the varying availability of tetracycline. A single capsule containing a combination of bismuth, tetracycline, and metronidazole with good initial results in different countries (see statement 27) was introduced to the pharmaceutical market, but it is not yet available in Brazil. The objective of this therapy is to optimize the dosage of quadruple therapy with bismuth.

Considering the failure of the second treatment using triple therapy with levofloxacin, a third treatment using quadruple therapy with bismuth and vice versa is recommended. In cases in which the first-line regimen did not include clarithromycin, the standard triple regimen with clarithromycin for 14 days is recommended as second-line therapy.

The main regimens recommended as the second or third option in cases of failure of standard triple scheme are shown in TABLE 3, and other therapeutic regimens used for retreating HP infection are shown in TABLE 4.

Statement 29
Treatment after three therapeutic failures should be restricted to special cases and guided by phenotypic or genotypic tests of antimicrobial susceptibility. The use of rifabutin, when available, may be an alternative.
Level of evidence: 3A **Grade of recommendation: B**

TABLE 3. Drugs, dosage, and duration of the main regimens recommended as the second- or third-line regimen in cases of failure of standard triple therapy

	Drug	Dose	Length of treatment
Recommended			
Triple therapy with levofloxacin	PPIs*	Full dose at 12/12 h	10–14 days
	Amoxicillin	1.0 g at 12/12 h	
	Levofloxacin	500 mg at 24/24 h	
Quadruple therapy with bismuth	PPIs	Full dose at 12/12 h	10–14 days
	Colloidal bismuth subcitrate	120 mg at 6/6 h or 240 mg at 12/12 h	
	Tetracycline hydrochloride**	500 mg at 6/6 h	
	Metronidazole	400 mg at 8/8 h	

*PPIs: proton pump inhibitors. Full dose: omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg, dexlansoprazole 60 mg, vonoprazan 20 mg, or esomeprazole 40 mg. **Tetracycline hydrochloride, if not available, may be replaced with doxycycline 100 mg at 12/12 h[3].

TABLE 4. Drugs, dosage, and duration of alternative regimens used as the second- or third-line regimen for eradicating *Helicobacter pylori* in cases of failure of the first regimen

	Drug	Dose	Length of treatment
Quadruple therapy with furazolidone[3]*	PPIs**	Full dose at 12/12 h	10–14 days
	Amoxicillin	1.0 g at 12/12 h	
	Furazolidone	200 mg at 12/12 h	
	Colloidal bismuth subcitrate	240 mg at 12/12 h	
Quadruple therapy with levofloxacin and bismuth [398,399]***	PPIs	Full dose at 12/12 h	14 days
	Colloidal bismuth subcitrate	240 mg at 12/12 h	
	Levofloxacin	500 mg at 24/24 h	
	Amoxicillin	1.0 g at 12/12 h	
Standard triple therapy with clarithromycin****	PPIs*	Full dose at 12/12 h	14 days
	Clarithromycin	500 mg at 12/12 h	
	Amoxicillin	1.0 g at 12/12 h	

*Doxycycline 100 mg at 12/12 h can replace amoxicillin. Eradication rates close to 80%[3]. **PPIs: proton pump inhibitors. Full dose: omeprazole 20 mg, lansoprazole 60 mg, pantoprazole 40 mg, rabeprazole 20 mg, dexlansoprazole 60 mg, vonoprazan 20 mg, or esomeprazole 40 mg. ***Few studies, with intention-to-treat eradication rates of 85%–90%. ****Recommended as a second regimen when the first regimen was quadruple therapy with bismuth or triple therapy with levofloxacin and as a third regimen when the first treatment was quadruple therapy with bismuth and the second treatment was triple therapy with levofloxacin.

Treatment after failure of three previous treatments is an exception and should be used in patients known to be adherent to treatment and in situations in which HP eradication is critical, such as patients with MALT lymphoma, GC resection, or a family history of GC. The choice of the antibiotic scheme should, whenever possible, be guided by sensitivity studies (culture or molecular genetic tests) of antibiotic resistance. Previous knowledge of earlier regimens also helps in establishing therapy. Rifabutin (not available in Brazil to date) is an antibiotic with high anti-HP activity, a mean HP resistance rate of only 1.3%, and a mean eradication rate of 73%[400]. A systematic review of 21 trials using rifabutin to retreat HP infection indicated that the eradication rates were 79% when used as second-line therapy and 66%–70% when used as third-line therapy or higher, with global mean eradication rates of 73% (95% CI: 67%–79%)[401]. The most widely used therapeutic regimen included a combination of full-dose PPIs, rifabutin 150 mg, and amoxicillin 1.0 g twice daily for 10 days[400,401]. A study using this dosage as the fourth-line treatment in 190 patients found that the eradication rates were 52% (95% CI: 45%–59%)[402]. The most common adverse event was reversible myelotoxicity at the end of treatment[400].

Statement 30
The recommendation for individuals with allergy to amoxicillin is PPI 2x day + clarithromycin 500 mg 2x day + levofloxacin 500 mg 1x day for 14 days; or IBP 2x day + doxycycline 100 mg 2x day; or tetracycline 500 mg 4x day + metronidazole 500 mg 3x day + bismuth 240 mg 2x day for 14 days.
Level of evidence: 4 **Grade of recommendation: C**

The actual prevalence of penicillin allergy in the population is controversial. Although some studies reported that 3%–10% of the population of Japan and the United States are allergic to penicillin, other studies found that approximately 90% of these patients had negative skin tests and could tolerate penicillin without hypersensitivity[354,403,404]. To date, few studies with adequate sampling have determined the best therapeutic regimen in the impossibility of use of amoxicillin. A recent prospective study reported that the eradication rate using quadruple therapy with PPI, bismuth, tetracycline, and metronidazole in patients allergic to penicillin was 75% compared with a triple regimen consisting of PPI, metronidazole, and clarithromycin (59%; $P<0.05$). The most effective regimen as a second treatment or retreatment option was the combination of PPI, clarithromycin, and levofloxacin[405].

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Authors' contribution

Coelho LGV: designed the meting, conceived the initial statements, writing one statement, discussion and voting all the statements, and manucript writing. Marinho JR: designed the meting, writing two statements, discussion and voting all the statements. Genta R: writing two statements, discussion and voting all the statements. Ribeiro LT: writing two statements, discussion and voting all the statements. Passos MCF: writing two statements, discussion and voting all the statements. Zaterka S: writing one statement, and discussion and voting all the statements. Assumpção PP: writing one statement, and discussion and voting all the statements. Barbosa AJA: writing one statement, and discussion and voting all the statements. Barbuti R: writing two statements, and discussion and voting all the statements. Braga LL: writing one statements, and discussion and voting all the statements. Breyer H: writing one statements, and discussion and voting all the statements. Carvalhaes A - discussion and voting all the statements. Chinzon D: writing two statements, and discussion and voting all the statements. Cury M: writing one statement, and discussion and voting all the statements. Domingues G: writing one statement, and discussion and voting all the statements. Jorge JL: writing one statement, and discussion and voting all the statements. Maguilnik I: writing one statement, and discussion and voting all the statements. Marinho FP: writing one statement, and discussion and voting all the statements. Moraes Filho JP: writing two statements, and discussion and voting all the statements. Parente JML: writing one statement, and discussion and voting all the statements. Paula e Silva CM: writing one statement, and discussion and voting all the statements. Pedrazzoli Júnior J: writing two statements, and discussion and voting all the statements. Ramos AFP: writing one statement, and discussion and voting all the statements. Seidler H: writing one statement, and discussion and voting all the statements. Spinelli JN: writing one statement, and discussion and voting all the statements. Zir JV: discussion and voting all the statements.

Conflicts of interest

Coelho LGV: consultant from EMS; Marinho JR: consultant from EMS and Farmoquímica; Passos MCF: consultant from Apsen, EMS, Farmoquimica, and Mantecorp; Zaterka S: consultant from Takeda, and EMS; Barbuti R: consultant from Ache, and EMS; Chinzon D consultant from Takeda, and Mantecorp; Pedrazzoli Júnior J: consultant from EMS; Marinho FP consultant from EMS, and Farmoquímica; Parente JML; Genta R, Assumpção P, Barbosa AJA, Braga LL, Breyer H, Carvalhaes A, Cury M, Domingues G, Jorge JL, Maguilnik I, JP Moraes Filho, Paula e Silva CM, Ramos AFP, Ribeiro LT, Seidler H, Spinelli JN, Zir JV: no conflicts of interest.

Coelho LGV, Marinho JR, Genta R, Ribeiro LT, Passos MCF, Zaterka S, Assumpção PP, Barbosa AJA, Barbuti R, Braga LL, Breyer H, Carvalhaes A, Chinzon D, Cury M, Domingues G, Jorge JL, Maguilnik I, Marinho FP, Moraes Filho JP, Parente JML, Paula e Silva CM, Pedrazzoli Júnior J, Ramos AFP, Seidler H, Spinelli JN, Zir JV. IV Consenso Brasileiro sobre a infecção por *Helicobacter pylori*. Arq Gastroenterol. 2018;55(2):97-121.

RESUMO – Os avanços significativos ocorridos desde o III Consenso Brasileiro sobre *H. pylori* realizado em 2012, em Bento Gonçalves, justificam este quarto consenso. O evento foi organizado pelo Núcleo Brasileiro para Estudo do Helicobacter e Microbiota, associação vinculada à Federação Brasileira de Gastroenterologia, tendo sido realizado novamente em Bento Gonçalves, RS, nos dias 25 a 27 de agosto de 2017. Participaram 26 delegados provenientes das cinco regiões brasileiras incluindo gastroenterologistas, endoscopistas e patologistas, além de um convidado internacional (EUA). Os participantes foram convidados pelo conhecimento e contribuição ao estudo da infecção por *H. pylori.* O encontro buscou rever diferentes aspectos relacionados ao tratamento da infecção, suas inter-relações com a dispepsia, microbiota e outras afecções, com ênfase especial ao câncer gástrico, além de promover uma reavaliação dos aspectos epidemiológicos e diagnósticos desta infecção. Os participantes foram alocados em quatro grupos, a saber: 1) Epidemiologia e diagnóstico, 2) Dispepsia, microbiota e outras afecções, 3) Neoplasias gástricas, e 4) Tratamento. Previamente à reunião do Consenso, os participantes receberam um tema a ser discutido e elaboraram texto com uma revisão recente da literatura, contendo uma assertiva de sua revisão. Todas as assertivas foram avaliadas em dois turnos de votação. Inicialmente, cada participante apresentava sua compilação e assertiva ao seu grupo, para eventuais modificações e votação. Posteriormente, em uma segunda votação, agora em sessão plenária, as assertivas eram novamente votadas e eventualmente modificadas. As votações obedeceram a cinco alternativas: 1) concorda fortemente; 2) concorda com reservas; 3) indeciso; 4) discorda e; 5) discorda fortemente. O índice de consenso adotado para cada afirmativa foi de 80% dos votantes respondendo que concorda fortemente ou concorda com reservas. As recomendações aqui apresentadas foram baseadas nas evidências científicas mais relevantes para o manuseio da infecção por *H. pylori* na população adulta no Brasil.

DESCRITORES – *Helicobacter pylori.* Infecções por *Helicobacter.* Infecções por *Helicobacter*, terapia. Infecções por *Helicobacter*, diagnóstico.

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