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Clinical Practice Guidelines of Russian Gastroenterological Association, Scientific Society for the Clinical Study of Human Microbiome, Russian Society for the Prevention of Non-Communicable Diseases, Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy for *H. pylori* Diagnostics and Treatment in Adults

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Aim: bring to the attention of practitioners indications for anti-Helicobacter therapy, methods and procedure for diagnostics and eradication therapy of *H. pylori* infection.

Key points. Chronic gastritis caused by *H. pylori* infection, including asymptomatic persons, may be considered as an indication for eradication therapy of *H. pylori* as etiological therapy and opportunistic screening for gastric cancer prevention. Indications, for obligatory anti-Helicobacter therapy include peptic ulcer, gastric MALT lymphoma, early gastric cancer (EGC) with endoscopic resection. *H. pylori* primary diagnostics methods include ^{13}C-urea breath test, *H. pylori* stool antigen lab test, rapid urease test and serological method. The serological method cannot be used after anti-Helicobacter therapy.

In Russia *H. pylori* strains' resistance to clarithromycin does not exceed 15 % in most regional studies. The first line therapy for *H. pylori* infection eradication is the standard triple therapy including a proton pump inhibitor (PPI), clarithromycin and amoxicillin, enhanced with bismuthate tripotassium dicitrate. A classic four-component therapy based on bismuthate tripotassium dicitrate or quadrotherapy without bismuth drug products which includes PPI, amoxicillin, clarithromycin and metronidazole, may be used as alternative to the first line eradication therapy. The standard triple therapy may be prescribed for 14 days only in those regions, where it has been proven to be effective.

Quadrotherapy with bismuthate tripotassium dicitrate is also used as main second line therapy in case of standard triple therapy, bismuth enhanced standard triple therapy or combined therapy failure. Another second line therapy includes PPI, levofloxacin and amoxicillin, to which a bismuth-containing drug product may be added. The third line therapy is selected individually based on previously used treatment settings.

Conclusion. In each case of *H. pylori* infection the decision for eradication therapy should be made, which is especially relevant as eradication of *H. pylori* has been recognized as an effective measure for the prevention of gastric cancer.

Key words: *Helicobacter pylori*, chronic gastritis, gastric MALT lymphoma, *H. pylori* eradication therapy, ^{13}C-urea breath test, rapid urease test

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Клинические рекомендации Российской гастроэнтерологической ассоциации, Научного сообщества по содействию клиническому изучению микробиома человека, Российского общества профилактики неинфекционных заболеваний, Межрегиональной ассоциации по клинической микробиологии и антимикробной химиотерапии и по диагностике и лечению *H. pylori* у взрослых

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Цель: ознакомить практикующих врачей с показаниями к проведению антигеликобактерной терапии, методами и порядком диагностики и эрадикационной терапии инфекции *H. pylori*.

Основное содержание. Хронический гастрит, вызванный инфекцией *H. pylori*, в том числе у бессимптомных лиц, может рассматриваться как показание к проведению эрадикационной терапии *H. pylori* в качестве этиотропного лечения и оппортунистического скрининга для профилактики рака желудка. Показаниями для обязательного проведения антигеликобактерной терапии служат язвенная болезнь (ЯБ) желудка и двенадцатиперстной кишки, MALT-лимфома желудка, ранний рак желудка с эндоскопической резекцией. В качестве методов первичной диагностики инфекции *H. pylori* служат дыхательный тест с мочевиной, меченной ^{13}C, определение антигена *H. pylori* в кале лабораторным способом, быстрый уреазный тест и серологический метод. Серологический метод после проведения антигеликобактерной терапии неприменим.

Показатели устойчивости штаммов *H. pylori* к кларитромицину в России не превосходят 15 % в большинстве региональных исследований. Терапией первой линии для эрадикации инфекции *H. pylori* служит стандартная тройная терапия, включающая ингибитор протонной помпы (ИПП), кларитромицин и амоксициллин, усиленная висмута трикалия дицитратом. Как альтернативный вариант эрадикационной терапии первой линии может быть назначена классическая четырехкомпонентная терапия на основе висмута трикалия дицитрата или квадротерапия без препаратов висмута, которая включает ИПП, амоксициллин, кларитромицин и метронидазол. Стандартную тройную терапию следует назначать продолжительностью 14 дней только в регионах, где ее эффективность доказана. Квадротерапию с висмута трикалия дицитратом применяют также как основную схему терапии второй линии при неэффективности стандартной тройной терапии, стандартной тройной терапии, усиленной висмутом, или сочетанной схемы. Другая схема терапии второй линии включает ИПП, левофлоксацин и амоксициллин, к которой может быть добавлен препарат висмута. Терапия третьей линии подбирается индивидуально в зависимости от выбора предшествующих схем лечения.

Заключение. В каждом случае обнаружения *H. pylori* целесообразно решить вопрос о проведении эрадикационной терапии, что особенно актуально в связи с признанием эрадикации инфекции *H. pylori* эффективной мерой профилактики рака желудка.

Ключевые слова: *Helicobacter pylori*, хронический гастрит, язвенная болезнь, MALT-лимфома желудка, эрадикационная терапия *H. pylori*, дыхательный тест с мочевиной, меченной ^{13}C, быстрый уреазный тест

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Terms and definitions

Helicobacter pylori (H. pylori) is a helical gram-negative bacteria that colonizes the gastric mucous membrane, being an etiological factor of chronic gastritis.

Gastritis is an inflammatory disease of gastric mucosa.

Chronic gastritis is a group of chronic conditions morphologically characterized with persistent inflammatory infiltrate and disturbed cellular renewal with the development of intestinal metaplasia, atrophy and epithelial dysplasia in gastric mucosa.

H. pylori eradication therapy means treatment aimed at eradication of *H. pylori* infection.

1st line eradication therapy is the scheme of *H. pylori* infection eradication that is prescribed in the first instance.

2nd line eradication therapy is the scheme of eradication that is prescribed at failure of the 1st line therapy H. pylori.

1. Brief information on the disease or condition (group of diseases or conditions)

1.1. Definition

Helicobacter pylori (H. pylori) is a helical gram-negative bacteria that colonizes the gastric

mucous membrane, being an etiological factor of chronic gastritis.

Gastritis is an inflammatory disease of gastric mucosa. There are two main types of gastritis: acute and chronic. Chronic gastritis is a group of chronic conditions morphologically characterized with persistent inflammatory infiltrate and disturbed cellular renewal with the development of intestinal metaplasia, atrophy and epithelial dysplasia in gastric mucosa.

1.2. Etiology and pathogenesis

The Helicobacter pylori bacteria that colonizes gastric mucosa is an etiological factor of gastritis. Establishment of *H. pylori* etiological roles has made gastritis a clearly defined and clinically significant nosological unit, i.e. a disease with the known cause, stages of pathogenetic development, definite prognosis and finally determined possibilities of etiotropic therapy. B.J. Marshall and J.R. Warren, who were able to isolate the culture of previously unknown gram-negative microorganism from human gastric biopsy material, in their first publication discovering a large-scale research of *H. pylori* associated this bacteria with infiltration of epithelium and own mucous membrane layer with polymorphonuclear leukocytes in addition to lymphoplasmacytic infiltration [1]. *H. pylori's* ability to colonize gastric mucosa and cause acute and then chronic gastritis was perfectly supported with self-infecting experiments, independently conducted by B. Marshall (1985) and A. Morris (1987). Animal experiments greatly contribute to pathogenetic study of *H. pylori*: models capable of reproducing Helicobacter-associated gastritis and some other *H. pylori*-associated diseases, include mice, Mongolian gerbilles, Guinea pigs, gnotobiotic pigs and primates [2]. A Mongolian gerbille model was used to reproduce the gastric carcinogenesis paradigm (the Correa cascade): chronic inflammation caused by *H. pylori*, intestinal metaplasia, atrophy, dysplasia/intraepithelial metaplasia and invasive adenocarcinoma. Various authors were able to reproduce gastritis in humans following volunteers deliberately infected with *H. pylori* culture [2, 3].

A vast number of factors facilitates gastric mucosa colonization by and survival of *H. pylori* in a special gastric environment. Urease, an enzyme that catalyzes the hydrolysis of urea, forming ammonium and carbon dioxide, is essential for acid neutralization around the microorganism. Cilia allow the bacteria moving in a target way in a layer of mucus above epithelium. Other bacterial enzymes may cause mucin degradation. About 10 % of *H. pylori* come to a direct contact with epithelium. *H. pylori* adhesion to epithelial cells is a complex process, in which a number of surface proteins take part. For instance, BabA (blood group antigen binding adhesin) — adhesin that binds to Le^b-blood group antigens on epithelial cells; this adhesin gene allele, *babA2*, is closely associated with gastric ulcer and gastric cancer development in certain populations [2, 4].

There is a *"pathogenicity island"*, *cag PAI*, in the bacterium's genome, which marker is *cagA gene*, *i.e. cytotoxin-associated gene A*. This gene is found in 50–70 % of *H. pylori* strains. Certain proteins coded by *cag PAI* are used to form type IV secretory system of the bacteria, which helps H. pylori when connecting to a gastric epithelial cell to introduce *CagA*, the peptidoglycane and possibly other of its molecules into a host cell. In an epithelial cell, H. pylori's proteins activate several signal paths resulting in the host cell's cytoskeleton changes, disturbance of intercellular contacts, modification of proliferation and apoptosis, as well as an anti-inflammatory effect. Gastric epithelial cells respond to presence of *H. pylori* with the release of IL-8 and chemokine expressed and excreted by T-cells upon activation (RANTES) triggering an active inflammatory reaction in the mucous membrane. About 50 % of *H. pylori* strains excrete a highly immunogenic protein, vaculoating cytotoxin A (VacA) that causes *in vitro* vacuolization of cells and is associated with inflammation and apoptosis *in vivo*, respectively [2, 4]. Thus, *H. pylori* colonization maintains inflammatory infiltrate persistence in the gastric mucous membrane. H. pylori-induced inflammation results in atrophy, i.e. irreversible loss of gastric glands with their replacement by fibrous tissue or metaplastic epithelium. Atrophic gastritis, especially with gastric body damage and hypoacidity, has been proven to be a risk factor for gastric adenocarcinoma [2, 5–8].

Chronic Helicobacter gastritis is an underlying disease for a number of *H. pylori*-associated conditions, including gastric cancer [3, 5].

1.3. Epidemiology

Based on the data of large epidemiological studies for 2004–2012, *H. pylori* infection was found in 65–92 % of adult patients in various regions of the Russian Federation [9]. A trend of decrease in the number of infected people in the population has been observed in recent years. *H. pylori* prevalence according to the results of ^{13}C-urea breath test in people without previous eradication therapy (n = 6480) was 38.8 % (41.8 % in 2017, 36.4 % in 2019, $p < 0.0001$). In 2019 the lowest prevalence was registered in the Ural Federal District (32,7 %), the highest one was registered in the South Federal District

(52.7 %). Significant reduction of *H. pylori* prevalence in 2019 compared to 2017 was revealed only in the Central, North-Western, Volga and Ural Federal Districts, while it remained the same in other regions. The lowest prevalence of *H. pylori* was established in the age group below 18 years (20.2 %), and the highest one in the group aged 41–50 years (43.9 %). In 2017 *H. pylori* prevalence was significantly higher than in 2019 in all age groups ($p < 0.05$) (except for children below 18 and above 70 years, where similar values were found during both study periods) [10].

Prevalence of *H. pylori* in our country complies with the reduction of gastric ulcer and cancer incidence. Incidence of gastroduodenal ulcer in 2010 was 1047.0 per 100,000 of population, and in 2020 it was 740.8 per 100,000 of population [11]. In 2010 gastric cancer incidence was 28.3 per 100,000 of population, and in 2020 it was 21.89 per 100,000 of population. The average annual incidence reduction rate was 1.56 %, and 14.37 % for 10 years [12].

1.4. ICD-10 Coding

A number of diseases is associated with *H. pylori* infection; that determines the need for *H. pylori* to be diagnosed and treated. These recommendations provide indications to anti-Helicobacter therapy in various clinical situations below.

Gastritis and duodenitis (K29)
Gastric ulcer (K25)
Duodenal ulcer (K26)
Dyspepsia (K30)
Extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue [MALT-lymphoma] (C88.4)
Iron deficiency anemia, unspecified (D50.9)
Other primary thrombocytopenias (D69.4)

1.5. Classification

This section is not applicable to Clinical recommendations on *H. pylori* diagnostics and treatment.

1.6. Clinical presentation

H. pylori infection is not always accompanied with clinical symptoms, and the symptoms are not specific. Dyspepsia includes such symptoms as epigastric pain or burning, the sense of epigastric fullness, the feeling of early saturation. Chronic gastritis characterized with certain morphological mucosa alternations rarely causes symptoms, including those of dyspepsia. However, clinical symptoms found in certain patients with dyspepsia may be caused by chronic H. pylori-associated gastritis supported with their persistent elimination after eradication of an infectious agent. Dyspepsia associated with *H. pylori* and chronic gastritis was suggested to be reviewed as an independent clinical form in the report of Kyoto Consensus. To the contrary, persistence of dyspeptic symptoms, despite successful eradication therapy of *H. pylori*, is considered to be a manifestation of the functional disease, i.e functional dyspepsia [6, 7, 9].

2. Diagnosis of a disease or condition (group of diseases or conditions), medical indications and contraindications to the use of diagnostic methods

2.1. Primary Diagnostic

• Reference *H. pylori* diagnostics methods should be used for primary diagnostics in all patients, including ^{13}C-urea breath test and monoclonal *H. pylori* stool antigen lab test [13, 14].

Class of recommendations A (Level of evidence 1).

Comments: Best *H. pylori* infection primary diagnostics methods are non-invasive (require no oesophagogastroduodenoscopy) ^{13}C-urea breath test and monoclonal *H. pylori* stool antigen test. According to Cochrane review and meta-analysis, sensitivity of ^{13}C-urea breath test is 94 % (CI 95 %: 0.89–0.97), and *H. pylori* stool antigen test is 83 % (CI 95 %: 0.73–0.90) with specificity of 90 % [13].

• Rapid urease test with collection of the biopsy material from the antrum and the gastric body [15–18] or PCR with gastric biopsy material [19–21] may be recommended as the primary diagnostics method to patients with indications to oesophagogastroduodenoscopy.

Class of recommendations B (Level of evidence 2).

Comments: The rapid urease test may serve as the primary diagnostics method when performing EGDS. When endoscopic methods are used for H. pylori diagnostics, at least 2 biopsy samples are collected from the gastric body and 1 sample from the antrum [15–18]. Rapid urease test has sensitivity from 85 % to 95 %, specificity from 95 % to 100 % [19]. The biopsy material previously placed in the medium of rapid urease test may be used for H. pylori PCR diagnostics [20, 21].

Comments: It should be considered that treatment with proton pump inhibitors (PPI) may lead to false-negative results of most diagnostic tests [6, 9, 22, 23]. PPIs are recommended to be discontinued at least 2 weeks prior to diagnostics [6, 9]. Antibiotics and bismuth drug products should be discontinued at least 4 weeks prior to diagnostic tests [6].

• Serologic analysis for anti-*H. pylori* IgG antibodies may be recommended for certain patients,

including in case of decreased bacterial colonization of the gastric mucous membrane, e.g., after recent administration of antibacterial medicines, in case of ulcerous bleeding, or atrophic gastritis, as the means of primary infection diagnostics [13, 24].

Class of recommendations B
(Level of evidence 3).

2.2. Diagnostics following the course of *H. pylori* eradication therapy

• ^{13}C-urea breath test [13, 14] or *H. pylori* stool antigen lab test [13, 25] is recommended for all patients to assess efficacy of the eradication therapy received at least 4 weeks after completion of anti-Helicobacter therapy course or after completion of therapy with anti-secretory drugs or bismuthate tripotassium dicitrate [6, 13].

Class of recommendations A
(Level of evidence 1).

•Serological methods of anti-*H. pylori* antibodies detection are not recommended for use to assess effectiveness of the eradication therapy received, since those are not applicable in this situation [6, 13].

Class of recommendations B
(Level of evidence 3).

• Where reference diagnostics methods are unavailable, it is appropriate to combine available diagnostic tests or (where methods of bacterial detection directly in the gastric mucosa biopsy sample, i.e. bacteriological, morphological, and rapid urease test, are used) to study at least two biopsy samples from the gastric body and one antrum sample [9, 15–18].

Class of recommendations B
(Level of evidence 3).

Comments: For eradication control to be performed no earlier than in 4 weeks following completion of the eradication therapy, the best suitable methods are ^{13}C-urea breath test or H. pylori stool antigen test [13]. To avoid false-negative results, PPI should be discontinued at least 2 weeks prior to the expected control test, while any anti-bacterial drugs or bismuthate tripotassium dicitrate should be discontinued 4 weeks prior to the scheduled control test [6].

3. Treatment, including drug and non-drug treatment, diet treatment, pain relief, medical indications and contraindications to use of treatment methods.

3.1. Indications for eradication therapy of *H. pylori* infection

• Eradication therapy is recommended for all patients with chronic gastritis, who tested positive for *H. pylori*, as etiologic treatment [26–32].

Class of recommendations B
(Level of evidence 2).

• Eradication therapy is recommended for all patients with atrophic gastritis, who tested positive for *H. pylori*, to prevent from atrophy progression [33–35].

Class of recommendations A
(Level of evidence 2).

Comments: H. pylori is an etiological factor of chronic gastritis.The eradication therapy of the infection makes it possible to recover from non-atrophic gastritis that is accompanied by well-studied histological changes: epithelial and proper mucous membrane infiltration with polymorphonuclear leukocytes is eliminated at an early stage, infiltration with lymphocytes and plasma cells is reduced at quite an early terms however it does not disappear completely for more than a year after eradication; lymphoid follicles also remain for more than a year after etiological treatment, however their count decreases [26–32]. Based on results of several meta-analyses, it was established that eradication therapy of H. pylori resulted in regression or at least stabilization of mucosa atrophy in the gastric body and antrum, however this may help to achieve only stabilization, but not reverse development of intestinal metaplasia [30, 33–35].

• All persons with *H. pylori* infection, in the absence of contraindications, are recommended to undergo eradication therapy to prevent gastric cancer [8, 36–41].

Class of recommendations A
(Level of evidence 2).

Comments: Eradication of H. pylori infection is recognized as the main method of prevention of gastric cancer, the effectiveness of which has been proven in a number of population-based studies and meta-analyses [36–40]. In a meta-analysis of 7 RCTs that included 8323 people H. pylori eradication reduced the incidence of gastric cancer compared with people who did not receive eradication therapy, with relative risk 0.54 (95 % CI 0.40–0.72; NNT = 72), as well as mortality from gastric cancer with relative risk 0.61 (95 % CI 0.40–0.92; NNT = 135) [37].

• *H. pylori* eradication therapy is recommended for all patients who have undergone endoscopic resection of adenoma/early gastric cancer to prevent metachronous gastric cancer [37, 41–44].

Class of recommendations B
(Level of evidence 1).

Comments: A decrease in the incidence of metachronous gastric cancer in patients after

H. pylori eradication compared with the group with persistent infection has been proven in RCTs and meta-analyses [37, 41–44]. Thus, in a meta-analysis of 3 studies, including 1841 patients with endoscopic resection of epithelial dysplasia / neoplasia, eradication therapy reduced the incidence of gastric cancer with a relative risk index of 0.49 (95 % CI 0.34–0.70, NNT = 21) [37].

• Eradication therapy is recommended for all patients with ulcer relapse who tested positive for *H. pylori* for ulcer healing [45].

Class of recommendations A
(Level of evidence 1).

Comments: Based on the meta-analysis data, eradication therapy of H. pylori was superior than anti-secretory drugs for duodenal ulcer healing (34 studies; relative risk (RR) of ulcer persistence is 0.66 (95 % CI 0.58–0.76)) [45].

• Eradication therapy is recommended for all patients with ulcer who tested positive for *H. pylori* in order to prevent relapse [45, 46].

Class of recommendations A
(Level of evidence 1).

Comments: The meta-analysis summarizing results of 5 randomized controlled studies, demonstrated that in the population of patients with ulcers complicated with perforation eradication therapy significantly reduced the risk of relapse within one year after defect closure (RR 1.49; 95 % CI 1.10–2.03) [46]. According to Cochrane meta-analysis, eradication therapy of H. pylori compared to no such treatment significantly reduced relapses of duodenal ulcer (27 studies; RR 0.20, 95 % CI 0.15–0.26) and gastric ulcer relapses (12 studies; RR 0.31, 95 % CI 0.22–0.45) [45].

• Eradication therapy is recommended for all patients with ulcer complicated with gastro-intestinal bleeding with positive test results for *H. pylori* to prevent recurrent bleeding [47].

Class of recommendations A
(Level of evidence 1).

Comments: The meta-analysis included seven studies with 578 patients in total: mean percentage of recurrent bleeding in the group of H. pylori eradication therapy was 2.9 %, while it was 20 % in the group without eradication therapy and without subsequent continuous maintenance anti-secretory therapy (odds ratio 0.17; 95 % CI 0.10–0.32; number needed to treat (NNT) was 7, 95 % CI 5–11). Another meta-analysis included three studies with 470 patients in total: mean percentage of recurrent bleeding in the group of H. pylori eradication therapy was 1.6 %, while it was 5.6 % in the group without eradication therapy, but with continuous maintenance anti-secretory therapy (odds ratio 0.25; 95 % CI 0.08–0.76; NNT was 20, 95 % CI 12–100) [47].

• Eradication therapy of *H. pylori* is recommended to all patients with unexamined dyspepsia, who tested positive for *H. pylori*, to recover from dyspepsia and to diagnose functional dyspepsia [48].

Class of recommendations A
(Level of evidence 1).

Comments: According to the systematic review of assessment of H. pylori eradication therapy efficacy in treatment of functional dyspepsia, analysis of 29 clinical studies with 6781 patients demonstrated that eradication therapy was significantly more effective in elimination (number needed to treat (NNT) 14 (95 % CI 11–21)) or reduction (NNT 9 (95 % CI 7–17)) of dyspepsia complaints. Therefore, a positive effect of anti-Helicobacter therapy in patients with functional dyspepsia has been proven to be statistically significant, but slight [48]. The report of Kyoto Consensus on Helicobacter gastritis has legalized the term of "H. pylori-associated dyspepsia", and such form of dyspepsia is considered as a distinct entity [7]. Symptoms in H. pylori-infected patients with dyspepsia may be caused by Helicobacter gastritis where successful eradication is followed by persistent remission. If dyspepsia remains after etiologic treatment of bacterial gastritis, functional dyspepsia should be diagnosed [7].

• Eradication therapy of *H. pylori* is recommended to patients, who continuously take aspirin or whose long-term therapy will be supplemented with non-steroid anti-inflammatory drugs (NSAIDs), and who are at greater risk of ulcer formation [48–50].

Class of recommendations B
(Level of evidence 2).

Comments: Anti-Helicobacter treatment reduces the risk of uncomplicated and complicated gastroduodenal ulcers while using NSAIDs and aspirin, including low doses of aspirin [48–50]. However, H. pylori eradication alone does not eliminate completely the risk of gastroduodenal ulcers and complications thereof, in the first instance, bleeding in patients already taking NSAIDs [48–50].

• Eradication therapy of *H. pylori* is recommended to patients with chronic Helicobacter gastritis in case of long-term use of proton pump inhibitors (PPI) [27, 51–53].

Class of recommendations A
(Level of evidence 1).

Comments: Under the conditions of drug-induced intra-gastric pH increase during treatment with PPI, H. pylori migrates from the antrum

to the gastric body with subsequent gastritis progression in the gastric body. Eradication of H. pylori infection helps to reduce severity of such gastric alternations irrespectively of continuation of acid-suppressive therapy [27, 51–53]. In the systematic review the risk of body atrophy was higher in H. pylori-positive persons compared to H. pylori-negative (odds ratio 11.45; CI 95 %: 6.25–20.99; p < 0.00001) where PPI treatment continued for more than 3 years [52].

• Eradication therapy of *H. pylori* is recommended to patients with gastric MALT lymphoma as an initial therapy course. Eradication of *H. pylori* may be also appropriate in patients without established *H. pylori* infection, as well as at late disease stages [6, 54–56].

Class of recommendations A
(Level of evidence 1).

Comments: Anti-Helicobacter therapy has been recognized to be effective initial treatment of localized gastric MALT lymphoma in H. pylori-positive patients that may lead to tumor regression and its long-term control in most patients [54]. The meta-analysis demonstrated recovery from lymphoma after eradication therapy in 30 % of patients without established H. pylori [55, 56]. Assessment of anti-Helicobacter therapy and initiation of the repeated treatment course where necessary are included in the MALT lymphoma management scheme [57]. Forwarding a patient to the specialized oncological institution for subsequent follow-up is mandatory [9].

• *H. pylori* eradication therapy is recommended to patients with autoimmune thrombocytopenia and iron deficiency anemia to normalize blood parameters [58, 59].

• ***Class of recommendations A***
(Level of evidence 1).

Comments: The systematic review that included 25 studies (1555 adult patients) demonstrated a trend to increased thrombocyte count following recovery from H. pylori [58]. The incidence of iron deficiency anemia in H. pylori-positive persons is significantly higher than in non-infected people; the meta-analysis of 7 studies showed increased ferritin (but not hemoglobin) level after completion of eradication therapy of H. pylori combined with iron-containing drug products compared to iron-containing drug products alone [59].

3.2. First line eradication therapy of *H. pylori*

Resistance to antibiotics is believed to be the main reason of *H. pylori* eradication failure [60]. Maastricht Consensus VI EHMSG recommends routine tests for susceptibility to antibiotics (molecular or via inoculation) even before initiation of the first line therapy to make sure that antibiotics will be effective [6]. At the same time, it is emphasized that the global use of the strategy involving determination *H. pylori* antibiotic susceptibility is yet to be introduced to the routine clinical practice [6].

Clinical Practice Guidelines of the Gastroenterological Association are based on the empirical selection of the effective eradication therapy regimen. According to the concept of V.T. Ivashkin, the RAS Academician, *in vitro* data on resistance to antibiotics obtained should be interpreted very carefully in assessment of the multi-component anti-Helicobacter therapy efficacy, including PPI, that significantly changes gastric pH and bacterial activity. Influence of gastric pH on susceptibility of *H. pylori* to antibacterials has not been studied. Therapy success depends on such characteristics of the eradication therapy being initiated as selection of medicinal products, in particular, PPI, doses and frequency of administration during the day, including regarding food intake, specific dosage form and treatment duration [61].

The meta-analysis by M. Espada et al. that included 54 studies was dedicated to eradication therapy efficacy initiated based on established antibiotic susceptibility of *H. pylori* (number of patients 6705) and treatment regimens selected empirically (n = 7895) [62]. Testing results did not show that eradication efficacy based on *H. pylori* antibiotic susceptibility assessment was higher than empirical treatments neither in general, nor when only randomized controlled studies were included, or when culture-based methods were used to assess resistance to antibiotics, or for the purpose of repeated anti-Helicobacter treatment. Several advantages of the approach based on antibiotic resistance determination were shown for the first line eradication therapy — relative risk (RR) 1.15; CI 95 %: 1.11–1.20; I 2: 79 %. However, the difference in efficacy for empirical four-component treatments (with bismuth-based drugs or without them, without assessment of CYP2C19 gene polymorphism was insignificant. Therefore, the meta-analysis does not support advantage of the eradication therapy initiated based on determination of *H. pylori* susceptibility to antibiotics neither for the first line therapy, nor for treatment after the first line therapy failure [62].

Data on *H. pylori* susceptibility to antibiotics in the Russian Federation are presented in the meta-analysis of domestic studies for 10 years [63]. Resistance of *H. pylori* to clarithromycin was 10.39 % (CI 95 % 7.103–14.219), metronidazole — 33.95 % (CI 95 % 15.329–55.639),

amoxicillin — 1.35 % (CI 95 % 0.281–3.202), levofloxacin — 20.0 % (CI 95 % 12.637–28.574), tetracycline — 0.98 % (CI 95 % 0.353–2.163). Double resistance to clarithromycin and metronidazole was registered in 2.37 % (CI 95 % 1.136–4.345) [63]. Therefore, on the one hand, most data available in the Russian Federation still demonstrate low resistance of *H. pylori* to clarithromycin (less than 15 %), on the other hand, it should be noted that antibiotic resistance levels are not known in most regions. Unavailability of data on *H. pylori* resistance to antibiotic for a certain region is not the reason to refuse from initiation of anti-Helicobacter therapy, since therapy strategy is based on empirical modulation of any treatment regimen.

• One of the following therapies (optionally) should be initiated in all patients, who tested positive for *H. pylori* infection with indications for eradication therapy as the first line eradication therapy ensuring high percentage of infection eradication:

— standard triple therapy including PPI (at a standard dose twice a day), clarithromycin (500 mg twice a day) and amoxicillin (1000 mg twice a day) enhanced with bismuthate tripotassium dicitrate (120 mg 4 times a day or 240 mg twice a day) for 14 days [64, 65]

or

— classic four-component therapy with bismuthate tripotassium dicitrate (120 mg 4 times a day) combined with PPI (at a standard dose twice a day), tetracycline (500 mg 4 times a day) and metronidazole (500 mg three times a day) for 10 or 14 days [66–68]

or

— quadrotherapy without bismuth-based drugs that includes the standard triple therapy (PPI at a standard dose twice a day), amoxicillin (at a dose of 1000 mg twice a day), clarithromycin (500 mg twice a day) enhanced with metronidazole (500 mg 3 times a day) for 14 days [68].

Class of recommendations A
(Level of evidence 1).

Comments: Empirical selection of the first line eradication therapy without determination of H. pylori susceptibility to antibiotics is based on the therapy with the greatest proven efficacy. Adding bismuthate tripotassium dicitrate to the standard triple therapy significantly increases achievement of recovery from infection at the level exceeding 90 % of cases according to the data of European Registry on the management of Helicobacter pylori infection [65]. According to the meta-analysis by S.W. Ko et al., enhancement of the standard triple therapy with bismuthate tripotassium dicitrate increases efficacy with the odds ratio of 2.81 (95 % CI 2.03–3.89), including in case of established H. pylori resistance to clarithromycin [64]. The classic four-component therapy based on bismuthate tripotassium dicitrate continues demonstrating eradication efficacy in more than 90 % of cases, according to both European Registry data [66] and data of meta-analyses [67, 68]. Quadrotherapy without bismuth-based drug products or a concomitant therapy including PPIs and a combination of amoxicillin, clarithromycin and metronidazole is non-inferior compared to classic quadrotherapy according to the meta-analysis data [68]. In fact, a concomitant therapy is the standard triple therapy enhanced with metronidazole [9].

• Standard triple therapy should be initiated in patients, who tested positive for *H. pylori* infection with indications for eradication therapy as the first line eradication therapy in regions where its effectiveness is proven for the duration of 14 days [69].

Class of recommendations A
(Level of evidence 1).

Comments: According to the data of European Registry, the standard triple therapy for 7 days results in successful eradication in 82.7 %; 10 days in 84.2 %; 14 days in 86.2 % [66]. Cochrane meta-analysis of 45 randomized, parallel group, controlled studies demonstrates higher percentage of H. pylori eradication as a result of the triple therapy when its duration is increased from 7 to 14 days (72.9 % vs 81.9 %), and the relative risk (RR) of H. pylori persistence is 0.66 (95 % CI 0.60–0.74), NNT is 11 (95 % CI 9–14). A significant effect was observed when PPIs were combined with clarithromycin and amoxicillin (34 studies. RR 0.65; 95 % CI 0.57–0.75; NNT 12, 95 % CI 9–16). Significantly greater H. pylori eradication success is seen when the triple therapy duration is increased from 7 to 10 days (24 studies, 75.7 % vs 79.9 %); RR 0.80, 95 % CI 0.72–0.89; NNT 21, 95 % CI 15–38) and from 10 to 14 days (12 studies, 78.5 %; 78,5 % vs 84.4 %; RR 0.72, 95 % CI 0.58–0.90; NNT 17, 95 % CI 11–46); especially for PPIs combined with clarithromycin and amoxicillin when the duration is increased from 7 to 10 days (17 studies, RR 0.80, 95 % CI 0.70–0.91) and from 10 to 14 days (10 studies, RR 0.69, 95 % CI 0.52–0.91) [69].

3.3. Measures aimed at improvement of efficacy of *H. pylori* eradication therapy

Clinical Guidelines of Russian Gastroenterological Association for *H. pylori* Infection Diagnostics and Treatment in Adults, 2018 [9], cover the measures

aimed at improvement of the eradication therapy effectiveness:

– increased duration of *H. pylori* eradication therapy up to 14 days;

– prescription of newer PPI, such as rabeprazole and esomeprazole;

– prescription of PPI at a high dose;

– inclusion of bismuthate tripotassium dicitrate in the *H. pylori* eradication therapy;

– inclusion of a probiotic in the *H. pylori* eradication therapy;

– inclusion of rebamipide in the *H. pylori* eradication therapy;

– increased patients' compliance to *H. pylori* eradication therapy.

Methods of anti-Helicobacter treatment improvement have been studied well [70–74]. It is clear that these measures should be universal and may be applied to any therapy line and combination of these may help to achieve the best result in a specific patient [9].

Increased duration of the standard triple therapy of *H. pylori* up to 14 days based on the meta-analysis data [60] is provided for in the recommendation above. Maastricht Consensus VI EHMSG provides for duration of 14 days for all eradication regimens [6].

The necessity to add bismuthate tripotassium dicitrate to the standard triple therapy supported in the meta-analysis [65] is provided in the recommendation above. Effectiveness of the standard triple therapy enhanced with bismuth-based drugs exceeds 90 % in the routine clinical practice according to Russian data [66, 75–78]. Addition of bismuth-based drugs to other eradication therapy regimens, including those with levofloxacin, also demonstrated high efficacy [79–81].

In addition to above mentioned methods, which increase efficacy of the eradication therapy, importance of proton pump inhibitors, rebapamide, probiotics and patient compliance measures should be considered.

• The dose of a proton pump inhibitor may be doubled in patients, who tested positive for *H. pylori infection* and with indications for eradication therapy, to improve anti-Helicobacter treatment efficacy [82].

Class of recommendations A
(Level of evidence 1).

Comments: The meta-analysis demonstrated increased percentage of H. pylori eradication following administration of PPIs at high doses [82]. In the Clinical Guidelines of Russian Gastroenterological Association for H. pylori Infection Diagnostics and Treatment in Adults, 2018, preference was given to newer PPIs, i.e. rabeprazole and esomeprazole [9]. Specific properties found in rabeprazole (own anti-Helicobacter effect, mucins secretion activation in the gastric mucosa) may provide additional benefits for H. pylori eradication [9]. An attempt to demonstrate through the meta-analysis increased treatment efficacy based on the dose of rabeprazole and esomeprazole was not supported (85.3 % of successful therapy at high doses of PPIs and 84.2 % at usual doses of PPIs, OR 1.09 (95 % CI 0.86–1.37), P = 0.47) [83]. This may be resulted from inclusion in the meta-analysis of studies with low daily dose of rabeprazole (10 mg twice a day) accepted in several Asian countries [83]. High efficiency of rabeprazole and esomeprazole in H. pylori eradication barely depends on phenotypically determined variants of hepatic metabolism. The meta-analysis of 16 randomized controlled studies (n=3680) demonstrated decreased efficacy of the triple therapy with omeprazole and lansoprazole at standard doses in rapid PPI metabolizers, where efficacy of the triple therapy with rabeprazole and esomeprazole at standard doses was independent of CYP2C19 genetic polymorphism and did not decrease in rapid PPI metabolizers [84].

• A potassium-competitive acid blocker may be initiated by patients, who tested positive for *H. pylori* infection and with indications for eradication therapy, to improve anti-Helicobacter treatment efficacy [85, 86].

Class of recommendations B
(Level of evidence 2).

Comments: The meta-analysis by Y.S. Jung et al. demonstrated increased percentage of H. pylori eradication following the triple therapy with vonoprazan compared to the triple therapy with classic PPI [85]. The meta-analysis by S. Shinozaki et al. comparing efficacy of various second line eradication therapies also demonstrated benefit of the eradication therapy with vonoprazan [86].

• Rabamipide may be added to eradication treatments of patients, who tested positive for *H. pylori* infection and with indications for eradication therapy, to improve anti-Helicobacter treatment efficacy [87–89].

Class of recommendations A
(Level of evidence 1).

Comments: 3 meta-analyses including 6, 11 and 6 randomized, controlled studies confirmed increased eradication frequency following rabamipide inclusion in the treatment [87–89].

• Compliance with the prescribed treatment should be ensured for patients, who tested positive for *H. pylori* infection and with indications for eradication therapy [90, 91].

Class of recommendations B
(Level of evidence 2).

Comments: Compliance must be reviewed as the key success factor for H. pylori eradication therapy. In the controlled study it was shown that when more than 60 % of drugs prescribed were taken, infection eradication was 96 %, when less than 60 % of such drug were taken (low compliance) eradication was 69 % [90]. In a large-scale randomized, controlled study, eradication percentage decreased with low compliance (less than 80 % of prescribed drugs were taken) by 34 %, with persistence of H. pylori observed on 59 % of cases of non-compliant patients [91]. Recommendations of the World Gastroenterology Organization on H. pylori provide for measures on increase of patients' compliance with eradication therapy as adherence to quality practice. Patients must be informed of that successful eradication depends on compliance with the treatment regimen. Certain amount of time should be spent on consulting a patient explaining how to receive the complex medicinal therapy and to assess possible side effects of antibacterial therapy. The need of therapy completion and taking the total dose of prescribed drug products is of great importance. It is emphasized that written or graphical information on the method of complex eradication therapy use may be helpful for compliance [https://www.worldgastroenterology.org/UserFiles/file/guidelines/helicobacter-pylori-russian-2021.pdf]. A combined drug product for ulcer treatment containing a set of capsules and tablets of the standard triple therapy is registered in the Russian Federation: every strip (blisterless pack) that includes 2 capsules of omeprazole 20 mg, 2 tablets of clarithromycin 500 mg, 4 capsules of amoxicillin 500 mg, is for one day where morning and evening intakes are clearly distinguished. A ready-to-use set of drug products for eradication therapy helps to ensure the correct dose and stable administration frequency increasing patient's compliance, which serves as the basis for infection eradication in ulcer patients at the level exceeding 90 % achieved in the domestic study [92].

• Strain-specific probiotics with proven efficacy may be initiated by patients, who tested positive for H. pylori infection and with indications for eradication therapy to decrease incidence of adverse events, including antibiotic-associated diarrhea [93–102].

Class of recommendations A
(Level of evidence 1).

Comments: Certain single-strain and multi-strain probiotics have proven efficacy for H. pylori eradication therapy [93–102]. Probiotics included in the anti-Helicobacter therapy are believed to reduce incidence of adverse events resulting in potential improvement of eradication efficacy [6].

The systematic review with the meta-analysis that summarized results of 42 RCTs showed that the risk of antibiotic-associated diarrhea in patients taking probiotics was significantly lower than in patients not taking these products (RR = 0.35; 95 % CI 0.27–0.47, p < 0.00001) or taking placebo during antibacterial treatment (RR = 0.69, 95 % CI 0.60–0.80, p < 0.00001). The review also presents data of the meta-analysis of 7 RCTs dedicated to probiotic use combined with antibiotics in the course of H. pylori eradication, where significant reduction of the risk of antibiotic-associated diarrhea by 45 % was observed (RR = 0.55; 95 % CI 0.41–0.73; P < 0.0001) [97].

According to data of Cochrane review with the meta-analysis of 31 RCTs, probiotics also reduce the risk of C.difficile-associated diarrhea by 60 % (RR = 0.40; 95 % CI 0.30–0.52) compared to placebo or in absence of probiotic support [102].

A controlled study demonstrated that inclusion of Saccharomyces boulardii (S. boulardii) CNCM I-745 probiotic in a three-component eradication therapy at a dose of 750 mg daily for the whole period of treatment significantly reduced the number of side effects related to the therapy received compared to the control group (5.3 ± 3.0 vs 9.0 ± 3.1, P = 0.028) [103]. H. pylori eradication in the group of patients receiving S. boulardii CNCM I-745 at a dose of 500 mg daily was significantly superior to that in control subjects (86.0 % and 74.7 %, respectively; p = 0.02). Eradication-related side effects, including antibiotic-associated diarrhea (2.0 % vs 46.4 %; P = 0.02) and greater treatment compliance (95.0 % of subjects in the experimental group completed the full therapy course vs 91.2 % in the control group, p < 0.001) were significantly fewer in patients of main group compared to the control group (17.0 % vs 55.7 %; p < 0.001) [104]. The meta-analysis of 18 studies (n = 3592) showed that adding S. boulardii to eradication therapy lead to decrease in the risk of the total number of side effects (dyspepsia, altered defecation pattern) by 53 % compared to patients not taking S. boulardii (RR = 0.47, CI 95 %: 0.36–0.61), diarrhea incidence was lower by 67 % (RR = 0.37, CI 95 %: 0.23–0.57), and achievement of successful eradication was higher (RR = 1.09, CI 95 %: 1.05–1.13) [94].

Results of the meta-analysis performed demonstrate that probiotics containing Lactobacillus acidophilus LA-5 and Bifidobacterium animalis subsp. lactis BB-12 (mainly as a part of functional food products) are effective in decrease of the total number of side effects (RR 0.31, CI 95 %: 0.20–0.47), prevention of antibiotic-associated diarrhea (RR 0.38, CI 95 %: 0.20–0.72) and improvement of H. pylori eradication outcomes (RR 1.16, CI 95 %: 1.05–1.28) [95].

3.4. *H. pylori* eradication therapy after the first line therapy failure

• The classic four-component therapy with bismuthate tripotassium dicitrate is recommended to patients, who tested positive for *H. pylori* infection following failure of the standard triple therapy, standard triple therapy enhanced with bismuthate tripotassium dicitrate, or concomitant therapy, as the second line therapy [81, 105].

Class of recommendations A (Level of evidence 1).

Comments: The systematic review with the network meta-analysis demonstrated great efficacy of quadrotherapy with a bismuth-based drug product as the second line therapy [81]. According to the meta-analysis by Z. Han et al., bismuth-containing drug products increase percentage of eradication in case of resistance to clarithromycin by 40 %, to metronidazole by 26 %, in case of double resistance by 59 % justifying their choice as the second line therapy [105].

• The triple treatment regimen with levofloxacin or quadrotherapy with levofloxacin is recommended to patients, who tested positive for *H. pylori* infection, following failure of the classic four-component therapy with bismuthate tripotassium dicitrate, as the second line therapy [79–81, 106].

Class of recommendations B (Level of evidence 2).

Comments: The triple therapy with levofloxacin (PPI, levofloxacin and amoxicillin) or quadrotherapy with levofloxacin (PPI, levofloxacin, amoxicillin, bismuth-based drug product) following failure of previous eradication therapy courses has been studied in controlled studies and systematic reviews [79–81, 106].

The algorithm of *H. pylori* diagnostics and treatment is shown in the figure (Annex B. Medical algorithms).

Annex A. Methodology of Clinical Recommendations Development

Proposed recommendations are to inform the practitioners about the indications for anti-Helicobacter therapy, methods and procedure for diagnostics and eradication therapy of *H. pylori* infection.

Target audience of these Clinical Guidelines:

1. Gastroenterologists.
2. General practitioners (family doctors).
3. Internists.
4. Surgeons.

Table 1. Levels of evidence (LOE) for diagnostic methods (diagnostic interventions)

LOE	Meaning
1	Systematic reviews of reference method-controlled studies or a systematic review of randomized clinical trials using meta-analysis
2	Separate reference controlled studies or separate randomized clinical trials and systematic reviews of studies of any design, with the exception of randomized clinical trials, using meta-analysis
3	Studies without sequential control by a reference method or studies with a reference method that is not independent of the method under study or non-randomized comparative studies, including cohort studies
4	Non-comparative studies, case study
5	There is only a justification of the mechanism of action or the opinion of experts

Table 2. Levels of evidence with specification of level of evidence (LoE) classification used

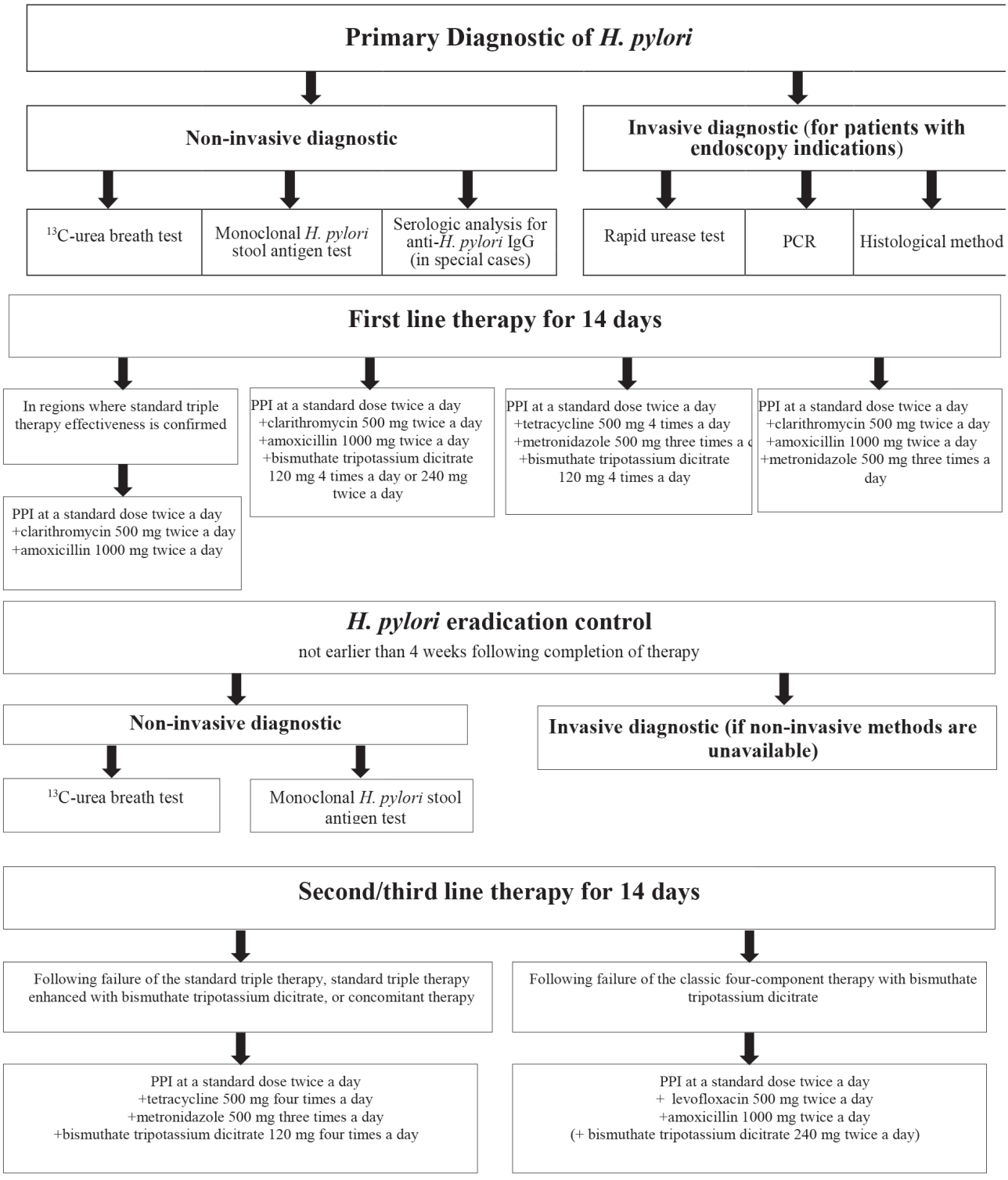
LOE	Meaning
1	Systematic review of randomized clinical trials using meta-analysis
2	Separate randomized clinical trials and systematic reviews of studies of any design, with the exception of randomized clinical trials, using meta-analysis
3	Non-randomized comparative studies, including cohort studies
4	Non-comparative studies, case studies or study of a series of cases, case-control study
5	There is only a justification of the mechanism of action of the intervention (preclinical studies) or expert opinion

Table 3. Classes of recommendation (CoR) with specification of classes of recommendation classification used

CoR	Meaning
A	Strong recommendation (all considered performance criteria (outcomes) are significant, all studies have high or satisfactory methodological quality, their conclusions on the outcomes of interest are consistent)
B	Conditional recommendation (not all considered performance criteria (outcomes) are significant, not all studies have high or satisfactory methodological quality and/or their conclusions on the outcomes of interest are not consistent)
C	Poor recommendation (lack of evidence of proper quality (all considered efficacy endpoints (outcomes) are insignificant, all studies have low methodological quality and their conclusions on the outcomes of interest are not consistent)

Annex B. Medical algorithms

Algorithm for the diagnosis and treatment of *H. pylori* infection in adults



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