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HELICOBACTER PYLORI-ASSOCIATED CHRONIC GASTRITIS: EPIDEMIOLOGY, DIAGNOSIS AND CHOICE OF ERADICATION THERAPY IN THE SETTING OF HIGH CLARITHROMYCIN RESISTANCE

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ABSTRACT

Aim. To summarize current evidence on the epidemiology, diagnosis and treatment of Helicobacter pylori-associated chronic gastritis, taking into account regional data on H. pylori antibiotic resistance in Central Asia and Uzbekistan.

Material and methods. International and national consensus documents (Maastricht VI/Florence, ACG 2024, Kyoto consensus, Taipei Global Consensus II, ESPGHAN/NASPGHAN 2023, etc.), systematic reviews, meta-analyses and randomized trials published predominantly in 2016–2026 and indexed in PubMed/MEDLINE, Scopus, eLIBRARY.ru and Google Scholar, as well as regional studies from Central Asian countries, were analysed.

Results. The global prevalence of infection among adults has declined to 43–44% but remains high in Central Asia (about 70%). H. pylori causes chronic active gastritis in all infected individuals and is the main cause of gastric cancer, which is the leading cause of cancer death in Uzbekistan. For primary diagnosis in adults without indications for endoscopy, the ^{14}C-urea breath test and the monoclonal stool antigen test are preferred; when endoscopy is indicated, biopsy-based methods with gastritis staging according to OLGA/OLGIM are used. According to a multicentre study, clarithromycin resistance of H. pylori in Uzbekistan reaches 41–45%, which precludes empirical use of clarithromycin-containing regimens. Fourteen-day bismuth quadruple therapy is the first-line regimen of choice; clarithromycin- and levofloxacin-containing regimens are appropriate when susceptibility is confirmed.

Conclusion. National surveillance of H. pylori antibiotic resistance and implementation in Uzbekistan of a strategy based on bismuth quadruple therapy and mandatory confirmation of eradication are needed.

Keywords: Helicobacter pylori; chronic gastritis; eradication therapy; antibiotic resistance; clarithromycin; bismuth quadruple therapy; gastric cancer; Uzbekistan.

Introduction

Helicobacter pylori is a Gram-negative microaerophilic bacterium that colonizes the human gastric mucosa and is classified as a group I carcinogen [1, 2]. The infection is acquired mainly in childhood, is transmitted predominantly within families and, if left untreated, usually persists for life [2–4]. According to the Kyoto global consensus, H. pylori gastritis is an infectious disease regardless of symptoms or complications, and the Maastricht VI/Florence consensus (2022) recommends eradication therapy for all infected individuals [1, 5].

The problem is particularly relevant for Uzbekistan because of the high prevalence of infection, the leading role of gastric cancer in cancer mortality and the high resistance of H. pylori to clarithromycin [6–8]. At the same time, most practice guidelines were developed for regions with a different antibiotic resistance profile, so their application requires consideration of local data [2].

The aim of this review was to summarize current evidence on the epidemiology, pathogenesis, diagnosis and treatment of H. pylori-associated chronic gastritis and to formulate practical approaches to the choice of eradication therapy that take into account regional antibiotic resistance data.

Material and methods

Publications were searched in PubMed/MEDLINE, Scopus, eLIBRARY.ru, CyberLeninka and Google Scholar up to September 2026. Keywords and their combinations in Russian and English were used: “Helicobacter pylori”, “chronic gastritis”, “eradication therapy”, “antibiotic resistance”, “clarithromycin”, “bismuth”, “gastric cancer”, “Central Asia”, “Uzbekistan”. The review included: 1) international and national clinical guidelines and consensus statements; 2) systematic reviews and meta-analyses; 3) randomized controlled trials and large cohort studies; 4) studies of H. pylori prevalence and antibiotic resistance in Central Asian countries. Priority was given to publications from 2016–2026; earlier works were included if they are of fundamental importance (classifications, key randomized trials). Conference abstracts and studies whose data had been updated in later publications were not included.

Epidemiology

According to J.K.Y. Hooi et al., approximately 4.4 billion people worldwide were infected in 2015, and prevalence in individual countries ranged from 18.9% in Switzerland to 87.7% in Nigeria [9]. In the systematic review and meta-analysis by Y.C. Chen et al. (1748 publications from 111 countries, 1980–2022), H. pylori prevalence among adults decreased from 52.6% before 1990 to 43.9% in 2015–2022, whereas among children and adolescents it remained high (35.1%) and did not decrease significantly; the decline in prevalence was accompanied by a decrease in gastric cancer incidence [3]. Similar results were obtained by Y. Li et al. (224 studies from 71 countries, approximately 3 million individuals): prevalence decreased from 58.2% in 1980–1990 to 43.1% in 2011–2022, with the most marked decline in the last decade [10]. Studies using serological diagnosis reported higher prevalence than those using non-serological methods (53.2% vs. 41.1%), which should be taken into account when comparing data [10].

The main determinant of infection prevalence is socioeconomic status in childhood, which reflects hygiene, sanitation, household crowding and education [2]. Lower prevalence is observed among

younger people and in high-income countries and countries with high universal health coverage [10]. In a multicentre study using the ^{13}C-UBT, the prevalence of H. pylori among primary care attendees in Russia in 2017–2019 was 38.8% [11].

Central Asian countries remain a poorly studied region in terms of H. pylori epidemiological surveillance [12]. In the regional meta-analysis by K. Dauyey et al., the pooled prevalence of infection in Central Asian countries was 70% (95% CI 59–80%), and pooled clarithromycin resistance was 29% (95% CI 10–53%) [12]. Prevalence estimates of 72–80% have been reported for Uzbekistan [6, 12].

According to GLOBOCAN 2022, gastric cancer ranks fifth worldwide in both incidence and mortality among malignant neoplasms, with approximately 969,000 new cases and 660,000 deaths per year [13]. H. pylori infection is the main cause of gastric cancer [14]. In Uzbekistan, gastric cancer is the leading cause of cancer death (approximately 13% of all cancer deaths) [7].

Pathogenesis

The survival of H. pylori in the acidic gastric environment is ensured by urease, which hydrolyses urea to ammonia and carbon dioxide, creating a neutral microenvironment around the bacterium; flagella provide directed motility within the mucus layer [15, 16]. Adhesion to epithelial cells is mediated by a number of surface proteins, in particular the BabA adhesin, which binds to the Lewis b blood group antigen; the babA2 allele is associated with peptic ulcer disease and gastric cancer in several populations [15, 16]. The key virulence factors are the cag pathogenicity island (cag PAI), whose marker is the cagA gene (found in 50–70% of strains), and the vacuolating cytotoxin VacA. Proteins encoded by cag PAI form a type IV secretion system through which the CagA protein is translocated into the epithelial cell; activation of intracellular signalling pathways leads to disruption of intercellular junctions, altered proliferation and apoptosis, secretion of interleukin-8 and other chemokines, and the development of chronic active inflammation [15, 16].

Long-standing inflammation, oxidative stress and DNA damage in epithelial cells trigger the sequence “non-atrophic gastritis → atrophy → intestinal metaplasia → dysplasia → adenocarcinoma” (the Correa cascade) [17–19]. Gastric cancer develops in only a small proportion of infected individuals (approximately 1–3%); the risk is determined by strain virulence, host genetic factors (in particular, interleukin-1 gene polymorphisms associated with hypochlorhydria and atrophy) and environmental factors [15, 17, 20].

Clinical manifestations and morphological diagnosis of gastritis

H. pylori causes chronic active gastritis in all infected individuals [1, 2, 5], yet in most of them (80–90% according to various data) the infection is asymptomatic [21–23]. The term “gastritis” is morphological and should not be used as a synonym for dyspeptic symptoms — epigastric pain or burning, postprandial fullness and early satiety [5, 24]. In infected patients with dyspepsia, after exclusion of organic disease, eradication may lead to sustained symptom relief (H. pylori-associated dyspepsia); persistence of symptoms after confirmed eradication allows a diagnosis of functional dyspepsia [1, 5].

Gastritis is diagnosed histologically [24, 25]. For staging, systematic biopsy according to the updated Sydney System is recommended — two biopsies each from the antrum and the corpus and one from the incisura angularis, placed in separate containers, with additional sampling of any visible lesions [26, 27]. The pathology report should assess inflammatory activity and the severity and topography of

atrophy and intestinal metaplasia, with staging according to the OLGA/OLGIM systems: stages III–IV are associated with an increased risk of gastric cancer and determine the indications for endoscopic surveillance [25, 27, 28]. High-definition endoscopy with narrow-band imaging (NBI) and chromoendoscopy increase the detection of precancerous lesions; the Kimura–Takemoto classification and the EGGIM system, which correlate with OLGA/OLGIM, are used for endoscopic assessment of the extent of atrophy and intestinal metaplasia [24, 27]. Serological markers (pepsinogens I and II, their ratio, gastrin-17) may be used for non-invasive identification of individuals with advanced corpus atrophy but do not replace endoscopy with biopsy [5, 24, 27].

Indications for H. pylori testing

Adults. International and regional guidelines (Europe, the United Kingdom, the United States, China, Japan, ASEAN countries and the Middle East) consistently recommend testing in the following situations: uninvestigated dyspepsia in individuals without alarm features (the "test-and-treat" strategy); current or past gastric or duodenal ulcer; gastric MALT lymphoma; precancerous mucosal changes (atrophy, intestinal metaplasia, dysplasia) and after endoscopic resection of early gastric cancer; first-degree relatives of patients with gastric cancer; before long-term use of aspirin or NSAIDs and during long-term PPI therapy; unexplained iron deficiency anaemia, ITP and vitamin B12 deficiency [1, 4, 29–33].

Children. According to the ESPGHAN/NASPGHAN guidelines (2023), testing is indicated in children with peptic ulcer disease or gastric and duodenal erosions; it is not part of the initial work-up of iron deficiency anaemia and is no longer recommended when investigating causes of chronic ITP [34]. The "test-and-treat" strategy is not recommended in children [34, 35]. Children with a first-degree relative with gastric cancer may be screened with reliable non-invasive tests [34]. The Chinese consensus additionally provides for testing children from families in which other family members are infected with H. pylori [4, 36].

Diagnostic methods for H. pylori infection

The choice of method depends on the clinical situation (primary diagnosis or confirmation of eradication), the need to assess the mucosa, and test availability. The diagnostic accuracy of the main methods is presented in Table 1.

Table 1. Diagnostic accuracy of methods for detecting H. pylori [37–41]

Method	Sensitivity, %	Specificity, %	Comments
Non-invasive methods			
^{13}C-urea breath test	90.0–96.0	94.0–98.0	Method of choice for primary diagnosis and confirmation of eradication; citric acid is required
^{14}C-urea breath test	96.0–97.3	91.0–97.0	Radioactive label; not used in children or pregnant women

Method	Sensitivity, %	Specificity, %	Comments
H. pylori stool antigen	73.9–95.0	86.8–100.0	Monoclonal antibody-based assays are recommended; suitable for primary diagnosis and confirmation of eradication
Anti-H. pylori antibodies (IgG)	72.7–90.0	68.4–100.0	Does not distinguish current from past infection; not used to confirm eradication
Invasive (biopsy-based) methods			
Rapid urease test	85.0–99.0	92.4–100.0	Biopsies from the antrum and corpus; result within 1–24 h
Histology	83.0–95.5	95.4–100.0	Simultaneous assessment of gastritis and OLGA/OLGIM stage
Culture	67.9–96.0	100*	Reference method; allows antibiotic susceptibility testing

Note: values depend on the assay, the population studied and the reference standard. * The specificity of culture is taken as 100% because it serves as the reference standard.

Non-invasive methods

For primary diagnosis in adults without indications for upper endoscopy, the ^{13}C-UBT and the laboratory stool antigen test based on monoclonal antibodies are preferred [1, 37, 41]. Citric acid is an essential component of the breath test protocol [1]. The ^{14}C-UBT uses a radioactive label and is not used in children or pregnant women [41, 42]. Serological tests cannot distinguish current from past infection and are not used to confirm eradication, because antibodies persist for a long time; validated assays may be used in situations that reduce the accuracy of other methods (PPI or antibiotic use, bleeding, advanced atrophy, MALT lymphoma) [1, 37, 40]. Rapid whole-blood antibody tests ("office" tests) are not recommended for diagnosis [1, 41].

The use of PPIs, antibiotics and bismuth preparations, gastrointestinal bleeding and advanced atrophy reduce the sensitivity of both non-invasive and biopsy-based tests. Therefore, PPIs should be stopped at least 2 weeks, and antibiotics and bismuth preparations at least 4 weeks, before testing [1, 41].

Invasive methods

When upper endoscopy is indicated, the RUT is used for primary diagnosis; taking biopsies from both the antrum and the corpus increases its sensitivity, especially in the presence of atrophy and PPI use [43–46]. Histology allows simultaneous detection of H. pylori and staging of gastritis. Molecular methods (PCR) detect H. pylori in biopsy specimens, including material previously used for the RUT and in patients taking PPIs, and identify mutations in the 23S rRNA gene responsible for clarithromycin resistance [41, 47–49]. Culture with antibiotic susceptibility testing is the reference method and is indicated after eradication failure; the availability of culture-based and molecular resistance tests is a prerequisite for susceptibility-guided therapy [1, 30].

Diagnosis in children

In children, invasive (biopsy-based) testing with antimicrobial susceptibility analysis of the strain is recommended for diagnosis and for selection of eradication therapy; molecular methods are acceptable for detecting H. pylori and resistance mutations in gastric biopsies [34]. The ^{13}C-UBT and the monoclonal stool antigen test are used in children primarily to confirm eradication; serological tests are not recommended [34]. The Japanese guidelines emphasize the value of culture for choosing therapy based on the strain's clarithromycin susceptibility [35].

Confirmation of eradication

Confirmation of eradication is mandatory in all treated patients. It is performed no earlier than 4 weeks after the end of therapy using the ^{13}C-UBT or the monoclonal stool antigen test [1, 14, 34].

Eradication therapy

General principles and the role of antibiotic resistance

Eradication cures non-atrophic gastritis: neutrophil infiltration disappears, followed by a reduction in mononuclear infiltration [5, 50, 51]. According to meta-analyses, atrophy may improve after eradication, mainly in the corpus (data on its regression in the antrum are conflicting), whereas intestinal metaplasia generally does not regress [52, 53].

The goal of treatment is eradication in at least 90% of patients. The choice of regimen depends on previous antibiotic exposure, drug allergy, local resistance and, where possible, individual strain susceptibility [1, 30]. Clarithromycin resistance is the main cause of treatment failure: in regions where it exceeds 15% or is unknown, empirical clarithromycin-based triple therapy should not be used [1].

In a multicentre retrospective study conducted in Uzbekistan (2020–2022), overall clarithromycin resistance of H. pylori among cagA-positive patients was 44.8% (genotypic resistance, based on 23S rRNA mutations, 41.2%) and increased with disease severity: 33.3% in chronic non-atrophic gastritis, 31.7% in atrophic gastritis, 59.3% in gastric ulcer, 54.1% in MALT lymphoma and 69.6% in gastric cancer [8]. Pooled clarithromycin resistance in Central Asian countries was 29% [12]; a review of regional data also points to high metronidazole resistance [6]. Uzbekistan should therefore be regarded as a region with high (more than 15%) clarithromycin resistance.

First-line therapy

When antibiotic susceptibility is unknown and in regions with high clarithromycin resistance, the regimen of choice is 14-day bismuth quadruple therapy: a standard-dose PPI twice daily, bismuth tripotassium dicitrate 120 mg four times daily (or 240 mg twice daily), tetracycline 500 mg four times daily and metronidazole 500 mg three to four times daily [1, 14, 30, 54]. Substituting doxycycline for tetracycline is not recommended [30]. The efficacy of bismuth quadruple therapy is largely preserved in strains resistant to clarithromycin and metronidazole [55–57]. According to the European Registry on H. pylori Management (Hp-EuReg), effectiveness above 90% was achieved with 10-day single-capsule (“three-in-one”) bismuth quadruple therapy and with 14-day bismuth-containing regimens that included tetracycline plus metronidazole, or amoxicillin plus either clarithromycin or metronidazole [57]. The main eradication regimens for adults are presented in Table 2.

Table 2. Main H. pylori eradication regimens in adults (duration 14 days) [1, 30, 54, 58, 59]

Regimen	Drugs and doses	Place in therapy
Bismuth quadruple therapy	Standard-dose PPI twice daily + bismuth tripotassium dicitrate 120 mg four times daily (or 240 mg twice daily) + tetracycline 500 mg four times daily + metronidazole 500 mg three to four times daily	First line when clarithromycin resistance is unknown or high (>15%), including in Uzbekistan; second line after non-bismuth regimens
Clarithromycin triple therapy ± bismuth	Standard- or double-dose PPI twice daily + amoxicillin 1000 mg twice daily + clarithromycin 500 mg twice daily (± bismuth tripotassium dicitrate 240 mg twice daily)	Only when clarithromycin susceptibility is confirmed
Non-bismuth concomitant quadruple therapy	PPI twice daily + amoxicillin 1000 mg twice daily + clarithromycin 500 mg twice daily + metronidazole 500 mg twice daily	Alternative to bismuth quadruple therapy per Maastricht VI (not favoured by ACG 2024); efficacy declines with dual clarithromycin–metronidazole resistance
Levofloxacin-containing regimen	Standard-dose PPI twice daily + amoxicillin 1000 mg twice daily + levofloxacin 500 mg once daily (± bismuth)	Second and subsequent lines, preferably when fluoroquinolone susceptibility is confirmed
High-dose dual therapy	High-dose PPI three to four times daily + amoxicillin 750 mg four times daily or 1000 mg three times daily	Alternative first- and second-line option
Rifabutin triple therapy	Omeprazole 40 mg three times daily + amoxicillin 1000 mg three times daily + rifabutin 50 mg three times daily	Alternative first-line option and after failure of bismuth quadruple therapy (ACG 2024); if available
Vonoprazan dual therapy	Vonoprazan 20 mg twice daily + amoxicillin 1000 mg three times daily	Alternative first-line option (ACG 2024); if available

Note: PPI — proton pump inhibitor. In children, doses are calculated by body weight according to the ESPGHAN/NASPGHAN recommendations.

For patients without penicillin allergy, ACG 2024 suggests 14-day alternatives for first-line treatment: rifabutin triple therapy (omeprazole, amoxicillin, rifabutin) and vonoprazan–amoxicillin dual therapy [30]. The Chinese guideline considers high-dose PPI–amoxicillin dual therapy to be as effective as bismuth quadruple therapy [54, 59]. Whether these regimens can be used in Uzbekistan depends on drug registration and availability.

Non-bismuth concomitant quadruple therapy (a PPI, amoxicillin, clarithromycin and metronidazole given together for 14 days) is regarded by the Maastricht VI consensus as the preferred non-bismuth quadruple regimen, acceptable also in regions with high clarithromycin resistance [1, 60]; however, ACG 2024 does not favour it over bismuth quadruple therapy [30]. With high clarithromycin resistance, especially combined with metronidazole resistance, the efficacy of this regimen declines [1].

Clarithromycin triple therapy (a PPI, amoxicillin and clarithromycin for 14 days) is acceptable only when the strain is confirmed to be susceptible to clarithromycin [1, 30]. Adding bismuth tripotassium dicitrate (240 mg twice daily) increases the efficacy of this regimen: in the Hp-EuReg registry (1141

patients), eradication rates were 88% (ITT) and 94% (PP), and 93% (ITT) with a 14-day course [58]. However, these results were obtained in a European population with a different resistance profile; in Uzbekistan, where clarithromycin resistance exceeds 40%, empirical use of this regimen requires confirmation of its efficacy in local studies [1, 61].

Factors that improve treatment efficacy

High-dose PPIs increase eradication rates [62]. In CYP2C19 rapid metabolizers, the efficacy of triple therapy with standard doses of omeprazole and lansoprazole is reduced, whereas the efficacy of regimens with rabeprazole and esomeprazole does not depend significantly on CYP2C19 genotype [63]. In Hp-EuReg, higher effectiveness was associated with treatment adherence, a double-dose PPI and a 14-day treatment duration [58]. The potassium-competitive acid blocker vonoprazan is superior to PPIs in triple therapy and in second-line regimens [64, 65]. Adding rebamipide may increase eradication rates and improve tolerability, but the evidence is heterogeneous, and rebamipide does not replace the antibacterial regimen [66–68]. Most regimens last 14 days; 10-day courses are acceptable for regimens with proven efficacy [1].

In children, the eradication regimen is chosen on the basis of susceptibility testing (culture or PCR), and drug doses are calculated by body weight according to the ESPGHAN/NASPGHAN recommendations and national guidelines [34, 35].

Second-line and subsequent therapy

After failure of a non-bismuth regimen (triple or concomitant), 14-day bismuth quadruple therapy is recommended [1, 30]. After failure of bismuth quadruple therapy, the Maastricht VI consensus allows fluoroquinolone-containing regimens (triple or quadruple) or high-dose PPI–amoxicillin dual therapy, and, in case of high fluoroquinolone resistance, bismuth combined with other antibiotics or rifabutin-based regimens [1]. In this situation, ACG 2024 suggests rifabutin triple therapy, and levofloxacin-containing regimens when levofloxacin susceptibility is confirmed or when alternatives are unavailable [30]. The efficacy of second-line levofloxacin-containing regimens has been confirmed by meta-analyses and clinical studies [69–71], but it decreases markedly with fluoroquinolone resistance [72]. Given the widespread use of fluoroquinolones and the limited data on H. pylori levofloxacin resistance in Uzbekistan, susceptibility testing is advisable before such regimens are prescribed. After two treatment failures, antibiotic susceptibility testing is indicated [1].

H. pylori eradication and gastric cancer prevention

Eradication of H. pylori reduces the risk of gastric cancer. In a meta-analysis of randomized trials in healthy infected individuals, eradication therapy reduced gastric cancer incidence (RR 0.54; 95% CI 0.40–0.72; NNT = 72) and gastric cancer mortality (RR 0.61; 95% CI 0.40–0.92), and in patients after endoscopic resection of gastric neoplasia it reduced the risk of metachronous cancer (RR 0.49; NNT = 21) [73]. Similar results were obtained in a meta-analysis of observational and randomized studies [74], in long-term randomized trials in China [75, 76] and in the mass eradication programme on the Matsu Islands [77]. The greatest benefit is achieved when eradication is performed before the development of atrophy and intestinal metaplasia [14, 75].

The Taipei Global Consensus II recommends offering eradication to all infected adults, prioritizing screening in high-risk groups, taking into account the intrafamilial transmission of the infection and, in regions with high antibiotic resistance, using primarily bismuth quadruple therapy for empirical treatment [4, 14]. Patients with extensive atrophy or intestinal metaplasia (OLGA/OLGIM III–IV) require endoscopic surveillance even after eradication [14, 27]. Given the leading position of gastric cancer in cancer mortality in Uzbekistan [7], evaluation of a "screen-and-treat" strategy in first-degree relatives of patients with gastric cancer and in other high-risk groups is warranted.

Conclusion

1. The global prevalence of H. pylori is declining, but in Central Asian countries, including Uzbekistan, it remains high (approximately 70–80%), and gastric cancer is the leading cause of cancer death in Uzbekistan.
2. H. pylori causes chronic active gastritis in all infected individuals; gastritis is diagnosed morphologically, using biopsies obtained according to the Sydney System, with OLGA/OLGIM staging.
3. For primary diagnosis in adults without indications for upper endoscopy, the ^{13}C-UBT and the monoclonal stool antigen test are preferred; confirmation of eradication is mandatory and is performed no earlier than 4 weeks after the end of treatment.
4. Clarithromycin resistance of H. pylori in Uzbekistan (41–45%) far exceeds the 15% threshold, so empirical clarithromycin triple therapy is unacceptable; 14-day bismuth quadruple therapy is the first-line regimen of choice.
5. National surveillance of H. pylori antibiotic resistance, wider availability of molecular resistance tests and the development of national clinical guidelines based on local data are needed.

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