OPTIMIZATION OF ERADICATION THERAPY IN PATIENTS WITH ANTIBIOTIC-RESISTANT HELICOBACTER PYLORI INFECTION: COMPARATIVE EFFICACY OF CURRENT REGIMENS

Tolibov Farrux Farhodivich
tolibovf1@gmail.com
orcid.org/0009-0001-0186-8499
Asia International University, Bukhara, Uzbekistan
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Annotation: Helicobacter pylori (H. pylori) infection is one of the most widespread chronic bacterial infections in the world; in 2015 the number of infected individuals was estimated at approximately 4.4 billion [1]. H. pylori is the principal etiological factor of chronic gastritis, peptic ulcer disease, MALT lymphoma and gastric adenocarcinoma; therefore, its effective eradication is regarded as a means of primary prevention of gastric cancer [2].

The leading factor reducing the effectiveness of eradication therapy is the growth of antibiotic resistance. According to a meta-analysis covering the World Health Organization regions, resistance to clarithromycin, metronidazole and levofloxacin exceeded the 15% threshold in most regions [3]. In Europe in 2018, primary resistance to clarithromycin was approximately 21% and to levofloxacin about 16%, and was shown to be associated with outpatient macrolide consumption [4]. According to the European Registry (Hp-EuReg), clarithromycin-based triple therapy failed to reach the target eradication rate of 90%, which was achieved mainly with optimized quadruple regimens [5].

The Maastricht VI/Florence consensus recommends abandoning empirical clarithromycin-based triple therapy in areas where clarithromycin resistance exceeds 15% or is unknown, and using regimens that ensure eradication rates of at least 90% [2]. Regional resistance data indicate the need to adapt the treatment algorithm to local conditions.

Keywords: Helicobacter pylori, antibiotic resistance, clarithromycin, bismuth quadruple therapy, vonoprazan, eradication therapy.

Aim: to develop practical recommendations for optimizing therapy based on an analysis of the comparative efficacy and safety of current eradication regimens in H. pylori infection resistant to clarithromycin and/or levofloxacin.

Materials and Methods. Randomized clinical trials, meta-analyses and international clinical guidelines (Maastricht VI/Florence [2], ACG 2024 [6], AGA 2021 [7]) published in 2015–2026 in the PubMed/MEDLINE, Cochrane Library and Google Scholar databases were systematically analysed; a total of sources were included. Inclusion criteria: patients older than 18 years; studies in which resistance to clarithromycin and/or levofloxacin was confirmed by culture (antibiogram, MIC) or molecular tests (PCR detecting 23S rRNA and gyrA mutations), or studies conducted in regions with high resistance. Studies in which eradication was assessed at least 4 weeks after the end of treatment (with PPIs discontinued 2 weeks beforehand) by ^{13}C-urea breath test or monoclonal stool antigen test were included. Compared groups: bismuth quadruple therapy, concomitant therapy, vonoprazan-based regimens and

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high-dose dual therapy. The primary outcome was the eradication rate by intention-to-treat (ITT) and per-protocol (PP) analysis; secondary outcomes were the frequency of adverse events and compliance.

Results and Discussion. The efficacy of bismuth quadruple therapy (PPI + bismuth + tetracycline + metronidazole, 14 days) does not depend on clarithromycin resistance, while the negative impact of metronidazole resistance is largely overcome by extending the course to 14 days and using higher doses. For this reason, the Maastricht VI and ACG (2024) guidelines recommend it as first-line therapy where resistance is high or unknown [2,6]. Meta-analyses have confirmed that the addition of bismuth reliably increases eradication rates in first-line therapy [8], as well as the high efficacy and favourable compliance of single-capsule bismuth quadruple therapy [9].

Concomitant (non-bismuth quadruple) therapy given for 14 days is an alternative when bismuth preparations are unavailable; however, its efficacy declines in regions where dual resistance to clarithromycin and metronidazole is widespread [2,5].

The potassium-competitive acid blocker vonoprazan provides faster and more stable acid suppression than PPIs and is virtually unaffected by CYP2C19 polymorphism. In the phase III PHALCON-HP trial conducted in the United States and Europe, vonoprazan triple and dual (vonoprazan + amoxicillin) therapy achieved eradication rates of 65.8% and 69.6%, respectively, in clarithromycin-resistant strains, compared with 31.9% for lansoprazole triple therapy [10]. Thus, vonoprazan substantially reduces the negative impact of resistance; however, when clarithromycin resistance is confirmed, the clarithromycin-free vonoprazan–amoxicillin regimen is preferable.

When first-line therapy fails, Maastricht VI recommends fluoroquinolone-containing quadruple (or triple) therapy, high-dose dual therapy or rifabutin-containing regimens [2]. Since levofloxacin resistance readily develops through gyrA mutations, its use is appropriate when susceptibility is confirmed or in regions with low resistance. The AGA expert review recommends avoiding the repeated use of clarithromycin and levofloxacin in refractory infection, taking the patient's history of antibiotic use into account, and performing susceptibility testing whenever possible [7].

In multicomponent regimens, adverse events (dyspepsia, metallic taste, diarrhoea) are the main reason for premature discontinuation of treatment, and according to Hp-EuReg data, compliance is one of the important determinants of eradication success [5]. In line with international guidelines, the analysis shows that the main ways to optimize therapy are extending the course to 14 days, potent acid suppression and susceptibility-based regimen selection [2,6].

Conclusions.

1. When clarithromycin resistance exceeds 15% or is unknown, empirical clarithromycin-based triple therapy should not be used; the first-line choice is 14-day bismuth quadruple therapy.
2. Where vonoprazan is available, the vonoprazan–amoxicillin dual regimen is a more effective alternative to PPI-based regimens in clarithromycin-resistant infection.
3. In rescue therapy, previously used clarithromycin and levofloxacin should not be repeated, levofloxacin should be prescribed only when susceptibility is confirmed, and rifabutin-containing or high-dose dual regimens should be used as reserve options.
4. It is necessary to educate patients in advance about compliance and adverse events, to confirm eradication with a breath test at least 4 weeks after treatment, and to establish local resistance monitoring.

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