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The Main Statements of the Consensus "Maastricht VI" (2022) on the Diagnosis and Treatment of *Helicobacter pylori* Infection

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Aim: to present an analysis of the published materials of the consensus "Maastricht-VI" on the management of patients with *Helicobacter pylori (H. pylori)* infection.
Key points. The content of the new consensus "Maastricht-VI" largely corresponds to that of the previous "Maastricht-V" consensus. This refers to the methods of diagnostics of this infection, indications for eradication. The introduction of eradication schemes of the 3rd and 4th lines, as well as a double scheme with increased doses of proton pump inhibitors (PPI) and amoxicillin can be considered new. The important role of measures that increase the effectiveness of eradication (14-day duration of the course, increasing the dose of PPI, the use of probiotics) is emphasized.
Conclusion. The publication of materials of the new consensus "Maastricht-VI" will contribute to improving the results of *H. pylori* eradication therapy.
Keywords: *Helicobacter pylori* infection, diagnostics, treatment, cancer prevention
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Основные положения согласительного совещания «Маастрихт-VI» (2022) по диагностике и лечению инфекции *Helicobacter pylori*

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Цель публикации. Представить анализ опубликованных материалов согласительного совещания «Маастрихт-VI» по ведению пациентов с инфекцией *Helicobacter pylori (H. pylori)*.
Основные положения. Содержание нового согласительного совещания «Маастрихт-VI» во многом соответствует таковому предыдущего консенсуса «Маастрихт-V». Это относится к методам диагностики данной инфекции, показаниям к проведению эрадикации. Новым можно считать введение схем эрадикации 3-й и 4-й линий, а также двойной схемы с увеличенными дозами ингибиторов протонного насоса (ИПН) и амоксициллина. Подчеркнута важная роль мер, повышающих эффективность эрадикации (14-дневная продолжительность курса, увеличение дозы ИПН, применение пробиотиков).
Заключение. Положения нового согласительного совещания «Маастрихт-VI» будут способствовать улучшению результатов эрадикационной терапии *H. pylori*.
Ключевые слова: инфекция *Helicobacter pylori*, диагностика, лечение, канцерпревенция
Конфликт интересов: автор заявляет об отсутствии конфликта интересов.

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In recent years, doctors diagnosing and treating patients with Helicobacter pylori (*H. pylori*) were guided by the statements of the consensus "Maastricht-V" held in 2016 [1]. In 2022 the materials of the consensus "Maastricht VI" held in September 2021 were published. [2]. His goal was to develop guidelines for the management of patients with *H. pylori* infection based on new data obtained in recent years in clinical studies.

41 experts from 29 countries took part at the consensus. 5 working groups were established in the following topics: indications/associations; diagnosis; treatment; prevention/gastric cancer; *H. pylori* and the gut microbiota.

The statement was considered adopted (in full or with restriction) if the number of experts who voted for it (agreement) was more than 80 %. The quality of evidence was assessed as high (A), moderate (B), low (C) or very low (D), and strength of recommendation as strong (1) or weak (2).

Each group of experts developed relevant statements, which were subsequently adopted by a general vote, the most important of which are presented below. Those relating to the first section of the consensus (indications and associations) can be attributed to the following.

Statement 1. H. pylori infection always causes gastritis, irrespective of symptoms or complications (Agreement — 100 %, Grade — A1).

The commentary indicates that the conduct of patients with *H. pylori*-associated gastritis eradication therapy can cause some of them, regarded as suffering from functional dyspepsia, the disappearance of clinical symptoms, and also minimizes the risk of complications such as peptic ulcer, adenocarcinoma and MALT-lymphoma of the stomach.

Statement 3. Test-and-treat is an appropriate strategy for uninvestigated dyspepsia (Agreement — 94 %, Grade — A1).

Experts stressed that the strategy "diagnose infection *H. pylori* and treat it" ("test-and-treat") using non-invasive testing methods effectively prevents the development of more serious diseases, but it can only be used in patients younger than 45–55 years with no "alarm symptoms". Given the high cost of esophagogastroduodenoscopy (EGDS), this method of diagnosing stomach diseases in patients with dyspepsia is provided only for those cases where dyspeptic complaints first appeared over the age of 50 years, in the presence of "alarm symptoms" and the absence of the effect of empirical therapy with proton pump inhibitors (PPI).

The experts confirmed the statements of the previous consensus that the presence of *H. pylori* increases the risk of developing erosive and ulcerative lesions of the stomach and duodenum when taking acetylsalicylic acid and nonsteroidal anti-inflammatory drugs (NSAIDs), which makes it advisable to test for this infection and its subsequent eradications in cases where the patient is scheduled to be prescribed NSAIDs.

Statements on the need for eradication of *H. pylori* infection were also confirmed in patients with idiopathic thrombocytopenic purpura, iron deficiency anemia with an unknown cause of its development, B12-deficient anemia, as well as in patients who are forced to take PPIs for a long time. As in the previous consensus, the experts considered that the causative role of *H. pylori* infection in the development of cardiovascular diseases, metabolic disorders, neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, multiple sclerosis) as not proven and found no negative association between this infection and such diseases as bronchial asthma, obesity and inflammatory bowel disease.

Statement 16. The COVID-19 pandemic has negatively impacted the management of H. pylori-related diseases (Agreement — 86 %, Grade — A1).

The presented statement should certainly be considered very important. Experts stressed that in the context of the pandemic of the new coronavirus infection, the quality of examination of patients with gastroenterological diseases has deteriorated, in particular, the ^{13}C-urease breath test (^{13}C-UBT) has become less common to test for *H. pylori* infection, there were difficulties in implementing the strategy of gastric cancer prevention.

The next section of the consensus "Maastricht VI" deals with the diagnostics of *H. pylori* infection. As in the previous consensus, in cases where EGDS is not performed during testing, non-invasive methods are considered optimal: ^{13}C-UBT, study of the antigen of *H. pylori* in feces and a serological method for determining antibodies to the *H. pylori* of the immunoglobulin G class, which can only be used for the primary diagnosis of this infection. At the same time, ^{13}C-UBT is recommended as the most optimal method for monitoring the effectiveness of eradication.

If the patient is given EGDS, then in order to diagnose *H. pylori* infection can be used a rapid urease test. In addition, in such cases, for a thorough analysis of the degree of gastritis changes it is necessary to use a modern operative system for assessing the severity of gastritis (Operative Link for Gastritis Assessment, OLGA) and the operative system for assessing the severity of intestinal metaplasia of the gastric mucosa (Operative Link on Gastric Intestinal Metaplasia, OLGIM).

The following statements of this section of the consensus should be considered important.

Statement 7. Molecular methods (in particular, real time-PCR, whole genome sequencing) can detect mutations, associated with resistance to clarithromycin, levofloxacin, tetracycline and rifampicin (Agreement — 100 %, Grade — A1).

As the experts emphasized, the significance of this statement is determined by the ever-increasing frequency of the resistance of *H. pylori* to antibiotics. These methods are now replacing the long-standing "gold standard" method of determining the sensitivity of *H. pylori* to antibiotics when it is cultured, which is time-consuming and equipped.

Statement 9. Clarithromycin susceptibility testing, if available through molecular techniques or culture, is recommended before prescribing any clarithromycin containing therapy (Agreement — 100 %, Grade — A1).

In the materials of the previous consensus "Maastricht-V", it was suggested that there is the possibility of empirical administration of standard triple therapy (PPI + amoxicillin + clarithromycin) in regions with a frequency of resistance to clarithromycin < 15 %. Given the key role of this antibiotic in many eradication regimens and a significant drop in the effectiveness of eradication in cases of resistance of *H. pylori* to this antibiotic, experts came to the conclusion that it is necessary to test for sensitivity *H. pylori* to clarithromycin in each case of its prescription. As follows from the assessmentand statements of the next section (treatment), the implementation of this recommendation was considered by the experts themselves to be difficult.

Statement 1. It is reasonable to recommend that susceptibility tests (molecular or after culture) are routinely performed, even before prescribing first-line treatment. However, the generalised use of such a susceptibility guided strategy in routine clinical practice remains to be established (Agreement — 91 %, Grade — D1).

Despite on the high level of agreement, attention is drawn to the low degree of evidence and the strength of this statement. The algorithm proposed further by experts for the appointment of eradication schemes of the 1st line proceeds, as in the consensus "Maastricht-V", from the frequencies of resistance of *H. pylori* strains to clarithromycin available in this region.

If it does not exceed 15 %, then standard triple therapy or quadrotherapy with bismuth preparations (PPI + bismuth tricalium dicitrate + tetracycline + metranidazole) are recommended as 1st line schemes. If standard triple therapy is ineffective, then for the 2nd line therapy, quadrotherapy with bismuth preparations is used, as well as triple (or quadrotherapy) with levofloxacin (in the first case, it includes PPI + amoxicillin + levofloxacin, in the case of quadrotherapy bismuth preparations are added to them). With the ineffectiveness of quadrotherapy with bismuth preparations as a 1st line scheme, a triple (quadrotherapy) with levofloxacin is prescribed as a 2nd line scheme.

With the ineffectiveness of the eradication regimens of the 1st and 2nd lines, the consensus "Maastricht-V" recommended the individual selection of antibiotics, taking into account the sensitivity of the *H. pylori* strains to antibiotics. The consensus "Maastricht VI" considered it expedient to introduce the eradication schemes of the 3rd and 4th lines into clinical practice. If the schemes of the 1st and 2nd lines were quadrotherapy with bismuth preparations or triple (quadrotherapy) with levofloxacin, then triple (quadrotherapy) with clarithromycin is recommended as a 3rd line therapy. In cases where the 1st and 2nd line regimens were standard triple therapy or quadrotherapy with bismuth preparations, then triple (quadrotherapy) with levofloxacin is indicated as the 3rd line therapy. If the 1st and 2nd line regimens were standard triple therapy and triple (quadrotherapy) with levofloxacin the appointment of standard quadrotherapy with bismuth preparations is recommended. If the schemes of the 1st, 2nd and 3rd lines are ineffective, a scheme with rifabutin (PPI + amoxicillin + rifabutin) is prescribed as the scheme of the 4th line.

In regions with high (>15 %) or unknown resistance *H. pylori* to clarithromycin as a scheme of the 1st line in the concensus "Maastricht-VI" positioned the appointment of quadrotherapy with bismuth preparations, with its ineffectiveness — the scheme of the 2nd line in the form of triple (quadrotherapy) with levofloxacin. If there is no effect as a 3rd line therapy, regimens with a combination of bismuth preparations and other antibiotics or a regimens with rifabutin are recommended.

As an alternative to quadrotherapy with bismuth preparations in the form of a 1st line scheme, the consensus "Maastricht-VI" considered it possible to prescribe quadrotherapy without bismuth preparations (PPI + amoxicillin + clarithromycin + metronidazole), as schemes of the 2nd and 3rd lines — sequentially triple (quadrotherapy) with levofloxacin and quadrotherapy with bismuth preparations (or in reverse order) as a scheme of the 4th line — triple therapy with rifabutin.

If in the consensus "Maastricht-V" it was allowed to reduce the duration of eradication therapy to 10 days (in those regions, where it gave the same good effect as the 14-day course), then in the new consensus "Maastricht-VI" in all cases (in particular, when prescribing standard triple therapy, quadrotherapy with bismuth preparations and without bismuth preparations) the duration of eradication therapy, which is 14 days, is positioned.

A higher frequency of eradication has also been confirmed when twice doses of PPIs are prescribed. At the same time, in the new consensus "Maastricht-VI", special emphasis is placed on inhibitors of hydrochloric acid secretion that are competitive with potassium. Representatives of this class (in particular, wonoprasan) are characterized by a rapid onset of action, a predictable antisecretory effect, a high efficiency of eradication (especially in patients with clarithromycin resistance). It should be noted that these drugs are used

in the countries of Southeast Asia and have not been registered in Russia.

In the consensus "Maastricht-VI", a double scheme of eradication therapy was also proposed, including a double dose of PPI and an increased dose of amoxicillin by 1.5 times (0.75 g 4 times a day). It is recommended, in particular, as a backup scheme for the ineffectiveness of quadrotherapy with bismuth preparations and triple (quadrotherapy) with levofloxacin.

The fourth section of the consensus "Maastricht VI" focuses on the role of *H. pylori* infection in the development of stomach cancer and its prevention.

Statement 1. H. pylori infection is the primary aetiological factor for gastric adenocarcinoma including proximal gastric cancer (PGC) (Agreement — 100 %, Grade — A1).

The commentary on this provision indicates that up to 90 % of cases of gastric cancer worldwide are associated with *H. pylori* infection.

Statement 5. Severe atrophy (OLGA III/IV) in the context of H. pylori gastritis carries a much higher risk for gastric cancer development as compared with atrophy in the context of autoimmune gastritis (AIG) (Agreement — 100 %, Grade — A1).

Evaluating this finding, the experts emphasized that AIG, which accounts for 2–5 % of all cases of chronic gastritis, is characterized by a more favorable prognosis for the development of stomach cancer compared to *H. pylori*-associated gastritis, which has reached the III-IV stages of atrophy according to the OLGA classification.

Statement 8. H. pylori eradication may reverse gastric atrophy and to some extent intestinal metaplasia (IM) and may halt the progression from chronic atrophic gastritis to neoplastic lesions in a subset of patients (Agreement — 97 %, Grade — A1).

Commenting on this statement, experts noted that in contrast to previous ideas that eradication therapy does not lead to the reverse development of atrophy and IM, recent studies have shown that this regression is possible and leads to a decrease in the incidence of gastric cancer.

Statement 10. H. pylori eradication is most effective for gastric cancer prevention before the development of severe chronic atrophic gastritis (Agreement — 100 %, Grade — A1).

When discussing this well-known conclusion, it was emphasized that in patients with severe atrophy and IM of the gastric mucosa after eradication therapy, the risk of developing stomach cancer remains, and therefore after eradication they are subject to dynamic observation with EGDS.

Statement 21. Eradication of H. pylori is mandatory to reduce the risk of metachronous gastric cancer after curative endoscopic resection (ER) or gastric subtotal resection of early gastric cancer (Agreement — 100 %, Grade — A1).

Commenting on this statement, experts noted that although the risk of developing of metachronic cancer in operated patients with gastric cancer after eradication of *H. pylori* infection decreases, in cases of severe atrophy and IM, it remains quite high, and therefore such patients are subject to dynamic observation with EGDS.

The last section of the published proceedings of the consensus "Maastricht VI" deals with the relationship between *H. pylori* infection and the gastrointestinal microbiota.

Statement 2. The human stomach is colonised by other bacteria beyond H. pylori, the so-called gastric microbiome (Agreement — 94 %, Grade — A1).

Describing this statement, the experts noted that in addition to *H. pylori*, bacteria belonging to *Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria*, etc. are found in the stomach, and in persons who are not infected with *H. pylori*, the diversity of these bacteria is more pronounced compared to those infected.

Statement 3. Gastric bacteria other than H. pylori may also affect H. pylori- related changes (Agreement — 91 %, Grade — B2).

In the commentary to this provision, it was emphasized that many studies had confirmed the involvement of other microorganisms in the development of changes in the stomach caused by *H. pylori*, however, the mechanisms of this interaction are not well understood and require further research.

Statement 5. H. pylori eradication therapy has the potential to select resistant strains of gut microbiota (Agreement — 89 %, Grade — B2).

Experts came to the conclusion that the use of various eradication regimens can lead to the appearance in the intestine of strains of microorganisms resistant to other antibiotics, however, noted that these consequences are not sufficiently studied and need further research.

Statement 6. Certain probiotics have been shown to be effective in reducing GI side effects caused by H. pylori eradication therapies (Agreement — 89 %, Grade — A2).

Statement 7. Certain probiotics may have a beneficial effect on H. pylori eradication therapy through reduction of antibiotic-related side effects (Agreement — 80 %, Grade — A2).

In the commentary to these statements, the experts emphasized the advisability of prescribing probiotics (in particular, lactobacilli, *Saccharomyces boulardii*), which, by reducing the severity of side effects and improving the tolerability of eradication therapy, increase its effectiveness.

Thus, summarizing the main statements of the consensus "Maastricht-VI", we can conclude that they largely correspond to those of the previous consensus "Maastricht-V". This applies to

diagnostic methods, indications for eradication. New can be considered the introduction of eradication schemes of the 3rd and 4th lines, as well as a double regimen with increased doses of PPI and amoxicillin. The important role of measures that increase the effectiveness of eradication. (14-day duration of the course, increase of the dose of PPIs, the use of probiotics) was emphasized. Undoubtedly, they will help improve the results of eradication therapy.

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