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Diagnostics and Treatment of Peptic Ulcer in Adults (Clinical Guidelines of the Russian Gastroenterological Association, the Russian Society of Colorectal Surgeons, the Russian Endoscopic Society and the Scientific Society for the Clinical Study of Human Microbiome)

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Aim. The guidelines set out the modern methods of diagnostics and treatment of peptic ulcer and are created for gastroenterologists, primary care physicians, general practitioners, surgeons, endoscopists.
Key points. The clinical guidelines contain modern views on the etiology and pathogenesis of peptic ulcer, its clinical features, methods of laboratory and instrumental diagnostics, the main approaches to conservative and surgical treatment. They include the criteria for assessment of the quality of medical care, the algorithm of the doctor's actions, as well as information for the patient.
Conclusion. Knowledge of modern methods of diagnostics and therapy of peptic ulcers will contribute to improving the results of its treatment.
Keywords: peptic ulcer, etiology, pathogenesis, diagnostics, treatment
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Диагностика и лечение язвенной болезни у взрослых (Клинические рекомендации Российской гастроэнтерологической ассоциации, Российского общества колоректальных хирургов, Российского эндоскопического общества и Научного сообщества по содействию клиническому изучению микробиома человека)

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Цель. В клинических рекомендациях, предназначенных для врачей-гастроэнтерологов, врачей общей практики (семейных врачей), врачей-терапевтов, хирургов, эндоскопистов, изложены современные методы диагностики и лечения язвенной болезни.

Основное содержание. Клинические рекомендации содержат современные представления об этиологии и патогенезе язвенной болезни, ее клинических особенностях, методах лабораторной и инструментальной диагностики, основных подходах к консервативному и хирургическому лечению. В них приводятся критерии оценки качества оказания медицинской помощи, алгоритм действий врача, а также информация для пациента.

Заключение. Знание врачами современных методов диагностики и терапии язвенной болезни будет способствовать улучшению результатов ее лечения.

Ключевые слова: язвенная болезнь, этиология, патогенез, диагностика, лечение

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

1.1. Definition of a disease or condition (group of diseases or conditions)

Peptic ulcer (PU) is a chronic relapsing disease that occurs with alternating periods of exacerbation and remission, the leading manifestation of which is the formation of a defect (ulcer) in the wall of the stomach and duodenum.

1.2. Etiology and pathogenesis of a disease or condition (group of diseases or conditions)

According to modern concepts, the pathogenesis of PU in general comes down to an imbalance between the factors of acid-peptic aggression of the gastric contents and the elements of protection of the mucous membrane of the stomach and duodenum [1].

The aggressive part of ulcer formation includes an increase in the mass of parietal cells (often hereditary), hyperproduction of gastrin, disruption of the nervous and humoral regulation of gastric acid secretion, increased production of pepsinogen and pepsin, disturbance of gastroduodenal motility (delay or, conversely, acceleration of evacuation from the stomach), contamination of the mucous membrane stomach lining with microorganisms *Helicobacter pylori* (*H. pylori*).

Weakening of the protective properties of the mucous membrane of the stomach and duodenum can result from a decrease in the production and disruption of the qualitative composition of gastric mucus, a decrease in the secretion of bicarbonates, a decrease in the regenerative activity of epithelial cells, a deterioration in the blood supply to the gastric mucosa, a decrease in the content of prostaglandins in the stomach wall (for example, when taking non-steroidal anti-inflammatory and antirheumatic drugs).

The decisive role in the development of peptic ulcer is currently assigned to the microorganisms *H. pylori*, discovered in 1983 by Australian scientists B. Marshall and J. Warren.

The spectrum of adverse effects of *H. pylori* on the mucous membrane of the stomach and duodenum is quite diverse. These bacteria produce a number of enzymes (urease, proteases, phospholipases) that damage the protective barrier of the mucous membrane, as well as various cytotoxins. The most pathogenic is the VacA strain of *H. pylori*, which

produces a vacuolating cytotoxin, leading to the formation of cytoplasmic vacuoles and death of epithelial cells, and the CagA strain, which expresses a gene associated with the cytotoxin. *H. pylori* promotes the release of interleukins, lysosomal enzymes, and tumor necrosis factor in the gastric mucosa, which causes the development of inflammatory processes in the gastric mucosa.

Contamination of the gastric mucosa with *H. pylori* is accompanied by the development of superficial antral gastritis and duodenitis and leads to an increase in gastrin levels with a subsequent increase in the secretion of hydrochloric acid. An excess amount of hydrochloric acid entering the lumen of the duodenum, in conditions of a relative deficiency of pancreatic bicarbonates, contributes to the progression of duodenitis and, in addition, causes the appearance in the duodenum of areas of gastric metaplasia (restructuring of the epithelium of the duodenal mucosa according to the gastric type), which are quickly populated by *H. pylori*. In the future, with an unfavorable course, especially in the presence of additional etiological factors (hereditary predisposition, 0(I) blood group, smoking, neuropsychic stress, etc.), an ulcerative defect is formed in areas of the metaplastic mucous membrane. About 80 % of duodenal ulcers and 60 % of gastric ulcers are associated with *H. pylori* [2]. *H. pylori*-negative gastroduodenal ulcers are most often caused by taking nonsteroidal anti-inflammatory and antirheumatic drugs.

1.3. Epidemiology of a disease or condition (group of diseases or conditions)

It has been shown that 11–14 % of men and 8–11 % of women may receive a diagnosis of peptic ulcer during their lifetime [3]. In the United States, 500,000 patients with newly diagnosed ulcers and more than 4 million patients with relapses of the disease are identified annually [2, 4]. Peptic ulcer localized in the duodenum is 4 times more common than ulcer localized in the stomach. Among patients with duodenal ulcers, men predominate over women, while among patients with gastric ulcers the ratio of men and women is approximately the same [5].

In recent years, there has been a trend towards a decrease in hospitalization of patients with uncomplicated forms of ulcer both in foreign countries [6] and in Russia. An analysis of the frequency and prevalence of PU in the Russian Federation, according to statistical data from the Ministry of Health of the Russian Federation for the period from 2006 to 2017, showed that the incidence of PU decreased from 128.7 to 79.5 per 100,000 population [7, 8]. At the same time, an increase in the incidence of complications of ulcerative disease (bleeding, perforation) has been noted all over the world, which is caused by the increasing use of nonsteroidal anti-inflammatory and antirheumatic drugs [6]. In the UK, more than 2,000 patients die annually from complications of gastric and duodenal ulcers associated with taking these drugs; in the USA, more than 16,500 patients die [9].

In recent years, there has been a worldwide trend toward a decrease in the number of patients with complicated forms of ulcer disease, largely due to the effectiveness of modern antiulcer therapy regimens, the increased availability of endoscopic diagnostics and the active use of screening tests to clarify the presence of *H. pylori*. According to the report of the Chief Surgeon of the Ministry of Health of the Russian Federation A.Sh. Revishvili dated October 25, 2018, in Russia from 2000 to 2017 there was a tendency towards a decrease in the absolute number of patients with perforated gastric and duodenal ulcers (from 37.6 to 19.1 thousand people), while the proportion of late hospitalizations increases (later than 24 hours — from 13.7 to 23.4 %) and an increase in postoperative mortality is observed. The absolute number of patients with gastrointestinal bleeding, including ulcerative etiology, also decreased over the analyzed period, but postoperative mortality decreased slightly. A similar situation was noted by a group of Japanese scientists who pointed out the reduced significance of the presence of *H. pylori* for patients with ulcer bleeding [10].

1.4. Features of coding a disease or condition (groups of diseases or conditions) according to the International Statistical Classification of Diseases and Related Health Problems

Stomach ulcer (K25):

K25.0 — acute with bleeding;
K25.1 — acute with perforation;
K25.2 — acute with bleeding and perforation;
K25.3 — acute without bleeding and perforation;
K25.4 — chronic or unspecified with bleeding;
K25.5 — chronic or unspecified with perforation;
K25.6 — chronic or unspecified with bleeding and perforation;
K25.7 — chronic without bleeding and perforation;
K25.9 — not specified as acute or chronic with out bleeding and perforation.

Duodenal ulcer (K26):

K26.0 — acute with bleeding;
K26.1 — acute with perforation;
K26.2 — acute with bleeding and perforation;
K26.3 — acute without bleeding and perforation;
K26.4 — chronic or unspecified with bleeding;
K26.5 — chronic or unspecified with perforation;
K26.6 — chronic or unspecified with bleeding and perforation;

K26.7 — chronic without bleeding and perforation;
K26.9 — not specified as acute or chronic without bleeding and perforation.

1.5. Classification of a disease or condition (group of diseases or conditions)

There is no generally accepted classification of PU. First of all, depending on the presence or absence of *H. pylori* infection, ulcers are distinguished as associated and not associated with *H. pylori* infection. The latter form is also sometimes called idiopathic. Peptic ulcers are also distinguished as an independent disease (essential ulcers) and symptomatic ulcers of the stomach and duodenum (drug-induced, stress related, associated with endocrine pathology, with other chronic diseases of internal organs), which arise against the background of other diseases and, according to the mechanisms of their development, are associated with special etiological and pathogenetic factors.

Depending on the location, there are gastric ulcers (cardial and subcardial sections, located in the body of the stomach, antrum, pyloric canal), duodenal ulcers (bulb, postbulbar section), as well as combined ulcers of the stomach and duodenum. In this case, ulcers can be located on the lesser or greater curvature, the anterior and posterior walls of the stomach and duodenum.

According to the number of ulcerative lesions, single and multiple ulcers are distinguished, and depending on the size of the ulcerative defect — ulcers of small (up to 5 mm in diameter) and medium (6–19 mm in diameter) sizes, large (20–30 mm in diameter) and giant (over 30 mm in diameter) ulcers.

When formulating a diagnosis, the stage of the disease is noted: exacerbation, healing, scarring (endoscopically confirmed stage of "red" and "white" scar) and remission, as well as the existing cicatricial ulcerative deformity of the stomach and/or duodenum, the presence of complications of ulcerative disease (including anamnestic): bleeding, perforation, penetration, cicatricial ulcerative stenosis, as well as the nature of surgical interventions, if any.

1.6. Clinical picture of a disease or condition (group of diseases or conditions)

The leading symptom of exacerbation of peptic ulcer is pain in the epigastric region, which can radiate to the left half of the chest and left shoulder blade, thoracic or lumbar spine. Pain occurs immediately after eating (with ulcers of the cardial and subcardial parts of the stomach), half an hour to an hour after eating (with ulcers of the body of the stomach). With ulcers of the pyloric canal and duodenal bulb, late pain is usually observed (2–3 hours after eating), "hunger" pain that occurs on an empty stomach and goes away after eating, as well as night pain. The pain resolves after taking proton pump inhibitors (PPIs) and H_2-histamine receptor blockers [5].

With exacerbation of ulcers, sour belching, nausea, and constipation are also common. Vomiting of acidic gastric contents, which brings relief and is therefore artificially induced by patients, has always been considered a sign of ulcerative disease, but nowadays it is relatively rare. During an exacerbation of the disease, weight loss is often observed, since, despite a preserved and sometimes even increased appetite, patients limit themselves to food for fear of increased pain.

Clinical symptoms observed during exacerbation of ulcer are not pathognomonic and can occur in other diseases (for example, chronic gastritis and duodenitis with functional dyspepsia syndrome), therefore the diagnosis of ulcer must be confirmed by other instrumental research methods.

During the period of exacerbation of ulcer, an objective examination can often reveal pain in the epigastric region on palpation, combined with moderate resistance of the muscles of the anterior abdominal wall. Local percussion pain in the same area (Mendel's symptom) may also be detected. However, these signs are not strictly specific for exacerbation of ulcerative disease.

Typical for ulcers are seasonal (spring and autumn) periods of increased pain and dyspeptic symptoms.

In uncomplicated cases, ulcer usually occurs with alternating periods of exacerbation (lasting from 3–4 to 6–8 weeks) and remission (lasting from several weeks to many years). Under the influence of unfavorable factors (for example, such as physical stress, taking non-steroidal anti-inflammatory and antirheumatic drugs and/or drugs that reduce blood clotting, alcohol abuse), complications may develop. These include bleeding, perforation and penetration of the ulcer, the formation of cicatricial ulcerative stenosis, and malignancy of the ulcer.

Ulcerative bleeding occurs in 15–20 % of patients with peptic ulcer. Risk factors for its occurrence include the use of nonsteroidal anti-inflammatory and antirheumatic drugs, *H. pylori* infection, and large ulcer sizes (> 1 cm) [6]. Ulcerative bleeding is manifested by vomiting coffee-ground-like contents (hematemesis) or black, tarry stools (melena). With massive bleeding and low secretion of hydrochloric acid, as well as localization of the ulcer in the cardia, an admixture of unchanged blood may be observed in the vomit. Sometimes general complaints (weakness, loss of

consciousness, decreased blood pressure, tachycardia) come first in the clinical picture of ulcer bleeding, while melena may appear only after a few hours.

According to the severity of bleeding, the most common classification in Russian Federation is one of A.I. Gorbashko (1982) [11] (Appendix D1), using a three-degree gradation and distinguishing mild, moderate and severe degrees of bleeding, taking into account both the amount of blood loss suffered and the condition of the patient himself. The American College of Surgeons Blood Loss Severity Scale (Appendix D2) distinguishes four classes (degrees) of blood loss — mild, moderate, moderately severe and severe.

To characterize the source of ulcerative gastroduodenal hemorrhage (UGDH), namely, stigmata of bleeding according to the results of endoscopic examination, it is generally accepted to use the classification of J. Forrest (F) (1974) [12] (Appendix D5).

Perforation occurs in 5–15 % of patients with ulcers, more often in men. Physical overexertion, alcohol intake, and overeating predispose to its development. Sometimes perforation occurs suddenly, against the background of an asymptomatic ("silent") course of ulcer. Perforation of an ulcer is clinically manifested by acute ("dagger-like") pain in the epigastric region and the development of a collaptoid state. When examining the patient, a "board-shaped" tension in the muscles of the anterior abdominal wall and sharp pain on palpation of the abdomen, a positive Shchetkin — Blumberg sign, are detected. Later, sometimes after a period of seeming improvement, the picture of diffuse peritonitis progresses.

Penetration refers to the ingress of a stomach or duodenal ulcer into the surrounding tissues: the pancreas, lesser omentum, gallbladder and common bile duct. When the ulcer penetrates, persistent pain occurs, which loses its previous connection with food intake, body temperature rises, and blood tests reveal an increase in the erythrocyte sedimentation rate. The presence of ulcer penetration is confirmed radiographically and endoscopically.

Pyloric stenosis usually forms after scarring of ulcers located in the pyloric canal or the initial part of the duodenum. Often the development of this complication is facilitated by the operation of suturing a perforated ulcer in this area. The most characteristic clinical symptoms of pyloric stenosis are vomiting of food eaten the day before, as well as belching with the smell of hydrogen sulphide. When palpating the abdomen in the epigastric region, a "late succussion splash" (Vasilenko's symptom) can be detected; in thin patients, gastric peristalsis sometimes becomes visible. With decompensated pyloric stenosis, patient exhaustion may progress, and electrolyte disturbances may occur.

Malignancy of a benign gastric ulcer is not as common a complication as previously thought. Cases of infiltrative ulcerative gastric cancer not recognized in a timely manner are often mistaken for malignant ulcers. Diagnosis of ulcer malignancy is not always simple. Clinically, it is sometimes possible to note a change in the nature of the course of ulcer with the loss of periodicity and seasonality of exacerbations. Blood tests reveal anemia and increased erythrocyte sedimentation rate. The final conclusion is made by histological examination of biopsies taken from various areas of the ulcer.

Certain features of the clinical picture are inherent in symptomatic ulcers that occur against the background of other diseases or when taking medications.

Thus, *stress gastroduodenal ulcers* include acute, usually multiple ulcers of the stomach and duodenum that occur with widespread burns (Curling ulcers), after traumatic brain injuries and neurosurgical operations (Cushing ulcers), after extensive abdominal operations, especially those associated with organ transplantation, with acute myocardial infarction, in patients with end-stage chronic kidney disease and liver failure and other critical conditions. Stress gastroduodenal ulcers are often asymptomatic, are prone to gastrointestinal bleeding, and are characterized by high mortality due to the often severe course of the underlying disease.

Among *medicinal ulcers* of the stomach and duodenum, the most important are acute erosive and ulcerative lesions associated with the use of nonsteroidal anti-inflammatory and antirheumatic drugs that block the enzyme cyclooxygenase 1, which is responsible for the synthesis of prostaglandins in the stomach wall. Gastroduodenal ulcers occur in 20–25 % of patients taking these medications for a long time, and erosive lesions occur in more than 50 % of patients. Risk factors for their development include the elderly age of patients, a history of ulcers, concomitant diseases of the cardiovascular system and liver, high doses of these drugs, and simultaneous use of antithrombotic drugs.

Gastroduodenal ulcers and erosions caused by the use of nonsteroidal anti-inflammatory and antirheumatic drugs are also often multiple in nature, often have few symptoms and are manifested by sudden gastrointestinal bleeding (melena or vomiting of "coffee grounds" type contents). The risk of their development in such patients increases 4–5 times [13].

2. Diagnostics, medical indications and contraindications for the use of diagnostic methods

Diagnosis criteria:

The diagnosis of peptic ulcer is established on the basis of:

1) anamnestic data (characteristic complaints, detection of peptic ulcer before);

2) physical examination (detection of pain and resistance of the abdominal wall muscles upon palpation);

3) instrumental examination (detection of an ulcerative defect during endoscopic and X-ray examination of the stomach and duodenum).

2.1. Complaints and anamnesis

Complaints and anamnesis data typical for patients with ulcer are listed in subsection 1.6.

2.2. Physical examination

Physical examination data typical for patients with ulcer are given in subsection 1.6.

2.3. Laboratory diagnostic tests

• To exclude anemia as a consequence of hidden ulcer bleeding, it is recommended that all patients with peptic ulcer undergo a general (clinical) blood test to determine the level of hemoglobin and hematocrit [14].

Grade of recommendations — B;
level of evidence — 3.

Comment. A general (clinical) blood test in an uncomplicated course of ulcer most often remains without significant changes, but anemia may also be detected, indicating obvious or hidden bleeding. To exclude hidden ulcerative bleeding, it is recommended that all patients with peptic ulcers undergo a stool test for occult blood [15].

Grade of recommendations — B;
level of evidence — 2.

Comment. A certain place in the diagnosis of exacerbations of ulcers is occupied by the study of stool for occult blood. When interpreting its results, it is necessary to remember that a positive fecal reaction to occult blood also occurs in many other diseases, which requires their mandatory exclusion.

2.4. Instrumental diagnostic studies

• In all patients with suspected ulcer, in the absence of contraindications, esophagogastroduodenoscopy (EGD) is recommended to confirm the diagnosis [2].

Grade of recommendations — C;
level of evidence — 5.

Comment. A planned endoscopic examination confirms the presence of an ulcerative defect, clarifies its location, shape, size, depth, condition of the bottom and edges of the ulcer, and allows to identify signs of penetration, cicatricial deformation and stenosis of the organ lumen. Routine endoscopic examination makes it possible to detect other concomitant changes in the mucous membrane of the stomach and duodenum and determine disorders of gastroduodenal motility. To assess the stage of the ulcerative process (exacerbation, healing, scarring), it is advisable to use the generally accepted Sakita and Miwa classification (Fig.):

— A (Active):

• A1 — the mucous membrane surrounding the ulcer appears swollen as a result of edema; there is no epithelial regeneration;

• A2 — swelling of the mucous membrane around the ulcer has decreased, the edge of the ulcer is clearly visible, and the first sprouts of regenerating epithelium have appeared in the edge of the ulcer; a red rim is often visible along the perimeter of the ulcer, and a circular white scab is often visible along the edge; usually converging folds of the mucous membrane can be traced right up to the edge of the ulcer;

— H (Healing):

• H1 — the layer of white fibrin covering the ulcer becomes thin, and the regenerating epithelium extends directly to the base of the ulcer; the gradient between the edge and the bottom of the ulcer is smoothed out; but the crater of the ulcer is still evident, and the edge of the ulcer is clearly visible; the diameter of the ulcer is approximately one-half to two-thirds the diameter of a stage A1 ulcer;

• H2 — the ulcerative defect is smaller than in stage H1, and the regenerating epithelium covers most of the bottom of the ulcer; the area of the white fibrin layer is approximately a quarter to a third of the area of the ulcer in stage A1;

— S (Scarring):

• S1 — regenerating epithelium completely covers the bottom of the ulcer; the white fibrin layer has completely disappeared; initially the regeneration zone looks bright red; upon close inspection, one can see a large number of capillaries; a “red scar” has formed;

• S2 — over a period of several months to several years, the initially red scar takes on the color of the surrounding mucous membrane; a “white scar” has formed.

When an ulcer is localized in the stomach, in almost all cases it is recommended to perform a multiple forceps biopsy from the edges of the ulcerative defect, followed by a pathomorphological examination to exclude the malignant nature of the ulcerative lesion.

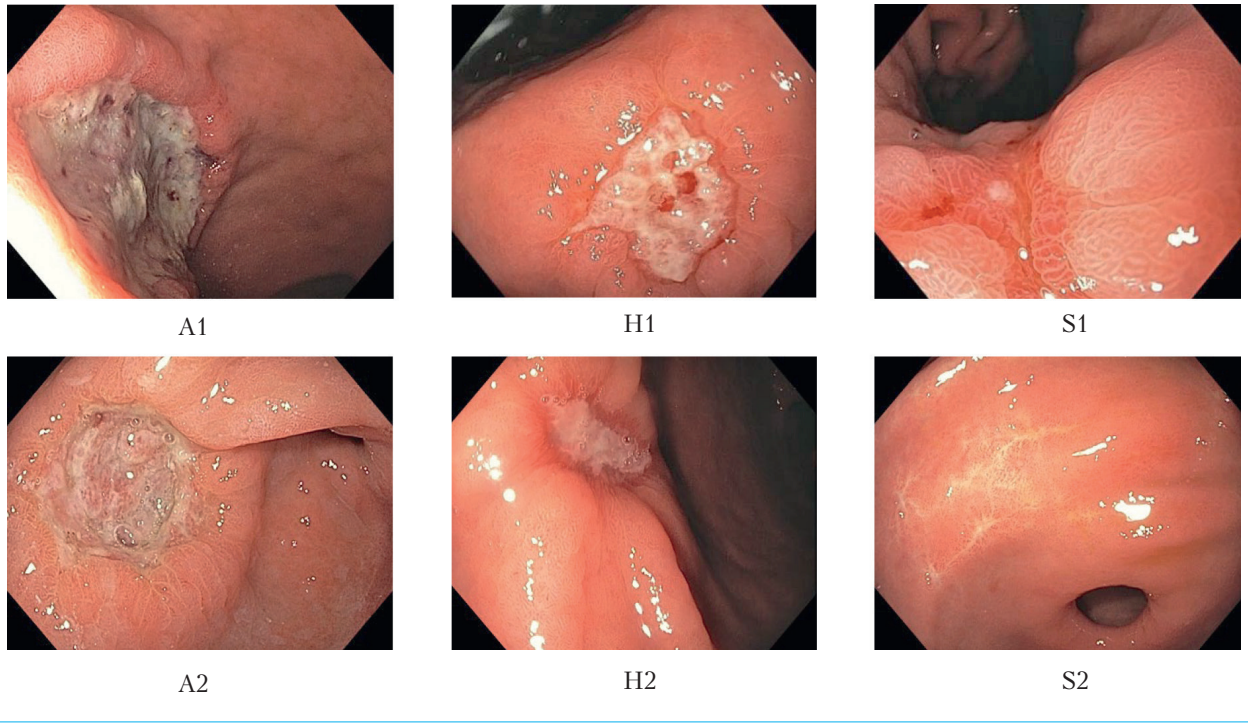

Figure. Stages of regression (healing) of a stomach ulcer and their characteristic features (according to Sakita and Miwa classification)

Рисунок. Стадии регрессии (заживления) язвы желудка и их характерные черты (согласно классификации Sakita и Miwa)

When the ulcer is localized in the duodenum, performing a biopsy from the edges of the ulcerative defect is usually not recommended, since such ulcers are extremely rarely malignant.

Benign ulcers of the duodenum should be differentiated from ulcerated forms of neuroendocrine and subepithelial tumors, as well as tumors from neighboring organs, most often the pancreas, growing into the duodenum. In these cases, a biopsy is definitely necessary.

Patients with gastric ulcers are recommended to undergo a control endoscopic examination with repeated multiple forceps biopsies at the end of the course of conservative treatment. This primarily concerns patients whose symptoms of ulcer persist despite an appropriate course of drug therapy, or the etiology of the ulcer remains insufficiently clear.

Patients with duodenal ulcers are recommended to undergo a control endoscopic examination in cases where clear clinical symptoms persist despite treatment, to exclude refractory ulcers and non-peptic etiologies of the ulcer.

• In patients with suspected peptic ulcer for whom endoscopic examination is not possible, X-rays of the stomach and duodenum are recommended to confirm the diagnosis [2].

Grade of recommendations — C; level of evidence — 5.

Comment. X-rays of the stomach and duodenum reveal a direct sign of ulcer — a "niche" on the contour or relief of the mucous membrane and indirect signs of the disease (local circular spasm of muscle fibers on the wall of the stomach opposite to the ulcer in the form of a "pointing finger", convergence of the folds of the mucous membrane towards a "niche", cicatricial and ulcerative deformation of the stomach and duodenal bulb, hypersecretion on an empty stomach, gastroduodenal motility disorders).

Currently, X-ray examination for the purpose of diagnosing ulcers is not used as often as before. It is used in cases where for some reason (for example, in the presence of contraindications) it is not possible to perform EGD, when, for the purpose of differential diagnosis with an infiltrative-ulcerative form of cancer, it is necessary to evaluate the peristalsis of the stomach wall, when it is necessary to evaluate the nature of evacuation from the stomach.

• In patients with suspected perforation of an ulcer, a computed tomography (CT) scan of the abdominal organs is recommended to confirm it [16–20].

Grade of recommendations — B; level of evidence — 4.

Comment. This method allows to determine the presence of free gas in the abdominal cavity, the volume and nature of the effusion, localize pathological changes, including determining the location of the perforation.

• In patients with suspected perforation or penetration of an ulcer, if CT is not possible, in order to diagnose these complications, it is recommended to perform an ultrasound examination and plain radiography of the abdominal organs [20, 21].

Grade of recommendations — B; level of evidence — 4.

Comment. An important criterion for preserving the patient's life and success in the treatment of perforated gastric and/or duodenal ulcers is the preoperative period — the time from the onset of the disease to the time of surgery. A long diagnostic search can lead to a deterioration in the patient's condition with a subsequent unfavorable prognosis. Only if a medical institution does not have a CT scan, it is possible to perform an ultrasound and radiography of the abdominal cavity to diagnose ulcer perforation. It must be remembered that the sensitivity and specificity of these methods are lower than those of CT, and the result largely depends on the qualifications of the ultrasound specialist.

• Urgent endoscopic examination/intervention (within 24 hours of the onset of bleeding and within the first two hours of hospitalization) is recommended for all patients with acute upper gastrointestinal bleeding [22, 23].

Grade of recommendations — A; level of evidence — 2.

Comment. The endoscopic method is of decisive importance for establishing the source and nature of bleeding, assessing the need and possibility of stopping/preventing bleeding using an endoscope, as well as predicting the risk of recurrent bleeding. That is why emergency EGD is indicated for all patients with bleeding from the upper gastrointestinal tract. It is advisable to carry out endoscopy with an operating endoscope with end optics and a wide instrumental channel, with the ability to supply a directed jet of liquid to wash away blood and clots and aspiration of the contents through the biopsy channel, parallel to the instrument inserted into it, on a functional table that allows to change the position of the patient. In necessary cases (when it is impossible to fully examine the source of bleeding and properly bring the appropriate instrument to the bleeding area), wide-channel operating duodenoscopes are used. Modern video endoscopic systems provide invaluable assistance for the coordinated work of the operating team, providing high-quality images of the source of bleeding on the monitor screen.

Refusal of emergency endoscopic diagnosis in exceptional cases may be justified in case of ongoing profuse bleeding, especially if, according to the anamnesis and medical documents available to the doctor, its ulcerative etiology can be assumed. However, with the availability of a 24-hour endoscopic service, emergency EGD is also possible in such patients; it is performed directly on the operating table and is considered as an element of pre- or intraoperative revision.

Endoscopic diagnosis is not indicated for patients who are in an agonal state and require resuscitation measures. The decision on the impossibility of performing EGD is made jointly by the surgeon in charge, anesthesiologist-resuscitator and endoscopist.

• To increase the diagnostic and therapeutic value of EGD, it is recommended to free the stomach from blood, clots, and food debris at the stage of admission to the hospital, by installing a wide-bore gastric tube, washing and evacuating the stomach contents [22, 23].

Grade of recommendations — B; level of evidence — 3.

Comment. For this purpose, it is also possible to use gastrointestinal motility stimulants, in particular, slow intravenous jet or drip administration of 200 mg of #erythromycin. If the anamnestic information and clinical picture suggest with a high degree of probability that the upper parts of the gastrointestinal tract are free of contents, EGD can be performed without installing a probe in the stomach and without administering gastrointestinal motility stimulants. This decision is made jointly by the surgeon in charge and the endoscopist.

• In severely ill patients, it is recommended to perform an urgent endoscopic examination with anesthetic management, including intensive treatment of blood loss, adequate analgesia/sedation and monitoring of vital signs [23, 24].

Grade of recommendations — A; level of evidence — 2.

Comment. Performing EGD in extremely critically ill patients with decompensated concomitant diseases is advisable only in a situation where "endoscopic intervention of desperation" is undertaken in parallel with intensive care, directly to stop ongoing bleeding.

• In patients with ongoing active hematemesis, encephalopathy, or agitation, tracheal intubation is recommended prior to endoscopy to protect the patient's airway from potential aspiration of gastric contents [12].

Grade of recommendations — A;
level of evidence — 2.

• If, during a diagnostic EGD, a large amount of blood, clots, or food masses are detected in the lumen of the stomach, which cannot be displaced or removed through the instrumental channel of the endoscope and, as a result, a full examination and hemostatic effect on the source of bleeding are carried out, it is recommended to remove the endoscope and wash/evacuate contents through a thick gastric tube [6, 10].

Grade of recommendations — B;
level of evidence — 3.

Comment. At the very beginning of the endoscopic examination, blood, clots and residual rinsing water, if possible, are completely removed from the lumen and from the mucous membrane through the biopsy channel of the device. If blood and clots cannot be removed completely, moving the source of bleeding to a position accessible for inspection and convenient for manipulation is achieved by changing the position of the patient on the endoscopic table, destroying and displacing the clots with instruments (polypectomy loop, Dormia basket), and targeted washing of the source of bleeding using intensive jet feeding fluids through a separate channel of the endoscope (preferred), or through a catheter. In conditions of ongoing bleeding, it is advisable to perform additional emergency preparation of the upper gastrointestinal tract for EGD directly on the endoscopic table, including the use of a fast-acting stimulator of gastrointestinal motility (#erythromycin).

• During emergency diagnostic EGD, the source of ulcerative gastroduodenal bleeding is recommended to be assessed according to the classification of J.F. Forrest (1974) (Appendix D) [12].

Grade of recommendations — A;
level of evidence — 1.

Comment. When conducting an emergency endoscopic examination in a patient with gastroduodenal bleeding, it is necessary to examine all parts of the gastrointestinal tract accessible to this type of examination, regardless of how many sources of bleeding are found in the esophagus or proximal parts of the stomach. To avoid diagnostic errors, the study should be especially carefully carried out in anemic patients, as well as in patients with a clear clinical picture of massive bleeding, but with "minimal" endoscopic manifestations ("discrepancy between the clinical picture and findings"). In doubtful cases, if the institution has the technical capabilities, it is necessary to analyze the video recording of the study in consultation with more experienced specialists or repeat it.

An urgent endoscopic examination confirms the presence and clarifies the localization of the ulcerative defect that served as the source of bleeding, its size, depth, condition of the bottom and edges. EGD allows to identify signs of penetration or covered perforation of an ulcer, cicatricial deformation and stenosis of the organ lumen, as well as additional erosive and ulcerative lesions of the stomach and duodenum.

• When a bleeding ulcer is localized in the stomach, it is recommended to perform a multiple forceps biopsy from the edges of the ulcerative defect, followed by a morphological examination to exclude the malignant nature of the ulcerative lesion [25].

Grade of recommendations — A;
level of evidence — 1.

Comment. If a biopsy during primary EGD is dangerous from the point of view of resumption of bleeding, or is technically difficult, a biopsy during control EGD is justified. The number of biopsies taken around the perimeter of the ulcer should be at least six.

• When the ulcer is localized in the duodenum, routine biopsy from the edges of the ulcer is not recommended, since such ulcers are extremely rarely malignant [25].

Grade of recommendations — A;
level of evidence — 1.

Comment. Benign ulcers of the duodenum should be differentiated from ulcerated forms of neuroendocrine and subepithelial tumors, as well as tumors from neighboring organs, most often the pancreas, growing into the duodenum. In these cases, a biopsy is definitely necessary.

2.5. Other diagnostic tests

• To determine indications for eradication therapy, all patients with peptic ulcer are recommended to be tested for the presence of *H. pylori* infection using a ^{13}C-breath urease test or determining the *H. pylori* antigen in stool, and with simultaneous EGD — using a rapid urease test [26, 27].

Grade of recommendations — C;
level of evidence — 4.

Comment. In accordance with the recommendations of the Maastricht V Consensus Meeting (2016) [26], the most optimal tests for the primary diagnosis of H. pylori infection are the ^{13}C-respiratory urease test and determination of the H. pylori antigen in stool. Thus, according to the latest Cochrane review and meta-analysis, the sensitivity of the ^{13}C-respiratory urease test is 94 % (95% confidence interval (95 % CI): 0.89–0.97), and the detection of H. pylori antigen in feces is 83 % (95% CI: 0.73–0.90) with a fixed specificity of 90 % [27].

If patients undergo EGD at the same time, a rapid urease test can be the primary diagnostic method. When using endoscopic methods for diagnosing H. pylori, at least two biopsies are taken from the body of the stomach and one biopsy from the antrum. The serological method for detecting antibodies to H. pylori can be used for the primary diagnosis of H. pylori infection, but only if the antibodies detected are of the IgG class. The microbiological (bacteriological) method is currently used to determine the individual sensitivity of H. pylori to systemic antibacterial drugs in cases of treatment failure.

*To monitor eradication, which is carried out 4–6 weeks after the end of eradication therapy, it is best to use a ^{13}C-urease breath test or determination of H. pylori antigen in stool. During this time, patients should not take antibiotics or tripotassium bismuth dicitrate**. To avoid false negative results, PPIs should be discontinued 2 weeks before the intended follow-up study. In addition, a negative test result for H. pylori infection must be confirmed by another diagnostic method.*

• In patients with ulcer bleeding, when determining whether they are infected with *H. pylori*, a ^{13}C-urease breath test is recommended due to the low sensitivity of the rapid urease test and histological pathological examination [28].

Grade of recommendations — A; level of evidence — 1.

Comment. A meta-analysis of works devoted to the use of various methods of testing for the presence of H. pylori infection in patients with ulcer bleeding showed low sensitivity of the rapid urease test and morphological examination. The highest accuracy of diagnosing H. pylori infection in patients with ulcer bleeding was noted when using the ^{13}C-urease breath test [51].

• In patients with refractory peptic ulcer disease, in order to exclude Zollinger — Ellison syndrome, it is recommended to determine the level of serum gastrin [29].

Grade of recommendations — C; level of evidence — 5.

Comment. The pathogenesis of gastroduodenal ulcers in Zollinger — Ellison syndrome is associated with a sharp hypersecretion of hydrochloric acid as a result of the presence of a gastrin-producing tumor (most often in the pancreas). These ulcers are usually multiple, localized not only in the stomach and duodenum, but also in the jejunum, and sometimes in the esophagus, and occur with severe pain and persistent diarrhea. When examining such patients, a sharply increased level of gastric acid secretion is noted (especially under basal conditions), and an increased content of serum gastrin is determined (3–4 times compared to the norm). Provocative tests (with secretin, glucagon), ultrasound and CT scan of the pancreas help in recognizing Zollinger — Ellison syndrome.

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

Treatment of ulcer should be comprehensive and include not only the prescription of medications, but also a wide range of different measures, including dietary nutrition, cessation of smoking and alcohol abuse, refusal to take drugs that have an ulcerogenic effect, normalization of work and rest, sanatorium spa treatment.

Patients with uncomplicated ulcer disease are subject to conservative treatment. In most cases it is performed on an outpatient basis. However, in cases of severe pain, a high risk of complications (for example, large and gigantic ulcers), the need for further examination to verify the diagnosis (for example, the nature of a gastric ulcer is unclear), and severe concomitant diseases, hospitalization of patients is advisable.

3.1. Diet therapy

• Diet therapy is recommended for all patients with ulcers in order to accelerate the healing of ulcers [30].

Grade of recommendations — C; level of evidence — 5.

Comment. The basic principles of dietary nutrition for patients with peptic ulcers, developed many years ago, remain relevant. Recommendations for frequent (5–6 times a day), fractional meals, corresponding to the rule "six small meals are better than three large ones", mechanical, thermal and chemical sparing. It is necessary to exclude from the diet foods that irritate the gastric mucosa and stimulate the secretion of hydrochloric acid: strong meat and fish broths, fried and peppered foods, smoked and canned foods, seasonings and spices (onions, garlic, pepper, mustard), pickles and marinades, carbonated fruit waters, beer, dry white wine, champagne, coffee, citrus fruits.

Preference should be given to products that have pronounced buffering properties (i.e., the ability to bind and neutralize hydrochloric acid). These include meat and fish (boiled or steamed), eggs, milk and dairy products. Pasta, stale white bread, dry biscuits and dry cookies, dairy and vegetarian soups are also allowed. Vegetables (potatoes, carrots, zucchini, cauliflower) can be cooked stewed or in the form of purees and steam

soufflés. The diet can include porridge, jelly from sweet varieties of berries, mousses, raw grated and baked apples, cocoa with milk, and weak tea.

A patient needs to remember such simple, but at the same time important recommendations as the need to eat in a calm environment, slowly, sitting, and chew food thoroughly. This promotes better saturation of food with saliva, the buffering capabilities of which are quite pronounced.

3.2. Conservative treatment

• In patients with exacerbation of ulcers, antisecretory therapy with proton pump inhibitors (PPIs) is recommended for 4–6 weeks in order to achieve healing of ulcers [2, 3].

Grade of recommendations — C; level of evidence — 5.

Comment. Currently, only H_2-histamine receptor blockers and PPIs can be considered as basic antiulcer therapy. In 1990, W. Burget et al. [31] published data from a meta-analysis of 300 studies, on the basis of which they came to the conclusion that gastric and duodenal ulcers are scarred in almost all cases if during the day it is possible to maintain the pH of the intragastric contents > 3 for about 18 hours ("Burget's rule"). According to one of the latest meta-analyses, H_2-blockers and PPIs are significantly more effective than placebo in achieving ulcer scarring (OR (odds ratio) = 3.49; 95% CI: 3.28–3.72; p < 0.0001) and reducing the risk of rebleeding in complicated disease (OR = 0.68; 95% CI: 0.60–0.78; p < 0.0001) [32].

Only drugs of the PPI group can fulfill, after taking them, the conditions for the necessary duration of increase in pH in the stomach, required for the healing of gastroduodenal ulcers. Currently, PPIs are a means of basic therapy for exacerbation of ulcerative disease. They are prescribed to relieve pain and dyspeptic disorders, as well as to achieve scarring of the ulcer in the shortest possible time. Numerous randomized comparative studies (including meta-analytic studies) have demonstrated significantly higher efficacy of PPIs compared with H_2-blockers in relieving clinical symptoms and achieving ulcer scarring [33, 34]. A recent meta-analysis demonstrated that PPIs are almost 1.5 times more effective than H_2-blockers in terms of epithelialization of ulcers (OR = 5.22; 95% CI: 4.00–6.80 vs. OR = 3.80; 95% CI: 3.44–4.20; p < 0.0001) [32].

*Currently, there is a protocol for the pharmacotherapy of ulcers, which involves prescribing the selected drug in a certain daily dose: #omeprazole** — at a dose of 20 mg, lansoprazole — at a dose of 30 mg, #pantoprazole — at a dose of 40 mg, #rabeprazole — at a dose of 20 mg, #esomeprazole** — at a dose of 20 mg. The duration of treatment is determined by the results of endoscopic monitoring, which is carried out at intervals of 2–4 weeks. Basic antisecretory therapy using PPIs is the main treatment method for idiopathic gastroduodenal ulcers.*

When using PPIs metabolized by the cytochrome P450 system, issues of competitive drug interactions with drugs that are also metabolized by this system may arise. Among all PPIs, pantoprazole and rabeprazole exhibit the lowest affinity for the cytochrome P450 system, the main metabolism of which occurs without the participation of this enzyme system.

• If PPIs are ineffective or there are contraindications to their use in patients with exacerbation of ulcers, in order to achieve healing of ulcers, it is recommended to prescribe H_2-histamine receptor blockers for 4–6 weeks [2].

Grade of recommendations — C; level of evidence — 5.

*Comment. H_2 blockers (famotidine**) suppress the secretion of hydrochloric acid by displacing histamine from binding to the H_2 receptors of parietal cells. These drugs maintain intragastric pH > 3 throughout the day for 8–10 hours. Numerous studies have shown that the use of H_2-histamine receptor blockers for 4–6 weeks leads to scarring of the ulcer in 70–80 % of patients with duodenal ulcers and in 55–60 % of patients with gastric ulcers [2]. A recent meta-analysis demonstrated that H_2 blockers were significantly more effective than placebo in achieving ulcer scarring (OR = 3.80; 95% CI: 3.44–4.20; p < 0.0001) [32]. However, after PPIs began to be widely used in clinical practice as basic antisecretory therapy, H_2-histamine receptor blockers have lost their position and are now rarely used, mainly when it is impossible to use PPIs or in combination with them to enhance antisecretory action.*

• Patients with exacerbation of ulcers are recommended to take #rebamipide to speed up the healing time of ulcers and improve the quality of the resulting scar [35, 36].

Grade of recommendations — B; level of evidence — 2.

Comment. #Rebamipide has both gastro- and enteroprotective effects. The mechanism of action of the drug is based on the induction of the synthesis of prostaglandins E_2 and I_2 in the mucous membrane of the stomach and intestines, which leads to the activation of its protective properties. As a result, blood flow in the wall of the stomach and intestines improves, the proliferation of epithelial cells increases, the

*permeability of the mucous membrane is normalized, oxygen radicals are absorbed, the secretion of gastric mucus increases, and an anti-inflammatory effect is realized. Studies have demonstrated higher effectiveness of rebamipide in healing gastric ulcers compared to placebo and similar effectiveness of #rebamipide and #omeprazole*** [35, 36].

• All patients with exacerbation of ulcer with positive test results for *H. pylori* infection are recommended to undergo eradication therapy to heal the ulcer [37].

Grade of recommendations — A;
level of evidence — 1.

Comment. According to a meta-analysis, the effectiveness of H. pylori eradication therapy in achieving ulcer healing was superior to that of drugs used to treat acid-related diseases (34 studies; relative risk (RR) of persistent ulcers = 0.66; 95% CI: 0.58–0.76) [37].

• All patients with ulcer who test positive for *H. pylori* infection are recommended to undergo eradication therapy to prevent subsequent relapses of ulcer [37–39].

Grade of recommendations — A;
level of evidence — 1.

Comment. A meta-analysis summarizing the results of five randomized controlled trials in a population of patients with peptic ulcer disease complicated by perforation showed that eradication therapy significantly reduces the risk of disease recurrence within a year after suturing the defect (RR = 1.49; 95% CI: 1.10–2.03) [28]. According to a Cochrane meta-analysis, eradication therapy for H. pylori in patients with ulcers, compared with no such treatment, significantly reduced the incidence of duodenal ulcer recurrence (27 studies; RR = 0.20; 95% CI: 0.15–0.26) and relapses stomach ulcers (12 studies; RR = 0.31; 95% CI: 0.22–0.45) [37].

• All patients with ulcer complicated by gastrointestinal bleeding with positive test results for *H. pylori* infection are recommended to undergo eradication therapy to prevent recurrent bleeding [12].

Grade of recommendations — A;
level of evidence — 1.

Comment. The meta-analysis included seven studies with a total of 578 patients: the average percentage of rebleeding in the group of patients who received eradication therapy for H. pylori infection was 2.9 %, and in the group without eradication therapy and without subsequent long-term maintenance antisecretory therapy — 20 % (OR = 0.17; 95% CI: 0.10–0.32; NNT (number of patients needed to treat to achieve benefit in one patient) was 7; 95% CI: 5–11). Another meta-analysis included three studies with a total of 470 patients: the mean rate of rebleeding in the H. pylori eradication therapy group was 1.6 %, and in the group without eradication therapy but with long-term maintenance antisecretory therapy it was 5.6 % (OR = 0.25; 95% CI: 0.08–0.76; NNT — 20; 95% CI: 12–100) [12].

• For all patients with ulcer with positive test results for *H. pylori* infection, it is recommended that the following be prescribed as first-line eradication therapy, providing a high percentage of infection eradication:

— *standard triple therapy*, including PPI (at a standard dose 2 times a day), clarithromycin** (500 mg 2 times a day) and amoxicillin** (1000 mg 2 times a day), enhanced with bismuth tripotassium dicitrate** (120 mg 4 times a day or 240 mg 2 times a day) for 14 days [40, 41];

— *classical four-component therapy with bismuth tripotassium dicitrate*** (120 mg 4 times a day) in combination with PPI (at a standard dose 2 times a day), #tetracycline** (500 mg 4 times a day) and #metronidazole** (500 mg 3 times daily) for 14 days [42–44];

— *quadruple therapy without bismuth preparations*, which includes standard triple therapy of PPI (at a standard dose 2 times a day), amoxicillin** (at a dose of 1000 mg 2 times a day), clarithromycin** (500 mg 2 times a day), enhanced with #metronidazole** (500 mg 3 times a day) for 14 days [44].

Grade of recommendations — A;
level of evidence — 1.

*Comment. Empirical selection of a first-line eradication therapy regimen without determining the sensitivity of H. pylori to systemic antibacterial drugs is based on therapy with the maximum proven effectiveness. The addition of bismuth tripotassium dicitrate** to standard triple therapy convincingly increases the eradication rate of H. pylori infection above 90 %, according to the European H. pylori Treatment Registry [41]. According to a meta-analysis by S.W. Ko et al., intensification of standard triple therapy with bismuth tripotassium dicitrate** increases its effectiveness with OR = 2.81 (95% CI: 2.03–3.89), including in cases of proven resistance of H. pylori to clarithromycin** [40]. Classic quadruple therapy based on bismuth tripotassium dicitrate** continues to demonstrate an eradication efficiency of more than 90 %, both according to the European registry [42] and according to meta-analyses [43, 44]. Quadruple therapy without bismuth tripotassium dicitrate** or concomitant therapy, including PPI and a combination of amoxicillin**, clarithromycin** and*

*#metronidazole**, according to a meta-analysis, is not inferior in effectiveness to classical quadruple therapy [44]. In essence, combination therapy is a standard triple regimen enhanced with #metronidazole**.*

• For patients with ulcer who test positive for *H. pylori* infection, 14 days of standard triple therapy is recommended as first-line eradication therapy in regions where its effectiveness has been confirmed [42, 44, 45].

Grade of recommendations — A;
level of evidence — 1.

*Comment. According to the European registry, standard triple therapy carried out within 7 days leads to successful eradication in 82.7 % of cases; within 10 days — in 84.2 %; 14 days — in 86.2 % [42]. A Cochrane meta-analysis of 45 randomized controlled trials in parallel groups shows an increase in the eradication rate of H. pylori with triple therapy when the duration of treatment was extended from 7 to 14 days (72.9 % vs. 81.9 %), and the RR of H. pylori persistence was 0.66 (95% CI: 0.60–0.74), NNT — 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). A significant increase in H. pylori eradication efficacy occurred when the duration of triple therapy was 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 % vs. 84.4 %; RR = 0.72; 95% CI: 0.58–0.90; NNT — 17; 95% CI: 11–46); especially when PPIs were combined with clarithromycin** and amoxicillin** when increasing the duration 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) [45].*

• For patients with ulcer who test positive for *H. pylori* infection, a double dose of a proton pump inhibitor is recommended during first-line eradication therapy to increase its effectiveness [46, 47].

Grade of recommendations — C;
level of evidence — 5.

*Comment. A meta-analysis demonstrated an increase in the eradication rate of H. pylori with high-dose PPIs [46]. However, an attempt to show, using a meta-analysis, an increase in treatment effectiveness with increasing drug dose for more modern PPIs (rabeprazole and #esomeprazole**) was not confirmed, possibly due to the inclusion of studies with a low daily dose of rabeprazole (20 mg per day), adopted in some Asian countries, or the effectiveness of these PPIs in eradicating H. pylori (85.3 % success with "high" doses and 84.2 % with "regular" doses of PPIs, OR = 1.09; 95% CI: 0.86–1.37; p = 0.47) [47]. A meta-analysis of 16 randomized controlled trials (n = 3680) demonstrated a decrease in the effectiveness of triple therapy with #omeprazole** and standard-dose lansoprazole in rapid metabolizers of PPIs. At the same time, the effectiveness of triple therapy with rabeprazole and #esomeprazole** in standard doses did not depend on the genetic polymorphism of CYP2C19 and did not decrease in rapid metabolizers of PPIs [48].*

• In patients with peptic ulcer who test positive for *H. pylori* infection, it is recommended that a potassium-competitive proton pump inhibitor be prescribed during eradication therapy to increase its effectiveness [49, 50].

Grade of recommendations — B;
level of evidence — 2.

Comment. A meta-analysis demonstrated an increase in the percentage of H. pylori eradication when prescribing triple therapy with vonoprazan compared with classical PPIs [49]. A meta-analysis by S. Shinozaki et al. [50] when comparing the effectiveness of various second-line eradication therapy regimens, also showed the advantage of vonoprazan.

• In patients with peptic ulcer who test positive for *H. pylori* infection after failure of standard triple therapy, standard triple therapy enhanced with bismuth tripotassium dicitrate, or combination therapy, classic quadruple therapy with bismuth tripotassium dicitrate is recommended as second-line therapy [51, 52].

Grade of recommendations — A;
level of evidence — 1.

*Comment. A systematic review with network meta-analysis demonstrated the high effectiveness of quadruple therapy with bismuth tripotassium dicitrate** as second-line therapy [51]. According to a meta-analysis conducted by Z. Han et al. [52], regimens containing bismuth tripotassium dicitrate** increase the percentage of eradication in the presence of resistance to clarithromycin** by 40 %, to #metronidazole** — by 26 %, in case of double resistance — by 59 %, which makes them the choice in justified as second-line therapy.*

• For patients with peptic ulcer testing positive for *H. pylori* infection after failure of classical quadruple therapy with bismuth tripotassium dicitrate, a triple regimen with #levofloxacin** or quadruple therapy with #levofloxacin** is recommended as second-line therapy [53, 54].

Grade of recommendations — B;
level of evidence — 2.

*Comment. The effectiveness of triple therapy with levofloxacin (PPIs, levofloxacin** and amoxicillin**) or quadruple therapy with levofloxacin** (PPIs, levofloxacin**, amoxicillin**, bismuth tripotassium dicitrate**) after unsuccessful results of previous courses of eradication therapy was noted in controlled studies and systematic reviews [53, 54].*

• In patients with peptic ulcer infected with *H. pylori*, to increase the effectiveness of eradication therapy, it is recommended to add #rebamipide to eradication regimens [55, 56].

Grade of recommendations — A;
level of evidence — 1.

Comment. Two meta-analyses, including 6 and 11 randomized controlled trials, confirmed an increase in eradication rates when #rebamipide was included in the regimen [55, 56].

• Patients with peptic ulcer with positive test results for *H. pylori* infection when prescribing eradication therapy are recommended to ensure adherence to the prescribed treatment (compliance) [57, 58].

Grade of recommendations — B;
level of evidence — 2.

*Comment. Compliance should be considered a key factor for the success of H. pylori eradication therapy. A controlled study showed that when taking more than 60 % of prescribed drugs, eradication of infection was 96 %, when taking less than 60 % (low compliance) — 69% [57]. In a large-scale randomized controlled trial, the eradication rate decreased with low compliance (less than 80 % of prescribed drugs taken) by 34 %, and in non-compliant patients, persistence of H. pylori was observed in 59 % of cases [58]. The recommendations of the World Organization of Gastroenterology regarding the eradication of H. pylori infection present measures to increase patient adherence to eradication therapy, ensuring a good treatment outcome. Patients should always be informed that successful eradication depends on compliance with the treatment regimen. Time should be taken to counsel the patient, explain how to administer complex drug therapy, and evaluate possible side effects of systemic antibacterial therapy. The need to complete treatment must be specifically emphasized. It is emphasized that written or graphic information about the procedure for carrying out complex eradication therapy can contribute to high compliance. For the treatment of peptic ulcer disease, a combination drug has been registered in the Russian Federation, which contains a set of capsules and tablets for standard triple therapy: each strip, including 2 capsules of #omeprazole** 20 mg each, 2 tablets of clarithromycin** 500 mg each, 4 capsules of amoxicillin** each 500 mg, designed for one day with a clear indication of morning and evening doses. A ready-made set of drugs for eradication therapy ensures the correct dose and stability of the frequency of dosing and increases patient compliance, which, as a domestic study has shown, makes it possible to achieve an eradication rate of H. pylori infection in peptic ulcers of over 90 % [59].*

• For patients with peptic ulcer who test positive for *H. pylori* infection during eradication therapy, it is recommended to prescribe strain-specific antidiarrheal microorganisms that have proven effective in reducing the incidence of adverse events, including diarrhea, associated with taking systemic antibacterial drugs [60–71].

Grade of recommendations — A;
level of evidence — 1.

Comment. Specific strains of single-strain or multi-strain antidiarrheal microorganisms have proven effectiveness in eradication therapy of H. pylori [60–67]. It is assumed that due to the prescription of these drugs during anti-Helicobacter treatment, the incidence of adverse events is reduced, which leads to a possible increase in the effectiveness of eradication [26].

A recent systematic meta-analysis review of 42 RCTs found that the risk of diarrhea associated with systemic antibacterial agents was significantly lower in patients taking antidiarrheal agents compared with patients not taking antidiarrheal agents (RR = 0.35; 95% CI: 0.27–0.47; p < 0.00001) or received a placebo during treatment with systemic antibacterial drugs (RR = 0.69; 95% CI: 0.60–0.80; p < 0.00001). The review also presents data from a meta-analysis of 7 RCTs on the use of antidiarrheal microorganisms together with systemic antibacterial drugs exclusively for the eradication of H. pylori. At the same time, there was a significant reduction in the risk of developing diarrhea associated with taking systemic antibacterial drugs in such patients by 45 % (RR = 0.55; 95% CI: 0.41–0.73; p < 0.0001) [68].

According to a Cochrane review of a meta-analysis of 31 RCTs, antidiarrheal microorganisms also reduced the risk of developing C. difficile-associated diarrhea by 60 % (RR = 0.40; 95% CI: 0.30–0.52) compared with placebo or no taking antidiarrheal microorganisms [69].

A recent controlled study demonstrated that the inclusion of CNCM I-745 at a dose of 750 mg per day for the entire treatment period in a three-component eradication regimen of the antidiarrheal microorganisms Saccharomyces boulardii (S. boulardii) significantly reduced the number of side effects during therapy compared

with the group control (5.3 ± 3.0 vs. 9.0 ± 3.1; p = 0.028) [70]. The effectiveness of S. boulardii CNCM I-745 in both improving tolerability and increasing H. pylori eradication rates was demonstrated in a recent controlled trial. The effectiveness of H. pylori eradication in the group of patients taking S. boulardii CNCM I-745 at a dose of 500 mg per day was significantly higher than that in the control group (86.0 and 74.7 %, respectively; p = 0.02). Compared with the control group, patients in the main group experienced significantly less undesirable side effects of eradication (17.0 % vs. 55.7 %; p < 0.001), including the development of diarrhea associated with taking systemic antibacterial drugs (2.0 % vs. 46.4 %; p = 0.02), and also showed higher adherence to treatment. In the main group, 95.0 % of patients completed the full course of therapy, in the control group — 91.2 % (p < 0.001) [71]. A meta-analysis of 18 studies (n = 3592) showed that when S. boulardii was added to eradication therapy, the risk of total adverse events was 53 % lower than without S. boulardii (RR = 0.47; 95% CI: 0.36–0.61), the incidence of diarrhea is 67 % lower (RR = 0.37; 95% CI: 0.23–0.57), and the achievement of successful eradication is higher (RR = 1.09; 95% CI: 1.05–1.13) [61].

According to the results of the meta-analysis, the effectiveness of some drugs containing Lactobacillus acidophilus LA-5 and Bifidobacterium animalis subsp lactis BB-12 (mainly in functional foods) is also noted in reducing the total number of adverse events (RR = 0.31; 95% CI: 0.20–0.47), preventing diarrhea associated with systemic antibacterial drugs (RR = 0.38; 95% CI: 0.20–0.72) and improved outcomes of H. pylori eradication (RR = 1.16; 95% CI: 1.05–1.28) [62].

• For patients with peptic ulcer and positive test results for *H. pylori* infection during eradication therapy, it is recommended to prescribe metabiotics (postbiotics) to increase the effectiveness and tolerability of treatment [72–74].

Grade of recommendations — B;
level of evidence — 2.

Comment. Metabiotics (postbiotics) include non-viable bacteria or their components, as well as products of microbial metabolism that are active in relation to the human body [72, 73]. The effectiveness of metabiotics in eradicating H. pylori infection was demonstrated in a multicenter randomized clinical trial involving 90 adult patients with gastritis and gastric ulcers. A significant improvement in the outcomes of standard triple eradication therapy was shown when a metabiotic containing inactivated Lactobacillus reuteri DSM 17648 at a dose of 1 × 10^{10} CFU 2 times a day was included in the treatment regimen (p = 0.024). According to the results of the ^{13}C-urease breath test, successful eradication was achieved in 86.7 % of those taking the metabiotic and in 66.67 % of patients in the control group who were treated only with components of the triple treatment regimen. Patients receiving the metabiotic were less likely to experience such treatment side effects as nausea (60 % vs. 86.67 %; p = 0.033), diarrhea (36.6 % vs. 50 %; p = 0.035), constipation (20 % vs. 33.3 %; p = 0.026) and taste disturbance (43.3 % vs. 60 %; p = 0.047), but bloating was more common (40 % vs. 13.3 %; p < 0.001) [74].

• In patients with laboratory and endoscopically confirmed ulcer bleeding, intravenous administration of PPI is recommended in order to stop it and prevent relapse as part of other measures to achieve hemostasis [75].

Grade of recommendations — A;
level of evidence — 1.

*Comment. The use of PPIs helps stop ulcer bleeding and reduce the risk of recurrent bleeding [24]. In this case, 80 mg of esomeprazole** is administered simultaneously intravenously as a bolus, followed by a continuous intravenous infusion of this drug (at a dose of 8 mg per hour) for 72 hours [76]. One recent meta-analysis found that intravenous PPIs significantly reduced the risk of rebleeding (OR = 2.24; 95% CI: 1.02–4.90) [31]. After transferring the patient to oral medication, eradication therapy is carried out.*

In addition to esomeprazole, lansoprazole can be used to stop ulcer bleeding. Intravenous administration of lansoprazole has been shown to be highly effective and well tolerated in the treatment of upper gastrointestinal bleeding caused by peptic ulcers and erosive gastritis [77]. Lansoprazole is used for short-term treatment (up to 7 days) in the form of a 30-minute intravenous infusion of 30 mg 2 times a day, followed by transfer to oral administration.

3.3. Endoscopic treatment

• If bleeding from an ulcer continues (FIa, FIb), it is recommended to stop the bleeding using endoscopic hemostasis methods [23, 78–80].

Grade of recommendations — A;
level of evidence — 2.

Comment. A number of studies confirm that performing therapeutic endoscopy to stop ulcer bleeding significantly reduces mortality, the need for surgical intervention, the risk of recurrent bleeding, as well as the time of ongoing bleeding in comparison with "isolated"

pharmacotherapy [25]. According to the literature, endoscopic bleeding control is the "gold standard" in the treatment of patients with ulcer bleeding. Timely and correct endoscopic assistance allows achieving stable hemostasis in 89–92 % of cases.

The rules for making a difficult decision on stopping endoscopic hemostasis in the event of intense ongoing bleeding cannot be prescribed with mathematical precision. Just as in any difficult clinical situation the doctor should be guided by the principle of "do no harm," so in the process of endoscopic hemostasis one should be guided by the principle of "do not overextend." Endoscopic hemostasis should be stopped when the possibilities currently available in the clinic for its implementation have been exhausted; when reasonable time limits have been exhausted (time limits mainly depend on the intensity of bleeding and the adequacy of blood loss replacement); when a relatively compensated patient shows clear signs of hemodynamic instability and, finally, when the performer himself has lost confidence in success. Organizationally, this decision is made jointly by the surgeon in charge, anesthesiologist and endoscopist, with the primacy and casting vote of the surgeon.

• In case of stopped ulcerative gastroduodenal hemorrhage (UGDH) with the presence of highly significant stigmas (traces) of previous bleeding at the bottom of the ulcer (FIIa — exposed visible vessel; FIIb — fixed thrombus-clot), it is recommended to perform endoscopic prevention of recurrent bleeding [78–80].

Grade of recommendations — B; level of evidence — 2.

Comment. If a blood clot is detected in the ulcer bed, it should be removed using targeted washing, and then a targeted effect should be applied to the underlying vessel — the direct source of the bleeding. If the patient has an indelible clot (FIIb), that is, fixed to a vessel at the bottom of the ulcer, it is advisable to remove it using the "guillotine method" — by cutting it off at the base with a polypectomy loop (without using or using an electrocoagulation unit) and then act through the endoscope on the underlying vessel — the direct source of the bleeding.

• In case of stopped UGDH with absence (FIII) or with insignificant stigmas (traces) of previous bleeding at the bottom of the ulcer (FIIc), endoscopic prevention of recurrent bleeding is not recommended [78–80].

Grade of recommendations — A; level of evidence — 1.

Comment. An important condition for refusing to perform endoscopic hemostasis for UGDH FIIc is the guaranteed provision of adequate drug prevention of recurrent bleeding after performing endoscopy.

• To perform endoscopic hemostasis and prevent recurrent bleeding during in UGDH, it is recommended to use mechanical (clipping), thermal (hydro-mono-/bi-/multipolar, argon plasma coagulation) and injection (sclerosants — polidocanol) methods — in isolated form or in combination with injections epinephrine solution** [23, 78–80].

Grade of recommendations — A; level of evidence — 1.

*Comment. Epinephrine** injections as monotherapy do not provide the necessary effectiveness and should be used in combination with other methods of endoscopic hemostasis. None of the thermal coaptive methods of endoscopic hemostasis has advantages over others. As an addition to combined endoscopic hemostasis, local agents can be used — hemostatic liquids and powders.*

• Repeated control endoscopic examination/intervention is recommended in case of incomplete initial examination/hemostasis and in patients with a high risk of recurrent bleeding [81].

Grade of recommendations — A; level of evidence — 1.

Comment. Routine endoscopic surveillance is not recommended in all patients with UGDH. The timing of repeated endoscopic examination/intervention is determined by the main task facing it. If the initial examination/hemostasis is incomplete, a repeat endoscopic examination is recommended to be performed in the coming hours after the first endoscopy after eliminating the reasons that prevented a full intervention (emptying of the stomach from clots and blood; adequate staffing, hardware, instrumental support, anesthesia). If a high risk of recurrent bleeding is determined, it is advisable to perform a control endoscopy and, if necessary, repeated endoscopic intervention the next morning/day after the initial intervention. Performing repeat EGD in patients with a low risk of recurrent bleeding does not affect the rate of recurrent bleeding and is not economically feasible [22, 82, 83].

• If bleeding recurs in the hospital, in most cases it is recommended to perform repeated endoscopic hemostasis [81].

Grade of recommendations — A; level of evidence — 2.

• After successfully diagnosing the source, stopping and/or preventing bleeding using a combination of clinical and endoscopic parameters, it is recommended to assess the risk of UGDH recurrence as high or low [78, 79].

Grade of recommendations — A; level of evidence — 2.

Comment. It is advisable to assess the risk of recurrence of UGDH immediately after completion of emergency endoscopy and document it in the report of the responsible surgeon. The criteria for a high risk of recurrent bleeding are clinical (history of collapse, severe blood loss, severe concomitant pathology) and laboratory signs, reflecting mainly the intensity of bleeding, as well as endoscopic signs (FIA-B, FIIA-B, depth, size and location of the ulcer), primarily giving an idea of the diameter of the bleeding vessel and bleeding activity. According to a systematic review by B.J. Elmunzer et al. [81], risk factors for recurrent bleeding are large size of the ulcer (more than 1 cm in diameter), location of the ulcer on the lesser curvature of the stomach and on the posterior wall of the duodenum, as well as unstable hemodynamics — a decrease in blood pressure during bleeding with its subsequent increase during replenishment of circulating blood volume. It is also important to note that taking anticoagulants and antiplatelet agents significantly increases the risk of developing ulcer bleeding, including recurrent bleeding, as well as a sharp increase in blood pressure (for example, as a reaction to pain or due to a missed dose of an antihypertensive drug). To assess the risk of relapse of UGDH and determine further treatment tactics, the repeatedly validated Rockall score (Appendix D6) can be used, which takes into account and ranks all significant clinical (age, hemodynamic shock, concomitant diseases) and endoscopic (source and stigmata of the gastrointestinal bleeding) signs that are taken into account when predicting recurrence of bleeding and the likelihood of an unfavorable outcome. The size, depth, including signs of penetration, as well as the localization of the ulcerative defect in the stomach along the lesser curvature, and in the duodenum along the posterior wall, are indirectly taken into account in the "Stigma of recent gastrointestinal bleeding" indicator of the Rockall score.

3.4. Endovascular treatment

• Transcatheter angiographic embolization of the arteries of the stomach and duodenum is recommended as an alternative to surgical treatment for repeatedly recurrent UGDH, resistant to endoscopic and drug hemostasis [81, 83].

Grade of recommendations — A; level of evidence — 1.

Comment. There are no recommendations for prophylactic (before the development of recurrent bleeding) embolization of the arteries of the stomach and duodenum in high-risk patients, and this issue is under study.

3.5. Surgical treatment

• Patients with complicated forms of gastric and duodenal ulcers (bleeding, perforation, etc.) are recommended to be hospitalized for the purpose of surgical treatment in a surgical hospital [18, 22, 23, 82, 84, 85].

Grade of recommendations — C; level of evidence — 5.

Comment. Patients suffering from a complicated course of peptic ulcer usually need to be hospitalized as an emergency. It is advisable to begin treatment of ulcer bleeding in the intensive care unit. The main goal of treatment in the intensive care unit is to stabilize the patient's condition — replenishment of circulating blood volume, combating the manifestations of hypovolemic shock, adequate pain relief, treatment of decompensated concomitant diseases and systemic inflammatory response syndrome, after which endoscopic, endovascular and surgical treatment methods can be used according to indications [10, 22, 82, 86, 87]. It is important to note that in case of ulcerative bleeding, the risk of death of a comorbid patient directly correlates with the number of concomitant diseases [88]. This, in turn, requires the doctor to be very careful when working with comorbid patients and to analyze all risk factors for the development of complications of ulcerative disease before their implementation [89].

• For patients with ongoing or recurrent ulcer bleeding with ineffectiveness (or impossibility) of endoscopic and endovascular hemostasis, as well as with a combination of bleeding and ulcer perforation, emergency surgical intervention is recommended [10, 22, 82, 90].

Grade of recommendations — C;
level of evidence — 5.

Comment. Surgical treatment of patients with ulcerative bleeding is indicated in cases where it is not possible to control it endoscopically (if bleeding continues or if it recurs). Untimely surgical treatment worsens the patient's prognosis and increases the risk of death. Surgery is necessary to achieve reliable hemostasis and reduce the risk of recurrent bleeding. The extent of the proposed operation depends on the patient's condition, but it is important to remember that the surgical intervention should be as gentle as possible. In patients at high risk of surgical intervention, it is preferable to perform X-ray endovascular selective angiography followed by occlusion of the bleeding vessel. According to foreign recommendations, the most preferable is to perform gastrotomy (pyloroduodenotomy) with suturing of the bleeding vessel and suturing of the ulcer, however, this method is inferior in its reliability to resection operations [10]. The best results in the treatment of refractory complicated ulcers were observed when combining gastric resection with gastrojejunostomy and vagotomy [91], however, in foreign literature, vagotomy is considered a complex, limitedly applicable option, for the full recognition of which studies of a high level of evidence must be conducted [83]. The Russian scientific surgical community recommends performing vagotomy, while limiting the indications for its implementation [23].

• For patients with perforated gastric and/or duodenal ulcers, emergency surgery is recommended to eliminate the perforation [18, 82, 92].

Grade of recommendations — B;
level of evidence — 2.

Comment. Ulcer perforation is a common complication that inevitably leads to the development of peritonitis and has a high mortality rate among patients, reaching 30 %. The highest mortality rate is observed among elderly patients, as well as in the group of patients with late hospitalization (more than 24 hours from the development of this complication). Laparotomic access has no advantages over laparoscopic. It is preferable to perform laparoscopic intervention — suturing the perforation with sanitation and drainage of the abdominal cavity [18, 82, 92]. However, the clinical picture of such a serious complication can be very diverse, and experts recognize that the extent of the operation depends primarily on the patient's condition [92]. Russian clinical guidelines for the treatment of perforated ulcers discuss surgical treatment options in more detail [84]. (For more details, see Clinical Recommendations of the Russian Society of Surgeons "Perforate ulcer" Approved by the Ministry of Health of Russia on June 22, 2021).

• Patients with peptic ulcer after surgical treatment are recommended to perform diagnostic studies aimed at identifying *H. pylori* (see section on diagnostics) and conduct eradication and maintenance therapy to prevent relapses of ulcer and its complications [22, 93, 94].

Grade of recommendations — A;
level of evidence — 1.

Comment. The completed stage of surgical treatment does not reduce the risk of developing a new round of surgical complications of peptic ulcer disease, primarily bleeding, so it is important to continue the course of conservative treatment of the disease until the patient is completely cured.

• In patients with pyloroduodenal stenosis, endoscopic balloon dilatation is recommended to eliminate it. If it is ineffective, pyloroplasty and drainage operations are recommended [82].

Grade of recommendations — C;
level of evidence — 5.

Comment. Indications for surgical treatment of patients with pyloroduodenal stenosis are determined by the degree of its compensation, as well as the condition of the patients. Endoscopic balloon dilatation is possible only in patients with subcompensated stenosis and with scar localization along the anterior wall of the duodenum. This endoscopic approach often brings temporary success and is accompanied by a high rate of recurrence of stenosis.

4. Medical rehabilitation, medical indications and contraindications for the use of rehabilitation methods

• For patients with gastric and duodenal ulcers in remission, to preserve it, sanatorium treatment is recommended in sanatorium-resort organizations in the climatic zone of the patient's residence [5].

Grade of recommendations — C;
level of evidence — 5.

Comment. For patients with peptic ulcer, 2–3 months after the exacerbation subsides, sanatorium-resort treatment lasting 14–21 days is recommended. Sanatorium-resort

treatment is carried out in the sanatoriums of Dorokhovo, Essentuki, Zheleznovodsk, etc., and includes mud and peat therapy, pine-sea baths, drinking alkaline mineral waters [5].

5. Prevention and clinical observation, medical indications and contraindications for the use of prevention methods

• All patients with *H. pylori* infection, in the absence of contraindications, are recommended to undergo eradication therapy to prevent ulcer disease and its exacerbations [95].

Grade of recommendations — C; level of evidence — 5.

Comment. Confirmation of the leading role of H. pylori infection in the development of peptic ulcer disease has made eradication therapy the main method of preventing this disease.

• Clinical observation of patients with gastric and duodenal ulcers is recommended to be carried out annually for 5 years from the moment of the last exacerbation [5].

Grade of recommendations — C; level of evidence — 5.

6. Organization of medical care

Indications for planned hospitalization of patients with gastric and duodenal ulcers are a pronounced clinical picture of the disease with persistent (more than 7 days) pain syndrome, the presence of ulcerations in the stomach requiring a differential diagnosis between benign ulcers and gastric cancer, exacerbation of peptic ulcer with a history of complications, peptic ulcer with concomitant diseases [95].

The duration of inpatient treatment for patients with exacerbation of peptic ulcer disease should, on average, be 10 days.

Indications for emergency hospitalization are the presence of signs of gastric bleeding, perforation and penetration of the ulcer.

Patients with uncomplicated exacerbation of gastric and duodenal ulcers are subject to treatment on an outpatient basis.

Patients with exacerbation of peptic ulcer disease are provided with specialized medical care both in outpatient and inpatient settings, in accordance with the standard of specialized medical care for gastric and duodenal ulcers.

All patients with signs of acute gastrointestinal bleeding or with reasonable suspicion of such are subject to immediate referral to hospitals that are fully prepared for the reception and treatment of patients of this profile organizationally, personnel and logistically. In large cities, it is advisable to refer patients with gastrointestinal bleeding to multidisciplinary hospitals or to specialized centers for the treatment of gastrointestinal bleeding.

Each clinic providing care to patients with acute ulcerative hyperplasia should have a protocol for the multidisciplinary management of such patients. The protocol for diagnosing and treating patients should be based on national clinical guidelines and consider the peculiarities of the structure of emergency care and the equipment of a particular medical institution.

In a clinic providing care to patients with acute ulcerative gastroduodenal bleeding, modern endoscopic video equipment, instruments and personnel proficient in the basic methods of diagnostic and therapeutic endoscopy should be available at any time of the day, as well as highly qualified surgical, resuscitation and anesthesiology and, if possible, X-ray intervention service.

All patients with acute gastrointestinal bleeding should be hospitalized in a surgical hospital or intensive care unit.

Patients with moderate to severe ulcerative gastroduodenal bleeding, a high risk of recurrent bleeding, and the presence of concomitant pathologies should be treated in hospital until the threat of relapse of ulcerative gastrointestinal tract is removed, complete correction of acute post-hemorrhagic disorders and compensation of concomitant diseases are performed, but not less than 4 days.

In compliant patients with mild ulcerative gastroduodenal bleeding, a low risk of recurrent bleeding, and the absence of concomitant pathology, discharge from the hospital is possible in the early stages (the first or second day) from admission.

7. Additional information (including factors that influence the outcome of the disease or condition)

7.1. Features of the course of peptic ulcer disease in certain groups of patients

7.1.1. Features of the course of peptic ulcer disease during pregnancy

The course of peptic ulcer disease during pregnancy generally differs little from that in non-pregnant women. The diagnosis is established on the basis of clinical manifestations,

anamnestic data, results of endoscopy and ultrasound examination of the abdominal organs [96]. X-ray examination of the stomach and duodenum is contraindicated for pregnant women.

In diagnostically unclear cases, if complications are suspected (bleeding, stenosis of the antrum, cancer), EGD, due to its safety for the fetus, can be performed at any stage of pregnancy [97]. To exclude occult bleeding, feces are examined for occult blood and a general (clinical) blood test.

Differential diagnosis of exacerbation of peptic ulcer must be carried out with erosive gastroduodenitis, pancreatitis, diseases of the biliary tract, acute appendicitis and early toxicosis — vomiting of pregnant women. A stenosing ulcer of the gastric antrum can simulate excessive vomiting of pregnancy. Early toxicosis is characterized by painful, almost constant nausea, aggravated by various odors, and drooling. In this case, vomiting occurs regardless of food, especially in the morning; abdominal pain, as a rule, is absent. Bleeding caused by peptic ulcer must be differentiated from that caused by erosive gastritis, Mallory — Weiss syndrome, stomach cancer, and bleeding from the respiratory tract.

Pregnancy has a beneficial effect on the course of peptic ulcer disease; 75–80 % of women experience remission of the disease, and it does not have a noticeable effect on its outcome. However, some patients may experience an exacerbation. This is most often observed in the first trimester of pregnancy (14.8 %), in the third one (10.2 %), 2–4 weeks before the due date or during early postpartum period. Uncomplicated peptic ulcer disease does not have a negative effect on fetal development.

Treatment includes adherence to generally accepted "regime" activities and diet, taking in usual therapeutic doses of adsorbent intestinal drugs (for example, dioctahedral smectite**). If there is no effect, H_2-histamine receptor blockers are prescribed.

For severe pain caused by motor disorders, it is possible to prescribe papaverine derivatives (drotaverine** 40 mg 3–4 times a day, if the benefit to the mother outweighs the potential risk to the fetus) and stimulants of gastrointestinal motility (it is possible to use metoclopramide in II and III trimesters of pregnancy 5–10 mg 2–3 times a day). Bismuth tripotassium dicitrate** is contraindicated for pregnant women. Eradication therapy for *H. pylori* infection is not carried out in pregnant women.

7.1.2. Features of the course of ulcerative disease in elderly and senile people

In the development of gastroduodenal ulcers in elderly patients, in addition to *H. pylori* infection and the acid-peptic factor, atherosclerotic changes in gastric vessels, some underlying diseases (for example, chronic nonspecific lung diseases) that reduce the protective properties of the gastric mucosa, and the use of medications (primarily non-steroidal anti-inflammatory and anti-rheumatic drugs) that have an ulcerogenic effect may also play a role.

Gastroduodenal ulcers in elderly and senile patients are localized mainly in the stomach (along the lesser curvature of the body or in the subcardial region), are sometimes very large in size, often occur with blurred and vague clinical symptoms, and are prone to the development of complications (primarily gastrointestinal bleeding). When ulcers in the stomach are detected in elderly patients, it is important to carry out a differential diagnosis with the infiltrative-ulcerative form of gastric cancer.

Gastroduodenal ulcers in elderly and senile people are characterized by slow scarring. Caution should be exercised when administering drug therapy, given the higher risk of side effects in elderly patients compared to young and middle-aged patients.

Criteria for assessing the quality of medical care

Quality criteria	Level of evidence	Grade of recommendations
EGD was performed	C	5
A biopsy was taken from the ulcer when it was localized in the stomach	C	5
A study of serum gastrin levels was performed in frequently relapsing (more than twice a year) course of peptic ulcer disease	C	5
Diagnostic tests aimed at identifying *H. pylori* were performed (^{13}C-breath urease test or rapid urease test (CLO test) or determination of *H. pylori* antigen in stool)	B	2
Eradication of *H. pylori* infection was carried out according to 1st line regimens (PPI, clarithromycin** and amoxicillin**, quadruple therapy with bismuth tripotassium dicitrate**) or 2nd line (quadruple therapy with bismuth tripotassium dicitrate** or triple therapy with #levofloxacin**)	B	2
Emergency EGD for ulcerative gastrointestinal bleeding was performed after adequate preparation, with anesthesia, in parallel with infusion-transfusion therapy, in a timely manner	A	1
Ulcerative gastroduodenal bleeding was stopped and/or its recurrence was prevented using endoscopic and/or drug hemostasis methods	A	1
Emergency endovascular or surgical intervention was performed if endoscopic hemostasis was ineffective or impossible	A	1
Emergency surgery was performed for perforation of a gastric and/or duodenal ulcer	B	2
Diagnostic studies aimed at identifying *H. pylor*i were performed, eradication and maintenance therapy was carried out after surgical treatment	A	1

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Appendix A. Reference materials, including compliance with indications for use and contraindications, methods of use and doses of drugs, instructions for use of the drug

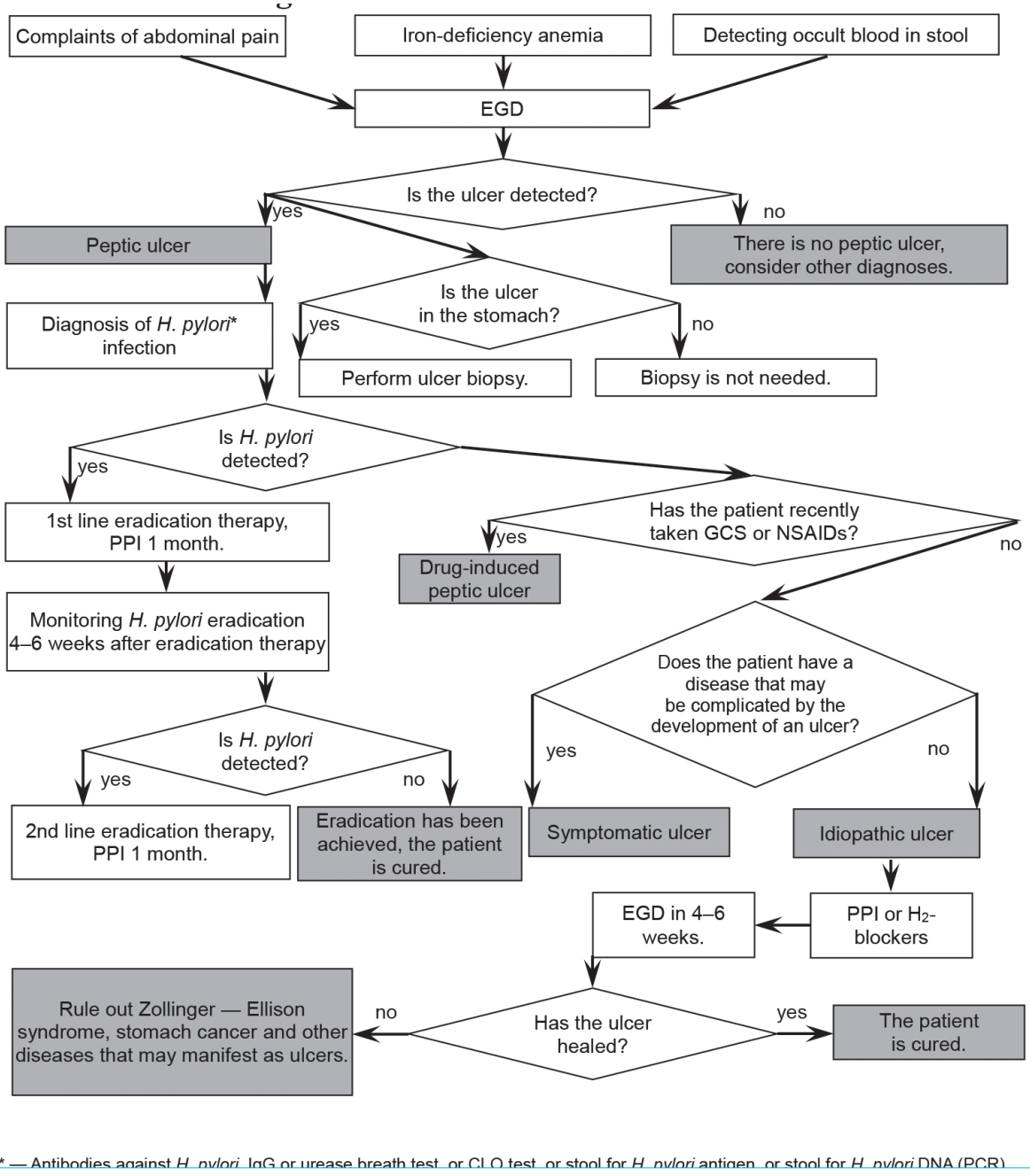
These clinical recommendations have been developed taking into account the following regulatory documents:

1. Order of the Ministry of Health of the Russian Federation dated November 12, 2012 No. 906н "On approval of the Procedure for providing medical care to the population in the field of gastroenterology".

2. Order of the Ministry of Health of the Russian Federation dated May 10, 2017 No. 203н "On approval of criteria for assessing the quality of medical care".

3. Order of the Ministry of Health of the Russian Federation dated June 10, 2021 No. 611н "On approval of the standard of medical care for adults with peptic ulcer disease (diagnosis and treatment)".

Appendix B. Doctor's action algorithm



* — Antibodies against *H. pylori* IgG or urease breath test or CLO test or stool for *H. pylori* antigen or stool for *H. pylori* DNA (PCR)

Appendix C. Information for a patient

The main factor causing peptic ulcer disease is currently recognized as a microorganism called *Helicobacter pylori*. Therefore, every patient diagnosed with a peptic ulcer should be examined for the presence of this infection. If it is confirmed, it is necessary to carry out treatment aimed at destroying these bacteria (eradication), followed by monitoring after 4–6 weeks. If the first course of eradication is ineffective, a second course of therapy should be carried out with a different drug regimen. It is important to adhere to treatment and strictly monitor medication intake. A patient with a peptic ulcer must follow a diet (frequent, small meals, chemically, mechanically and thermally gentle food), and be very careful when taking drugs that have a damaging effect on the mucous membrane of the stomach and duodenum (acetylsalicylic acid, non-steroidal anti-inflammatory drugs). If it is necessary to take them, a mandatory "cover" of drugs that protect the mucous membrane of the stomach and duodenum is recommended.

Appendix D. Rating scales, questionnaires and other assessment tools for the patient's condition given in clinical guidelines

Appendix D1. Severity of blood loss (Gorbashko A.I., 1982)

Blood loss rate	Degree of blood loss		
	mild	average	severe
Red blood cell count	> 3.5×10^{12}/L	2.5–3.5 × 10^{12}/L	< 2.5×10^{12}/L
Hemoglobin level, g/L	> 100	83–100	< 83
Pulse rate per minute	< 80	80–100	> 100
Systolic blood pressure (mmHg)	> 110	110–90	< 90
Hematocrit number, %	> 30	25–30	< 25
Deficiency of globular volume, % of the expected	≤ 20	20–30	≥ 30

Appendix D2. ACS (American College of Surgeons) blood loss severity scale

Parameter	Class 1 "Mild blood loss"	Class 2 "Moderate blood loss"	Class 3 "Moderately severe blood loss"	Class 4 "Severe blood loss"
Approximate blood loss, mL (% of total blood volume)	**< 750 (< 15 %)**	**750–1000 (15–30 %)**	**1500–2000 (30–40 %)**	**> 2000 (> 40 %)**
Heart rate (bpm)	N	N / ↑	↑	↑ / ↑↑
Blood pressure	N	N	N / ↓	↓↓
Pulse pressure	N	↓	↓	↓
Capillary refill time ("spot symptom")	N	↑	↑	↑↑
Breathing rate	N	N	N / ↑	↑
Diuresis (mL/hour)	N	N	↓	↓↓
Glasgow Coma Scale	N	N	↓	↓
Base excess (BE), mmol/L	0–2	–2–6	–6–10	less than – 10
Requirement for blood components	Observation	Possible	Necessary	Massive blood loss protocol

Note. N — norm; ↑ — increase; ↓ — decrease; ↑↑ — significant increase; ↓↓ — significant decrease.

Appendix D3. AIMS65 scale

Feature	Value	Points
Albumin (g/dL)	< 3.0	1
INR	> 1.5	1
Mental status	Modified	1
Age	> 65	1
Systolic blood pressure	< 90	1

In the absence of the above risks, in-hospital mortality is 0.3 % compared to 31.8 % in patients with a score of 5.

Appendix D4. Glasgow-Blatchford bleeding score (2000)

Signs of risk on admission	Points
Blood urea, mmol/L	
6.5–7.9	2
8.0–9.9	3
10.0–24.9	4
≥ 25.0	6
Hemoglobin in men, g/L	
120–129	1
100–119	3
< 100	6
Hemoglobin in women, g/L	
100–119	1
< 100	6
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
< 90	3
Other signs	
Pulse ≥ 100 per minute	1
Presence of melena	1
Loss of consciousness	2
Presence of liver diseases	2
Heart failure	2

Scores > 6 are associated with more than twice the risk of requiring endoscopic, endovascular, or surgical intervention.

Appendix D5. Endoscopic classification of the source of ulcerative bleeding according to J. Forrest (1974)

- F1 — bleeding from the ulcer continues at the time of endoscopic examination:
  - F1a — ongoing jet arrosive bleeding, often pulsating;
  - F1b — ongoing bleeding, in the form of diffuse seepage/leakage of blood (usually from small capillaries).
- F2 — at the time of endoscopic examination, bleeding from the ulcer had stopped; at the bottom of the ulcerative defect, stigmas (traces) of previous bleeding are visible:

○ F2a — at the bottom of the ulcer, a naked (clearly visible) large thrombosed vessel is determined, usually in the form of a grayish-pink column;
○ F2b — at the bottom of the ulcer, a fixed thrombus-clot is detected, which cannot be washed away/removed with a directed stream of liquid through an endoscope;
o F2c — at the bottom of the ulcer, colored (red, burgundy-brown, black) flat pinpoint spots are identified, which are small thrombosed vessels.
● F3 — at the time of endoscopic examination, bleeding from the ulcer had stopped; at the bottom of the ulcerative defect, which served as the source of the bleeding, no stigmas (traces) of this bleeding were found (the ulcerative crater is covered with "pure" fibrin).

Appendix D6. Rockall Risk Scoring System* (1996)

Parameter	Points			
	0	1	2	3
Age (years)	< 60	60–79	≥ 80	
Shock	No shock	Tachycardia	Hypotension	
Heart rate (bpm)	< 100	≥ 100	–	
Systolic BP	≥ 100 mmHg	≥ 100	< 100 mmHg	
Comorbidities	Absent	–	IHD, heart failure, other "serious" diseases	Renal, liver failure, disseminated malignant tumors
Diagnosis	Mallory – Weiss syndrome or absence of lesions and stigmata of the gastrointestinal tract	All other diagnoses	Malignant tumors of the upper digestive tract	–
Stigma of recent gastrointestinal bleeding	Absent or there are dark spots at the bottom of the ulcer	–	Blood in the upper digestive tract, fixed clot, visible vessel, or streak bleeding	–

Note: * System for assessing the risk of recurrence of gastrointestinal bleeding and the likelihood of death in patients with bleeding from the upper digestive tract. Total score: 0–2 — minimal risk of relapse (< 6 %), mortality is < 2 %; 3–7 — high risk of relapse (< 40 %, mortality is < 40 %; ≥ 8 — patients in critical condition, risk of relapse is ≥ 40 %, mortality is ≥ 40 %.

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