https://doi.org/10.22416/1382-4376-2024-34-5-111-135
UDC 616.329-002-008.6-07/-08

Diagnosis and Treatment of Gastroesophageal Reflux Disease (Clinical Guidelines of the Russian Gastroenterological Association, Russian Scientific Medical Society of Internal Medicine, Russian Society for the Prevention of Noncommunicable Diseases, Scientific Community for Human Microbiome Research)

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Aim. These recommendations are developed for practitioners in order to familiarize them with modern diagnostic methods, management features and pharmacotherapy of patients with gastroesophageal reflux disease (GERD).
General provisions. GERD is the most common reason for patients to visit clinics. There are esophageal and extraesophageal manifestations of GERD. Patients' complaints of heartburn and regurgitation remain the most sensitive and specific clinical manifestations of GERD. The diagnosis of GERD is established on the basis of anamnestic data, instrumental examination (detection of reflux esophagitis during upper gastrointestinal endoscopy, detection of pathological gastroesophageal reflux with 24-hour pH-metry or/and 24-hour pH-impedance monitoring). Patients with suspected GERD and the absence of erosive and ulcerative changes in the mucous membrane of the esophagus or the presence of erosive esophagitis of Grade A according to Los Angeles Classification of Gastroesophageal Reflux Disease are recommended to conduct 24-hour pH-metry on PPI off to exclude or confirm the diagnosis

of GERD. Patients with extraesophageal manifestations of GERD without classic symptoms (heartburn, regurgitation) are recommended to undergo 24-hour pH-impedance monitoring with discontinuation of proton pump inhibitor therapy. When deciding on surgical treatment, all patients need to perform high-resolution esophageal manometry and 24-hour pH-impedance monitoring. Complications of GERD include bleeding, strictures, Barrett's esophagus and esophageal adenocarcinoma. The main groups of medications used in the treatment of GERD are proton pump inhibitors (PPIs), potassium-competitive acid blockers (P-CABs), alginates, antacids, and prokinetics. PPIs are the drugs of choice in the treatment of both symptoms of gastroesophageal reflux disease and existing erosive esophagitis. Combination therapy Rebamipide with PPIs increases the effectiveness of relief of GERD symptoms, as well as reduces the frequency of relapses.

Conclusion. These clinical recommendations will improve the quality of medical care for patients with GERD.

Keywords: gastroesophageal reflux disease, gastroesophageal reflux, extraesophageal manifestations, Barrett's esophagus, high-resolution esophageal manometry, 24-hour pH-impedance monitoring

Conflict of interest: the authors declare no conflict of interest.

For citation: Ivashkin V.T., Trukhmanov A.S., Maev I.V., Drapkina O.M., Livzan M.A., Martynov A.I., Lapina T.L., Paraskevova A.V., Andreev D.N., Alexeeva O.P., Alekseenko S.A., Baranovsky A.Yu., Zayratyants O.V., Zolnikova O.Yu., Dronova O.B., Kliaritskaia I.L., Korochanskaya N.V., Kucheryavy Yu.A., Rumyantseva D.E., Mammaev S.N., Osipenko M.F., Pirogov S.S., Poluektova E.A., Saifutdinov R.G., Storonova O.A., Uspenskiy Yu.P., Khlynov I.B., Tsukanov V.V., Sheptulin A.A. Diagnosis and Treatment of Gastroesophageal Reflux Disease (Clinical Guidelines of the Russian Gastroenterological Association, Russian Scientific Medical Society of Internal Medicine, Russian Society for the Prevention of Noncommunicable Diseases, Scientific Community for Human Microbiome Research). Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2024;34(5):111–135. https://doi.org/10.22416/1382-4376-2024-34-5-111-135

Диагностика и лечение гастроэзофагеальной рефлюксной болезни (Рекомендации Российской гастроэнтерологической ассоциации, Российского научного медицинского общества терапевтов, Российского общества профилактики неинфекционных заболеваний, Научного сообщества по изучению микробиома человека)

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Цель. Настоящие рекомендации разработаны для практикующих врачей с целью их ознакомления с современными методами диагностики, особенностями ведения и фармакотерапии пациентов с гастроэзофагеальной рефлюксной болезнью (ГЭРБ).

Основные положения. ГЭРБ является наиболее частой причиной посещения пациентами поликлиник. Выделяют пищеводные и внепищеводные проявления ГЭРБ. Жалобы пациентов на изжогу и регургитацию остаются наиболее чувствительными и специфичными клиническими проявлениями ГЭРБ. Диагноз ГЭРБ устанавливается на основании анамнестических данных, инструментального обследования (обнаружение рефлюкс-эзофагита при эндоскопическом исследовании пищевода, выявление патологического гастроэзофагеального рефлюкса при pH-метрии и/или pH-импедансометрии). Пациентам с подозрением на ГЭРБ и отсутствием эрозивно-язвенных изменений слизистой оболочки пищевода или наличием эрозивного эзофагита степени А по Лос-Анджелесской классификации по данным эзофагогастродуоденоскопии рекомендовано проведение суточной pH-метрии на фоне отмены ингибиторов протонной помпы для исключения или подтверждения диагноза ГЭРБ. Пациентам с внепищеводными проявлениями ГЭРБ без классических симптомов (изжога, регургитация) рекомендовано проведение суточной pH-импедансометрии с отменой терапии ингибиторами протонной помпы. При решении вопроса о хирургическом лечении всем пациентам необходимо проведение манометрии пищевода высокого разрешения и суточной pH-импедансометрии. К осложнениям ГЭРБ относят кровотечения, стриктуры, пищевод Баррета и аденокарциному пищевода. Основными группами препаратов, используемых в лечении ГЭРБ, являются ингибиторы протонной помпы, калий-конкурентные блокаторы протонной помпы, альгинаты, антациды, прокинетики. Ингибиторы протонной помпы являются препаратами выбора при лечении и симптомов гастроэзофагеальной рефлюксной болезни, и имеющегося эрозивного эзофагита. Комбинированная терапия ребамипидом с ингибиторами протонной помпы повышает эффективность купирования симптомов ГЭРБ, а также сокращает частоту рецидивов.

Заключение. Настоящие клинические рекомендации позволят улучшить качество оказания медицинской помощи пациентам с ГЭРБ.

Ключевые слова: гастроэзофагеальная рефлюксная болезнь, гастроэзофагеальный рефлюкс, внепищеводные проявления, пищевод Баррета, манометрия пищевода высокого разрешения, суточная pH-импедансометрия

Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Ивашкин В.Т., Трухманов А.С., Маев И.В., Драпкина О.М., Ливзан М.А., Мартынов А.И., Лапина Т.Л., Параскевова А.В., Андреев Д.Н., Алексеева О.П., Алексеенко С.А., Барановский А.Ю., Зайратьянц О.В., Зольникова О.Ю., Дронова О.Б., Кляритская И.Л., Корочанская Н.В., Кучерявый Ю.А., Маммаев С.Н., Осипенко М.Ф., Пирогов С.С., Полуэктова Е.А., Румянцева Д.Е., Сайфутдинов Р.Г., Сторонова О.А., Успенский Ю.П., Хлынов И.Б., Цуканов В.В., Шептулин А.А. Диагностика и лечение гастроэзофагеальной рефлюксной болезни (Рекомендации Российской гастроэнтерологической ассоциации, Российского научного медицинского общества терапевтов, Российского общества профилактики неинфекционных заболеваний, Научного сообщества по изучению микробиома человека). Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2024;34(5):111–135. https://doi.org/10.22416/1382-4376-2024-34-5-111-135

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)

Gastroesophageal reflux disease (GERD) is a chronic esophageal disorder characterized by a primary impairment of disorders in motor-evacuation function of the digestive tract, disorders of the function of the esophagogastric junction and the presence of pathological gastroesophageal reflux. Esophageal inflammation can be caused by the reflux either stomach or mixed, including duodenal contents. Clinical symptoms are formed as a result of the pathological effect of gastroesophageal reflux on the mucous membrane of the esophagus, that lead to inflammatory, dystrophic, erosive-ulcerative and metaplastic changes of the esophagus.

One of the most serious complications of GERD is multilayered squamous epithelium transitions into intestinal metaplasia (Barrett's esophagus). Barrett's esophagus (BE) is at high risk of progress to esophageal adenocarcinoma (EAC).

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

The pathogenesis of GERD is based on dysfunction of the esophagogastric junction in combination with impaired esophageal clearance. The integrity of the esophageal mucosa is determined by the balance between aggressive factors (frequent and/or prolonged gastroesophageal reflux (GER)) and the ability of the mucous membrane to counteract pathological GER [1].

The most common cause of GERD is transient lower esophageal sphincter relaxations (TLESRs) and delayed gastric emptying [9]. Abnormal relaxation of the esophagogastric junction is the reason of transient lower esophageal sphincter (LES) relaxations. Despite the fact that they are physiological in nature, an increase in the number of TLESRs in the postprandial period leads to the appearance of pathological GER in patients with GERD [10].

A hiatal hernia (HH) is an important pathogenetic factor in the development of GERD [1, 3]. The esophagogastric junction forms an antireflux barrier, represented by the smooth muscles of the LES and surrounded by the oblique muscles of the stomach. HH is a proximal displacement of the esophagogastric junction, increasing the failure of the antireflux barrier and the amount of GER. Moreover, patients with HH have disturbances of esophageal clearance, increase in the number and duration of TLERS, more often [11].

Esophageal clearance protects the esophageal mucosa from the pathological effects of GER. There are volume and chemical esophageal clearance. Volume clearance is the clearing of the mucous membrane from refluxate during esophageal peristalsis, and chemical clearance is due to the neutralizing effect of salivary bicarbonates [12].

Delayed gastric emptying leads to increase gastric distension and stomach pressure, which consequent TLESR events, which increase number of pathological GER [11].

Pathological GER causes the release of proinflammatory cytokines and chemokines, which contribute to the development of esophagitis and its clinical manifestations [1, 3]. In patients with reflux esophagitis, an increase in the expression of interleukin (IL)-1β, IL-8, and interferon-γ (IFN-γ) is observed [4]. Patients with high levels of IL-8 have a more "vivid" clinical and endoscopic picture of GERD [5].

An important element in the pathogenesis of GERD development is the violation of the mucous-epithelial barrier of the esophagus, represented by preepithelial, epithelial and postepithelial levels [6]. Violation of the integrity of the epithelium of the esophageal mucosa and changes in its barrier function lead to the effects of GER at the subepithelial level, which leads to visceral hypersensitivity [6, 8].

In patients with GERD, attention should also be paid to the nature of the intercellular spaces in the mucous membrane of the esophageal epithelium. In a study conducted by N.A. Tobey et al., it was demonstrated that the size of intercellular spaces in biopsies of the esophageal mucosa was significantly larger in patients with complaints of heartburn than in a group of healthy volunteers [7].

Systematic analysis of development risk factors of GERD demonstrated that symptoms are more common in subjects ≥ 50 years, smokers, NSAID and/or aspirin use. An analysis of 30 studies has shown that the prevalence of GERD has increased among smokers compared with non-smokers: OR — 19.6 (95 % CI: 14.9–24.7) vs. 15.9 (95 % CI: 13.1–19.0). An analysis of 10 studies has shown that in NSAID and/or aspirin users prevalence of GERD symptoms was significantly higher than in patients who did not take these medications: OR — 25.5 (95 % CI: 18.4–33.3) and 19.6 (95 % CI: 14.5–25.1), vs OR — 1.44 (95 % CI: 1.10–1.88) [13].

Another important risk factor for GERD is obesity. Patients with excess body weight have high intra-abdominal pressure that leads to gastric emptying and to a decrease in resting pressure of the LES, an increase in the number of TLESRs and frequent pathological GER [13, 14]. Many studies demonstrate the effect of obesity on the severity of GERD. A systematic review and meta-analysis of 40 papers has shown a link between abdominal obesity and erosive esophagitis, BE and EAC. Patients with central adiposity had a higher risk of EE (OR — 1.87; 95 % CI: 1.51–2.31), BE (OR — 1.98; 95 % CI: 1.52–2.57) and EAC (OR — 2.51; 95 % CI: 1.54–4.06) compared with patients with normal body habitus [15]. The latest meta-analysis clearly showed that the lowest prevalence of GERD was found in people with a BMI < 18.5 kg/m^2 (OR — 6.64; 95 % C: 3.40–110.82), whereas the highest prevalence was recorded in people with BMI ≥ 30.0 kg/m^2 (OR — 22.63; 95 % CI: 17.33–128.41) [16]. Speaking about the lifestyle of patients with obesity and GERD, it should be noted that in this group of patients, the development of pathological GER is influenced by a late dinner (< 3 hours before bedtime) and eating in a flat position [17].

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

GERD is the most common reason for patients to visit clinics. According to the latest meta-analysis summarizing the results of 102 studies, the global pooled prevalence of GERD was 13.98 % (95 % CI: 12.47–15.56) [16]. GERD symptoms reduce the quality of life and may require lifestyle changes, lifelong medication, and surgical intervention [18].

Several major studies have been published in Russia to analyze the prevalence of GERD [19–21]. In a major study on the prevalence of heartburn (Heartburn prevalence analysis: national epidemiologic examination of adult urban population (ARIADNE)) published in 2008, 15,208 people were interviewed with a final analysis of the data of 14,521 respondents. The study was conducted in such large Russian cities as Yekaterinburg, Tyumen, Krasnodar, Samara, Perm, Kazan, Moscow, Nizhny Novgorod, Kemerovo, Novosibirsk, Krasnoyarsk. The results showed that 2/3 of the respondents experienced heartburn constantly, 22.7 % of the respondents experienced heartburn more than twice a week [19].

In another study conducted from 2006 to 2007 using a questionnaire based on the Mayo Clinic questionnaire, it was found that among 7828 respondents, 47.5 % had ever experienced heartburn. This study was conducted in 6 cities of Russia — Kazan, Kemerovo, Krasnoyarsk, Ryazan, Saint Petersburg, Saransk. According to the results of this study, the prevalence of GERD among the population was 13.3 % [20].

Most recently, in 2022, the results of a multicenter study on the prevalence of GERD symptoms in polyclinic patients in Russia were published. The study was conducted from 2015 to 2017 in Moscow, Kazan, Omsk, Novosibirsk, Rostov-on-Don, Ryazan, Tver and Chelyabinsk. 7216 people were surveyed, 6132 questionnaires of patients aged 18 to 90 years were analyzed. The prevalence of GERD among polyclinic patients was 34.2 % [21].

The results of large-scale epidemiological studies demonstrate an increase in the prevalence of GERD among the Russian population. As previously noted, one of the serious complications of GERD is BE, which in turn is a risk factor for the development of EAC. According to a recent meta-analysis by L.H. Eusebi et al. (2021), summarizing the results of 44 studies, frequency of histologically confirmed BE in patients with GERD is 7.2 % (95 % CI: 5.4–9.3), whereas pooled prevalence for endoscopically suspected BE revealed 12.0 % (95 % CI: 5.5–20.3) [22]. The risk of developing EAC in patients with BE without dysplasia is 0.2–0.5 % per year, if available low-grade dysplasia the risk of developing cancer increases to 0.7 % per year, and for patients with high-grade dysplasia the risk of neoplastic progression is 7 % per year [23]. In Russia, the incidence of esophageal cancer in 2010 was 5.2 per 100,000 population, and in 2020 — 5.4 per 100,000 population [24]. The average annual rate of increase in morbidity was 0.96 %, the increase in morbidity over 10 years was 10.18 % [25].

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

K21 — Gastroesophageal reflux
K21.0 — Gastroesophageal reflux with esophagitis
K21.9 — Gastroesophageal reflux without esophagitis
K22.1 — Esophageal ulcer
K22.7 — Barrett's esophagus

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

According to the Montreal Classification, there is GERD with esophageal and extraesophageal manifestations [26].

Esophageal manifestations of GERD primarily include symptoms such as heartburn and regurgitation. Patients may also complain of epigastric pain, sleep disorders [26]. The clinical picture of GERD is nonspecific and it is necessary to make a differential diagnosis with diseases such as achalasia of the cardia, eosinophilic esophagitis, hypersensitivity to reflux, functional disorders, paraesophageal hernia, as well as heart and lung diseases [27].

Patients' complaints of heartburn and regurgitation remain the most sensitive (30–76 %) and specific (62–96 %) clinical manifestations of GERD [28].

Nocturnal heartburn is the most debilitating because it causes sleep disorders that can lead to daytime fatigue, decreased performance of daily tasks, poor mood and deterioration in the quality of life of patients with GERD [29–31]. Up to 75 % of patients with nocturnal heartburn report its negative impact on sleep quality [30].

Among the main symptoms of GERD, belching can also be distinguished, which occurs in 52 % of patients, dysphagia and odynophagia, detected in 19 % of patients [32].

Non-cardiac chest pain is another symptom of GERD. Pathological GER can cause chest pain, along the esophagus, simulating coronary pain, without heartburn or regurgitation. Non-cardiac chest pain, although it can be relieved by taking nitrates, but during differential diagnosis,

attention should be paid to the fact that it is not associated with physical activity and is caused by esophageal motor disorders (ineffective esophageal peristalsis, esophagospasm). Also, non-cardiac pain is affected by a decrease in the resting pressure of the lower esophageal sphincter, which contributes to frequent pathological GER [26, 32, 33].

According to the Montreal Classification, two groups of symptoms are classified as extraesophageal manifestations of GERD, including established associations: reflux cough syndrome, reflux laryngitis syndrome, reflux asthma syndrome, reflux dental erosion syndrome and proposed associations: pharyngitis, sinusitis, idiopathic pulmonary fibrosis, recurrent otitis media [26, 32]. At the same time, extraesophageal manifestations of GERD rarely occur in isolation, without the main complaints characteristic of GERD [26].

For the diagnosis of GERD, these symptoms have low sensitivity and specificity. Using only a positive response to antisecretory therapy as the main method of diagnosing GERD with extraesophageal manifestations may lead to delayed diagnosis of other possible causes of these complaints, namely diseases of the larynx and lungs [3].

A recently published meta-analysis included 28 studies involving 4379 people (2309 GERD patients and 2070 control subjects) showed that the pooled prevalence of dental erosion was 51.524 % (95 % CI: 39.742–63.221) in GERD patients and 21.351 % (95 % CI: 9.234–36.807) in controls [34]. The treatment of extraesophageal manifestations of GERD is a difficult task. Even with confirmed GERD, it is difficult to trace the causal relationship of GERD with extraesophageal symptoms, especially in the absence of a response to antisecretory therapy with proton pump inhibitors [35]. The results of a meta-analysis published in 2016 demonstrated that there was no statistically significant difference between patients with laryngopharyngeal reflux (LPR) took PPIs and placebo (OR = 1.22; 95 % CI: 0.93–1.58; $p = 0.149$) [36].

Sore throat, hoarseness of voice, dry cough may be the result of LPR [32]. LPR represents retrograde movement of gastric contents into the pharynx and larynx, causing a variety of symptoms [36]. The mechanism of development of LPR in GERD consists in stimulation by gastric contents of the afferent pathways of the vagus nerve and direct action on the mucous membrane of the larynx in GERD. Compared with the mucous membrane of the esophagus, the mucous membranes of the larynx and pharynx are less resistant to the action of pathological reflux [36–38].

Complications of GERD

Complications of GERD include bleeding, strictures, BE and EAC [26, 32]. GERD, complicated by bleeding, is rare and is observed mainly in patients with esophageal ulcers [39].

Esophageal strictures develop as a result of severe GERD, when inflammation in the mucous membrane of the esophagus leads to a narrowing of its lumen, which makes it difficult for food to pass. The main complaint of patients with esophageal stricture is dysphagia. In the management of patients with stricture, in addition to antisecretory therapy, endoscopic dilation is necessary [26].

The risk of developing BE in patients with GERD is 10–15 %. Risk factors for the development of BE include long-term GERD, male gender, obesity and age over 50 years [23]. A major systematic review and meta-analysis published in 2020 demonstrated that ~12 % of EAC had in the anamnesis BE [40].

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

2.1. Complaints and anamnesis

• All patients with GERD symptoms are recommended to confirm the diagnosis and determine further management tactics [41].

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

Comment. Heartburn and regurgitation are the main characteristic symptoms of GERD. Traditionally, heartburn has been the main symptom evaluated in clinical trials conducted in patients with GERD [42, 43]. Heartburn is a typical symptom of GERD with high sensitivity and specificity [41]. Thus, to analyze the epidemiology of GERD in large systematic reviews and meta-analyses, the authors often consider complaints of heartburn and regurgitation as the main symptoms of GERD [44, 45].

2.2. Instrumental diagnostic studies

• Upper Gastrointestinal Endoscopy (Upper GI Endoscopy) is recommended for patients with GERD symptoms to confirm the diagnosis in the absence of contraindications.

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

Comment. When performing endoscopy of the upper gastrointestinal tract and detecting erosive changes in the mucous membrane of the esophagus, the Los Angeles classification (LA classification) is used, according to which four degrees of erosive esophagitis Grades A–D are distinguished [46]:

Grade A — one (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

Grade B — one (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds.

Grade C — one (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75 % of the circumference.

Grade D — one (or more) mucosal break which involves at least 75 % of the oesophageal circumference.

In addition, an endoscopic examination can diagnose PB with its assessment according to the Prague C&M classification in the presence of morphological confirmation [41, 47].

It is quite difficult to assess the closure function of the cardia during Upper GI Endoscopy, since the cardia opens reflexively in response to the introduction of an endoscope and air insufflation [32].

The changes that unambiguously establish the presence of GERD in a patient based on the results of Upper GI Endoscopy include LA Grade C and D oesophagitis, BE, esophagus strictures [48]. Erosive esophagitis is detected in only 30 % of patients with heartburn who have not previously received therapy. Among patients with heartburn who received antisecretory therapy, erosive esophagitis is diagnosed in less than 10 % of cases [49]. Erosive esophagitis of Grade A according to the LA classification can be detected in 5–7.5 % of healthy volunteers [1, 50–52]. According to the Lyon Consensus, the presence of Grade A esophagitis in patients without clinical manifestations is not sufficient to establish the diagnosis of GERD [1, 3, 53].

LA Grade B oesophagitis in the presence of typical clinical symptoms is considered conclusive evidence of GERD. LA Grade D oesophagitis is the manifestation of severe GERD [32, 41].

While maintaining the complaints endoscopy should be performed 2–4 weeks after discontinuation of antisecretory therapy to clarify the diagnosis and make a differential diagnosis with eosinophilic esophagitis. In turn, eosinophilic esophagitis is a diagnosis that requires morphological confirmation. In biopsies of the esophageal mucosa stained with hematoxylin and eosin at high magnification (400) microscope defined by > 15 eosinophils per high-power field (eos/hpf) [54].

• Patients with suspected GERD and the absence of erosive and ulcerative changes in the mucous membrane of the esophagus or the presence of erosive esophagitis of LA Grade A are recommended to conduct 24-hour pH-metry on PPI off to exclude or confirm the diagnosis of GERD.

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

Comment. 24-hour pH-impedance monitoring — a diagnostic method aimed at detecting pathological gastroesophageal reflux. Acid exposure time (AET) < 4,0 units in the esophagus is the main indicator of 24-hour pH-metry. According to the Lyon Consensus, AET < 4,0 units in the esophagus < 4 % is normal, 4–6 % is doubtful about the diagnosis of GERD, > 6 % is diagnostic of GERD [53].

Additional pH-impedance monitoring parameters such as mean nocturnal baseline impedance (MNBI) and postreflux swallow induced peristaltic wave (PSPW) allow to assess the clearance of the esophagus, reduction of resistance of the mucous membrane of the esophagus and the effectiveness of peristalsis in the esophagus, thereby increasing the diagnostic value of pH-impedance monitoring in establishing the diagnosis of GERD [32, 48]. MNBI is a parameter that determines the average level of basal impedance of the mucous membrane of the esophagus. MNBI correlates with inflammatory changes in the esophagus. The results of the conducted studies have demonstrated that this indicator is lower in patients with erosive esophagitis compared with patients with non-erosive reflux esophagitis [56, 57].

PSPW index is another parameter of the pH-impedance monitoring to assess the chemical esophageal clearance and the effectiveness of the motor function of the esophagus. It can also be considered as an additional criterion for the differential diagnosis between erosive and non-erosive forms of GERD [56].

The relationship between symptoms and gastroesophageal reflux can be assessed using the symptom index (SI) and the symptom association probability (SAP). To calculate SI, the total number of reflux episodes associated with symptom episodes is divided by the total number of symptom episodes during the entire monitoring period. The SI ≥ 50 % and the SAP > 95 % are considered positive [3].

• Patients with GERD with persisting symptoms on PPI therapy with complaints heartburn, regurgitation and/or non-cardic chest pain are recommended to carry out pH-impedance monitoring against the background of therapy with proton pump inhibitors to exclude refractory GERD.

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

Comment. The role of 24-hour pH-impedance monitoring in the diagnosis of GERD, including refractory GERD, has been increased over the past three decades [58]. Patients with persisting

clinical manifestations of GERD are recommended to carry out pH-impedance monitoring on antisecretory therapy. In order to diagnose possible hypersensitivity to reflux, it is necessary to conduct 24-hour pH-impedance monitoring, which is the "gold standard" examination of patients with refractory GERD [59]. The mechanism of development of hypersensitive esophagus is not completely clear. One of the possible mechanisms is the effect of gastroesophageal reflux on the nerve endings of the mucous membrane of the esophagus [7, 60].

The reasons to the GERD refractory by proton pump inhibitors, in addition to hypersensitive esophagus, may be persistent pathological GER or other diseases (achalasia cardia or extraesophageal manifestations of GERD, or functional heartburn, heart disease) [61].

When detected according to the data of 24-hour pH-impedance monitoring AET > 6 % on the antisecretory therapy, it can be concluded that the ongoing antisecretory therapy is ineffective.

When detected according to the data of 24-hour pH-impedance monitoring AET < 4 %, the physiological total reflux episodes (< 40/day) it are possible to assume a functional disorder of the esophagus [35].

• Patients with extraesophageal manifestations of GERD without classic symptoms (heartburn, regurgitation) are recommended to undergo 24-hour pH-impedance monitoring with the off proton pump inhibitors.

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

Comment. To study extraesophageal manifestations of GERD, 24-hour pH-impedance monitoring is performed with the abolition of antisecretory therapy [32]. The SI > 95 %, the SAP > 50 % and AET > 4.0 increases the reliability of the diagnosis of GERD [62]. Early studies of oropharyngeal pH were promising and demonstrated an association with LPR. However, subsequently, the results of 24-hour pH-impedance monitoring showed that a decrease in pH in the oropharynx may be associated not only with LPR [63, 64]. For the diagnosis of LPR, it is recommended to use modern combined pH-impedance probes with at least one sensor located 1 cm above UES [65, 66].

• When deciding on surgical treatment, all patients need to perform high-resolution esophageal manometry and 24-hour pH-impedance monitoring. High-resolution esophageal manometry and 24-hour pH-impedance monitoring are the gold-standard for examining patients with GERD when deciding on surgical treatment.

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

Comment. Before the antireflux surgery, high-resolution esophageal manometry is recommended to assess the contractile reserve of the esophagus and exclude achalasia cardia [32]. High–resolution esophageal manometry is a diagnostic method aimed at studying esophageal motor function, assessing the resting pressure of the upper and lower esophageal sphincters [67]. Low resting pressure of the lower esophageal sphincter and ineffective esophageal peristalsis often accompany severe forms of GERD. In addition, high-re-solution esophageal manometry makes it possible to assess the level of the lower esophageal sphincter for subsequent installation of a probe for 24-hour pH-impedance monitoring [3].

Modern high-resolution esophageal manometry makes it possible to determine the reserve of contractility of the thoracic esophagus, which can be used to predict the likelihood of complications in the postoperative period after fundoplication [67]. Conducting the test of multiple rapid swallows makes it possible to predict the appearance of dysphagia, which is the most common complication in patients in the postoperative period after antireflux surgery [68]. Dysphagia is a potential complication of antireflux surgery [69].

High-resolution esophageal manometry is recommended for patients with non-cardiac chest pain and patients who do not respond to therapy with proton pump inhibitors to clarify the diagnosis [3].

Performing high-resolution esophageal manometry allows to exclude the presence of primary esophageal dysmotility disorders, such as the achalasia cardia or diffuse esophagospasm, and also allows you to set the level to which it will be necessary to subsequently install a probe for 24-hour pH-impedance monitoring [70]. Surgical treatment is not indicated for patients with proven hypercontractile esophagus, GERD with normal function of esophageal gastric junction [1].

• Barium radiographs should not be used as a diagnostic test for GERD [1, 3]. The detection of pathological reflux by the barium esophagram is less sensitive and specific compared to 24-hour pH-impedance monitoring [3]. However, this study is necessary to identify the hiatal hernia and determine its type.

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

3.1. Conservative treatment

Most patients with a mild form of GERD note positive dynamics of regression and symptom

control in lifestyle modifications and nutrition, weight normalization, and the use of pharmacotherapy, especially PPI. The main groups of medications used in the treatment of GERD are proton pump inhibitors, potassium-competitive acid blockers (P-CABs), alginates, antacids, and prokinetics [71].

• Lifestyle modifications for GERD patients include the following recommendations: weight loss in overweight patients, elevating head of bed for nighttime GERD symptoms, avoidance of smoking and alcohol, avoiding a late dinner, avoidance of "trigger foods" for pathological gastroesophageal reflux (coffee, chocolate, carbonated beverages, spicy and sour foods, citrus, fatty meals).

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

Comment. Improper eating habits, overeating and eating snacks at night, affect the development of GERD. An analysis of 50 articles on dietary and lifestyle factors related to GERD showed positively correlated between frequent consumption of coffee, tea and reflux esophagitis. Data analysis of 60,718 patients there were 38,104 males, 22,614 females, and 1438 showed reflux esophagitis patients, that fatty meals, smoking and alcohol are positively correlated with reflux esophagitis. While a vegetarian diet, the consumption of vegetables and fruits are negatively correlated with GERD [72].

In a systematic review in 2017, it was demonstrated, that the prevalence of gastro-oesophageal reflux symptoms was more common in subjects ≥ 50 years with obesity [13].

The first step in the management of GERD is lifestyle modification, with dietary recommendations such as increasing fiber intake and lowering dietary fat [73].

The general recommendation for patients are to avoid foods and beverages, which in their opinion, is the "trigger food" for GERD symptoms [73].

In a prospective cohort study M. Singh et al. demonstrated, that patients with overweight enrolled in structured weight loss program in combination with increased physical activity, not only did they lose weight, but they also demonstrated a decrease in the severity of GERD [74].

The results of a meta-analysis published in 2019 showed that there was no significant relationship between tea consumption and the risk of GERD overall [75].

There are many studies on the risk of GERD and coffee consumption. However, the results of a meta-analysis published in 2014 demonstrated that there was no significant association between coffee intake and GERD [76].

Speaking about the relationship between the development of GERD symptoms and alcohol consumption should be noted that LES function was unaffected when serum concentration of alcohol was < 70 mg/dL. When analyzing the frequency of alcohol consumption, subjects who drank more often than 3–5 times a week had a stronger correlation with the risk of development GERD compared with those who drank less often [77].

A recent systematic review revealed that GERD is related to many irregular dietary and lifestyle habits such as a habit of midnight snacking: OR — 5.08 (95 % CI: 4.03–6.4); skipping breakfast: OR — 2.7 (95 % CI: 2.17–3.35); eating quickly: OR — 4.06 (95 % CI: 3.11–5.29); eating very hot foods: OR — 1.81 (95 % CI: 1.37–2.4); and eating beyond fullness: OR —2.85 (95 % CI: 2.18–3.73). High-fat diet (OR — 7.568; 95 % CI: 4.557–8.908) consumption was positively related to GERD. An interval of less than three hours between dinner and bedtime (OR — 7.45; 95 % CI: 3.38–16.4) was positively related to GERD. And proper physical exercise > 30 minutes more than 3 times a week (OR — 0.7; 95 % CI: 0.6–0.9) was negatively correlated with GERD. Speaking about smo-king and alcohol consumption, it should be noted that they also affect the development of GERD (OR — 1.19; 95 % CI: 1.12–1.264 and OR — 1.278; 95 % CI: 1.207–1.353, respectively) [72].

• Patients with GERD are recommended PPIs therapy for the treatment of erosive esophagitis.

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

Comment. PPI treatment are effective in patients with symptoms of gastroesophageal reflux disease and existing erosive esophagitis [79, 80].

Currently, the following PPIs are used: omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole and dexlansoprazole. The conducted meta-analyses do not show significant differences in their effectiveness as GERD therapy [81, 82]. All PPIs should be taken 30–60 minutes before meals to ensure their maximum effectiveness. Although the change of PPIs is common in clinical practice, there is limited evidence to support this practice. Results of randomized, double-blind trial demonstrated that patients with GERD who do not respond to therapy with lansoprazole once daily note the same clinical effect when increasing the dosage of lansoprazole to twice daily, as from its replacement with esomeprazole once daily. The need to switch from one PPIs to another with a partial clinical response to therapy or no response should be

confirmed during 24-hour pH-impedance monitoring. Patients with identified side effects may be considered changing the PPI [3].

Due to the high dissociation constant (pKa) rabeprezole able to quickly accumulation at their site of action in a large number of parietal cells and lead to a rapid and pronounced suppression gastric acid secretion by blocking the proton pump, which provides a high rate of action and allows to achieve a stable antisecretory effect after the first dose of the PPI [83-88]. The pharmacokinetic features of rabeprazole determine the effective relief of daytime and nighttime heartburn from the first day of therapy [89,90]. By stimulating the synthesis of mucus and mucins, its own cytoprotective effect is ensured, which ensures a high rate of healing of esophageal erosions [83] and maintenance of long-term remission of GERD, including when taken on demand [89,90].

PPIs are more effective in the treatment of erosive esophagitis compared to H2 receptor antagonists (H2RAs) [80]. Optimization of the therapy of PPIs consists in giving PPIs in an adequate dose with the possibility of increasing to a double dose and/or switching to another PPIs. About 40 % of patients with GERD symptoms do not respond to PPIs therapy [26]. Long-term use of PPIs is recommended for patients with severe erosive esophagitis or BE.

According to the upper endoscopy, the absence of erosive and ulcerative changes in the esophagus in patients, normal indicators of total time with AET < 4.0 (less than 4 % of the study time) indicate in favor of functional esophageal disease. In this case, patients need additional examination and high-resolution esophageal manometry to exclude motor disorders of the esophagus. It is necessary to recommend discontinuation of therapy with proton pump inhibitors and compliance with lifestyle recommendations. Patients without GERD are likely to have an alternative explanation for the symptoms that bother them, which can be considered within the framework of a functional disorder [3].

Patients with NERD and other non-complicated GERD forms of consideration can be gi-ven to on-demand PPI therapy. In one randomized controlled trial published in 1999, 83 % of NERD patients who took omeprazole 20 mg on demand felt satisfactory were in remission at 6 months compared with 56 % of patient on placebo [90].

If erosive esophagitis of LA Grade A is detected the probability of its healing within 4 weeks of treatment is high. The course can be 4 weeks with a standard dose of PPIs (rabeprazole 20 mg per day or esomeprazole 40 mg per day or omeprazole 20 mg 2 times a day or dexlansoprazole 60 mg per day or pantoprazole 40 mg per day) preferably with a control upper GI endoscopy [1].

In patients with erosive esophagitis LA Grade B, C, D, according to upper endoscopy and AET > 6 % of the study time, on the background of a positive clinical and endoscopic picture, when taking PPIs at a standard dosage, it is recommended to reduce the dose of PPIs followed by maintenance therapy [3]. If multiple erosions of the esophagus are detected, as well as complications of GERD, the course of treatment for PPIs should be at least 8 weeks [1].

Taking PPIs at a standard dose from 4 to 8 weeks is considered safe and suitable for patients with typical symptoms of pathological GER [9]. Clinical improvement is noted in most patients with GERD at 8 weeks standard course of PPIs therapy [91].

At the same time, according to randomized clinical trials, about a third of patients with GERD who took PPIs at a standard dose for 8 weeks do not respond to therapy. The results of randomized clinical trials have shown that taking PPIs at a standard dose for 8 weeks is the least effective in the treatment of severe erosive esophagitis. As a result of which, in patients with such erosive esophagitis the duration of PPIs therapy can be extended to 12 weeks [35].

In patients with refractory GERD complaints are persisting despite medical therapy. Also, erosive esophagitis by upper endoscopy and/or changes on reflux monitoring are characteristic of pathological GER. The term refractory GERD symptoms refer to previously diagnosed GERD which remains clinically resistant despite medical therapy. Refractory GERD is most common by females with low BMI, with dyspepsia and irritable bowel syndrome, and with sleep disturbances [35].

Regarding the treatment of GERD, gastroenterologists agree that the generally recognized benefits of PPIs far outweigh their theoretical risks [3]. In a previously published systematic review, it was demonstrated that patients with GERD have positive dynamics during PPI treatment. Up to 93 % of GERD patients noted a decrease in reflux symptoms during therapy [92]. 1691 patients with NERD, erosive esophagitis and noncardiac chest pain (NCCP) were included in a systematic review published in 2023. The PPI test based on the results of a study concerning the diagnosis of GERD had high pooled sensitivity 79 % (95 % CI: 72–84), but not so high 45 % pooled specificity (95 % CI: 40–49). Moreover, the results were similar for both

NERD and erosive esophagitis. With regard to the diagnosis of NCCP, both the sensitivity and specificity of the PPI test were high and pooled sensitivity and specificity were 79 % (95 % CI: 69–86) and 79 % (95 % CI: 69–86), respectively [93].

PPIs are used not only for treatment of GERD, but also for treatment dyspepsia, Zollinger — Ellison syndrome and other disease [94]. In recent years, much attention has been paid to the issues of PPI deprescribing [95]. The strategy of canceling the appointment of PPIs is aimed at reducing the dose of PPIs or switching to on-demand therapy after achieving the desired effect of PPIs [95].

PPIs, like other drugs, have side effects. Side effects include headache, abdominal pain, nausea, vomiting, diarrhea, constipation and flatulence [3]. These relatively minor side effects occur infrequently and decrease after discontinuation of their use. Sometimes these side effects may be specific to a particular drug from the PPIs group, and when switching to another PPIs, the side effects are leveled [3]. PPIs generally show a low incidence of side effects (<2 %) [1]. When prescribing PPIs in high doses for a long period, the potential for adverse effects such as bacterial overgrowth, Clostridium difficile (C. difficile) infection, osteoporosis, and pneumonia in patients over 65 years of age should be considered [1].

In a recently published large placebo-controlled randomized trial P. Moayyedi et al. investigated 17,598 patients aged 65 years and older given a rivaroxaban and/or aspirin. All patients assigned to groups given pantoprazole (40 mg daily, n = 8791) or placebo (n = 8807). After randomization, data were collected and analyzed at 6-month intervals over 3 years to identify potential side effects of PPIs, including pneumonia, Clostridium difficile infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, dementia, cardiovascular disease, cancer, hospitalizations, and all-cause mortality every 6 months. In the study, there were not statistically significant different between groups who took PPIs and received a placebo. With the exception of enteric infections (1.4 % vs. 1.0 % in the placebo group; OR —1.33; 95 % CI: 1.01–1.75). The authors concluded that pantoprazole is not associated with any adverse event when used for 3 years, with the possible exception of an increased risk of enteric infections [96].

Additional pharmacotherapy

• Clinicians should personalize additional pharmacotherapy depending on the GERD phenotype, as opposed to the empirical use of these drugs. Adjunctive agents include alginate for relief of symptoms, esophagoprotective therapy acceleration of the epithelialization of esophageal erosions and protection of the mucous membrane, nighttime H2 receptor antagonists for nocturnal symptoms, prokinetics when the motor evacuation function of the stomach slows down, ursodeoxycholic acid preparations with duodenogastroesophageal reflux.

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

Comment. As an additional therapy, can be use histamine2 receptor antagonists, the H2RA not decrease the acid suppressive ability of the PPI, but on the contrary it improved gastric acid control [97]. The reason why PPIs therapy may be ineffective in patients with GERD may be that the patient does not have acidic, but weakly acidic or alkaline reflux, which can be diagnosed during 24-hour impedance pH monitoring. Gastroesophageal reflux is predominantly acidic in 50 % of GERD patients, acidic — with a bile component — in 39.7 %, and 10.3 % of patients have bile reflux [1]. In this case, the following drugs should be added to the therapy of PPIs in various combinations: antacide, esophagoprotectors, prokinetics, ursodeoxycholic acid, rebamipide [1].

Rebamipide has a special mucoprotective mechanism in the esophagus, positively affecting epithelial permeability, the main cause of violation of the protective mechanisms of the mucous membrane. Rebamipid stimulates the synthesis of tight junction proteins (claudin-3, claudin-4) [1, 6, 95, 98]. S.M. Yoon et al. demonstrated in their study that about histologic examination of biopsies of the mucous membrane of the esophagus of patients with NERD during Rebamipide at 8 weeks was determined a more pronounced positive dynamics - a significant decrease in the number of lymphocytes and the size of dilated intercellular spaces in the epithelium of the esophagus compared to the placebo group (p = 0.024 and p = 0.026, respectively) [99, 100]. In another study, it was demonstrated that Rebamipide reduces IL-8 mRNA expression thereby preventing the recurrence of GERD symptoms [101, 102].

• Combination therapy Rebamipide with PPIs increases the effectiveness of relief of GERD symptoms, as well as reduces the frequency of relapses.

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

Comment. The effect of Rebamipide on the mucous membrane of the esophagus in reflux esophagitis continues to be studied. In the study involving a total of 501 patients over

a 4-week treatment course, esomeprazole and rebamipide combination therapy was more effective in decreasing the symptoms of reflux esophagitis than esomeprazole monotherapy [103]. S.M. Yoon et al. demonstrated in their study that a decrease in the severity of symptoms by 50 % or more was recorded in 74.1 % of patients taking lansoprazole in combination with rebamipide and in 51.7 % of patients in the lansoprazole and placebo group, p = 0.020 [100]. Patients with esophagitis of Los Angeles Grade A or B on the background of PPI therapy during 12 months after completion of the course of treatment had a recurrence of symptoms was 52.4 % of cases, unlike patients receiving PPIs in combination with rebamipide was observed only 20 % of cases, p < 0.05 [101].

Prokinetics

• The use of prokinetics in the treatment of GERD is due to their ability to restore the physiological state of the esophagus indirectly through normalization of gastric peristalsis, improvement of esophageal clearance and reduction of TLESRs. Prokinetics have the greatest effect in combination with GERD and functional dyspepsia.

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

Comment. Data on the use of prokinetic agents for patients with GERD are limited. Metoclopramide indirectly increases lower esophageal sphincter pressure, enhance esophageal peristalsis, and augment gastric emptying [3]. In patients with refractory GERD, the addition of prokinetics to therapy is impractical [35]. GERD is often combined with functional dyspepsia, which is associated with impaired accommodation of the fundal stomach and an increase in the frequency of episodes of TLESRs [104]. In an early meta-analysis was demonstrated that combined therapy (PPI and prokinetics) for GERD improves patients' quality of life and reduces the symptoms of GERD. During the meta-analysis, it was shown that the combination of prokinetics with PPIs in the treatment of GERD leads to a significant decrease in the number of reflux episodes compared with PPIs monotherapy (95 % CI: –5.96:–1.78; p = 0.0003) [105]. A recent meta-analysis by L. Xi et al. (2021), summarizing the results of 14 studies (1,437 patients), demonstrated that the addition of a prokinetic to PPIs contributes to a more pronounced regression of the symptoms of the disease in comparison with monotherapy (OR — 1.185; 95 % CI: 1.042–1.348; p = 0.010) [106]. The effectiveness of prokinetics in the treatment of GERD is due to their ability to influence the pathogenesis of GERD: to increase indirectly the tone of the lower esophageal sphincter, augment gastric emptying [107]. Augment gastric emptying under the action of prokinetics leads to a decrease in the effect of pathological GER on the esophagus in patients with reflux esophagitis. A meta-analysis that included 16 randomized controlled trials on the addition of prokinetics to GERD therapy, with a population of 1,446 patients, showed a significant reduction in GERD symptoms compared with PPIs monotherapy (OR of reflux symptoms resolution — 1.22; 95 % CI: 1.11–1.35; p < 0.0001); at the same time, the clinical course of GERD improved both for patients with non-refractory form (OR — 1.186; 95 % CI: 1.07–1.30), so it is with the refractory form (OR — 1.47; 95 % CI: 1.15–1.88). The effectiveness of the combination of PPIs and prokinetics does not depend on ethnic characteristics and is observed in both "western" and "eastern" populations. It was noted that a persistent clinical effect is observed with a duration of therapy of at least 4 weeks (OR — 1.26; 95 % CI: 1.10–1.43) [108]. According to the recommendations of the Japanese Society of Gastroenterologists for the diagnosis and treatment of GERD, the addition of prokinetics to therapy is advisable if PPIs monotherapy is ineffective [71]. A new prokinetic drug acotiamide 100 mg 3 times a day is a promising drug for the treatment of symptoms of dyspepsia, GERD and NERD. Acotiamide significantly reduced the frequency of regurgitation, pain and burning in the epigastric region in a study in patients with refractory to PPIs. Acotiamide reduces the total number of acid reflux [109]. Against the background of the use of acotiamide, the degree of inefficiency of esophageal peristalsis decreases with a small (2–5 cm) rupture length of its wall contraction (fragmentation of peristalsis). The effect of acotiamide on the fragmentation of the peristalsis of the proximal esophagus prevents the spread of reflux to the proximal esophagus [110]. Combination therapy with acotiamide and PPIs reduces the severity of clinical symptoms of GERD [111-113].

• Among the group of prokinetics for the treatment of patients with GERD, the drug itopride hydrochloride highlights the absence of restrictions on the duration of use, as well as a favorable safety profile.

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

Comment. The prokinetic drug itopride hydrochloride 50 mg 3 times a day belongs to the means of pathogenetic treatment of GERD, since it normalizes the motor function of the upper gastrointestinal tract, reduces the episodes of TLESRs [114-117]. When using itopride as part of combination therapy with PPIs in GERD, it was found that it significantly enhances the contractile activity of the LES and gastric motility, accelerates gastric evacuation, restores gastroduodenal coordination [118,119] and it has a significant effect on the relief of heartburn [120]. Itoprid in combination with rabeprazole has been proven to improve the clinical course of chronic cough caused by GERD [121]. The duration of therapy with itopride hydrochloride should be at least 8 weeks.

Esophagoprotectors

• Esophagoprotectors are a new group of drugs based on hyaluronic acid and chondroitin sulfate in a bioadhesive form. The combination of hyaluronic acid and chondroitin sulfate protects the mucous membrane of the esophagus.

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

Comment. hyaluronic acid affects the renewal of the epithelial cells of the mucous membrane and promotes the healing of erosions. Chondroitin sulfate is a glycosaminoglycan that has a healing effect on the mucous membrane of the esophagus and stomach, and the bioadhesive formula of the drug contributes to the effective protection of the mucous membrane, forming a barrier between the mucosa and pathological GER. The healing effect of ulcers and erosion of esophagoprotectors is due to the combined action of two compounds [122]. A recently published systematic review and meta-analysis of three studies involving 181 patients demonstrated that combined therapy with PPI and esophagoprotectors is significantly more effective than PPI monotherapy for the epithelialization of esophageal erosions on the day 28 of treatment (OR — 1.267; 95 % CI: 1.082–1.483; p = 0.003) [123].

Alginate and antacid

• In the treatment of reflux esophagitis, the main group of drugs are PPIs. However, the results of the conducted studies demonstrate that alginates and antacids are effective in relieving the symptoms of GERD. Antacide and alginate can be used both as monotherapy for heartburn, which is not accompanied by the development of erosive esophagitis, and in the complex therapy of GERD.

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

Comment. Alginate have been used in the treatment of reflux esophagitis for the past 30 years. Alginate create a protective barrier on the surface of gastric contents, thereby reducing the number of gastroesophageal and duodenogastroesophageal reflux [1, 124]. Due to this ability to form a barrier, alginate antacids have found application in the fight against postprandial heartburn and regurgitation. For patients with partial response to PPIs, the addition of alginate antacids serves as a useful supplement [125]. A meta-analysis involving 14 studies (2095 patients) demonstrated that alginate therapy reduced GERD symptoms significantly better than placebo and antacids (OR — 4.42; 95 % CI: 2.45–7.97; p = 0.001) [124]. Antacids and alginates should be taken depending on the severity of symptoms, usually after meals and at night until persistent relief of symptoms, then in the "on demand" mode [1].

Potassium-competitive acid blocker

• Potassium-competitive acid blocker (P-CAB) are promising antisecretory agents that marked suppression of gastric acid secretion and are considered as drugs for the treatment of acid-dependent diseases of the gastrointestinal tract in the future.

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

Comment. PPIs are widely prescribed as first-line therapy for the treatment of GERD. In PPIs metabolism cytochrome P450 (CYP) 2C19 play an important role, which determines the different metabolic rate of PPIs, in particular, in different ethnic groups. P-CAB (not registered in Russian Federation) developed for further improvement of acid-suppressive therapy. Studies of the physicochemical properties of this group of drugs have shown that P-CAB have high solubility and stability over a wide pH range in the acidic environment of the stomach. Studies have also demonstrated that P-CAB accumulate and retain their antisecretory effect for more than 24 hours [126].

According to modern Japanese guidelines, patients with GERD are prescribed P-CAB at a dose of 20 mg per day for 4 weeks. In case of positive dynamics, it is recommended to switch to a maintenance dosage, if there is no effect after 4 weeks, it is necessary to continue therapy for up to 8 weeks [71].

In the systematic review and meta-analysis published in 2021 was demonstrated that P-CAB vonoprazan is also effective in the treatment of GERD, as well as PPIs. An analysis of 56 stu-dies showed that the efficacy and frequency of adverse

events in patients taking vonoprazan and PPIs is 1.06 (0.99–1.13) and 1.08 (0.96–1.22), respectively [127]. Currently, a large number of clinical studies are underway on the effectiveness of P-CAB in the treatment of GERD.

Management of pregnancy with GERD

• Managing pregnancy with complaints of heartburn is quite a difficult task. First of all, it is necessary to give recommendations on lifestyle changes. Drugs used in patients at all stages of pregnancy include alginates.

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

Comment. The prevalence of gastroesophageal reflux disease (GERD) symptoms in pregnancy is very high, up to 80 %, with a maximum peak during the third trimester. Alginates are safe drugs as a therapy for heartburn in pregnancy [128].

3.2. Surgical treatment

• Surgical treatment is indicated for the complicated course of GERD (repeated bleeding, peptic strictures of the esophagus, the development of BE with high-grade epithelial dysplasia, frequent aspiration pneumonia). In some cases, when a patient cannot receive conservative therapy for one reason or another for objective or subjective reasons, surgical treatment should also be considered for an uncomplicated course.

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

Comment. Laparoscopic fundoplication is often used in patients without obesity. Choosing the type of fundoplication can be individual, with partial fundoplication in patients with esophageal hypomotor or reduced peristaltic reserve according to high-resolution esophageal manometry, if the risk of postoperative dysphagia is suspected. Studies show a relief of GERD symptoms in patients, which persists for a long time during 5–10 years of follow-up [41, 129].

Surgical treatment of GERD is more effective in those patients with GERD who have effective PPIs [130, 131]. With the ineffectiveness of PPIs and extraesophageal manifestations of GERD, surgical treatment is also less effective [1].

It is necessary to consider surgical treatment together with an experienced surgeon, after taking measures to normalize the lifestyle, conducting 24-hour impedance pH-monitoring to confirm the presence of pathological gastroesophageal reflux, as well as high-resolution esophageal manometry to identify possible contraindications to surgical treatment in the form of pronounced esophageal peristalsis defects of the thoracic esophagus [1].

4. Organization of medical care

The provision of planned specialized medical care to patients with gastroesophageal reflux disease is carried out both on an outpatient and inpatient basis, in accordance with the standards of medical care for adults (diagnosis and treatment approved by the Order of the Ministry of Health of the Russian Federation No. 722н dated November 9, 2012).

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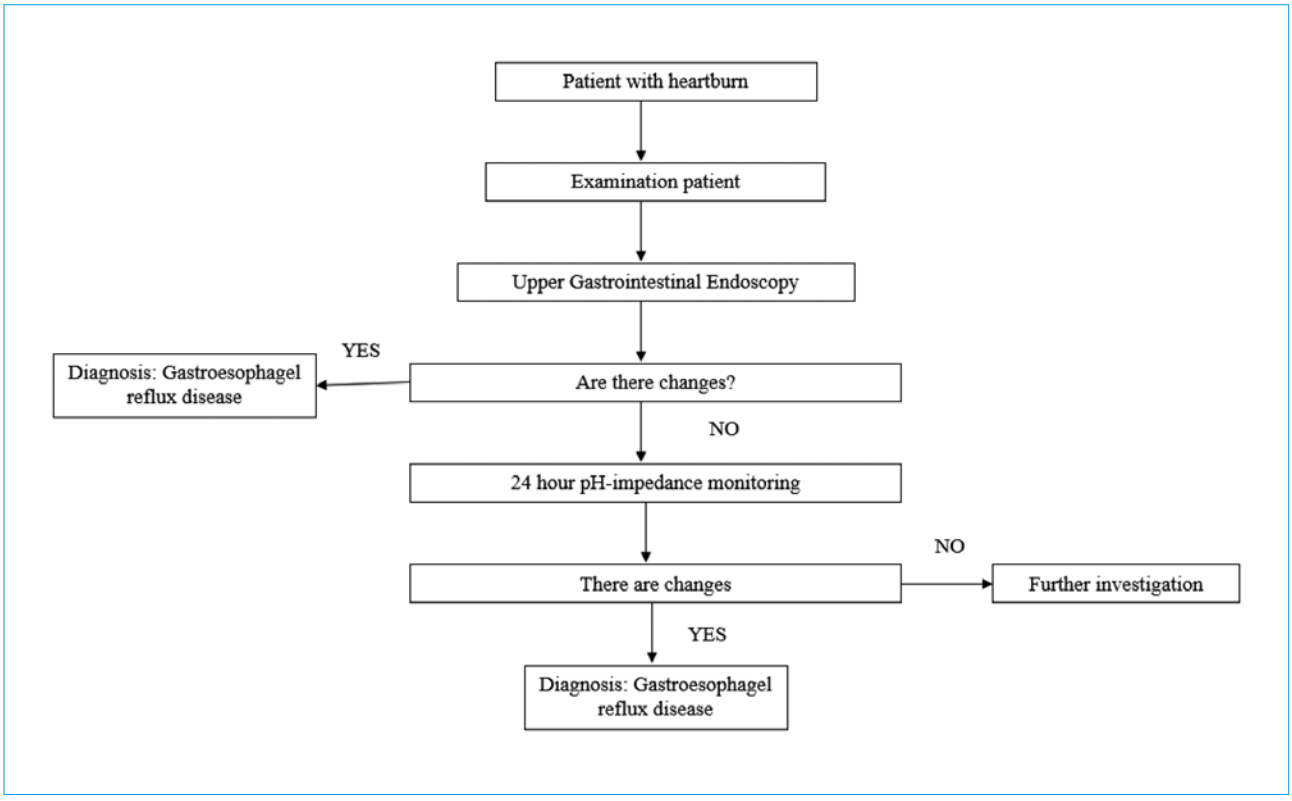
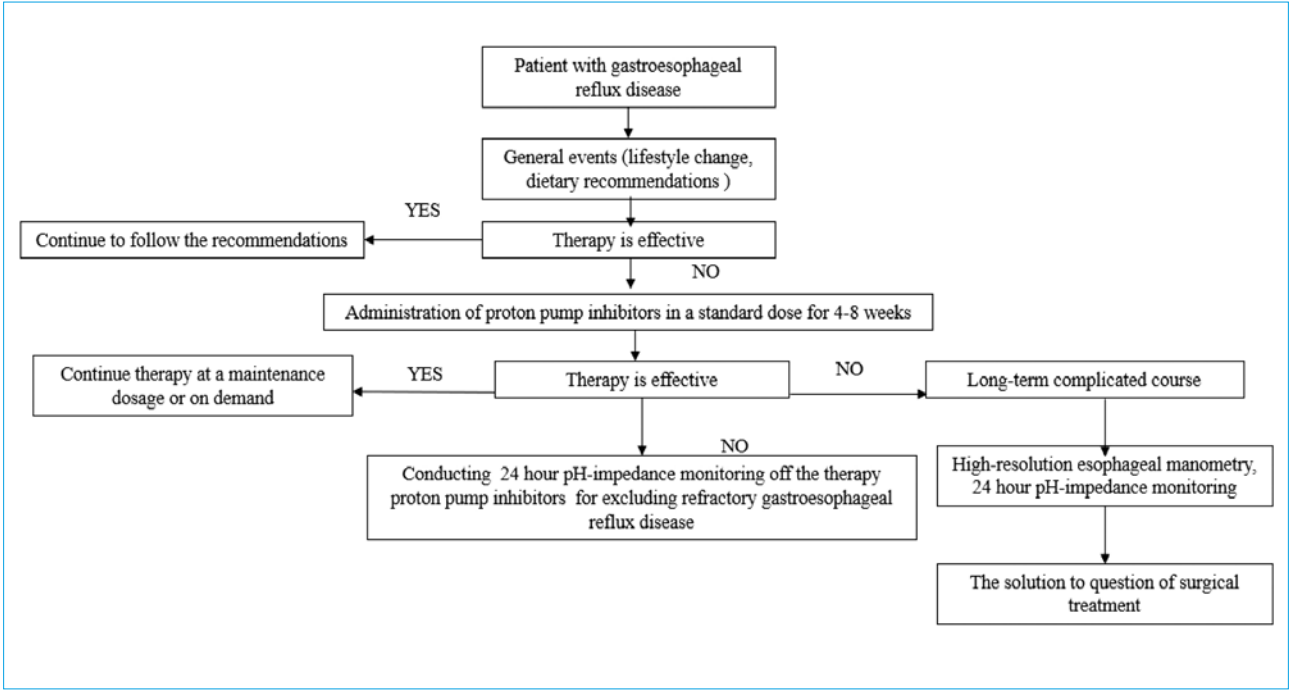
Appendix A.
Reference materials, including compliance with indications for use and contraindications, methods of use and doses of drugs, instructions for use of the drug

These clinical recommendations have been developed taking into account the following regulatory documents:
1. Order of the Ministry of Health of the Russian Federation No. 906н dated November 12, 2012, "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 No. 203н dated May 10, 2017, "On approval of criteria for assessing the quality of medical care".
3. Order of the Ministry of Health of the Russian Federation No. 247н dated November 22, 2004, "On approval of the standard of medical care for adults with gastroesophageal disease (diagnosis and treatment)".

Appendix B.
Doctor's action algorithm





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Submitted: 23.08.2024 Accepted: 27.09.2024 Published: 30.10.2024
Поступила: 23.08.2024 Принята: 27.09.2024 Опубликована: 30.10.2024