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ГАСТРОЭЗОФАГЕАЛЬНАЯ РЕФЛЮКСНАЯ БОЛЕЗНЬ: ДИАГНОСТИКА, МЕДИКАМЕНТОЗНОЕ ЛЕЧЕНИЕ, БАЛЬНЕОТЕРАПИЯ

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Gastroesophageal Reflux Disease: Diagnosis, Medication, Balneotherapy

Резюме

В статье приведены современные взгляды на проблему гастроэзофагеальной рефлюксной болезни (ГЭРБ). Представлены данные о распространенности и факторах риска развития заболевания. Сделан акцент на особой роли слабокислых и слабощелочных рефлюксов в патогенезе ГЭРБ, которые, в сочетании с дисфункцией нижнего пищеводного сфинктера и нарушениями моторно-эвакуаторной функции желудка, являются важными факторами, определяющими недостаточную эффективность стандартной антисекреторной терапии. Подчеркивается исключительная важность метода 24-часовой pH-импедансометрии для дифференциальной диагностики неэрозивной формы ГЭРБ с функциональной изжогой и гиперчувствительностью пищевода к рефлюксу (т.н. гиперсенситивный пищевод). Приведены данные результатов отечественных и зарубежных исследований, посвященных оценке эффективности применения физиотерапевтических методов и питьевой бальнеотерапии у больных ГЭРБ.

Ключевые слова: *гастроэзофагеальная рефлюксная болезнь, нижний пищеводный сфинктер, мониторинг pH пищевода, бальнеотерапия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The article presents modern views on the problem of gastroesophageal reflux disease (GERD). Data on the prevalence and risk factors for the development of the disease are presented. Emphasis is placed on the special role of slightly acidic and slightly alkaline reflux in the pathogenesis of GERD, which, in combination with dysfunction of the lower esophageal sphincter and impaired motor-evacuation function of the stomach, are important factors, determining the the lack of effectiveness of standard antisecretory therapy. The exceptional importance of the 24-hour pH impedanceometry method is emphasized for the differential diagnosis of the non-erosive form of GERD with functional heartburn and

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hypersensitivity of the esophagus to reflux (the so-called hypersensitive esophagus). The data of the results of domestic and foreign studies devoted to the evaluation of the effectiveness of the use of physiotherapeutic methods and drinking balneotherapy in patients with GERD are given.

Key words: *gastroesophageal reflux disease, lower esophageal sphincter, esophageal pH monitoring, balneotherapy*

Conflict of interests

The authors declare no conflict of interests

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FH — functional heartburn, GERD — gastroesophageal reflux disease, HE — hypersensitive esophagus, LES — lower esophageal sphincter, NO — nitric oxide, PPIs — proton pump inhibitors

For years, gastroesophageal reflux disease (GERD) has been one of the most complex challenges in gastroenterology and therapy. In the guidelines for the diagnosis and management of GERD developed by the Russian Gastroenterological Association, this nosology is defined as a chronic relapsing disease caused by impaired motor-evacuation function of organs of the gastroesophageal zone. It is characterized by regularly repeated reflux of gastric and, in some cases, duodenal contents into the esophagus, leading to the development of clinical symptoms that worsen the quality of life of patients. It also results in damage to the mucous membrane of the distal esophagus, with the development of dystrophic changes of the non-keratinizing stratified squamous epithelium, catarrhal or erosive and ulcerative esophagitis (reflux esophagitis), and in some patients, cylindrical metaplasia [1].

Epidemiology of GERD

Epidemiological studies show that GERD prevalence in the population varies from 8.8 to 33.1 %, and incidence rates have a steady upward trend in all regions of the world. The highest rates of GERD prevalence are in Europe and North America, and the lowest rates are in Asia [1, 2]. In our country, according to various sources, the incidence of GERD ranges from 11.3 to 23.6 %. Esophagitis in the overall population is registered in 5–6 % of cases; in 65–90 % of such patients, the process has moderate severity, and 10–35 % of them have signs of severe esophagitis. The prevalence of Barrett's esophagus (replacement of the squamous epithelium in the mucosa of the distal esophagus with the glandular metaplastic cylindrical epithelium, which increases the risk of developing esophageal adenocarcinoma) among individuals with esophagitis is close to 8 %, with fluctuations ranging from 5 to 30 % [1, 3].

The past decade has seen significantly more cases of GERD in the young population and more erosive and ulcerative forms of reflux esophagitis [4]. GERD is characterized by an extremely negative impact on the quality of life of patients; in this regard, this disease even "surpasses" such nosologies as peptic ulcer, angina and chronic heart failure [5].

Some pathophysiological mechanisms of GERD development

The following predisposing factors are important for the development of GERD: psycho-emotional disorders, smoking, excessive alcohol consumption, repeated pregnancies, hiatal hernia [4]. Overweight and obesity, conditions that are extremely common in the population, are essential in the pathogenesis of this disease [6]. It is known that obesity is accompanied by a significant increase in blood leptin level, which stimulates the production of gastrointestinal peptides, primarily ghrelin, as well as neuropeptides (vasoactive intestinal peptide), which, in turn, causes the formation of nitric oxide (NO) in the myocytes of the esophagus and stomach. It is known that NO reduces the tone of the lower esophageal sphincter (LES), which is the primary mediator that determines the degree of its relaxation; in addition, NO reduces peristaltic movement of the esophagus, which ultimately leads to a decreased antireflux barrier [7]. On the other hand, adipose tissue is "responsible" for the hyperproduction of pro-inflammatory cytokines (interleukins-1β and -6, tumor necrosis factor α) that play an important role in the pathogenesis of GERD; the latter cause inflammation of the esophageal mucosa and impair its barrier properties, making the mucosa particularly susceptible to disease-induced damage [8, 9].

According to experts, GERD is a complex disease with heterogeneous symptoms and multifactorial pathogenesis. Therefore, simplified diagnostic algorithms and classifications are unacceptable for its management [10, 11]. Although GERD is a so-called acid-related disease, its pathogenesis is complex and multicomponent in nature, which apparently causes the problem of insufficient control of symptoms, even with

the most advanced pharmacotherapy available. In addition to the effects associated with aggressive refluxate containing hydrochloric acid and pepsin in the lower third of the esophagus, the failure of the antireflux barrier is of great importance in the pathogenesis of GERD; it occurs due to the impaired intramural innervation of LES, as well as its spontaneous functional relaxation [12, 13].

In most cases, current antisecretory drugs allow controlling intragastric acidity at pH 5–6. However, they have no effect on the function of the lower esophageal sphincter and cannot prevent the reflux of contents neutralized to slightly acidic values into the esophagus; this fact probably explains the persistence of GERD symptoms when taking proton pump inhibitors (PPIs). Studies show that reflux of acidic nature occurs only in 50 % of patients with GERD, while acid reflux with a bile component is detected in 39.7 % of cases, and reflux is registered in 10.3 % of patients. These non-acidic (slightly acidic and slightly alkaline) refluxes are apparently why antisecretory therapy is not sufficiently effective [14]. It should be noted that multichannel daily impedance pH-metry plays a key role in the diagnosis of the so-called non-acidic refluxes [15].

An important role in the pathogenesis of GERD is played by the so-called impaired esophageal clearance, which is manifested by the failure of the secondary esophageal peristalsis, which determines the reverse "evacuation" of the refluxate into the stomach [16]; researchers emphasize the importance of reduced production of bicarbonates in the esophagus [4, 12]. Increased intragastric pressure due to impaired motor-evacuation function, as well as duodenostasis, are of particular importance in the development of this disease [17]. In cases of chronic duodenostasis and duodenogastric reflux, alkaline reflux enters the stomach, which increases the risk of developing erosive and ulcerative reflux esophagitis and Barrett's esophagus [18].

According to Ya. S. Zimmerman et al. (2016), one of the key pathogenetic factors in the development of GERD is decreased resistance of the esophageal mucosa to aggression factors due to an imbalance of pre-epithelial, epithelial, post-epithelial and functional protective components [4]. The pre-epithelial protective barrier is brought into action by the mucous membrane and bicarbonate ions that neutralize the protons of acid reflux in the esophagus; it maintains pH in the esophagus in the range of 7.3–7.4. In case of GERD, the formation of pre-epithelial protective factors is significantly reduced. Structural and functional features of esophageal epitheliocytes, as well as the process of their continuous regeneration, are the basis of the epithelial level of protection, which prevents damage to the mucous membrane. The state of microcirculation of the esophageal mucous membrane determines the so-called post-epithelial level of protection and is the basis of cellular resistance, which counters the proton aggression of gastric juice.

More on the differential diagnosis of GERD

A very important and challenging clinical aspect of GERD is the differential diagnosis of the non-erosive form of this disease with the so-called functional heartburn (FH) and hypersensitivity of the esophagus to reflux — hypersensitive esophagus (HE). It has recently been suggested that visceral hypersensitivity due to the state of vanilloid receptors 1 is significant in the occurrence of reflux symptoms [19]. In clinical practice, the "gold standard" for the differential diagnosis of these conditions in patients with heartburn and normal endoscopic results is the 24-hour pH impedance test [20]. In accordance with the Rome IV criteria for functional esophageal disorders, patients with complaints of heartburn and no pathological changes in the esophageal mucosa according to endoscopic results can be divided into two groups (Fig. 1): patients with no previously verified GERD, and patients with already confirmed diagnosis of GERD (for example, based on the results of pH-metry). Before the prescription of PPIs or after the so-called "washout" period (discontinuing PPIs in seven days), individuals of group 1 should take a 24h intraesophageal pH-impedance test; based on the results of this test, patients of group 1 are divided into three subgroups: individuals with increased exposure of the esophageal mucosa to hydrochloric acid (non-erosive GERD); individuals with normal acid exposure and association between the onset of symptoms and episodes of physiological reflux (that is, esophageal reflux hypersensitivity), and finally, individuals with normal acid exposure in the esophagus and no association between the onset of symptoms and reflux episodes (FH). For patients with an established diagnosis of GERD (group 2), an intraesophageal pH-impedance test should be performed while these patients take PPIs. The diagnosis of "refractory GERD" is established if increased exposure of the esophageal mucosa to hydrochloric acid is established despite ongoing antisecretory treatment. Patients with normal acid exposure during treatment with PPIs and episodes of physiological reflux (usually non-acidic) are considered patients with GERD and esophageal reflux hypersensitivity simultaneously; patients with symptoms during therapy that are not compliant to reflux episodes are most likely to have a combination of GERD and FH [21].

GERD management: problems and approaches

One of the biggest challenges in the case of GERD is ineffective acid suppression therapy. Despite the high efficacy of PPIs, there is a lot of evidence of their clinical "failure" in a number of patients. It is known that at least a third of patients with GERD continue to experience symptoms caused by reflux while taking PPIs [22].

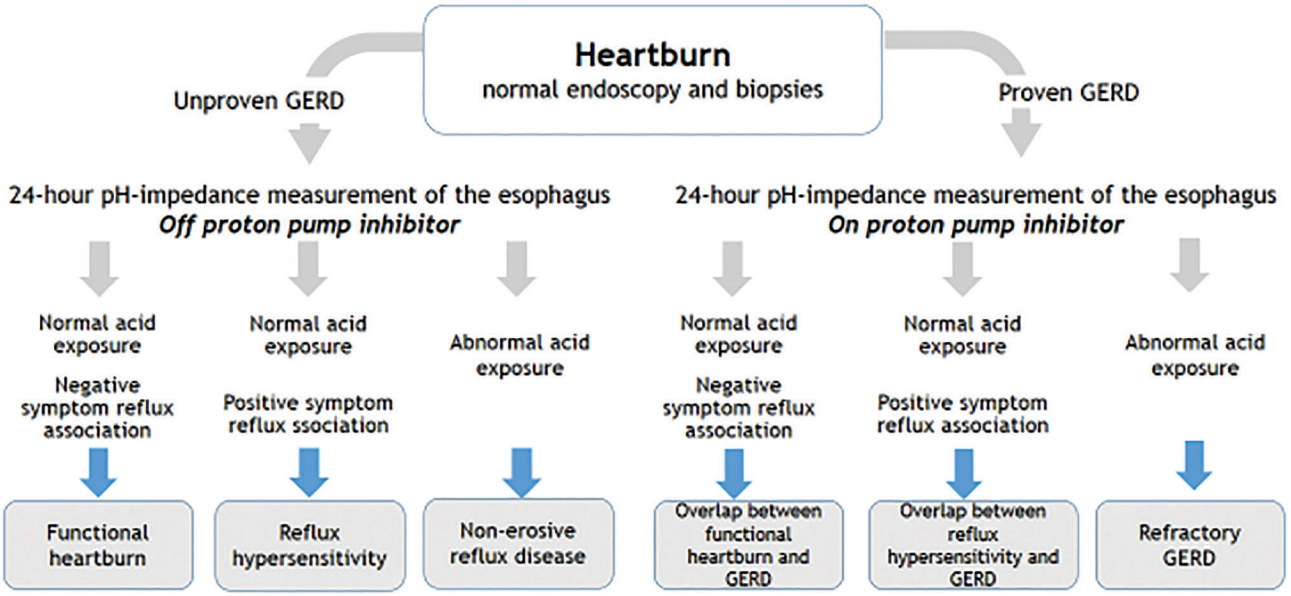

Figure 1. *Differential diagnosis of heartburn against the background of a normal endoscopic and histological picture of the esophageal mucosa [21]*

Refractory GERD usually occurs in the absence of complete healing of the esophageal mucosa and/or satisfactory relief of bothersome symptoms after a full course of PPIs at a standard (once a day) dose (treatment course for erosive esophagitis lasts eight weeks, and for non-erosive GERD — four weeks) [1]. There are several reasons for the ineffectiveness of acid suppression therapy for GERD. The first reason is the genetically determined inability of PPIs to maintain pH in the esophagus above 4 for at least 16 hours a day due to the rapid metabolism and elimination of the drug (the problem of genetic polymorphism of the cytochrome P450 isoenzyme CYP2C19) [23]. Secondly, slight acidic reflux, as well as the predominance of generally alkaline duodenal contents in the refluxate can be the reason for the ineffectiveness of PPIs. As mentioned already, reflux is mainly acidic in only half of patients with GERD [24]. The ineffectiveness of PPIs is often due to non-compliance with the physician's recommendations or the wrong choice of the daily dose and treatment duration [25]. In addition, one of the mechanisms for the development of resistance to therapy in patients with GERD may be an imbalance between cellular and humoral components of immunity, determined both by the macrophage phenotype and by other immune and non-immune cells that secrete cytokines. In particular, it was found that a high level of tissue interleukin-1β is a predictor of the torpid course of GERD, especially in the long-term presence of acid reflux. A high tissue level of interleukin-8, which is a potent chemoattractant and activator of WBC and other non-immune cells, predetermines the recurrence of GERD within three years despite ongoing therapy [26].

Approaches to the management of refractory GERD include: doubling the dose of PPIs, using modified-release PPIs, adding histamine H2-blockers (to control nocturnal secretion), prokinetic agents and ursodeoxycholic acid preparations [1, 4]. In this regard, we ought to mention the results of recent studies that suggest an increased risk of contracting COVID-19 for individuals taking PPIs at high doses [27].

Approaches to the management of FH and HE deserve special attention. Individuals with HE, who have physiological acid reflux, tend to respond well to treatment with PPIs. Patients with slightly acid and alkaline refluxes are usually refractory to antisecretory agents. Considering the role of visceral hypersensitivity, disorders of perception and signal processing in the central nervous system in the development of these conditions, tricyclic antidepressants in low doses (imipramine 50 mg per day, and amitriptyline 10–20 mg per day), as well as selective serotonin reuptake inhibitors (sertraline 50–200 mg per day, paroxetine 50–75 mg per day, citalopram 20 mg per day) are effective for the treatment of patients with FH and HE [20].

The high prevalence of GERD in the population and the ineffectiveness of acid suppression therapy raise the need for alternative methods of managing this disease, with physiotherapy and balneotherapy as important treatment options. Physiotherapeutic methods used for the management of GERD include sinusoidal modulated current (SMT) therapy, pulsed low-frequency electrotherapy using the electrosleep technique and transcranial electrical stimulation, ultrahigh frequency electromagnetic fields, structural resonance electromagnet therapy, low-frequency alternating magnetic

field, low-intensity laser radiation; the therapeutic use of these methods is based on complex reflex reactions of the body that lead to the normalization of changes in the nervous and endocrine systems, with an improvement in adaptive, protective and compensatory functions [28]. In particular, A. M. Korepanov and M. D. Mikhailova (2011) suggested using SMT-phoresis of chloride-iodine-bromine brine in patients with GERD. Positive changes in several clinical and functional parameters were registered, specifically, the disappearance or abatement of dyspeptic signs and pain syndrome, favorable changes in the esophageal mucosa, and decreased level of anxiety [29].

Earlier studies showed the effectiveness of balneotherapy in patients with GERD. Back in 2006, M. T. Efendieva et al. presented the results of the therapeutic use of hydrocarbonate-sulfate magnesium-sodium mineral water in patients with non-erosive GERD with cardiac manifestations. It was observed that a course of balneotherapy with potable mineral water contributes to the improvement of LES function (reflux index decreased by three times), resolution of hyperemia and edema of the esophageal mucosa (in 62 % of patients); the authors attribute the positive effects to the normalization of autonomic regulation processes [30]. L. G. Vologzhanina and E. V. Vladimirsky conducted an analysis of the treatment of 30 patients with GERD, who were divided into two groups. Group 1 patients received drug treatment (omeprazole 20 mg twice a day, motilium 10 mg three times a day) and Klyuchi sulfate-magnesium-calcium mineral water (200 ml three times a day). Group 2 patients received the same medications but no mineral water; the effectiveness of treatment was assessed based on the results of EGD fibroscopy, morphological analysis of gastric and esophageal biopsy specimens, 24h pH-metry of the esophagus and stomach. The results obtained by the authors revealed that the addition of Klyuchi mineral water to the standard treatment of GERD reduces the time required to stabilize the clinical, endoscopic, and morphological signs of the disease [31]. A study performed in Bashkortostan demonstrated that a course of potable Kazanchinskaya low-mineralized bicarbonate-sulphate calcium-magnesium mineral water in patients with non-erosive GERD improves the functional state of LES, with a significant decrease in reflux index (apparently due to the normalization of the production of the vasoactive interstitial polypeptide); it also has a pronounced anti-inflammatory effect that persists for six months [32]. A. N. Kazyulin et al. (2016) presented the results of a study of the effectiveness of mineral natural bicarbonate sodium water of the Borjomi deposit in patients with GERD and with no esophagitis. The group of patients who received combined treatment (PPIs and mineral water) experienced a faster resolution of such GERD signs as heartburn, belching, bitter taste in the mouth, and sleep disturbances than the group that received monotherapy with PPIs. The authors suggest that the positive clinical effect in patients who received combination therapy was due to its more pronounced acid suppression effect, as well as the normalizing effect of micronutrients in mineral water on the functional state of the upper digestive tract [33]. An open-label, single-center, experimental clinical trial conducted in Germany evaluated the efficacy and safety of high bicarbonate mineral water in patients with GERD [34]. The high efficacy of balneotherapy in reducing the frequency and severity of heartburn episodes was demonstrated; this improved the quality of life of patients. The study conducted by Dragomiretska N. et al. (2020) included 90 patients with GERD. After a preliminary assessment, all patients were randomly divided into three groups of 30 individuals. The control group (group 1) received PPIs; group 2, in addition to PPIs, received highly mineralized boron-bicarbonate-sodium water. In addition to basic therapy, group 3 patients were prescribed a course of treatment with highly mineralized sulfate-hydrocarbonate sodium-magnesium water. Basic therapy for one month in the control group resulted in no significant resolution of dyspeptic and asthenic syndromes. Using highly mineralized boron-bicarbonate water led to a significant decrease in abdominal pain and dyspeptic signs and improved acid secretion function of the stomach. However, there were no significant changes in the parameters of cytolytic, mesenchymal-inflammatory and cholestatic syndromes. Using highly mineralized sulfate-bicarbonate sodium-magnesium water contributed to the elimination of dyspepsia and pain syndrome, as well as to the normalization of the functional state of the liver [35].

Investigation of the mechanisms of the effect of mineral water on the functional state of the gastrointestinal tract in patients with GERD deserves special attention. Among the probable ones are the direct buffering effect of mineral water anions on gastric fluid protons [36], decreased activity of lipid peroxidation [37], anti-inflammatory effect of balneotherapy with potable mineral water [38], neurohumoral regulation of the motility of the lower esophageal sphincter due to the normalization of the production of the vasoactive interstitial polypeptide [32], positive effect of balneotherapy on carbohydrate metabolism in patients [39]. Many aspects of the rationale for the therapeutic use of potable mineral water in patients with GERD require thorough analysis.

Therefore, the issue of controlling signs and improving the prognosis for patients with GERD remains relevant despite the availability of advanced diagnostic methods and pharmacotherapy. This disease has a complex and multicomponent pathogenesis; many of its components require thorough analysis and clarification, and approaches to its treatment should be improved and individualized. Balneotherapy with potable mineral water can be one of the methods to increase the effectiveness of treatment of patients with GERD.

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