Gastroesophageal reflux disease: current state of the problem and prospects

Y. S. Tsimmerman, L. G. Vologzhanina
Perm State Medical University n. a. E. A. Vagner, Perm, Russia

Let's see what we know, and we will try to formulate it as best as possible.
Niels Bohr (1885–1962)

Key words: gastroesophageal reflux disease, definition, epidemiology, etiology and pathogenesis, clinical manifestattions, diagnosis, classification, treatment

Gastroesophageal reflux disease (GERD) is one of the unsolved problems of modern gastroenterology.

The term "GERD", or reflux disease of the esophagus, was first proposed in 1999 at the Genval Symposium [52].

Definition. We consider GERD as a chronic, recurrent disease characterized by characteristic clinical signs (heartburn, acid regurgitation, dysphagia) caused by spontaneous, regularly repeated retrograde reflux of acidic gastric and/or alkaline duodenal contents in food of water with damage to its distal sections (inflammation, erosion, peptic ulcer), and in some cases also with extra-oesophageal manifestations ("masks") [12, 14, 30, 32].

Prevalence. GERD is one of the most common gastroenterological diseases. In Western Europe, North and South America, its prevalence in the population is 10 — 20%. In Asia, GERD is much less common: in China, 2.5%, in South Korea — 3.5%, which may indicate the importance of ethnic differences, as well as the role of lifestyle and nutrition [50].

According to the population study (under the program) in 12 major cities of Russia periodically experiencing heartburn, 61.7% men and 63.6% of women [6, 18], and GERD is diagnosed in 13.3% of the Russian population with a certain tendency towards hedgehog Useful growth. Recently, there has been an increase in GERD in young people and an increase in erosive-ulcerative forms of reflux esophagitis (RE).

At 8 — 20% of patients with GERD regi striruyut development esophagus Bar Rett (PB) at which the substitution multilayer squamous neorogovevayuschy epithelium of the esophagus cylindrical enteric epithelium with the development of intestinal metaplasia, and epithelial dysplasia (pre- cancer) and increased risk of adeno carcinoma of the esophagus (20 — 30 times). According to Japanese authors PB frequency in GERD (endoscopy) is 0.1 — 0.3%, and adenocarcinoma frequency — 0.08 in 100 thousand people. [54]. The higher the degree of dysplasia in PB, the higher the risk of adenocarcinoma of the esophagus: at a low degree of dysplasia — 0,5%, at a high — 6% [27, 29]. It should also be noted that with GERD, adenocarcinoma is much more likely to develop than squamous cell carcinoma of the esophagus: in a 9: 1 ratio [27].

GERD dramatically reduces the quality of life (QOL) of patients, surpassing in this respect such diseases as untreated ulcer disease (IB), angina pectoris and chronic heart failure [53]. Thus the productivity and quality of the work performed are reduced by 20 — 30%. Insomnia develops in 64% of GERD patients [17, 22, 48].

Etiology and pathogenesis. The etiology of GERD has not been established. Of predisposing factors are most often called: psychoemotional disadaptation; excess body weight (obesity); malignant smoking and chronic alcoholism; repeated pregnancies; a hernia of the esophageal aperture of the diaphragm (hiatal hernia) and lesion of the esophagus with systemic scleroderma [1, 22, 31].

Thus, patients with GERD were diagnosed with *psychoemotional lability,* an increased level of reactive anxiety, depression, as well as a depressed mood and poor state of health (the SUN test). In addition, there was a change in the personal characteristics of patients with GERD with

a predominance of hypochondriacal traits and asthenia, panic attacks, as well as signs of autonomic dystonia, manifested by imbalance of its parasympathetic and sympathetic divisions [3, 24, 26, 31, 73, 77].

Overweight (obesity) is diagnosed in cases where the body mass index (BMI)>30 In obesity observes a high level of ***leptin*** in the blood: it stimulates the production of gastrointestinal peptides ***(ghrelin)***and neuropeptides (vazoak tive intestinal peptide — VIP) which, in turn, causes the release of nitric oxide (N O), which inhibits the peristaltic activity of the esophagus and reduces the tone of the lower esophageal sphincter (NPS). If in healthy people the pressure in the NPS is, on average, 19.7 ± 7 mm Hg, in patients with GERD it decreases to 11 ± 3 and even up to 3 ± 1 mm Hg. Art. (2 to 6 times). The content of nitrogen oxide increases is 5 — 8 times — up to 130, 7 ± 10,8 mmol/l (at a rate of 32.15 ± 0.51 mmol/l), and for the development of ER reaches 215,52 ± 12 02 μmol/l [8, 19, 70]. In 1998, D. P.Hirsch found that it is a neurotransmitter N0 performing relaxation NPC — it is the main inhibitory neurotransmitter, which determines the degree of relaxation of the NPC in GERD. It is synthesized in the cytoplasm of the esophagus and stomach myocytes, activating the guanylate cyclase with the formation of cGMP, and the receptor is the iron atom in the active center of this enzyme, causing the relaxation of the NPS and thereby reducing the antireflux barrier of the esophagus [63].

In addition, the adipose tissue produces pro-inflammatory cytokines (IL-1 (3, IL-6, TNFα), promoting the development of ER [21].

Long-term systematic smoking (indicator: "pack- years") reduces the tone of the NPS and increases the risk of adenocarcinoma in GERD (up to 40%) [56].

Relaxation NPCs also cause: regular use of strong coffee and tea, chocolate, coca-cola, concentrated alcoholic beverages, sour fruit juices, fatty and fried foods.

Of great importance in the development of GERD is the *long-term use of therapeutic agents*, relaxing NPCs: cholinolytics, and calcium antagonists, antidepressants, p-adrenoblockers, myopic antispasmodics, nitrates, glucocorticoids, theophylline [56].

Repeated pregnancies are accompanied by a significant increase in intra-abdominal pressure, especially in 2- yu half of pregnancy, which helps reduce the tone of NPS and GER. It is noted that if there are 4 genera in the anamnesis, the frequency of GERD reaches 22% [35]. Intra-abdominal pressure also increases with ascites and pronounced meteorism.

With hiatal hernia and lesion of the esophagus with systemic scleroderma, the deficiency of the NPS develops as a result of partial or complete disruption of its anatomical structure and primary muscular lesion — connective tissue dysplasia, respectively [60].

Pathogenesis. The most important factor in the pathogenesis of GERD is the failure of the antireflux barrier, represented by the NPS and the diaphragm stems. It is based on a defect of neuromuscular control of the NPS function or its primary muscular lesion (chiatal hernia, systemic scleroderma with esophageal lesions) [13, 30, 32, 36, 47].

In the pathogenesis of GERD are important:

1. The frequency of relaxation (episodes of relaxation) NPC. The inconsistency of the antireflux barrier can be caused by a violation of the intramural innervation of the NPC; spontaneous functional relaxation of the NPS; a violation of the anatomical integrity of the NPC (chiatal hernia) or primary lesion of the NPC (esophageal damage in systemic scleroderma) [17, 47, 61].

2. Penetration of the lower third (n/3) of the esophagus of refluxate containing hydrochloric acid and pepsin of gastric juice, and (with duodenal gastral reflux — DGR) of toxic bile acids and lysolecithin (detergents) with a high damaging potential.

3. Slowing down (decreasing) clearance of the esophagus, manifested by a violation of the secondary peristalsis of the esophagus, which expels the refluxatum that entered the esophagus, back into the stomach.

4. Reduction in the production of bicarbonates in the esophagus and saliva swallowed from the mouth, partially neutralizing acid reflux, penetrated into the esophagus from the stomach with GER.

5. Reducing the resistance of esophageal mucosa, develops scheysya for various reasons — its ability to resist the damaging influences (refluxate).

6. Violation of the motor-evacuation function of the stomach, accompanied by stagnation of its contents and increased intragastric pressure.

7. Duodenal stasis (chronic duodenal obstruction), which occurs with hypertension in the duodenum (DUK) and creates conditions for GDR with the entry into the stomach of duodenal contents, which includes detergents (toxic bile acids and lysolecithin).

8. Development of autonomic dystonia, which causes hypotension (weakness) of NPCs, which contributes to GER.

9. In the presence of osteochondrosis of the thoracic spine with involvement of the spinal cord in the pathological process (segments Th 6 and Th 7), which regulate the motor function of the digestive tract, there is sympathicotonia, which reduces tone and peristaltic activity of the esophagus and stomach and causes impairment of blood supply in the pool of the celiac artery. This leads to a decrease in the tone of the NPS, a shortening of the cardia and a decrease in the pressure gradient in the zone of cardioesophageal transition (CEP), promoting GER and penetration of refluxate into higher regions of the esophagus. Decreased peristaltic activity of the esophagus and episodic antiperistaltic disease cause high (proximal) GERs reaching the oral cavity, larynx and bronchi [6, 5, 13, 30, 47, 61, 63].

The source of acid GER is postprandial *"acid pocket"* ("acid lake"), which is a layer of non-brewed (not mixed with food) hydrochloric acid, located in the cardiac part of the stomach, below the CEP and NPS. It is formed after eating food on the surface of the contents of the stomach due to poor mixing of the hydrochloric acid of gastric juice and nutrients in the proximal part of the stomach (cardia) due to its expansion (from 2 up to 4 — 6 cm) for up to 2 hours and due to weak peristalsis in this part of the stomach. Here a layer of refluxate with a high acidity accumulates, which is thrown into the esophagus with each GER, causing excruciating heartburn and damage to its mucous membrane [3, 13, 17, 68].

In addition to acidic GER, mixed (acid-alkaline) and alkaline GER are possible, which develop as a result of increased pressure in the duodenum (with chronic duodenal obstruction — HDN) and DGR with the entry of DHK contents (bile, pancreatic juice) into the stomach [33]. Alkaline GER affects the risk of erosive ulcer ER and PB [5, 27, 29, 30, 41, 53, 54]. The damaging effect of alkaline refluxate on the esophageal mucosa is largely due to its effect on the cellular genome in which chromosomal aberrations occur [29].

In the pathogenesis of GERD, a certain imbalance in the peptide system is given some importance. Thus, the pathogenetic role of endothelium, calretinin, melatonin, serotonin and neurotensin-producing cells, as well as disturbances in cellular renewal (regeneration), with an increase in the proliferative activity of esophageal epitheliocytes, which are controlled by such *regulatory molecules as Ki-67, Bcl-2 and p53,* as well as nitrogen oxide (N0). The majority of patients with GERD have increased proliferative activity of epitheliocytes of the esophageal mucosa and excessive expression of Bcl-2 and p53 [62].

One of the important pathogenetic factors of GERD is a *decrease in tissue resistance of the esophageal mucosa* due to dysfunction of pre-epithelial, epithelial and post-epithelial mechanisms of its defense. First of all, the *mechanism of pre-epithelial protection,* consisting of an aqueous layer, a mucous coating and a layer of bicarbonate ions, neutralizing the acid refluxate, thrown into the esophagus from the stomach, is violated. It ensures the maintenance of the pH in the esophagus in the range of 7.3 — 7.4.

Saliva entering the esophagus from the oral cavity, which has a slightly alkaline reaction, has a certain significance, it also contains mucin, mussel proteins, epidermal growth factor (EGF), and prostaglandins Er. They stimulate mucus formation, secretion of bicarbonates, provide adequate

blood supply and physiological regeneration of multilayered squamous epithelium of the esophagus. With GERD, the formation of pre-epithelial protective factors is significantly reduced. *The epithelial level of protection* is represented by the structural and functional features of the esophageal epitheliocytes themselves and is carried out by continuous physiological regeneration of the basal cells of the esophageal epithelium that prevents erosion and ulceration. *Postepithelial level of protection is* provided by adequate blood supply to the esophageal mucosa and maintenance of tissue pH in the range of 7.3 — 7.4, which serves as the basis for its cellular resistance, which opposes the aggression of H^+-ions of gastric juice in the ED. As studies have shown, it is the disorders in the microcirculatory bed of the esophageal mucosa that are detected already in the initial stage of GERD in 84.5% of cases, preceding the development of ER and erosive-ulcerative lesions in the distal part of the esophagus [7, 15].

During the last 20 — 25 years, supporters of the concept of the leading role of Helicobacter pylori (Hp) -infections in the development of gastroduodenal diseases tried to prove the involvement of Hp in the development of GERD, but these attempts were unsuccessful. Moreover, evidence-based studies have established: 1. With GERD, the frequency of detection of Hp in the stomach is lower than in the general population: 52.4% versus 76 — 91% [76]; 2. after eradication (destruction) Hp number GERD patients does not decrease, but rather increases by 1.5 — 2 times and increasing the number of its severe complications — PB (precancer) and adenosine esophagus nokartsinomy [42, 58, 59]; 3. The presence in the stomach of Hp, especially its CagA- positive strains, plays a protective role, preventing somehow the development of GERD and its menacing complications [71]. In the latest revision of the *"Maastricht Consensus"* (MC) — "MK-4" (2010, Florence), regulating indications for Hp eradication, methods for its diagnosis and treatment of diseases associated with the Hp-infection, its authors-compilers were are forced to make an important recognition: *"Hp does not affect the severity, frequency of symptoms and the effectiveness of treatment with GERD, and epidemiological studies demonstrate a negative correlation between the prevalence of Hp and the development of GERD and adenocarcinoma of the esophagus"*[51], i.e. indicate an increase in GERD and its menacing complications.

Using multivariate analysis, it was found that after successful eradication of Hp symptomatic GERD occurs in 37% of patients, and if unsuccessful — only 13%, as determined by endoscopic signs RE y 21 and 4%, respectively [64]. These facts acquire special significance in connection with the proclaimed adherents of the concept of the leading role of Hp infection in gastroduodenal diseases and other diseases of the strategy for total destruction of Hp (test and treat strategy).

We found that the presence of Hp in the lower third of the esophagus does not exceed 14.2%, and they colonize only the centers of gastric metaplasia [30, 32].

Clinical picture. The GERD clinic is diverse and variable. In addition to the typical clinical picture display characteristic for GERD symptoms — such as heartburn (85%), acid regurgitation (52%) and dysphagia (20%), frequently observed atypical manifestations of the disease, its *clinical "mask":* psevdokoronarny syndrome, bronchopulmonary and laryngopharyngeal syndromes.

Heartburn is perceived by patients as a burning sensation that spreads up the esophagus, up to the neck, and is a consequence of penetration into the esophagus of acid refluxate (pH <4.0), which irritates its mucous membrane. The intensity of heartburn is determined by the concentration of H^+ ions in refluxate, the frequency of GER and the duration of its contact with the mucosa of the esophagus. Frequent and prolonged heartburn significantly reduces the quality of life (QOL) of patients with GERD.

Acid regurgitation is the second most important clinical symptom of GERD. It is based on an acidic GER spreading high in the proximal direction (up the esophagus) and reaching the oral

cavity. It is with a high GER with acidic regurgitation that the laryngopharyngeal and broncho-pulmonary "masks" of GERD develop.

Dysphagia with uncomplicated GERD is rare, appearing sporadically, and is caused by motor dyskinesia of the esophagus and its spastic contraction. Syndrome of dysphagia quickens and becomes persistent, progressive character with complications of GERD esophageal stricture scar, and especially — during his defeat adenocarcinoma.

The episodes of a *night "acid breakthrough" with a* duration of 60 min or more, aggravating the course of the underlying disease, are described in GERD [6, 13].

The severity of the clinical symptoms of GERD is assessed according to the *"Severity Scale of Clinical Symptoms"* (symptom burden): *"0 points" — there* are no clinical symptoms; *"1 point"* — mild symptoms; *"2 points"* — pronounced but tolerable symptoms (tolerable); *"3 points"* — pronounced symptoms that cause trouble (troublesome); *"4 points"* — intense symptoms [3].

Approximately 50% of GERD patients do not go to the doctor for a long time, limiting themselves to self-medication.

Non-esophageal "masks" of GERD. First of all, should be discussed bronchopulmonary (respiratory) "mask" GERD manifested persistent chronic cough with occasional appearance of dyspnea (in 10 -20%); chronic bronchitis with recurrent course; bronchoobstructive syndrome; bronchial asthma; aspiration pneumonia; paroxysmal nighttime apnea.

To explain the mechanism of bronchopulmonary symptoms in GERD, 2 theories are proposed: 1. reflux and 2. reflex.

According to the reflux theory, bronchopulmonary symptomatology with GERD appears due to a high proximal GER reaching the oral cavity, with multiple microaspiration of acidic and acid-alkaline reflux in the respiratory tract. An additional factor may be the hypotonia of the upper esophageal sphincter, as well as the features of the epiglottis structure and its dysfunction, leading to a violation of the closure of the glottis during the swallowing act. Aspiration of refluxate in the respiratory tract leads to damage to the bronchial mucosa with destruction of the surfactant layer and pulmonary alveoli.

Reflex theory attaches importance to the specific esophago- bronchial reflex resulting from the constant irritation with acid and acid-alkaline reflux of the esophagus receptor apparatus that is transmitted to the respiratory tract and accompanied by hyperreactivity of the bronchi with the development of chronic bronchitis, bronchospasm, and GERD-dependent bronchial asthma (BA). It was found that GERD is diagnosed in 30 to 90% of patients (on average, in 57%) who suffer from this form of asthma. Attacks of suffocation appear in them as a result of reflex bronchospasm, usually after eating, increasing in an inclined position.

A correlation was established between the severity of ER in patients with GERD, the level of pH decrease in the esophagus and the frequency of respiratory disorders. Epitheliocytes of the esophagus and stomach that produce endothelium-1, melatonin and NO- sint-alu take part in this process [13, 16, 25, 30, 49, 57].

Less common is the *laryngopharyngeal "mask" of GERD.* It is caused by the penetration of acid refluxate into the mouth, the larynx and pharynx with repeated regurgitation. Clinically, it manifests itself as a rough barking cough, a sore throat, hoarseness (dysphonia), especially in the morning, and significantly increases the risk of developing laryngeal cancer [4].

Some authors additionally distinguish *dental lesions* in GERD, which occur with the erosion of tooth enamel, dental caries, periodontitis and stomatitis.

Important is *pseudo-coronary "mask" GERD*, which is characterized by the appearance of burning, pressing pains in the lower part of the sternum with a broad irradiation (in the jaw, in the arms, in the back), simulating angina, and is described as *"pop cardiac chest* pain ". It is believed that in 52.4% of cases the appearance of chest pains not associated with coronary artery disease is due to GERD [74]. Noncranial chest pain with GERD appears, usually after eating, accompanied by a sensation of a coma in the throat and pain when swallowing (*lonely phagia)*,

is strengthened when the body tilts forward and is stopped by the use of antacids and inhibitors proton pump, but can also be facilitated by taking nitroglycerin.

Complications. The most serious complications of GERD are: *Barrett's esophagus* — PB (precancer) and *adenocarcinoma of the esophagus.*

In PB, substitution of a multi-layered flat neo- sparing epithelium of the esophagus with metaplastic small intestinal cylindrical epithelium occurs. In the development of PB, an important role is played by *alkaline refluxate, which* first enters the stomach (DGR), and then into the esophagus with duodenogastroesophageal reflux. It contains toxic bile acids and lysolecithin (detergents) [41].

Factors that increase the risk of development of PB are also malignant smoking and overweight (obesity), in which the frequency of PB increases by 2.5 times.

As a result of the action of refluxate on the epithelium of the esophagus, the cellular genome is damaged, — chromosome aberrations occur, translocation in chromosomes 7 and 11 and absence of Y — xpo- mosoma are noted [54]. In the processes of cellular interaction of many genes, *catherins* (catherin), which are representatives of a large family of cellular adhesion molecules, participate. They join the special cytoplasmic proteins — *catenin* (catenin), which are associated with the actin of the cell cytoskeleton, influencing the adhesion processes and promoting both nasal growth and metastasiro tumors. When PB dysplasia and esophageal epithelium expression of E-ka d Guerin and P-catenin in the cell membrane decreases and increases their expression in the cytoplasm and nuclei of cells [11].

There are no pathognomonic clinical symptoms in the PB. Moreover, in some cases it can proceed asymptomatically and remain undiagnosed for a certain time. According to the results of autopsy, the prevalence of PB was 16 to 21 times higher than the frequency of clinically diagnosed cases [53, 54].

When endoscopy of the esophagus PB is diagnosed on the basis of pink and red coloration of the affected area of the mucosa, extending from below upwards along the esophagus, resembling *"tongues of flame"*.

"Stepwise" biopsy of diseased mucosa of the esophagus IB reveals foci specialized metaplasia cylindrical enteric epithelium with goblet (goblet) cells.

It is accepted to distinguish: PB short (<3 cm) and long (> 3 cm) and the stages of its development: *stage 1* — small intestinal metaplasia and goblet- cells; *Stage 2* — easily Separated heavy and epithelial dis plasia (neoplasia). *Morphological criteria of dysplasia are:* enlargement of nuclei; change in the nuclear-plasma ratio; the growth of cellular and nuclear polymorphism and mitotic activity. With the integrity of the basal membrane, epithelial dysplasia is diagnosed, and when the mucous membrane is invaded — early esophageal cancer [2, 27, 29, 53, 54, 72].

Erosive-ulcer ER in 2% of cases is complicated by bleeding, which is never *excessive*, but with frequent repetition can lead to iron deficiency anemia.

Peptic ulcer of the esophagus, being a complication of GERD, is usually localized in its distal part and only in the centers of gastric metaplasia with replacement of the flat epithelium of the esophagus by the cylindrical epithelium of the stomach of the base or cardial type. When scarring a peptic ulcer, esophageal stricture may form.

GERD can be combined with a syndrome of functional (gastroduodenal) dyspepsia (SFA), irritable bowel syndrome (IBS) and ulcer disease (IB) [3, 32].

Diagnostics. *Mayo criteria are* proposed *for the* diagnosis of GERD. They include the presence of heartburn and/or acid regurgi tation at least 1 times a week for the last 12 months. In addition, *in the diagnosis of GERD, the following are used:* 1. *esophagofibroscopy*, which allows visually to detect the presence of changes in the diastolic part of the esophagus (catarrhal inflammation, erosion, ulceration, peptic ulcer, stricture, PB, cancer). Classifications have been developed reflecting the extent (stage) and nature of endoscopically detected changes in the esophageal mucosa.

I. *Classification Savary — Miller* (1978) in the modification of Carrison et al. (1998) proposes to distinguish the following stages: *" 0 stage* ": endoscopic signs of the ER are absent; *"I stage* ": presence of catarrhal RE; " *II stage* ": single linear erosion, occupying less than 10% of the area of the distal esophagus; *«III stage":* the presence of multiple erosions drain rounded and/or ulceration by 10 — 50% area of the distal esophagus; *"IV stage":* there are multiple circularly located erosions and/or ulcers occupying more than 50% of the area of the distal esophagus; *"V stage":* the presence of complications of GERD (deep peptic ulcers, esophagus stricture, Barrett's esophagus).

II. *Los Angeles classification: "stage A": the* presence of one or more erosions or ulcers longer than 5 mm, limited to the limits of one fold of the esophageal mucosa; *"Stage B":* one or more lesions of the esophageal mucosa in the form of erosions or ulcers longer than 5 mm, limited to the limits of two folds; *"Stage* C": defeat of the esophagus mucosa, extending to 2 or more folds, occupying less than 75% of the esophagus circumference; *"Stage D* ": esophageal lesion, which captures more than 75% of the circumference of the esophagus.

We prefer the Savary — Miller classification.

With GERD, the *endoscopically negative form of the disease* predominates (65%). At the same time, as our studies have shown, when supplementing the esophagogic fibroscope with targeted biopsy with a morphological study of biopsy specimens with endoscopically negative GERD, a catarrhal RE is often identified. Thus, a comparison of the results of visual and morphological studies of the esophagus showed that the signs of catarrhal RE are determined in 23.8 and 64.3%, respectively. morphologically, ER is diagnosed 2.5 — 3 times more often than with endoscopy [30, 32]. Therefore, only a histological examination of biopsy specimens from the distal esophagus allows us to establish the true frequency of the ER in GERD. And the initial signs of the inflammatory process should be sought in the zone of cardioesophageal transition (CEP), from where the inflammation spreads to the esophagus. To diagnose ER with endoscopically negative GERD, in addition, *video endoscopy is used* to detect the presence of edema and hyperemia in the esophagus mucosa, as well as *fluorescent endoscopy* using a 437-nm blue light source: it performs visual registration of the intrinsic glow of various esophagus tissues. In this case, a sensitive chamber is used which records the *autofluorescence of* \ the camera is attached to the eyepiece of the endoscope and to the processor that enhances the fluorescent signal [29, 55].

Morphologically, the presence of the ER is confirmed by: thinning of the epithelial layer due to dystrophy and atrophy; presence of necrosis of calcitons in the surface layers; thickening of the basement membrane and its sclerosis; disruption of stratification of the epithelium of the esophagus; the fullness of the vessels; an increase in the number of papillae; inflammatory lymphoplasmocytic and nifiltration with an admixture of eosin fils, neutrophils and macrophages; defibration of muscle fibers; the appearance of interepithelial lymphocytes (MEL), as well as the presence of a *"dentate line"* (linea serrata; Z — linea), which delimits the area of metaplastic cylindrical epithelium from the flat epithelium of the esophagus [13, 30, 32, 72].

For visual detection of BOP and esophageal adenocarcinoma can use *hromoezofagoskopiey*, coloring is time -conjugated sites of esophageal mucosa with using 1.5% solution Liu hoľa or 0.5% solution of methylene blue (20 ml): dye selectively accumulates at sites of intestinal metaplasia (PB), and tumor growth (adenocarcinoma), facilitating the choice of site for targeted biopsy [66].

One of the most informative methods for diagnosing GERD is the multichannel diurnal and pH-metry of the esophagus, the cardial and antral parts of the stomach, which reveals the presence of the disease in 88 to 95% of cases. Diagnosis of GERD is based on the identification of acidic GERs, which reduce the pH level in the food to < 4.0. At the same time, the amount of acidic GER should exceed 50 per day, and the total duration of time, during which the pH in the esophagus < 4.0, is more than 1 hour/day. To confirm the diagnosis of GERD it is necessary to

establish that the clinical symptoms of GERD (heartburn, acidic eructation) arise within the first 5 minutes after registration on the pH meter of the next acidic GER.

With the daily pH-metry of the esophagus, the following parameters are determined: 1. the total time during which the pH in the distal part of the esophagus is < 4.0 (in the vertical and horizontal positions of the patient); 2. the number of acidic GER per day, and also (separately) the amount of zakie fusion of the esophagus lasting> 5 min; 3. maximum duration of one acid reflux; 4. *De Meester index is an* integral indicator reflecting the exposure of acid in the esophagus during the entire Study Time (per day) in the vertical and horizontal positions of the patient (norm < 14.72) [9, 30]. Pathological GERs are recognized that exceed the norm by 95% and more, and especially dangerous are considered acidic GER at night (" *night acidic breakthrough* ") [3, 13, 30, 32].

The peristaltic activity (motor) of the esophagus and the tone of the NPS in GERD are determined *by the method of esophagomanometry* recording the decrease in the amplitude of the esophageal contractions and the tone of the NPS.

More informative is the *multichannel intraluminal impedance of manometry,* which registers the change in impedance (impedance) and allows estimating the violation of the spatial geometry of the esophagus and the magnitude of the amplitude of peristaltic waves. A promising trend in impedance-manometry is the creation of combined probes combining 2 electrodes: to record intraluminal pressure (impedance) in the esophagus and to determine the pH level, providing the possibility of esophageal im- pedance-pH monitoring [3, 30, 32].

Other methods of instrumental diagnosis of GERD are also used.

The presence of an alkaline GER can be *ascertained by intralespiratory bilimetry, which* records the transfer to the distal part of the esophagus of the alkaline refluxate, and also when bilirubin is determined in the stomach contents (spectrometric method at a wavelength of 420 nm) and by biochemical analysis of the stomach contents for the presence of bile acids and phospholipids [5, 10].

Stand out 2 diagnostic tests: 1. Test Bernstein (Bernstein) and 2 omeprazole (rabeprazole) test.

With the Bernstein test, the esophagus is irrigated with 0.1 N. solution of hydrochloric acid (15 ml): it is considered positive if it causes a feeling of heartburn and other symptoms characteristic of GERD.

The omeprazole (rabeprazole) test consists in taking the patient daily for 7 days before breakfast 40 mg of omeprazole (or 20 mg of rabeprazole) and 20 mg of omeprazole (10 mg of rabeprazole) before lunch. If after 4 to 5 days of "trial treatment" (ex juvantibus) the clinical symptoms of GERD (heartburn, acid regurgitation) disappear, then the diagnosis of GERD is considered the most probable [48, 65, 69].

The quality of life (QoL) of patients with GERD is assessed using a general questionnaire SF- 36 (SF- 36, Healt Status Survey) [6].

Classification. In 2005, a clinical classification of GERD was proposed in Montreal, Canada. It provides for the allocation of several headings.

I. *Esophageal syndromes.* 1. Clinical (heartburn, acid regulation, dysphagia) in the absence of structural changes in the esophagus; 2. syndromes with structural damage to the esophagus (reflux esophagitis, esophageal stricture, Barrett's esophagus, adenocarcinoma of the esophagus);

P. *Extra-oesophageal syndromes:* 1. recurrent cough; laryngitis; pharyngitis; bronchial asthma of reflux nature; 2. pseudo-coronary syndrome (pain in the chest); 3. erosion of tooth enamel, dental caries, periodontitis, stomatitis; recurrent otitis media, sinusitis [67].

In the same year 2005, we proposed a *clinico-pathogenetic working classification of GERD,* in which we propose to distinguish:

According to clinical features

1. Isolated endoscopically negative GERD with typical clinical symptoms (heartburn, acid regurgitation, dysphagia).

2. Endoscopically positive GERD: a) with catarrhal RE; b) with erosive ulcer ER.

3. GERD with complicated course: a) with peptic ulcer of esophagus; b) with esophageal stricture; c) with Barrett's esophagus; d) with adenocarcinoma adenoma or (rarely) squamous cell carcinoma of the esophagus.

4. GERD with extra-oesophageal manifestations: a) with pseudo-coronary syndrome; b) bronchopulmonary syndrome (chronic cough, chronic bronchitis, broncho-obstructive syndrome, aspiration pneumonia, aspiration bronchial asthma); c) with JIOP-organ damage (laryngitis, pharyngitis, otitis media, laryngeal cancer).

On pathogenetic features

1. with acidic gastroesophageal reflux; 2. with alkaline duodenogastroesophageal reflux; 3. with hypomotor disks of the esophagus; 4. with spontaneous relaxation of the lower esophageal sphincter; 5. with reduced alkalinity of the esophagus; 6. with hernia of the esophageal opening of the diaphragm (chiatal hernia); 7. with esophageal damage in systemic scleroderma; 8. with iatrogenic effects (a long-term administration of pharmacological preparations that reduce the tone of the NPS and peristaltic activity of the esophagus) [30, 32].

Treatment. Objectives of GERD treatment: elimination of clinical complaints and improvement of patients' quality of life; elimination of risk factors; epithelization of erosion and ulceration; improvement of the histological picture of the mucosa of the distal esophagus; prevention of complications; lengthening of remission [30].

Begin treatment with ordering lifestyle (lifestyle modification) and establishing psychological contact with the patient, ensuring strict compliance with their doctor's recommendations (compliance), which include: regular fractional (4 — 5 times a day in small portions) eating at certain hours of the day; last meal for 2 — 3 hours before bedtime; refusal of products and dishes that have a sodic and irritating effect (meat broths, ears, cabbage and beetroot broths, sour fruit and berry juices, fried and smoked meat and fish, spicy seasonings, pickles and spices, etc.); maximum restriction of alcoholic and carbonated beverages, including beer and champagne; restriction of physical activity, work in tilt; a dream with a head raised 15- to 20 cm; with obesity — weight loss; women — refusal of corsets and pulling the waist; men — from tight belts; refusal of strong coffee, chocolate and Coke, reducing the tone of the NPS; cessation of smoking of tobacco products; abolition (if possible) of pharmacological drugs that inhibit peristalsis esophagus and tone-reducing NPS (they were previously listed); when flatulence — limiting the intake of legumes, as well as vegetables and fruits containing coarse vegetable fiber [6, 30, 56].

Pharmacotherapy. GERD is a type of classical ("classical") acid- dependent disease, so the main goal of treatment is to suppress acidic gastric secretion and control the pH level in the stomach and esophagus.

There is a definite hierarchy of pharmacological preparations that neutralize H^+ ions in the stomach or suppress their formation in parietal cells of the gastric glands: 1. antacids and algae; 2. blockers of Hg-histamine receptors (Hg-GH) of the gastric glands; 3. proton pump inhibitors (PPI).

Two different tactics for prescribing antisecretory drugs are proposed: 1. start treatment immediately with the use of the most potent antisecretory drugs — PPI in standard or doubled doses, and after reaching the clinical effect, switch to the use of less active drugs (Ng-BH, antacids and alginates): step — down therapy; 2. use sequentially antisecretory pharmacological preparations with increasing activity, starting with antacids and alginates, and if they are not effective, proceed to Ng-BH and IPP: step — up therapy.

Most gastroenterologists adhere to the first of the proposed tactics with the use of adequate doses of PPI from the very beginning [6, 30, 36].

The use of PPI in GERD is a basic therapy. PPIs are derivatives of benzimidazole. These are prodrugs: first they accumulate in the acidic environment of the tubules of the parietal cells of the gastric glands, where they are converted to *sulfenamide,* which interacts with the sulfhydryl (SH) groups of the proton pump (enzyme H7K $^+$ ATPase), causing irreversible

inhibition of the production of hydrochloric acid (HC1); while H^+ ions are replaced by K^+ ions. This acid-suppressive effect lasts up to 24 hours. The effectiveness of PPI depends on the polymorphism of the gene encoding the cytochrome P 450- CYP 450 2C19 enzyme [1, 6, 14, 24, 30, 46, 67].

Currently, there are 5 drugs of PPI, which are used in the treatment of GERD in standard or doubled doses (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole). Their effectiveness is approximately the same, although some authors prefer rabeprazole, since it has the highest dissociation constant (4.53), while in omepra ash and esomeprazole it is 4.0 6, and in lansoprazole and pantopra, ash is 3, 83. This provides rabeprazole a faster transition into an active form [68]. Standard doses of IPP are: omepra ash — 20 mg, lansoprazole — 30 mg, pantoprazole — 40 mg, rabeprazole — 10 mg, esomeprazole — 20 mg; the course of treatment — 4 — 6 weeks [30, 36].

After cancellation of IPP, relapses of GERD within the next 6 months develop in 80% of patients. Therefore, after the end of the main course of treatment, *long-term maintenance therapy is* needed: within 16 to 24 weeks.

There are several options for maintenance treatment:

1. regular (systematic) reception of PPI in a half dose; 2. *"on-demand"* therapy (pro re nata), which is performed with relapse of typical for GERD clinical symptoms (heartburn, acid regurgitation, dysphagia) lasting more than 5 days; 3. *"Weekend therapy"* (on Saturdays and Sundays); 4. *"therapy by necessity»* (on demand), when, along with recurrent clinical symptoms of GERD symptoms appear ER [21, 22, 30].

Blockers, H2 receptor histamine (Hl-RG) located on the apical membrane of the parietal cells of the gastric glands, significantly inhibit acid production in the stomach for 8 h (ranitidine) and 10 — 12 hours (famotidine), and famotidine 6 — 8 times more potent than ranitidine, but they are both inferior to the IPP effect. In addition, N-RH blockers have serious disadvantages: 1. after their cancellation, production of hydrochloric acid in the stomach increases sharply ("rebound symptom"); 2. with a re-appointment, their effectiveness is rapidly reduced ("the phenomenon of tachyphylaxis"). In the treatment of GERD blockers Ng-RG their dose is usually 2 times higher than the standard: ranitidine administered with 300 — 600 mg/day; famotidine — for 40 — 80 mg/day; take them after eating and before going to bed [45].

At the same time, monotherapy of GERD with the use of IPP or blockers Ng-RG (singl e — agent therapy) can hardly be called the optimal method of treatment, — *complex therapy* with the use of other pathogenetic and symptomatic drugs is needed.

Prokinetics are a means of pathogenetic therapy of GERD: they strengthen and normalize peristalsis of the esophagus, stomach and duodenum; increase the tone of the NPS; prevent GER and improve the esophageal clearance, reducing the time of direct contact of refluxate with the mucosa of the food. At the same time, the mo- tor-evacuator function of the stomach and PDC improves, alkaline DHS is prevented. From prokinetic use in the treatment of GERD: *mochi lium* (domperidone) 10 mg 3-4 times/day *Ganaton* (itopride hydrochloride) 50 mg 3 times/day for 3 — 4 weeks [20, 30]. Received recognition as a means to normalize the motor and evacuation function of the digestive tract in GERD *the trim butyne* (debridat, trimedat) — antagonist opioid receptor enkephalinergic acting on the motor regulation system. It has a normalizing effect on the motor skills of the esophagus, stomach and intestines, both in hyperdiscine and in hypodesis. Take it at a dose of 200 mg 3 times/day 30 minutes after eating, 3 — 4 weeks.

With regard to the use of *motilium (domperidone),* which is a blocker of dopamine receptors with prokinetic properties, it has recently been established that it blocks the potassium channels of the cardiac conduction system and increases the Q — T interval, contributing to heart rhythm disturbances.

However, recent studies have shown that it can still be used as a prokinet in the treatment of GERD, with the exception of patients suffering from both moderate and severe hepatic insufficiency, as well as during pregnancy, lactation and children under 12 years of age [43].

Modern nonabsorbing antacids (maalox suspension, fosfalugel, Almagel-neo, etc.) are used in the treatment of GERD as symptomatic agents, if necessary, to urgently stop painful heartburn and epigastricgia. They also have adsorptive properties, neutralizing toxic bile acids and lysolecithin in DGR. An tatsidy not control the acid formation, but only chemically neutralize the hydrochloric acid which has accumulated in the stomach. The duration of their action does not exceed 40 — 60 min, so they have to be taken often. Therapeutic dose: 15 ml 4-5 times/day and at bedtime [6, 30]. Recently, the *combined antacids,* which include *si methicone,* reducing the manifestation of meteorism (alugel-forte, hestide) and containing alginic acid — *alginates* (Gaviscon, topalcane), which form an alkaline foam on the surface of the gastric contents, thrown into the n/3 esophagus with each GER, neutralizing the acid reflux in the esophagus. They take 10 — 15 ml at 1.5 hours after meals and at bedtime [3, 6, 14, 30,].

Taking into account psychoemotional and personality disorders revealed by us in patients with GERD, we recommend the use of an atypical neuroleptic *eglonil* (suppyrid), which also has a kinetic effect: 50 mg 2 to 3 times a day, 3 to 4 weeks [30, 32]. Useful also receiving *trazodone* — and ntidepressanta with anksiolitiche Skim properties; a dose of 50 mg 2 — 3 times/day.

When alkaline ERT increases risk of BOP, requires reception of *UDCA preparations* (ursofalk ur Sosan) — 10 — 12 mg/kg/day [5, 22, 23, 30, 32]. Complex therapy of GERD is more effective than PPI monotherapy.

Recently, new synthesized (combined) PPI drugs: 1. *ezolong,* in a Technical contents are subject which comprises ezomepra sol (20 — 40 mg) and sodium hydrogen carbonate (1080 mg); 2. *dexlansso prazole* (dexylant), which is a capsule with innovative technology with the release of active substance in the small intestine at various pH levels (5.5 and 7.5), providing a prolonged effect of the PPI preparation (within 24 hours). The therapeutic dose for erosive ER is 60 mg/day, for non — erosive — 30 mg/day [17, 40, 44].

At PB, there is no special medication. In therapy, PB use: high doses of PPI; laser photocoagulation, photodynamic destruction of the affected esophageal mucosa, as well as *ablative (destroying) endoscopic therapy:* argon-plasma coagulation; multipolar electrocoagulation with high-frequency currents; mucosectomy [27, 30, 72, 75].

Surgery. If the pharmacotherapy of GERD is ineffective, there is a need for surgical treatment. The main type of surgical intervention is laparoscopic fundoplication according to K. Nissen. Its essence is that a cuff around the abdominal esophagus is created by sewing the edges of the bottom of the stomach around the esophagus with the restoration of disturbed relationships in the field of cardioesophageal transition (CEP) — in fact an artificial gateway (gatekooper reflux repair system: shut-off valve) is created.

According to the testimony, other operations can be performed: according to Toupet, according to Dor:

1. back partial or bilateral classical operation by Toupet or
2. anterior partial operation of Dor, after which patients report less complaints about dysphagia and the impossibility of eructation [34, 39].

GERD is still an incurable disease with a chronic, recurrent course. Joint efforts of physiologists, pathologists, biochemists, gastroenterologists, neurologists and surgeons are required to study all the unresolved problems of its etiology, pathogenesis, timely diagnosis, prevention and effective treatment.

References:

1. Анищенко В. В. PPI-тест как дифференциальный критерий отбора к хирургическому лечению гастроэзофагеальной рефлюксной болезни / В. В. Анищенко, Е. А. Шмакова // Экспер. и клин, гастроэнтерол. — 2005. — №4. — С. 59–66.
2. Белоус Т. А. Пищевод Барретта: морфологические основы развития / Т. А. Белоус /// Российск. журн. гастроэнтерол., гепатол. и колопроктол. — 2002. — №5. — С. 63–66.

3. Бордин Д. С. Значение альгинатов в диагностике и лечении гастроэзофагеальной рефлюксной болезни / Д. С. Бордин, С. В. Колбасников, А. Г. Кононова // Русск. мед. журн. — 2014. — №15. — С. 1108–1111.
4. Бронхолегочные и орофарингеальные проявления гастроэзофагеальной рефлюксной болезни / К. В. Маев, Г. Л. Юренев, С. Г. Бурков, Сергеева Т. А. // Consilium medicum. — 2006. — №2. — С. 22–21.
5. Буеверов А. О. Дуоденогастроэзофагеальный рефлюкс, как причина рефлюкс-эзофагита / А. О. Буеверов, Т. Л. Лапина // Фарматека. — 2006. — №1. — С. 1–5.
6. Гастроэзофагеальная рефлюксная болезнь — лидер кислотозависимой патологии верхних отделов желудочно-кишечного тракта / И. В. Маев, А. А. Самсонов, П. А. Белый, Е. Г. Лебедева // Consilium medicum: Гастроэнтерология. — 2012. — №1. — С. 18–24.
7. Диагностика нарушений микроциркуляции при гастроэзофагеальной рефлюксной болезни методом допплеровской флуометрии / К. В. Маев, К. М. Щербенков, Е. Г. Лебедева, Д. Т. Дичева // Российск. журн. гастроэнтерол., гепатол. и колопроктол. — 2002. — №5. — С. 8–12.
8. Звенигородская Л. А. Регуляция оксида азота и терапия при гастроэзофагеальной рефлюксной болезни у больных с абдоминальным ожирением / Л. А. Звенигородская, Т. В. Нилова, Е. Ю. Бондаренко // Рус. мед. журн. — 2011. — №19 (17). — С. 1097–1099.
9. Значение суточного мониторирования внутрижелудочного pH в диагностике гастроэзофагеальной рефлюксной болезни и оценке эффективности лекарственных препаратов / В. Т. Ивашкин, А. А. Шептулин, А. С. Трухманов [и др.] // Клин. мед. — 1999. — №7. — С. 39–42.
10. Иванов А. И. Количественное определение желчных кислот с помощью листов SILUFOL / А. И. Иванов // Лабор. дело. — 1973. — №8. — С. 504–506.
11. Ивашкин В. Т. Пищевод Барретта / В. Т. Ивашкин, К. В. Маев, А. С. Трухманов. — 2011. — В 2-х т. — Т. 1. — С. 157–158.
12. Исаков В. А. Эпидемиология гастроэзофагеальной рефлюксной болезни: восток и запад / В. А. Исаков // Экспер. и клин, гастроэнтерология (спец. выпуск). — 2004. — №5. — С. 117–126.
13. Коварство гастроэзофагеальной рефлюксной болезни (редакц. статья) // Участковый врач. — 2015. — №1. — С. 50–52.
14. Лапина Т. Л. Гастроэзофагеальная рефлюсная болезнь: изменчивая и консервативная позиция / Т. Л. Лапина // Болезни органов пищеварения. — 2009. — №9 (1). — С. 1–4.
15. Ленберг В. В. Рефлюкс-ассоциированные гипоксические поражения слизистой оболочки пищевода / В. В. Ленберг, В. Л. Полуэктов, В. И. Кузьмин // Российск. журн. гастроэнтерол., гепатол. и колопроктол. — 2002. — №5. — С. 13–16.
16. Маев И. В. Внепищеводные проявления гастроэзофагеальной рефлюксной болезни / И. В. Маев // Экспер. и клин. гастроэнтерол. — 2005. — №5. — С. 56–66.
17. Маев И. В. Перспективы применения ингибитора протонной помпы нового поколения — декслансопразола в терапии гастроэзофагеальной рефлюксной болезни / И. В. Маев, А. А. Самсонов, Д. Н. Андреев // Фарматека. — 2015. — №2. — С. 6–11.
18. Многоцентровое исследование «Эпидемиология гастроэзофагеальной рефлюксной болезни в России (МЭГРЕ)»: первые итоги / Л. Б. Лазебник, А. А Машарова., Д. С. Бордин [и др.] // Экспер. и клин, гастроэнтерол., 2009. — №6. — С. 4–12.
19. Особенности метаболизма оксида азота при гастроэзофагеальной рефлюксной болезни / К. В. Маев, А. Н. Казюлин, Г. А. Бусарова [и др.] // Российск. журн. гастроэнтерол., гепатол. и колопроктол. — 2006. — №5. — С. 8–11.
20. Оценка клинической эффективности прокинетика ганатона (итоприд) в виде монотерапии и в комбинации с ингибитором протонной помпы при

гастроэзофагеальной рефлюксной болезни / М. Н. Подлесских, С. Г. Терещенко, Е. В. Волчкова [и др.] // Фарматека. — 2010. — №15. — С. 74–80.
21. Поддерживающее лечение у пациентов с гастроэзофагеальной рефлюксной болезнью / В. И. Симаненков, С. В. Тихонов // Фарматека. — 2014. — №2. — С. 54–60.
22. Полунина Т. Е. Поэтапное лечение гастроэзофагеальной рефлюксной болезни / Т. Е. Полунина // Фарматека. — 2013. — №6. — С. 59–67.
23. Применение урсодезоксихолевой кислоты при щелочном варианте гастроэзофагеальной рефлюксной болезни / М. М. Каримов, Г. Н. Сабирова, А. М. Ахматходжаев, З. З. Саатов // Вестн. клуба панкреатол. — 2013. — №2. — С. 39–40.
24. Психовегетативные аспекты у больных гастроэзофагеальной рефлюксной болезнью и функциональные расстройства пищевода / А. П. Погромов, Г. М. Дюкова, С. М. Рыкова, А. М. Вейн // Клин. мед. — 2005. — №12 (41). — С. 14.
25. Пульмонологическая маска гастроэзофагеальной рефлюксной болезни / К. В. Маев, Г. Л. Юренев, Д. Т. Дичева [и др.] // Consilium medicum. — Прил.: Гастроэнтерология. — 2012. — №1. — С. 15–18.
26. Рыкова С. М. Психовегетативные аспекты функциональных расстройств пищевода и желудка и гастроэзофагеальной рефлюксной болезни / С. М. Рыкова, А. П. Погромов, Г. М. Дюкова // Экспер. и клин, гастроэнтерол. — 2003. — №1. — С. 105–106.
27. Старостин Б. Д. Пищевод Барретта: выявление, мониторинг, лечение / Б. Д. Старостин // Российск. журн. гастроэнтерол, гепатол. и колопроктол. — 2003. — №3. — С. 84–90.
28. Стоматологические проявления гастроэзофагеальной рефлюксной болезни / К. В. Маев, Г. М. Барер, Г. А. Бусарова [и др.] // Клин. мед. — 2005. — №11. — С. 33–38.
29. Трухманов А. С. Пищевод Барретта: эпидемиология, патогенез, клиническое течение, профилактика / А. С. Трухманов // Российск. журн. гастроэнтерол, гепатол. и колопроктол. — 2002. — №5. — С. 59–62.
30. Циммерман Я. С. Гастроэзофагеальная рефлюксная болезнь / Я. С. Циммерман // Гастроэнтерология. — М., 2012. — С. 22–51.
31. Циммерман Я. С. Гастроэзофагеальная рефлюксная болезнь: состояние проблемы и дискуссионные вопросы / Я. С. Циммерман // Экспер. и клин, гастроэнтерол. — 2004. — №2. — С. 70–78.
32. Циммерман Я. С. Особенности язвенной болезни двенадцатиперстной кишки и гастроэзофагеальной рефлюксной болезни при их сочетанном течении / Я. С. Циммерман, Л. Г. Вологжанина // Клин. мед. — 2007. — №3. — С. 53–58.
33. Циммерман Я. С. Синдром хронической дуоденальной непроходимости: современный взгляд на проблему / Я. С. Циммерман // Клин. мед. — 2009. — №10. — С. 9–16.
34. Черноусов Ф. А. Результаты фундопликации при лечении рефлюкс-эзофагита / Ф. А. Черноусов, А. Л. Шестаков, Л. К. Егорова // Вестн. хирургич. гастроэнтерол. — 2009. — №4. — С. 64–69.
35. Шептулин А. А. Обсуждение проблемы гастроэзофагеальной рефлюксной болезни в докладах объединенной Европейской недели гастроэнтерологии (Копенгаген, 2005) / А. А. Шептулин, В. А. Киприанис // Клин. мед. — 2006. — №6. — С. 69–72.
36. Шептулин А. А. Гастроэзофагеальная рефлюксная болезнь: от мифов прошлого к реалиям настоящего / А. А. Шептулин // Клин. мед. — 2003. — №6. — С. 4–8.
37. Эффективность комбинированного антисекреторного препарата эзолонг в лечении гастроэзофагеальной рефлюксной болезни / Н. Б. Губергриц, П. Г. Фоменко, Г. М. Лукашевич [и др.] // Вестн. клуба панкреатол. — 2013. — №2. — С. 31–38.
38. American Gastroenterological Association Institute, Technical Review on the Management of Gastroesophageal Reflux Disease / P. J. Kahrilas, N. J. Shaheen, M. F. Vaezi [et al.] // Gastroenterology. — 2008. — Vol. 135. — P. 1392–1413.
39. Bagneto V. J. Laparascopic Nissen — fundoplication / V. J. Bagneto // Surg. Laparosc. Endosc. — 1992. — Vol. 2. — P. 188–190.

40. Behm B. W. Dexlansoprazole-MR for the management of gastroesophageal reflux disease / B. W. Behm, D. A. Peura // Expert. Rev. Gastroenterol., Hepatol. — 2011. — Vol. 5, No 4. — P. 439–445.
41. Bile reflux gastritis and Barrett's esophagus: further evidence of role duodenogastroesophageal reflux? / M. F. Dixon, P. M. Neville, N. P. Mapstone [et al.] // Gut. — 2001. — Vol. 49. — P. 359–363.
42. CagA-positive strains of Helicobacter pylori may protect against Barrett's esophagus / M. F. Vaezi, G. W. Falk, R. M. Peek [et al.] // Am. J. Gastroenterol. — 2000. — Vol. 95. — P. 2206–2211.
43. Cardiovascular safety profile and clinical experience with high-dose domperidone therapy for nausea and vomiting / A. Ortiz, C. L. Cooper, A. Alvares [et al.] // Am. J. Med. Sci. — 2015. — Vol. 10. — P. 1–4.
44. Clinical trials: healing of erosive oesophagitis with dexlansoprazole-MR, a proton pump inhibitor with a novel dual delayed-release formulation-results from two randomized controlled studies / P. Sharma, N. J. Shaheen, M. C. Perez [et al.] // Aliment. Pharmacol. Ther. — 2009. — Vol. 29. — P. 731–741.
45. Clossen J. R. Gastroesophageal reflux disease: rational approach inhibitor / J. R. Clossen // Drugs. — 2005. — Vol. 65, Suppl. 1. — P. 1–3.
46. Comparison of the inhibitory effects of the proton pump inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole on human cytochrome P 450 activities / X. Li, T. Andersson, M. Alstrom [et al.] // Drug Metab. Dispas. — 2004. — Vol. 32. — P. 821–827.
47. De Meester T. K. Spontaneos gastroesophageal reflux desease: evaluation of primary repair in 100 consecutive patients / T. K. De Meester, L. Bonavina, M. Albertucci // Ann. Surg. — 1986. — Vol. 204. — P. 9–20.
48. The diagnostic significance of coapplying a rabeprazole test with the SF-36 for gastroesophageal reflux disease / Y. Chen, F. Wang, Y. Jiang [et al.] // Gastroenterol. Res. Pract. — 2013. — P. 7.
49. Dobashi K. Chronic respiratory disease and gastroesophageal reflux / K. Dobashi // Nippon Rinsho. — 2002. — Vol. 60, No 8. — P. 1595–1600.
50. Epidemiology of gastroesophageal reflux disease : a systematic review / J. Dent, H. B. El-Serag, M. A. Wallender, S. Johnson // Gut. — 2005. — Vol. 54. — P. 710–717.
51. European Helicobacter Study Group. Management of Helicobacter pylori infection — the Maastricht-4, Florence consensus report / Malfentheiner P., Megraud, C. O'Morain [et al.] // Gut. — 2010. — Vol. 61, No 5. — P. 646–664.
52. An evidence-based appraisal of reflux disease management — the Genval Workshop Report / J. Dent, J. Brun, A. M. Fendrick [et al.] // Gut. — 1999. — Vol. 44, Suppl. 2. — P. 1–16.
53. Falk G. W. Barrett's esophagus: screening, surveillance and decisions on dysplasia and cancer risk / G. W. Falk // Scientific session handouts / Digestive disease week. — 2003. — P. 248.
54. Falk G. W. Reflux disease and Barrett's esophagus / G. W. Falk, J. E. Richter // Endoscopy. — 1998. — Vol. 30. — P. 61–72.
55. Fluorescence endoscopy in the gastrointestinal tract / H. Tajiri, M. Kobayashi, K. Izuishi [et al.] // Dig. Endosc. — 2000. — Vol. 12, Suppl. — P. 28–31.
56. Gammon M. D. Tabacco, alcohol and socioeconomic status and adenocarcinoma of the esophagus and gastric cardia / M. D. Gammon // J. Natl. Cancer Inst. — 1997. — Vol. 89. — P. 1277–1284.
57. Gibella F. Nocturnal asthma and gastroesophageal reflux / F. Gibella, G. Cuttitta // Am. J. Med. — 2001. — Vol. 111, Suppl. 8A. — P. 31S–36S.
58. Helicobact pylori infection is associated with a descreased risk of developing esophageal neoplasms / J. H. Simon, A. Forsgren, G. Berglund, C. H. Floren // Helicobacter. — 2001. — Vol. 6. — P. 310–316.

59. Helicobacter pylori infection and the risk of development of esophageal adenocarcinoma / E. de Martel, A. E. Llosa, S. H. Farr [et al.] // J. Infect. Dis. — 2005. — Vol. 191. — P. 761–767.
60. Hiatal hernia size in the dominant of esophagitis presense and severity in gastroesophageal reflux disease / M. P. Jones, J. C. Sloan, J. C. Rabine [et al.] // Am. J. Gastroenterol. — 2000. — Vol. 96. — P. 1711–1717.
61. Holloway R. H. The anti-reflux barrier and mechanisms of gastroesophageal reflux / R. H. Holloway // Baillieres Best. Pract. Res. Clin. Gastroenterol. — 2000. — Vol. 14. — P. 681–699.
62. Immunohistochemical analysis of Ki-67, p53 and Bcl-2 expression related to hislogical features in gastroesophageal reflux disease / S. Ayhan, O. A. Nalbant, A. Isisag [et al.] // Turk. J. Gastroenterol. — 2010. — Vol. 21, No 3. — P. 199–205.
63. Involvement of nitric oxide in human transient lower esophageal sphincter relaxantions and esophageal primary peristalsis / D. P. Hirsch, R. H. Holloway, G. N. J. Tytgat, G. E. E. Bolckxtaens // Gastroenterology. — 1998. — Vol. 115. — P. 1347–1380.
64. Is Helicobacter pylori eradication associated with gastroesophageal reflux disease? / C. A. Fallone, A. N. Barcum, G. Friedman [et al.] // Am. J. Gastroenterol. — 2000. — Vol. 95. — P. 914–920.
65. Is proton pump inhibitor testing an effective approach to diagnose in patients with non-cardiac chest pain? / W. Wang, J. Huang, G. Zheng [et al.] // Arch. Intern. Med. — 2005. — Vol. 165. — P. 1222–1228.
66. Methylene blue selectively strains intestinal metaplasia in Barrett's esophagus / M. I. Canto, S. Setranian, R. E. Petras [et al.] // Gastrointest. Endoscopy. — 1996. — Vol. 44. — P. 7–13.
67. Montreal definition and classification of gastroesophageal reflux disease. A global evidence-based consensus / N. van Vakil, S. V. Zanten, P. Kahritas [et al.] // Am. J. Gastroenterol. — 2006. — Vol. 101. — P. 1900–1920.
68. Orlando R. C. Overview of the mechanisms of gastroesophageal reflux / R. C. Orlando // Am. J. Med. — 2002. — Vol. 111, Suppl. 8A. — P. 174S–177S.
69. Pace F. The proton pump inhibitor test and the diagnosis of gastroesophageal reflux disease / F. Pace, M. Pace // Expert. Rev. Gastroenterol., Hepatol. — 2010. — Vol. 4, No 4. — P. 423–427.
70. Physiological studies on nitric oxide in the lower esophageal sphincter of patients with reflux esophagitis / R. Tomita, K. Tanjoh, S. Fujisaki, M. Fukuzawa // Hepatogastroenterology. — 2003. — Vol. 50, No 49. — P. 110–114.
71. Prospective evaluation of the prevalence of gastric Helicobacter pylori infection in patients with GERD, Barrett's dysplasia and Barrett's adenocarcinoma / A. P. Weston, A. S. Badr, M. Topolovski [et al.] // Am. J. Gastroenterol. — 2000. — Vol. 95. — P. 914–920.
72. Rajandra S. Barrett's esophagus / S. Rajandra, P. Sharma // Curr. Options Gastroenterol. — 2014. — Vol. 12, No 2. — P. 169–182.
73. Reflux symptoms are associated with psychiatric disease / B. Avidan, A. Sonnenberg, N. Giblovich, S. J. Sontag // Aliment. Pharmacol. Ther. — 2001. — Vol. 15. — P. 1907–1912.
74. Risk factor for non-cardiac chest pain in the community / J. L. Wise, G. R. Locke, A. R. Zinmeister, N. J. Talley // Aliment. Pharmacol. Ther. — 2005. — Vol. 22. — P. 1023–1031.
75. Sharma P. Ablation therapies for Barrett's esophagus / P. Sharma // Medcape Gastroenterol. — 2001. — Vol. 3, No 4. — P. 64–67.
76. Sontag S. J. Helicobacter pylori infection and reflux esophagus in children with chronic asthma / S. J. Sontag // J. Clin. Gastroenterol. — 2004. — Vol. 38, No 1. — P. 3–4.
77. Stress, personality and social support in gastroesophageal reflux disease / B. T. Johntson, S. A. Levis, A. H. Love // J. Psychosom. Res. — 1995. — Vol. 39, No 2. — P. 221–226.
78. Suncel M. Pharmacokinetics (PK) and effect on pentagastrin stimulated peak acid output (PAO) of omeprazole (O) and its 2 optical isomers S-omeprazole (esomeprazole (E) and R-

omeprazole (R-O) / M. Suncel // Gastroenterology. — 2000. — Vol. 118, No 4. — Suppl. 2. — A1210.

Gastroesophageal reflux disease: current state of the problem and prospects

Y. S. Tsimmerman, L. G. Vologzhanina
Perm State Medical University n. a. E. A. Vagner, Perm, Russia

Key words: gastroesophageal reflux disease, definition, epidemiology, etiology and pathogenesis, clinical manifestattions, diagnosis, classification, treatment

The article is a lecture for doctors which includes modern ideas about gastroesophageal reflux disease: its etiology and pathogenesis, risk factors, clinical features and diagnostics. The classification, strategy and tactics of treatment are explained in detail. The author critically evaluated the literature data and expressed his reasoned critical point of view concerning the basic concepts, diagnostics and treatment of the disease.