What is common between functional dyspepsia and bacterial overgrowth syndrome

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Functional dyspepsia (FD) is one of the most common disorders of the upper gastrointestinal tract. According to the III Rome criteria, it is determined by postprandial weight in the epigastrium, a sense of early satiety, epigastric pains or burning in the absence of an organic disease that explains the symptoms of the patients. III Roman criteria further divide FD into postprandial distress syndrome (PDS) and epigastric pain syndrome (EBS). The cardinal features of the PDS — this early satiety and a feeling of heaviness in the epigastrium after eating, while the main feature of EBS is a pain or a burning sensation in the epigastric region. [32]

The definition of functional dyspepsia has always been difficult, and despite numerous changes in the definition of FD, the problem has not been completely solved. In addition, the diagnosis, as well as the treatment of this disease remain a clinical dilemma for physicians. One of the important tasks in determining a, therefore, in the treatment of FD is the presence gastroesophageal reflux disease (GERD) and gastritis in patients. Gastroenterologists offer various options to share symptoms of reflux and postprandial distress syndrome. For example, recent studies have shown that 37% of patients complaining of dyspepsia that correspond to the EBS category also have acidic esophageal reflux, proven by monitoring the pH, despite a normal endoscopic pattern [45]. In patients diagnosed with FD, there is a high prevalence of such a complaint as heartburn [27].

A number of researchers have demonstrated the effect of H. pylori (Hp) on the increase in the thickness of the muscular layer of the stomach, which leads to accelerated emptying of the stomach [25]. Other, a military blind, randomized controlled study of the effect of eradication Hp in patients with FD gave conflicting results [50]. While Miwa H. et al. reported no change symptomatology of FD after eradication Hp, another study in the Asian population showed a significant improvement [22]. However, histological studies did not show a correlation between the severity of inflammation and the presence of dyspepsia.

To violations of motor function in FD are abnormal accommodation of the bottom of the stomach and abnormal emptying of the stomach. J. Tack et al. showed that in patients who suffered from early saturation, the accommodation of the stomach bottom was sharply reduced or there was no accommodation [51]. In addition, more than two-thirds of patients with FD had electrophysiological indices, reflecting delayed waves of stomach contraction during and after food intake [53]. When thus, slowing of gastric emptying in patients with FD were due to the effects of ghrelin and motilin associated with gastrointestinal peptide, but these effects and has not been confirmed, and s in further studies [20, 28, 44].

The study by M. Kusano et al. in 8 patients with PDS it was shown that a feeling of heaviness after eating is associated with accelerated rather than delayed gastric emptying [49]. They associated this phenomenon with the intake of liquid fatty foods and attributed this effect to reflex stimulation of the secretion of cholecystokinin.

Visceral hypersensitivity is associated with gastric distension, gastric acid and bile [7, 11, 18]. Studies have shown that patients with FD who complain of epigastric pain after ingestion experience pain even with a slight increase in stomach pressure, which may be a source of epigastric discomfort.

MJ Collen et al., have shown that the level of hydrochloric acid secretion in patients with FD is not increased [18], but they have hypersensitivity to the mucous membrane of the duodenum even to the normal level of gastric acid [11]. Current theory of hypersensitivity, which takes the lead in central sensory neurotransmission to the neurotransmitter glutamate. This theory suggests that an increase in the presynaptic release of glutamate in the central sensory

areas speeds up the transmission of visceral sensory signals, which leads to an increased response to pain stimuli and disrupts the perception of pain. In addition, central hypersensitivity can potentially lead to the activation of previously inactive visceral pain receptors through the painful pathways of the neurons of the spinal cord [34].When studying the functional parameters of the brain in patients with FD, abnormal regional brain activity is registered, which suggests an interest in the central nervous system [8]. Zeng et al. revealed that in patients with functional dyspepsia the cerebral metabolism of carbohydrates is significantly different from healthy people. Anterior cingulate cortex, middle cingulate cortex, bilateral insula,cerebellum, thalamus are key brain structures that determine the severity of FD symptoms [9].

The role of genetic factors in the formation of FD was demonstrated in studies that showed that patients with a positive family history of FD are more likely to develop dyspepsia [22].

Psychosocial factors are well known factors in the pathogenesis of FD. There is a high prevalence of psychological symptoms in patients who complain of dyspepsia. A large-scale epidemiological study showed that anxiety is most common in patients diagnosed with FD, and they did not have a depressive level [12]. Another recent prospective large-scale cohort study involving 1175 patients showed that among people without a FD at the beginning of the study, a higher level of anxiety but not depression at the beginning of the study was a significant independent predictor of development FD 12 years later [16]. Mental tension determines the appearance of postprandial symptoms of dyspepsia, which can be associated with sympathetic hyperactivation, which in turn slows the emptying of the stomach [32]. A recent study by YC Hsu et al. revealed a correlation between FD subtypes, mental disorders and personality traits. PDS was independently associated with psychosomatic manifestations — depression and phobia, whereas EBE did not reliably correlate with these psychic factors [48]. Various physical problems were also associated with the prevalence and severity of FD symptoms in a number of other studies [19, 23, 52].

Finally, a number of other factors are also associated with symptoms of dyspepsia, including lifestyle, environmental, dietary and some others. There are separate reports on the role of melatonin and neuronal autoantibodies in the pathogenesis of dyspepsia symptoms, but their relevance remains to be proved [42, 52].

Treatment of functional dyspepsia should be aimed at both eliminating the etiologic factor, for example Hp, and affecting pathogenetic mechanisms. In the treatment of FD, it is necessary to take into account the option — EBS and/or PDS. With EBS, as a rule, the basis of treatment is the use of proton pump inhibitors (PPI), sometimes with ineffectiveness of standard doses, it is necessary to assign double doses. Drugs in Ismut compared with placebo in nine RCTs showed a tendency to improve the effectiveness of treatment, but were not statistically significantly more effective. Most researchers assumed that this is due to the anti-Helicobacter activity of the drug, but there was no difference in the efficacy of treatment between infected and non-infected Hp patients with FD [61]. Antacids and sucralfate did not exceed placebo in functional dyspepsia based on the Cochrane review [43]. If double doses of PPI are also ineffective, and the results of a daily pH-metry within the limits of the age physiological norm, adjuvant therapy with psychotropic drugs that includes "somatic" antipsychotics and/or antidepressants is necessary [62, 63]. Some antidepressants, such as paroxetine, amitriptyline, have shown a positive effect in studies [33, 65]. Other antidepressants, such as sertraline and venlafaxine, did not differ from placebo when used in patients with FD to reduce visceral hypersensitivity [36, 66].

When prescribing treatment for patients with a dyskinetic form of FD, it is necessary to include prokinetics in the treatment regimen. A meta-analysis on the effectiveness of prokinetics, including metoclopramide, domperidone, trimebutin, cisapride, itopride and mozapride, which included all studies from 1951 to 2005, showed that prokinetic agents are significantly more effective than placebo in the treatment of FD [40]. O gastric emptying in FD can be disrupted by the type of evacuation slowdown or the violation of fundamental accommodation, therefore prokinetic drugs can be divided into two main groups: modifying the base relaxation and affecting the emptying of the stomach.

With prolonged reception of PPI, a syndrome of excessive bacterial growth in the small intestine can form. Under the syndrome of excessive bacterial growth (BOS) is understood a pathological condition, which is based on the increased colonization of the small intestine by a fecal or oropharyngeal microflora, accompanied by chronic diarrhea and malabsorption, especially fats and vitamin B_{12}. An increase in the number of opportunistic microflora in the small intestine is revealed in 70-95% of cases of chronic intestinal pathology. With BOS, not only the amount increases, but the spectrum of microorganisms changes with a shift towards gram-negative bacteria and anaerobes. In 30% of healthy people jejunum normally sterile, the rest — has a low population density, which increases as we approach the colon and only in the distal ileum revealed microflora fecal type: enterobacteria, streptococci, anaerobes kind Bacteroides and others [3].

The most important etiologic factors of BOS are:

- dysfunction of the ileocecal valve (inflammatory, tumor processes, primary functional failure);
- consequences of surgical operations (anatomical or surgically formed blind loop, small intestine anastomosis or fistula, vagotomy, cholecystectomy, small intestine resection);
- gastrointestinal diseases associated with motor disorders — gastrostasis, duodenostasis, stasis of contents in the small and large intestine (chronic constipation, including in diabetic patients);
- disorders of the cavity digestion and absorption (maldigestia and malabsorption), including those associated with: achlorhydria of various origins (operated stomach, with chronic atrophic gastritis, prolonged intake of proton pump inhibitors), exocrine pancreatic insufficiency (chronic pancreatitis), bile duct pathology (cholelithiasis, chronic cholecystitis);
- Enteropathy (disaccharidase insufficiency and other food intolerance);
- prolonged food imbalance;
- chronic inflammatory bowel disease, diverticulitis, short bowel syndrome;
- the entry of bacteria from the extraintestinal reservoir (for example, with cholangitis);
- local and systemic immune disorders — radiation, chemical effects (cytostatics), AIDS;
- antibiotic therapy;
- stresses of different origin;
- tumors of the intestine and mesenteric lymph nodes;
- various diets for weight loss, "cleansing" with the use of voluminous enemas, and especially hydrocolonotherapy, which has a certain popularity, but is persistently not recommended by gastroenterologists all over the world, as they violate the microbial biotopes [55], have a negative effect on the microbial intestinal landscape.

Verification of excess bacterial growth in the small intestine is performed with the help of direct and indirect methods of diagnosing this syndrome. The "gold standard" for diagnosing BOS is the sowing of microflora, this requires the aspiration of the contents of the small intestine with the immediate sowing of aspirate on the nutrient medium. But excess bacterial growth can affect the most distal parts of the small intestine, which is beyond the reach of the instrument [54]. In 2008, the Roman consensus on hydrogen tests was adopted, which sets out the recommendations of international experts for clinical practice regarding indications and methods for conducting H_2 -breath tests in diseases of the digestive canal [1]. The method is cheap, simple, but many practitioners not only do not know the basic provisions of the consensus, but still, in general, are not familiar with this test, do not know their diagnostic capabilities, certain limitations and shortcomings. Today, in many Russian clinics, the hydrogen breath test (HBT) method with lactulose is used for BOS screening diagnostics, including inhibition of proton pump inhibitors.

The positive effects of PPI are undeniable, they are the main drugs in the treatment of functional dyspepsia, but, like all other medicines, they also have a number of side effects. Most often, the side effects are mild, go away spontaneously and do not depend on the dose of the drug or the age of the patient. Side effects from the gastrointestinal tract (GIT): diarrhea,

flatulence, abdominal pain, constipation.The appearance of gastrointestinal symptoms (intestinal hypermotorics) is associated with the oppression of acid production, and flatulence is a consequence of the syndrome of excessive bacterial growth [2].

IPPs are potent antisecretory drugs leading to hypochlorhydria, which in turn is a risk factor for BOS development. The presence of gastric acid is the main protection against oropharyngeal and intestinal infection. Thus, it is not surprising that the removal of this natural defense inevitably leads to clinically significant disorders intestinal flora in a number of patients taking PPI. It has long been established that PPI can alter the bacterial profiles of the stomach, duodenum and jejunum. For example, J. Thorens et al. 47 randomized patients with peptic ulcer who received 4 weeks of cimetidine or omeprazole were examined and then aspirates from the small intestine to the condition of the microflora were examined. The authors found a higher level of bacterial growth after taking omeprazole (53% vs. 17%) [13]. This finding was duplicated by Fried M. et al., Who showed that PPI-induced BOS was due not only to the oropharyngeal microflora but also to the colonic one [24].

J. Theisen and his colleagues found that suppressing gastric acid with omeprazole led to a high prevalence of BOS, which in turn led to a marked increase in the concentration of unconjugated bile acids. In addition, Lewis et al. Documented that omeprazole-induced BOS was associated with shorter intestinal transit [59]. These studies have shown that PPI-induced BOS can potentially lead to the development of symptoms of irritable bowel syndrome (IBS), such diarrhea, as a result of increased osmotic load from bile acids combined with faster intestinal transit. It should be noted that the most common side effects of PPIs in all studies were abdominal pain, bloating, flatulence, constipation, diarrhea, symptoms that intersect with IBS and occur in 5% IPP host [57].

Attention deserves two cohort studies conducted in medical centers New England. It was attended by 1166 patients and the cause-effect relationships of the influence of proton pump inhibitors on theincrease the risk of re-colitis C. difficile etiology. In the first study, the use of PPI during treatment infection C. difficile was associated with higher risk of recurrence infection C. Difficile in 42% of patients. The second study showed that with increasing the "dose-response" effect with a decrease in gastric acid production in inpatients receiving PPIs, the risk increases nosocomial C. difficile infection [41].

In the study L. Lombardo and with about the author. 450 participants were examined, which were examined using a respiratory hydrogen test with glucose (GDTV) to detect the metabolic activity of small intestinal bacteria. 200 of the examined patients took one of several IPPs on average for 36 months for GERD. BOS was detected in 50% of patients taking PPI in 24.5% of patients with IBS, and only 6% healthy. In addition, the researchers found a correlation between the duration of treatment of STIs and the detection of BOS, more than 70% of those taking PPI for more than 13 months, were three times more likely to acquire BOS, unlike those who took IPPs for a year or less. Many researchers suggest the use of respiratory hydrogen tests in patients to monitor BOS as an assessment of the effect of PPI. This, they say, is an "important oversight" of the use of PPI. Lombardo L. and his colleagues studied the appointment of an antibiotic α- rifaximin 400 mg three times a day for 14 days in patients with PPI-induced BOS. Normalization of the clinical picture and HDTV occurred in 87% of patients taking PPI, and in 91% of patients in the IBS group [56].

A year ago, an article was published in the American Gastroenterology Journal in which the role of the influence of STIs on the formation of BOS on the data of the results of GDVT and LDTV was reduced. This article analyzes the results of 10 studies conducted from 2004 to 2010. The data of observation of 1,191 patients (70% of the female) are given, 566 (48%) of whom received IPP. Positive HDT was associated with age (odds ratio (OR) 1.03, 95% confidence interval (CI) 1.01-1.04) and diarrhea (1.99, 95% CI 1.15-3.44) where the exhaled $H_2 > 20$ pmm; with the elderly age (OR 1.01, 95% CI 1.00-1.02) and diarrhea (OR 1.53, 95% CI 1.13-2.09) where the level of exhaled $H_2 > 10$ pmm and with the older age (OR 1.01, 95% CI 1.00-1.02), where the level of exhaled $H_2 > 20$ pmm or $CH_4 > 15$ pmm was noted [47]. L. Lombardo

responded to this article with comments, indicating that the duration of the use of PPIs, which directly affects the formation of BOS in patients using IPPs, was not assessed in the study [38].

The basis of BOS treatment is antibacterial therapy [31]. Some foreign authors advocate the empirical treatment of suspected BOS patients without diagnostic testing [15]. However, this approach is problematic because of the frequent placebo effect, the high cost of antibiotics, the high potential of complications (eg, drug interactions, side effects), and the need for a repeat course of antibiotics. Study M. Di Stefano et al. It showed that the average duration of clinical improvement at the empirical treatment lasts only 22 days, and this treatment strategy leads to the need for at least 12 seven-day course of antibiotic therapy in the year to provide relief of patients with constipation and ARIS [10].

Many authors recommend the appointment of broad-spectrum antibacterial drugs effective against anaerobic bacteria — rifaximin (400-600 mg twice daily), tetracycline (inside 0.25 g 4 times daily), ampicillin (inside 0.5 g 4 times daily), metronidazole (inside 500 mg 3 times a day), ciprofloxacin (500 mg twice a day), norfloxacin (800 mg per day), vancomycin (125 mg 4 times a day) [1, 55]. Sometimes repeated courses lasting from 7 to 14 days are required.

As adjuvant therapy BOS it is expedient to use preparations of bismuth. Due to the known antidiarrheal properties, bismuth compounds are widely used to treat episodic diarrhea in children and adults throughout the whole century [14, 21, 30, 60].

In addition to its antibacterial properties [58], bismuth also has anti-inflammatory effects [26] when passing through the intestine. There are experimental data confirming the role of bismuth in inhibiting the activity of inducible nitric oxide synthase in epithelial cells of the intestine, as well as in the induction of hemoxygenase-1, thereby causing a therapeutic effect in inflammatory and oxidative reactions associated with inflammatory bowel diseases [17]. Another experimental study has shown the ability of bismuth to absorb free radical oxygen in the context of chemical damage to the gastric mucosa [39]. Given these antibacterial and anti-inflammatory mechanisms, it can theoretically be suggested that bismuth should play a role in the pathogenetic treatment of BOS, acute and chronic diarrhea, as an antibacterial and antitoxic agent [64]. Active active substance Novobismol ® (produced by Pharmproject, Russia) is bismuth titrate dicitrate, which can be recommended for complex entero -septic therapy of BOS [4].

Separate attention deserves the experience of using probiotics in the complex treatment of BOS. L. Richard and R. Parker in 1977. used the term "probiotic" to refer to living microorganisms and their fermentation products, which have antagonistic activity against the pathogenic microflora. According to WHO/FAO definition of probiotics — live microorganisms applied in adequate amounts, which have a healing effect on the human body. Probiotics are also defined as preparations based on intestinal commensals, capable of performing biological control in the body and possessing regulatory and trigger properties.

Potential effects of probiotics [35, 37, 46, 67]:

- modulation of intestinal immunity, changes in inflammatory cytokine profiles, and reduction of proinflammatory cascades or activation of regulatory strain-specific mechanisms;
- inhibition of pathogenic gas-producing and deconjugating bile salts of bacteria, reducing their adhesion;
- change in bacterial flora by acidifying the colon by fermenting the nutrient substrate;
- increased epithelial barrier function;
- induction of μ-opioid and cannabinoid receptors in epithelial cells of the intestine;
- reduction of visceral hypersensitivity, spinal afferentation and reaction to stress.

Modern probiotics should meet the following criteria [5]:

- contain microorganisms, the probiotic effect of which has been proven in randomized controlled trials;
- have stable clinical efficacy;
- be phenotypic and genotypically classified;
- remain alive;
- be non-pathogenic and non-toxic, do not cause side effects with prolonged use;

- have a positive effect on the host organism (eg, increase resistance to infections);
- have the colonization potential, i.e. remain in the digestive tract until the maximum positive effect is reached (be resistant to high acidity, organic and bile acids, antimicrobial toxins and enzymes produced by pathogenic microflora);
- be acid-fast or encapsulated in an acid-fast capsule;
- be stable and retain viable bacteria for a long shelf life [29].

Principal requirements are also applied to strains of bacteria, on the basis of which probiotics are created. They have to:

- be isolated from healthy people and identified to a species by phenotypes and genotypes;
- have a genetic passport;
- have a broad spectrum of antagonistic activity against pathogenic and opportunistic microorganisms;
- should not inhibit normal microbiocenosis;
- be safe for people, including immunological safety;
- The production strains must be stable in terms of biological activity and meet technological requirements.

Maxilak® (production «Genexo Sp zoo.», Poland) — synbiotic, which contains 9 cultures of intestinal bacteria in a concentration of — 4.5 billion cfu. Contained in the Maxilak® lactobacillus, suppress the growth of pathogenic microflora, process lactose into simple sugars, which is useful for individuals with lactase deficiency, intolerance to milk and dairy products. Bifidobacteria, which are also included in Maxilak®, support the normal processes of parietal digestion, suppress the growth of pathogenic microflora, promote the stimulation of immunity, help to reduce the pH of the diet. Oligofructose stimulates the rapid proliferation of beneficial bacteria and inhibits the development of pathogenic bacteria of external origin, reduces the contamination of the intestine with toxins and improves its functioning, stimulates peristalsis, serves to prevent constipation, diarrhea, and improve gastrointestinal function.

Through the use of innovative technology MURE (Multi Resistant Encapsulation), bacteria present in Maxilak®, protected from the acidic gastric contents, bile salts, and digestive enzymes. This protection allows them to adapt and settle down in the lumen of the intestine, while retaining high biological activity. Moreover, thanks to this technology, most of the probiotic bacteria gets into the intestines, but does not dissolve in the stomach, which has a positive effect on the recovery of the gastrointestinal microflora, as the concentration of colonies of microorganisms increases from the stomach to the large intestine. The original composition of the drug is the result of a unique production process that ensures the preservation of bacteria during their passage through the stomach even after dissolving the gelatin capsule shell with gastric juice. Bacteria remain under the protection of the matrix of microcapsules from polysaccharides are converted into acid-fast gel upon contact with hydrochloric acid in the stomach. With increasing Ph in the intestine, the gel dissolves, releasing live bacteria. Thus, the bacteria contained in the gelatin capsules live into the small and large intestine, that is, where they can begin their action.

In the bacteriological control of drug contamination, there was no growth on the Endo medium, nutrient agar with 9% sodium chloride and Saburo medium, i.e. the drug was characterized by the absence of extraneous microflora (E. coli, fungi, staphylococci).

The method of dilution was used to determine the amount of microorganisms in each capsule. In one dose of the drug contains 20×10^{10} cfu of bacteria, i.e. not less than the amount declared by the manufacturer. The high concentration of bacteria in vitro (6 times higher than indicated in the documentation) is probably due to the stimulating effect of oligofructose. Acid-forming ability of bacteria was 124.2^{0} T. In general, the adhesive ability was good, as the adhesion index is 3.61.

The definition of susceptibility to antibiotics of the whole consortium of bacteria was carried out, without the isolation of pure cultures. It was found that the bacteria were resistant to

the following antibiotics: imipenem, ceftazidime, cefazolin, amoxicillin, ofloxacin. The consortium of bacteria was sensitive to ciprofloxacin, levofloxacin, sparfloxacin, roxithromycin, meropenem, gentamicin, amikacin.

Thus, Maxilak® is characterized by the following microbiological features: the bacterial content in 1 dose of the drug was not less than 20×10^{9} cfu/g, the consortium includes microorganisms of the genus Bifidobacterium, Lactobacillus, Streptococcus. The acid formation activity was 124.2^{0} T, the adhesion index of microorganisms was 3.61 — average. A consortium of bacteria resistant to antibiotics of β-lactam (imipinemu, ceftazidime, cefazolin, amoxicillin) and to ofloxacin that can assign Maxilak® while taking appropriate antibiotics.

Conclusion. Syndrome of excessive bacterial growth and functional dyspepsia can be combined. The etiology of BOS is usually associated with a breach of protective antibacterial mechanisms (eg, achlorhydria, with PPI) and/or motor disorders that underlie functional dyspepsia.

BOS is often underestimated, misdiagnosed and, in general, not an independent disease. Clinical symptoms can be nonspecific (dyspepsia, bloating, abdominal discomfort), which are often found in FD. Nevertheless, BOS can cause severe disorders by the type of maldigestia and malnutrition. Non-invasive breathing hydrogen tests with lactulose are most often used to diagnose BOS. ARIS Therapy should be integrated and include treatment of the underlying disease, normal food and course bowel sanation antibiotic, enteroseptikov (Novobismol®) and then restoration of the microflora using pre- and probiotics or synbiotics. Syn biotics of choice may be the preparation of Maxilak®, which is highly effective in the complex treatment of intestinal diseases, including in the syndrome of excessive bacterial growth. The prognosis of BOS is usually serious and is determined by the course of the underlying disease that led to its formation.

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What is common between functional dyspepsia and bacterial overgrowth syndrome

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Key words: functional dyspepsia, proton pump inhibitors, bacterial overgrowth syndrome, pathogenetic link, probiotics

The article presents the results of a review of various syndromes that occur in the pathology of the digestive system. Functional dyspepsia and the principles of its treatment are considered in detail. Proton pump inhibitors are one of the main groups of drugs used to treat functional dyspepsia. A serious complication of prolonged use of proton pump inhibitors is the syndrome of small intestinal bacterial overgrowth. The main principles of treatment of this complication are antibacterial therapy and probiotics. Enterobseptic Novobismol® and modern probiotic Maxilak® can be drugs of choice in this situation.