Study of intestinal dysbiosis (“dysbacteriosis”): state of problem and new trends

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To explore is to see what everyone sees, but to think as no one thought.
Hans Selye (1907–1982)

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Definition. Dysbiosis ("dysbacteriosis") of the intestine is a clinical and laboratory (clinical and microbiological) syndrome, which develops secondarily in a number of diseases and clinical syndromes and is characterized by a change in the quantitative and qualitative (species) composition of microbial associations (normoflastic cytopathies).) with the translocation of its various representatives into unusual biotopes, proceeding with metabolic and immunological disorders, which, gradually increasing, cause the appearance of ycheskoy symptoms [6, 15, 25].

It is believed that the term "intestinal dysbiosis" was coined by the prominent Russian infectious scientist A.F. Bilibin [4, 5]. However, as shown by a retrospective analysis, the priority in the use of the term belongs to A. Nissle, who first applied it in 1916 [47].

For the sake of justice, it should be noted that the founder of the doctrine of dysbiosis ("dysbacteriosis") of the intestine should be recognized by one and the coryphaeus of domestic medicine, the Nobel laureate I.I. Mechnikov (1845–1916), who first drew attention to the role of the intestinal microflora (normobiocenosis) in the vital activity of the human body and its importance in counteracting infection, due to the phenomenon of bacterial antagonism. He wrote: "Numerous associations of germs that inhabit a person’s intestines, to a large extent, determine his spiritual and physical health." At the same time, various processes that cause disturbances of the quantitative and qualitative composition of the intestinal flora can contribute to the development of various pathological processes. In addition, he suggested that by altering the composition of the intestinal microflora by modifying it, it is possible to protect the human body from the development of intestinal infections, prolong its life and improve the quality of life [20, 23].

We consider the term "intestinal dysbiosis" not quite accurate, since not only bacteria but also viruses and yeast-like fungi colonize the human intestine. Therefore, we prefer the term "intestinal dysbiosis", which, moreover, is better associated with the term "eubiosis" corresponding to the concept of "normomicrobiosis" or "normomicroflora" of the intestine [23, 24].

Normobiocenosis can be disturbed not only in the colon, but also in the small intestine, which in foreign medical literature has been dubbed the "bacterial overgrowth syndrome". As early as 2000, we proposed, in order to unify the terminology, to refer to these disorders of the intestinal flora as "colonic dysbiosis" and "small intestinal dysbiosis", which reflect both the change (violation) of the quantitative and qualitative composition of the bacterial microflora of the intestine [24] and its localization.

Main indicators of the norm flora (eubiosis) of the intestine and its function. The bacteriological community, which is part of the system "macroorganism — endosymbiont bacteria", has an ancient phylogenetic origin and in its development has passed several historical stages. In the first stage, it is the relationship of the confrontation, the confrontation of the person and the microflora introduced into the macroorganism; in the second stage — coexistence on the principles of commensalism; in the third stage, the interaction of the macroorganism and the microbiota on the principle of mutualism ("mutual services"). The fourth stage came from the beginning of the “antibiotic era” (the middle of the XX century), when in the uncompromising fight against pathogenic microbes, the symbiotic microflora needed for the normal life of the macroorganism were also destroyed [22, 23]. The human body coexists with a myriad of microorganisms whose number is many times the total number of eukaryotic cells in organs and tissues [32]. Moreover, 70% of them colonize the intestines, mainly the colon [2, 32]. As shown by the latest data obtained by analysis of sequenced 16Sr RNA genes, the gut microbiota is represented by 395 phylogenetically separated groups (philotypes) of microorganisms, whose total mass exceeds 2.5 kg, which is 4–5% of body weight [6, 32, 37, 41, 44]. Human microbial contains 400 thousand of genes [41].

Main facts established in the study of the intestinal flora.

1. Despite the huge diversity of intestinal microflora, its main composition is formed by 15–20 associations of microorganisms, namely: Bacteroides, Bifidumbacterium, Eubacterium, Fusobacterium, Clostridium, Lactobacillus, Veilonella, etc. [1, 6, 19].
2. Bifido and lactobacilli are recognized as the central link of the colon microbiota.
3. The interaction between humans and the gut colonizing microbiota is carried out on the basis of mutualism (from the Latin Mutuari — interaction) — on the principle of "mutual services", as well as commensalism (from the French commensal — "sotrapeznik"), when the bacteria use favorable conditions for their activity in the human intestine, but do not cause harm to it [1, 9, 23, 32, 37, 57].
4. Among the bacteria that colonize the human digestive tract, the

following are distinguished: a) strict (obligate) anaerobes (bifidobacteria, fusobacteria, veylonelles, clostridia, etc.); b) strict aerobes (bacilli, micrococci, pseudomonads, etc.) and c) optional aerobes (anaerobes) — lactobacilli, enterococci, enterobacteria, streptococci, staphylococci, etc. [6, 9, 32, 44].

5. In the stomach of a healthy person, where gastric juice with high acidity and enzymatic activity, having bactericidal (bacteriostatic) properties is formed, the number of microorganisms does not exceed 10^3-10^4/ml, including Helicobacter pylori 6-36%; in 10% the stomach remains sterile.
6. In the duodenum, 10^3-10^5/ml bacteria are detected; Helicobacter pylori are absent. In a small proportion of cases, the duodenum is sterile.
7. In the small intestine, the bacterial count increases to 10^4–10^5/ml, and in the ileum, adjacent to the large intestine, from which it is separated only by the ileocecal sphincter of Vorolius (Bauginian flap), increases to 108/ml, and if in the proximal divisions — the intestinal tract is dominated by strict aerobes and optional anaerobes, then a significant number of strict anaerobes is determined in the ileum.
8. The colon is colonized by a large number of microorganisms in excess of 10^{10}-10^{11}/g with anaerobic dominance (up to 90%); aerobes account for less than 10% and their mass is less than 1000 times.
9. Among the bacteria that inhabit the human intestine, it is customary to distinguish: a) saccharolytic bacteria, which are certainly beneficial to humans (bifidobacteria and lactobacilli, enterococci) and b) proteolytic bacteria, which in certain conditions can become potentially dangerous to his health [9].
10. The intestinal wall (its epithelial cover) is a sealed physical and chemical barrier that prevents microbes and toxic substances from entering the macroorganism (into the blood and lymph); barrier function also involves the intestinal mucosa and the layer of near-wall endosymbiotic bacteria [19, 45].
11. Most of the gut microbiota are located near the wall in the form of micro colonies fixed (adhesion) on the outer membrane of epitheliocytes due to the presence of special protein compounds called lectins, which include glycoproteins. Lectins are complementary to receptors on the outer membrane of the intestinal epitheliocytes containing sphingolipids.
12. Bacterial wall microcolonies are protected from external adverse effects of exopolysaccharide-mucin film consisting of mucin — secret of goblet cells and exopolysaccharides of microbial origin (so-called exopolysaccharide-mucin, which provides the contents of the intestine

and the near-walled micro-colonies of bacteria [39, 55].

13. The smaller part of the microflora is localized in the lumen of the intestine (intraluminal microflora), being "in free swimming". Its amount is 6 times less than the wall microflora [9].
14. The microorganisms that inhabit the human gut can be modified and evolved under the influence of the environment [6, 26, 44].
15. The intestinal epithelium is continuously updated. In this case, the torn epitheliocytes, together with the fixed colonies of the near-walled bacteria, are “discharged” into the lumen of the intestine (up to 250 g/day) and are excreted together with the feces, accounting for 30–50% of its mass. A complete renewal of the intestinal epithelial cover occurs every 3-4 days. I.I. Mechnikov compared this process with a tightly-fitting lady’s glove, which, when turned inside out, is removed from the hand.
16. The gut microbiota performs a number of vital functions in the human body: a) provides its colonization resistance (protection against conditionally pathogenic and pathogenic bacteria) due to the phenomenon of microbial antagonism; b) has antibacterial activity, forming bacteriocins and microcins, as well as lysozyme (proteolytic enzyme myromidase); c) saccharolytic bacteria form short-chain fatty acids (HCF) — acetic, oily, valeric and propionic, which are the product of carbohydrate fermentation, which serve as the main energy resource of epitheliocytes, affecting their proliferation and trophic activity; participate in lipogenesis and glyconeogenesis, amino acid synthesis, cholesterol metabolism; have a detoxifying effect on various toxic substances of exogenous and endogenous origin due to their adsorption and subsequent removal (natural sorbent); d) synthesize vitamins (B-complex, K, folic and nicotinic acids); promote the absorption of vitamin D and calcium salts needed to strengthen bone tissue; e) have immunomodulatory action, stimulating the gut-associated lymphoid tissue (GALT), Peyer’s plaques, solitary lympho-follicles, etc., promoting its maturation; provide secretory immunoglobulin A (sIgA) synthesis, phagocytosis activation; synthesis of cytokines and interferons [19, 43, 50, 61]; the immunomodulatory effect of the intestinal microflora is largely due to its effect on the differentiation of T-suppressors in Peyer’s plaques and depends on the antigen presenting system — HLA (Human Leucocyte Antigen) [19]; e) participate in metabolic (metabolic) processes, producing enzymes, mediators, histamine, (3-alanine, y-aminobutyric acid, etc.; g) affect the digestive processes, providing the final enzymatic hydrolysis of undigested

nutrients (target of nutrients), dietary fiber, oligo- and polysaccharides, protein substances); promote the conversion of primary bile acids into secondary; h) have a morphokinetic (trophic) effect, stimulating the physiological activity of the intestine, its motor function due to the synthesis of nitric oxide (NO) from arginine under the influence of NO synthase (NOS) [52]; improve water absorption; provide transmembrane exchange of Na + ions for H + ions (Na +/H + exchanger) and Cl− ions for HCO3– (Cl–/HCO3 ions) ions [19, 44].

17. Given the diversity of vital functions performed by the intestinal microflora, some authors consider it justified to regard it as a kind of extracorporeal organ providing homeostasis of the macroorganism, along with the liver and pancreas [9, 12, 49].
18. Regulation of intestinal functions is carried out by remote regulation with the help of "signaling molecules", which act as neurotransmitters, which are represented by GLC, histamine, serotonin, putrescine, cadaverine, etc., as well as through contact interaction through the receptor apparatus on the epithelium; intracellular endocytosis also takes part in this process [1, 19].

Colonic dysbiosis.

1. The main causes of colonic dysbiosis are: a) antibacterial therapy with the use of broad-spectrum antibiotics; b) hormone therapy; c) use of cytostatics; d) radiation therapy; e) surgery on the intestine; e) acute intestinal infectious diseases (dysentery, salmonellosis, etc.); g) immunodeficiency states of different genesis; h) unbalanced nutrition; food fiber deficiency; excessive consumption of preservatives and xenobiotics; i) motor disorders of the intestine (chronic constipation, diarrhea); k) mental stress states, etc. [1, 20, 23, 37, 40, 42, 57].

2. In the colon microbiota distinguish: a) permanent (obligate, autochthonous, indigenous, resident) microflora (90%); b) additional (accompanying, optional) microflora (<10%) and c) transient (random, residual, allochthonous) microflora (<1%) [1, 6, 37, 57].

3. It is customary to distinguish 4 degrees of colonic dysbiosis:

I degree (compensated) is characterized by a decrease in the obligate microflora (especially bifidobacteria and lactobacilli) to 10^7–10^8/g of faeces at a normal amount of high-grade Escherichia coli; increasing the number of pathogenic microflora to 10^3/g; by changing the TLC pool, increasing the content of phenylacetic acid and methylamine.

II degree (subcompensated) is characterized by a decrease in the number of obligate bacteria up to 10^5/g and a full E. coli — up to 10^4/g; further increase of conditionally pathogenic bacterial species (proteas, staphylococci, Klebsiell, etc.); the presence of pseudomonads, carboxylic and aromatic amino acids.

III degree (decompensated, uncomplicated) proceeds with further reduction of obligate bacterial species to 10^3/g; appearance of qualitatively modified (enteropathogenic) Escherichia coli; an increase in the pool of pathogenic bacteria and fungi of the genus Candida — up to 10^5-10^6/g; reducing the content of phenolic compounds; increasing the level of phenylpropionic acid.

IV degree (decompensated, complicated) is characterized by a sharp decrease or complete absence of bifidobacteria, lactobacilli and normal species of Escherichia coli; the dominance of pathogenic bacteria and fungi of the genus Candida, the number of which reaches 10^8/g faeces and more; deep imbalance of the entire bacterial ecosystem of the colon with the accumulation of entero- and cytotoxins in it and the presence of signs of endotoxemia [2, 13, 23].

4. In I and II degrees of colonic dysbiosis, clinical symptomatology is most often absent; sometimes there are some symptoms of intestinal dyspepsia (flatulence, unstable stools, decreased appetite) and the initial signs of hypovitaminosis; at III and IV degrees — clear clinical signs (abdominal pain, belching, heartburn, diarrhea, skin allergic rashes; pathological impurities in the feces; symptoms of general intoxication); bacteremia is possible. In these cases, colonic dysbiosis is transformed from a purely laboratory concept into a clinical-laboratory syndrome [6, 20].

5. In decompensated (III-IV) degrees of colonic dysbiosis, diseases such as antibiotic-associated diarrhea (AAD) and its most severe form, life-threatening pseudomembranous colitis, are diagnosed. In its etiology, the leading role belongs to Clostridium difficile — a spore-forming bacterium that produces enterotoxins A and B with cytotoxic properties that damage colonocytes, induce the formation of inflammatory mediators, increase the permeability of the intestinal cell barrier with lesions 16, 31, 48].

The authoritative "Therapeutic Directory of the University of Washington", which has withstood more than 30 editions, testifies: "Antibiotics inhibit the normal intestinal microflora, which leads to dysbacteriosis, the most severe clinical form of which is pseudomembranous colitis." In addition, the clinical forms of colonic dysbiosis are recognized as diarrhea of travelers (tourists) and (with reservations) irritable bowel syndrome (IBS) [2, 21, 35].

6. *Predispose to the development of colonic dysbiosis:*

a) immunodeficiency states [33]; b) endocrine dysfunction; c) a sharp deterioration of the ecology of the environment [1, 2].

All of these pathogenetic and predisposing factors lead to local and systemic disorders in the colon.

7. The criteria for the virulence of microflora are: a) pathogenicity (the ability to cause disease); b) infectivity (the ability to colonize and implant into the tissue of the affected organ); toxicity (the ability to produce toxic substances).

Conditionally pathogenic and pathogenic bacteria that dominate the colon with high degrees of dysbiosis (III-IV), synthesize: adhesins, cyto- and enterotoxins; anti-lysocyme factor having complex resistance plasmids that promote endotoxemia

8. *Colonic dysbiosis* most often develops: with ulcerative colitis; in Crohn's disease of the colon (granulomatous colitis), with diverticulosis of the colon, complicated by diverticulitis and peridverticulitis, etc. [1, 2, 23].

Intestinal dysbiosis.

1. *Pathogenesis of small bowel dysbiosis.* Conditionally pathogenic microflora penetrate into the small intestine in two ways:

a) from the stomach — with achlorhydria and gastric achilles, when it does not contain gastric juice, which due to its high acidity and enzymatic activity has bactericidal (bacteriostatic) properties; with prolonged administration of proton pump inhibitors (PPIs) that suppress active gastric secretion; after resection of the stomach;

b) from the colon — in violation of the function of the ileocecal sphincter of Vorolius (Bauginian flap) due to its functional failure or resection.

2. *Promote the development of small intestinal dysbiosis:*

a) various diseases of the hepatobiliary system and pancreas, occurring with violation of their functions; b) syndromes of maldigestion and malabsorption in the small intestine; c) celiac disease (gluten enteropathy); d) various inflammatory and infectious processes in the small intestine; e) surgery on the small intestine; e) various medicines and their side effects; radiation damage to the small intestine.

3. *Cytotoxins produced by conditionally pathogenic microflora*, penetrating into the small intestine, damage the enterocytes, cause the development of productive inflammation with subsequent atrophic process and impaired barrier function of the intestinal wall; it should be borne in mind that its permeability is higher than that of the large intestine; enzymes that form pathogenic bacteria inactivate and destroy the enzymes of the digestive juices, causing bacterial fermentation of nutrients.

4. Clinical manifestations of small intestinal dysbiosis are: a) osmotic and excretory diarrhea; b) syndromes of maldigestion and malabsorption of different severity, developing as a result of metabolic disorders, impaired hydrolysis and nutrient absorption, which causes fermentation and putrefactive processes, deterioration of the absorption of water and electrolytes.

Patients develop abdominal pain; signs of general intoxication appear and accrue; the formation of abscesses and even the development of sepsis is possible.

5. Most often in small intestinal dysbiosis find: enteropathogenic Escherichia coli, proteas, pseudomonads, bacteroids, enterococci, fusobacteria, etc.

6. *It is proposed to distinguish the following gradations of small intestinal dysbiosis:*

I degree: increase in the amount of aerobic microflora — gram-positive and gram-negative (more than 10^5-10^6/ml at a norm less than 10^5/ml), mainly due to streptococci, micrococci, enterococci, Escherichia coli and fungi of the genus Candida;

II degree: increase of contamination of small intestine with conditionally pathogenic microflora to 10^6-10^7/ml; appearance along with the aerobes of representatives of anaerobes (bacterioids, clostridia, etc.);

III degree: the amount of opportunistic microflora in the small intestine reaches 10^9/ml and more, with anaerobic microflora (fusobacteria, clostridia, etc.) predominating [2, 10, 23, 34, 51, 53, 54, 60].

Diagnosis. There are direct and indirect methods of diagnosing bowel dysbiosis.

1. In the diagnosis of colonic dysbiosis, the classical (direct) method of bacteriological examination of feces still retains significance. The most important prerequisite for obtaining reliable and reproducible results is strict adherence to methodological guidelines*:*

a) the feces should be collected in a clean glass jar with a lid and immediately (within 15–20 min) delivered to a bacteriological laboratory;

b) the sample to be sampled from the middle or last portion of feces;

c) with a sterile instrument 0.3–1.0 g of faeces should be placed in a sterile hermetically sealed container;

d) for the study of anaerobic microflora, test the stool portion into the tubes with ground tubes filled with a gas mixture of a certain composition (carbon dioxide, propane, hydrogen, nitrogen) or in tubes with a special nutrient medium for growing anaerobes (thioglycol buffer);

e) to make sowing on special nutrient media (Endo, yolk and salt agar, Saburo medium, 5% blood agar, Wilson-Blair medium, semi-liquid MRS, Blorocco, etc.) [1, 7]. The sensitivity of the method is 81–100%, and the specificity is 84–95%. The answer is received after 24-48 hours [11].

2. An indirect method for the study of feces was developed by determining short-chain (volatile) fatty acids (GFA) by gas-liquid chromatography, which allows to determine the metabolic activity of the microflora of the colon, in a short time and sufficiently accurately detect the presence of indigenous, conditionally pathogenic and pathogenic microflora.

3. Respiratory tests are also proposed to determine the presence of microbial metabolites in exhaled air and other methods for the diagnosis of colonic dysbiosis.

4. Determination of the microbial composition of the large intestine by polymerase chain reaction (PCR) is of absolute value, but it is not available for

daily practice.

5. In the diagnosis of intestinal dysbiosis, the most informative direct method of studying the microbial composition of the small (small) intestine by duodenojunoscopy and aspiration of the contents of the small intestine with subsequent sowing on bacterial media. If the level of microbial contamination of the small intestine exceeds 105/ml and the presence of anaerobic bacteria (bacterroids, clostridia, bifidobacteria, etc.) is detected in the aspirate, then small intestinal dysbiosis is diagnosed.

In addition, use of a hydrogen load test with lactulose. Bacteria break down lactulose, increasing the concentration of hydrogen in the exhaled air. First, establish the basic concentration of hydrogen, then after ingestion of 10 g of lactulose every 15 minutes for 3 hours determine the content of hydrogen in the exhaled air with the construction of its concentration curve.

Discussion terminological issues. In 1998, as part of the annual Russian Gastroenterology Week, a “round table” was held on irritable bowel syndrome, which also discussed the problem of “colon dysbiosis”. In 1999, a roundtable transcript was published in the journal [8]. The chairman (V.T. Ivashkin) called the term "dysbacteriosis" "awful" and referred to the foreign term "bacterial overgrowth syndrome" as a role model.

However, in our view, this description of intestinal syndrome can hardly be recognized as a medical term that should be short and accurate. In addition, only quantitative but not qualitative disturbances of normobiocenosis are reflected in this term.

With substantiation of the position of V.T. Ivashkina was delivered by A.V. Kalinin, who gave the following arguments:

1. The term "intestinal dysbiosis" does not exist in foreign literature.
2. When sowing feces on bacterial media, only 14-15 species of bacteria can be identified, while the microflora of the colon is represented by more than 500 species.
3. In bacterial examination of faeces, it is possible to determine only the intraluminal, but not the wall microflora, localized mainly in the distal colon.

We believe that none of these arguments withstand objective criticism, so we considered it possible to speak in favor of the term "dysbacteriosis" of the colon. Our position was supported by well-known enterologist I.L. Khalifa [8].

In 2000, we published a discussion paper in the same journal on the essence of the concept of "intestinal dysbiosis" (dysbiosis) and the lawfulness of using the term "[24]. In brief, our position is as follows.

1. In foreign medical literature, indeed, the term "dysbacteriosis" is rarely found, but the importance of disorders of normomicrobiosis (eubiosis) of the large intestine and the need for its correction with the help of pre- and probiotics and

intestinal antiseptics are constantly considered and discussed [3, 36, 38, 56, 58].

With regard to the use of the term "dysbacteriosis" (dysbiosis), we believe that not only Russian scientists have the right to borrow the terms offered by foreign scientists, but they could also adopt the terms used by Russian gastroenterologists, especially when they are so obscure, as the term "intestinal dysbiosis (dysbiosis)".

2. The basic microbial composition of the large intestine (more than 90%) is formed by 15-20 associations of dominant bacteria, so it is not necessary to identify all 500 species of colonizing colon colonies each time — it is sufficient to establish the number and presence of 15-20 representatives of the dominant microflora. It should be borne in mind that the gut microbiota also includes uncultured microorganisms.

3. In the intestines, as previously indicated, the epithelial cover is continuously updated with enterocyte rejection (up to 250 g/day) together with microbial colonies of wall bacteria located on their outer membrane, and complete replacement of the entire intestinal epithelium is observed every 3-4 days. Therefore, in bacteriological examination of feces determine both the intraluminal and the wall microflora.

4. Fecal masses are formed throughout the colon, and, consequently, the study of feces "on dysbacteriosis" is an integral reflection of the bacterial composition of the entire colon, not just its distal part.

5. The foreign term "bacterial overgrowth syndrome" can not serve as an alternative to the term "dysbiosis (dysbiosis)", as it refers to the study of the bacterial composition of the small rather than large intestine (as evidenced by its full name: small interstinal bacterial overgrowth syndrome — SIBOS) [34, 51].

Principles of treatment. Treatment of dysbiosis ("dysbacteriosis") of the intestine should be individualized and complex, take into account its severity (degree), the predominant localization (colon, small intestine), the nature of the predominantly conditionally pathogenic microflora, the presence of clinical symptoms and its characteristic features.

1. The main objectives of therapeutic activities are:

a) adequate treatment of the underlying disease that caused intestinal dysbiosis; b) restoration of impaired bowel functions, its parietal (contact, membrane) and cavity digestion; c) increase of general resistance of the organism by restoring its immunological and nonspecific protection; d) correction of intestinal and small bowel dysbiosis [23, 44]. Empirical treatment of bowel dysbiosis is unacceptable.

2. Functional nutrition. This is due to the use of products of plant, animal and microbial origin, capable of eliminating the disturbances of the gut microbiocenosis and restore the biochemical parameters of the macroorganism.

Functional nutrition includes: soy milk, pectins, proteins, minerals, vitamins, natural antioxidants, which are figuratively called "nutritional drugs"; they also contain bifidobacteria and lactobacilli [29].

The most important component of functional nutrition is dietary fiber. They increase the volume of feces; stimulate the motor activity of the colon, contributing to the elimination of constipation; serve as a source of QOL, membrane phospholipids, proteins and amino acids (arginine, glutamine); increase absorption of water and sodium, secretion of bicarbonates; improve the proliferation and trophism of colonocytes, cholesterol metabolism, lipogenesis and glyconeogenesis; contribute to the restoration of normobiocenosis of the colon, performing the function of a matrix for fixation of obligate bacteria [14].

3. Pre-, pro- and synbiotics. Probiotics are preparations made on the basis of the most valuable strains of living representatives of the obligate microflora of the colon. They are excreted in healthy people.

Prebiotics are substances that serve as a substrate for the selective growth of a population of obligate bacteria.

Synbiotics are drugs that contain both pro- and prebiotics.

The most commonly used probiotics are bifiform and lineex.

Bifiform is available in enteric coated capsules and contains Bifidobacterium longum ($>10^7$) and Enterococcus faecium ($>10^7$); Linex — Lactobacillus acidophilus, Bifidobacterium infantis and Enterococcus faecium. Dose of both drugs: 2 capsules. 3 times/day; 3-4 weeks.

From the new preparations it is necessary to name bifistim-forte — a balanced synbiotic, which includes: Lactobacillus acidophilus, L. plantarum and L. casei; Bifidobacterium longum, B. bifidum; prebiotics inulin and oligofructose; vitamins B-complex, C, E, folic and pantothenic acids; biotin and niacin; apple pectin (European Patent EP No. 1514553). Available in chewable tablets. Accepted 1 time/day, 20-30 days.

Other synbiotics are also used: fly's in 4 variants; bactistatin containing Bacillus subtilis — 3, bacteriocins, lysozyme, catalase and zeolite sorbent; probibor, bisporin and more.

Strains of obligate bacteria included in the composition of pro- and synbiotics, as a rule, have a wide range of antagonistic activity against conditionally pathogenic microflora, restoring eubiosis of the corresponding intestinal biotope; do not cause damage to the intestinal flora and are safe for the macro-organism. In addition, they synthesize antioxidants, strengthen the intestinal epithelial barrier, stimulate the formation of anti-inflammatory cytokines, improve nutritional status, providing nutrient synthesis [1, 3, 23, 25, 36, 38, 56, 58].

Of prebiotics, lactulose (duphalac, normase), inulin, and hilak-forte are most commonly used [1, 23, 36, 38, 44].

4. At high degrees of colorectal dysbiosis (III-IV) occurring with clinical symptoms, there is a need for preliminary administration of antibacterial agents, since pro- and synbiotics can no longer independently restore normomicrobiosis of the intestine. Start with intestinal antiseptics, which selectively suppress the pathogenic microflora, thereby contributing to the restoration of normo-flora. Representatives of intestinal antiseptics are: a) combined antibacterial drugs: intrex and enteroseed; 8-oxyquinolone derivatives: nitroxoline and chloroquinaldol; c) nitrofuran derivatives: furazolidone and ersefuril; d) non-absorbable antibiotic rifaximin; e) biological preparations with antimicrobial activity: enterol and baktisubtil, etc. More often others use intrex (2 caps. 3 times/day; 5-7 days), enterosev (1–2 tables. 2–3 times/day; 7 — 10 days) rifaximin (alpha-normix: 200–400 mg 2–3 times/day; 5–7 days), as well as enterol containing the freeze-dried yeast of Saccharomyces boulardii, which inhibits the growth and reproduction of pathogenic gut microflora, including Clostridium difficile and fungi of the genus Candida. Dose: 5000-1000 mg/day; 3-4 weeks [46].

5. In clinically manifest, severely flowing forms of colon intestinal dysbiosis prescribed a short course of antibiotics of general-destructive action, more often than others from the group of fluoroquinolones (levofloxacin, ciprofloxacin, sparfloxacin); course 5-7 days.

In pseudomembranous colitis, treatment should be started immediately. To combat the causative agent of this disease — Clostridium difficile — use: vancomycin (125-500 mg 4 times/day; 7-10 days) and/or metronidozole (250-500 mg 4 times/day; 7-10 days), and at their insufficient effectiveness — a backup antibiotic bacitracin (125 thousand ME 4 times/day; 7-10 days). To prevent recurrence of the disease, enter enterol in the usual dosage.

6. 6. According to the testimony, adjuvant (adjunctive) treatment can be additionally prescribed: a) enterosorbents (enterosgel, enterodesis, smecta); b) motility regulators (trimebutin — trimedat); c) drugs that reduce flatulence (espumizan, meteospasmil); d) antidiarrheal drugs (imodium — loperamide); e) mukofalk (psyllium) — a drug made from plantago ovata seeds, which in action is close to dietary fiber; e) immunomodulators (immunophane, galavit, gapon), etc. [1, 12, 21, 23].

7. There was a recommendation to treat severe forms of intestinal dysbiosis by transplantation of fecal masses from healthy people (“New England Journal of Medicine”), named “Intestinal Microbiota Transplantation” (IMT). The method is that with the help of a nasoduodenal probe, a solution of faeces from a healthy donor (1-2 procedures) is introduced into the human intestine. Restoration of normomicrobiosis was observed in 94% of cases. The method is certainly noteworthy, though not very aesthetic.

New directions in the doctrine of intestinal dysbiosis

I. In 2009, French microbiologists from the National Institute for Agricultural Research (INRA) hypothesized the existence of a key colon microbiota, its filometabolic nucleus, represented by the dominant bacterial species found in most healthy people. This filometabolic nucleus was isolated from a study of 17 healthy people 28–54 years old. It featured: Bacteroides, Eubacterium, Bifidobacterium, Clostridium, Faecalibacterium, Streptococcus, Klebsiella, Veilonella, Escherichia, Peptostreptococcus, etc. Among the dominant bacterial species, 3 bacterial types prevailed: 1. Fermicutes (Eubacterium, Faecalibacterium и др.) — 100%; 2. Bacteroides — 100%; 3. Actinobacteria (Bifidobacterium longum) — 82%. Noteworthy is the absence in this list of Lactobacillus, which are known to colonize the entire gastrointestinal tract — from the stomach to the colon.

The authors of the hypothesis believe that the physiological role of the filometabolic nucleus of the colon microbiota is to regulate metabolic processes in the intestine. This concept, which has yet to be substantiated, aims primarily at assessing the metabolic activity of major microbiota functional groups. For example, celiac disease and ulcerative colitis have been shown to increase the number of butyrate-producing bacteria that play a leading role in the energy supply of intestinal epithelium [17, 59].

II. The concept of symbiotic digestion, introduced in 2013, and its importance in the digestive process. The authors of this concept — Russian gastroenterologists and microbiologists — believe that the gut microbiota, especially the colon, has proteolytic, lipolytic and amylolytic activity. Thus, it contributes significantly to the mechanism of digestion by enzymes of the digestive juices of the stomach, pancreas and small intestine, expanding the ability of digestion and digestion of food ingredients in the colon, where there is practically no digestion. They believe that the inclusion of symbiotic digestion in the mechanism of their own digestion greatly expands and complements its functionality.

In various diseases, signs of colonic dysbiosis are observed, accompanied by a violation of symbiotic digestion. The use of pro-, pre- and synbiotics is the basis for the recovery of colon eubiosis and symbiotic digestion [27, 28].

Both concepts are certainly of scientific interest. However, the long and painstaking work of gastroenterologists, microbiologists, physiologists and geneticists is still needed to confirm their validity and scientific significance.

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Study of intestinal dysbiosis ("dysbacteriosis"): state of problem and new trends

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Key words: intestinal dysbiosis, history of study, terminology, diagnosis, treatment

Intestinal dysbiosis ("dysbacteriosis") is a clinical and laboratory (clinical and microbiological) secondary syndrome that develops in a number of diseases and clinical syndromes and is characterized by changes in the quantitative and qualitative (species) composition of microbial associations (normal flora) in certain biotopes (large and small intestine) with the translocation of its various representatives into unusual biotopes.

The main causes of the development of colic dysbiosis are: antibacterial therapy with the use of broad-spectrum antibiotics; hormone therapy; use of cytostatics; radiation therapy; bowel surgery; acute intestinal infectious diseases (dysentery, salmonellosis, etc.); immunodeficiency states of various genesis; unbalanced nutrition; lack of dietary fiber; excessive consumption of preservatives and xenobiotics; intestinal movement disorders (chronic constipation, diarrhea); mental stress conditions, etc.

There are direct (bacteriological cultures) and indirect (determination of short-chain volatile fatty acids by gas-liquid chromatography, respiratory tests, etc.) methods for diagnosing intestinal dysbiosis.

Treatment of intestinal dysbiosis ("dysbacteriosis") should be individualized and complex, taking into account its severity (degree), preferential localization (colon, small intestine), nature of the prevailing conditionally pathogenic microflora, presence of clinical symptoms and its characteristic features. Adequate treating of the underlying disease that caused intestinal dysbiosis; restoration of the impaired functions of the intestine, its parietal (contact, membrane) and abdominal digestion; increasing the overall resistance of the organism due to the restoration of its immunological and non-specific protection; correction of dysbiosis of the colon and small intestine are crucial. Diet, intestinal antibiotics, pro-, prebiotics, synbiotics are important components of treatment. In recent years, fecal transplantation has been more widely applied.