

EUBIOSIS AND DYSBIOSIS OF GASTROINTESTINAL TRACT: MYTHS AND REALITY

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An evolutionary-ecological functional system macroorganism — endosymbiotic bacteria has formed in the long process of evolution and natural selection for thousands of years [33]. In its development and formation it passed (schematically) several historical stages.

At the first stage it was a relationship of mutual antagonism and confrontation: the human body violently resisted the invasion of alien organisms. This opposition is believed to kill more than one human line [45].

At the second stage, when the elimination of bacteria, for some reasons did not succeed, microorganism and penetrated microflora entered into a compromise by smoothing relations of mutual antagonism and coexistence based on the principles of commensalism (French “commensal”).

At the third stage by overcoming commensalism a mutually beneficial symbiosis was formed on the principle of mutual services — mutualism (Latin “mutuus”), when macroorganism and penetrated microflora recovered some advantages of co-existence. Endosymbiotic bacteria occupy an ecological niche with favorable (comfort) and stable conditions that ensure the safety of the microbial population, and the macroorganism receives reliable protection against penetration of opportunistic and pathogenic bacteria and viruses that threaten its health and uses complicity of bacteria colonizing his gastrointestinal tract in metabolism, synthesis of vitamins, enzymes, neurotransmitters etc. [22, 38, 39].

The fourth stage emerged with the beginning of the era of antibiotics (the middle of the 20th century), when there was a gradual loss of many beneficial for human endosymbiotic bacteria, historically adapted to macroorganisms, and

antibiotic resistant virulent strains-mutants replaced them, including the L-forms of bacteria, chlamydia, and viruses that threaten the health and life of human [38, 39, 45, 46].

It is recalled that there is an evolutionary-ecological antagonism between bacteria and viruses, being an important defense mechanism of the human body from the long-term persistence of viruses. In the presence of endosymbiotic bacteria in the gastrointestinal tract, "buffering unit" (bacteria) between the microorganism and viruses is preserved, that constrains expansion of viruses due to nucleolytic enzymes (DNase and RNase) produced by them, capable of dissolving the viral nucleic acid, irrespective of the virus type [45]. With the destruction of the biological barrier, viruses acquire the ability to affect directly the human body, causing viral infections dangerous for life [45, 46].

Terminological problems. Eubiosis (normobiocoenosis, normal flora) is an evolutionarily and phylogenetically established set of microbial communities colonizing the gastrointestinal tract of healthy humans and characterized by a certain quantitative and qualitative (species) composition in different places its habitats (biotopes), which are able to maintain the biochemical, metabolic and immune balance necessary for human health [8, 18, 39, 60, 61, 69].

Eubiosis of gastrointestinal tract of a healthy person is marked with relative constancy and persistence of dynamic equilibrium between the macroorganism and the association of microorganisms colonizing its digestive tract. The total mass of bacteria associated with the digestive tract of a healthy person reaches 2.5-3 kg, which is approximately 5% of the weight of his body. Endosymbiotic microflora is the most numerous in the large gut, where it is represented by 17 families, 45 genera and 500 species of bacteria. According to the latest data obtained by analysis of homology of 16 S rRNA sequenced genes, gastrointestinal microflora includes 395 phylogenetically isolated groups (phylotypes) microorganisms [8, 58].

In our country, to refer to various violations in microbiocenosis of gut, term "dysbiosis" is most often used [1, 3, 8, 14, 27], or "dysbiosis" [8, 11, 12, 29, 68], which was first used by A. Nissle in 1916 [68].

We consider the term "dysbiosis" more accurate, and there are compelling reasons for this. Firstly, the term "dysbiosis" reflects the qualitative and quantitative changes in intestinal microbiocenosis and is alternative to the term "eubiosis", denoting normobiocoenosis. Secondly (and this is the most important), the composition of microorganisms colonizing the gut is not limited to bacteria, as yeast-like fungi live in it, including fungi of the genus *Candida*, and several species eiteroviruses (rotavirus, astrovirus etc.), which does not "fit" the term "dysbacteriosis" [3, 4, 8, 22, 39, 41].

In a broader sense, we consider dysbiosis as a condition of the ecosystem of the intestine when functions of all of its components are disturbed: the macroorganism, its resident microflora and the environment of its habitat, and the mechanisms of their interaction [39].

The important role of the microflora colonizing the gastrointestinal tract in human health and disease, for the first time was marked by outstanding domestic microbiologist I. I. Mechnikov (1845-1916), awarded with the Nobel Prize for Medicine (1908) [3, 8, 47]. He believed that "the numerous associations of microbes that inhabit the human gut largely determine its mental and physical health". In 1907, Mechnikov declared the protective role of the microflora colonizing the large intestine of healthy people, as well as the possibility of the occurrence of various diseases under the influence of endotoxins and microbial metabolites formed during the life of opportunistic and pathogenic bacteria penetrated to the bowels.

We believe that the doctrine of eubiosis and dysbiosis of gut created by our scientist should be proud of.

However, some gastroenterologists in our country do not recognize the doctrine of dysbiosis (dysbacteriosis) of gut and carefully avoid this term [34], and mention it with the derogatory epithet "notorious" [10, 50]. Instead of the term "dysbiosis (dysbacteriosis)", they strongly recommend to use the term "bacterial overgrowth syndrome" borrowed from thr foreign medical literature or "wrong colonization of bacteria" (German "bacterielle Fehlbesidlung") [5, 22, 39, 49].

Trying to justify their position, these authors usually use two arguments:

1. The term "dysbiosis (dysbacteriosis)" is missing in the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10, 1995). But this term should not must appear in ICD-10, as dysbiosis of the gut is not a disease, but clinical and laboratory syndrome developing secondarily upon broad-spectrum antibiotics intake, in different gastroenterological diseases (and not only, in acute intestinal infections etc. [8, 13, 17, 18, 34, 39]. Incidentally, the term "bacterial overgrowth syndrome" is also absent in ICD -10.
2. The term "dysbiosis (dysbacteriosis)" with few exceptions [31], not referred to in medical foreign literature — it is true [57, 60, 61, 63], but many publications of foreign authors are dedicated to the violations of microbiocenosis of gut upon different diseases and its correction with help of pro- and synbiotics containing representatives of normal (obligate) colonic microbiota (bifidobacteria and lactobacilli). The question arises: if the problem of dysbiosis (dysbacteriosis) of gut does not exist, why correction could be conducted [39, 54, 57, 59]?

Distribution of various representatives of the microbiota in the large gut is uneven. Bifidobacteria colonize mostly blind, ascending and descending colon, lactobacillus — all parts of the large gut, with the exception of rectum, E. coli — all its departments, opportunistic pathogenic strains — descending colon and sigmoid colon; streptococci are be found in all parts of the large gut, but they are especially numerous in the transverse colon and rectum [8, 16].

The term "syndrome of excessive microbial growth" can hardly be attributed to medical terms. It is rather verbose description and not a term which should be notable for brevity and accuracy. Furthermore, it indicates only quantitative but not qualitative changes in the microflora. However, the main objection is that the term was proposed and used by foreign researchers to refer violations of microbiocenosis in the small intestine, not the large one, which is clearly indicated by its full title: «small intestinal bacterial overgrowth syndrome (SIBOS)» [19, 30, 41].

Thus, the term "syndrome of bacterial overgrowth" is not synonymous with the term "dysbiosis" and can not serve as an alternative to it, since these terms reflect different processes in different habitats of the intestine (in the small and large intestine).

While the microflora of the large intestine performs multiple useful functions in healthy humans (eubiosis), bacterial overgrowth in the small intestine, especially in its proximal parts, is almost always fraught with negative consequences (syndrome of impaired digestion and absorption, chronic diarrhea, etc.) [30, 37, 42, 73, 77]. Furthermore, it is a narrower term than dysbiosis [22].

Number of microflora in the duodenum and jejunum of a healthy person is less than 10^4 /ml (streptococci, staphylococci, micrococci, peptostreptococci, lactobacillus, yeast-like fungi); *Helicobacter pylori* (Hp) are absent. In the ileum, adjacent to the ileocecal valve (Voroilio sphincter, valva ileocaecalis), the amount of the microbiota, as well as its species composition, is substantially increased, including the anaerobes up to 10^5 to 10^8 /ml (enterococci, E. coli, bacteroides, bifidobacteria) [4, 8, 13, 22, 30, 37, 42, 71, 73, 76, 77].

We should recognize pathogenetic link between dysbiosis of the large intestine and development of so-called syndrome of bacterial overgrowth in the small intestine, as increased microbial contamination of the small intestine develops largely due to cases of penetrating microbiota of the large intestine in it, especially in case of (for different reasons) function violation and/or structure of the ileocecal valve. Another possible route of microflora entering the small intestine — from the stomach with the development of widespread atrophic process occurring with achlorhydria and gastric achylia when natural barrier of active bactericidal action of gastric juice disappears.

In order to unify the terminology, we offered new terms in 2000: "colonic dysbiosis" and "enteric dysbiosis", which reflect the quantitative and qualitative abnormalities in microbiocenosis of large and small intestine and their localization [41].

Classification of colonic dysbiosis.

It is proposed to distinguish the following types of flora.

I. By the composition of microbial associations colonizing the colon:

1. obligate (indigenous, autochthonous) microflora, which is the most numerous: more than 90% of all microorganisms colonizing the colon healthy person (bifidobacteria and lactobacilli, bacteroides, complete *E. coli*);
2. facultative microflora: 9.5% (micrococci, streptococci, peptostreptococci, staphylococci, *Proteus*);
3. transient (random, residual, allochthonous) microflora: 0.5% (*Clostridium*, *Pseudomonas aeruginosa*, fungi of the genus *Candida*).

II. By the localization:

1. parietal (mucosal) microflora (M-flora), fixed (adhesion) on epithelial cells (colonocytes) of the large intestine with formation of microcolonies. Adhesion occurs due to the presence of the protein compounds on the surface of bacteria, known as lectins, which contain glycoproteins, and are complementary to specific receptors located on the colonocytes. Microcolonies formed by the bacteria are protected from external influences by specific biofilm composed of microbial exopolysaccharides and mucin — the secret of goblet cells. Formed exopolysaccharide-mucin matrix performs the function of "placenta", through which the exchange of substances between microorganisms disposed on the wall surface, and contains of the large gut is done [25, 35, 47];
2. intraluminal microflora, less numerous, which is located in the cavity of the large gut ("free floating"). Parietal microflora is about 6 times larger than the cavity one.

III. By the regard to molecular oxygen:

1. strict aerobes which livelihoods are impossible without oxygen (most prokaryotic microorganisms);

2. strict anaerobes, for which, on the contrary, oxygen is toxic (bacteroides, clostridia, bifidobacteria, eubacteria);
3. facultative aerobes (lactobacilli, enterococci). Anaerobes significantly prevail in the large gut (10 times).

IV. By the dominant type of opportunistic pathogens:

1. staphylococcal;
2. streptococcal;
3. klebsiellous;
4. proteus;
5. bacteroidal;
6. clostridial (*Clostr. Difficile*);
7. candidomycotic;
8. mixed dysbiosis [12].

V. By the quantitative and qualitative disorders of normal flora of the large gut, 4 stages (degrees) are distinguished:

1. compensated, at which there is a change (decrease or increase) in the population of *E. coli*; violation of the pool of short-chain fatty acids (SCFA); increase in the content of phenylacetic acid and methylamine;
2. subcompensated, which is characterized by a moderate decrease in the number of representatives of the major obligate microflora of the large intestine (bifidobacteria and lactobacilli), quantitative and qualitative changes of *E. coli*, the population growth of opportunistic pathogenic microflora (*Proteus*, *Klebsiella*, *Staphylococcus* and others), emergence of *Pseudomonas*, carboxylic and aromatic amino acids, change in the content of serotonin and histamine;
3. decompensated uncomplicated, with a significant decrease (up to 10^5 - 10^6 /g of faeces) of bifidus- and lactobacilli in the contents of the large gut, evident qualitative changes of *E. coli*, a significant growth of opportunistic pathogens and the manifestation of their virulent properties; metabolic

disorder (decrease in the content of phenolic compounds, higher levels of phenylpropionic acid, etc.);

4. decompensated complicated, that is characterized by a sharp decrease or complete absence of bifidobacteria and lactobacilli, a significant decrease in the amount of *E. coli*, the dominance of the opportunistic pathogenic and pathogenic bacteria and fungi of the genus *Candida*, deep lack of balance of biochemical regulatory mechanisms of microbial ecosystem of the large intestine with the accumulation of entero- and cytotoxins in it with signs of endotoxemia, gastrointestinal dysfunction, sometimes with destruction of the intestinal wall; possible bacteremia and sepsis developing upon reducing macroorganism resistance and its immune protection [4, 14, 23, 29, 35, 39].

At the initial (I-II) stages of colonic dysbiosis, obvious clinical symptoms are absent, but there is a variety of metabolic disorders. Upon decompensation (III-IV stages), there is a wide range of clinical symptoms (bloating, constipation, diarrhea, abdominal pain, food allergies, disorders of water and electrolyte metabolism, signs of endotoxemia occurring with liver lesion, etc.), resulting in the large intestine dysbiosis being transformed from the laboratory (microbiological) syndrome in clinical-microbiological one [39].

The main function of the colon microbiota. Currently microbiocaenosis of the human gastrointestinal tract has been already studied at the genetic and molecular levels [8, 12]. It is found that the microflora of the large gut in healthy person (eubiosis) performs a number of vital functions, ensuring its homeostasis. Among them must be mentioned:

- providing colonization resistance of the macroorganism through the phenomenon of microbial antagonism between obligate microflora of the large gut (mainly bifidobacteria and lactobacilli) and opportunistic pathogens [40, 45, 46];

- formation of substances with antibiotic properties (bacteriocins, microcins), as well as organic acids, biasing the pH to 5.3-5.8 that prevents growth of gassing and putrefactive microflora;
- detoxification of endogenous and exogenous toxic substances due to their absorption (natural sorbent) and excretion from the human body (metals, phenols, various poisons of animal, plant and microbial origin);
- synthesis of vitamins (vitamin B complex, vitamin K, folic and nicotinic acid), the assimilation of vitamin D and calcium salts, synthesis of amino acid, production of cytokines;
- strengthening the disease-resistance of the macroorganism by stimulating lymphatic system of the large gut, immunoglobulin synthesis of interferon, and maintenance of non-specific defense factors (lysozyme, properdin, complement);
- synthesis of biologically active substances which stimulate metabolic processes in macroorganism (neurotransmitters, enzymes, p-alanine, γ -aminobutyric acid, etc.); taking part in the recirculation of bile acids, cholesterol, steroid hormones;
- enzymatic digestion of nutrients, not hydrolyzed in the small intestine, including dietary fiber, with forming amines, phenols, SCFA which serve as energy source for colonocytes and affect the synthesis of DNA (butyrate), are involved in lipogenesis, gluconeogenesis, synthesis of amino acids, cholesterol metabolism (propionate);
- morphokinetic (trophic) action, providing for the physiological activity of the digestive tract [3, 12, 14, 21, 24, 25, 48, 55, 62, 64, 65, 66, 72, 75].

All the above-mentioned justifies the recognition of the fact that the microbiota of the large gut is a kind of extracorporeal body providing vital aspects of human life [24, 41, 47, 48].

Eminent physiologist A. M. Ugolev asserted: "The microflora is a mandatory component of the normal life of the human body" [32, 33].

Intestinal eubiosis and dysbiosis: myths and realities. In the process of studying the intestinal microbiocenosis, numerous myths developed that have no connection with the reality, that "migrate" from one publication to another. However, their authors, apparently, do not seriously think about their sometimes categorical assertions.

We tried as much as possible to understand the validity of some the most enduring myths concerning gastrointestinal eubiosis and dysbiosis, and argue our position, based on the existing realities.

Myth 1: "The stomach of a healthy human almost has no microbes" [29, 34]. Formed opinion about the impossibility of a long (over 30 minutes) existence of the microflora in the strongly acidic environment of the stomach with a high proteolytic activity proved to be wrong. Previously it was argued that only Hp, due to genetic polymorphism and the unique ability to recombinant mutations and the formation of urease, was able to adapt to living in the acidic environment of the stomach and take up free ecological niche. In case of finding another microflora in the stomach, it was declared transient, unable to adhesion and colonization of its mucosa.

Research of clinicians and microbiologists using modern methods of microbiological examination, however, proved that it was not so. It was found that, besides Hp, other mucosal microflora (M-microflora) was living in the stomach of healthy and having adhesiveness and urease activity; a significant portion of it was characterized by invasiveness (unlike Hp) and virulence. Number of M-microflora in the stomach of healthy people is 10^3 - 10^4 /ml. Only in 10% the medium in the stomach was sterile [8, 44].

Microflora of the stomach is divided into 2 types by origin: the oral-respiratory (type 1) and fecal (type 2) [8, 62].

The total number of species of microorganisms colonizing the stomach of healthy people is 10-14. Thus, in the stomach of healthy persons were detected: staphylococci — 61.1% (3.6 lg CFU/g), streptococci — 55.5% (4 lg CFU/g), Hp — 44.4% (5.3 lg CFU/g), *Lactobacillus* — 50% (3.2 lg CFU/g), *Bacillus* — in 22.2% (2.9 lg CFU/g), fungi of the genus *Candida* — 22.2% (3.5 lg CFU/g) [8, 13]. It seems

important to emphasize that in HEALTHY people Hp is found in the stomach only in combination with other types of bacteria — not in monoculture [8]. S. Roos et al. [70] established an important fact: they were able to identify new species of *Lactobacillus*, colonizing the stomach of a healthy person (*L. gastricus*, *L. antri*, *L. kalixensis* and *L. ultenensis*), adapted (like Hp) to the existence in the acidic medium of the stomach. According to the latest data, the microflora of the gastric mucosa of healthy individuals is represented by 128 phylotypes [56, 67].

Myth 2: "Unfortunately, in domestic practice, the method of stool culture continues to be applied, in which intraluminal microflora dominates" [12, 18, 34]. This classic method of identification of the microflora of the large gut, indeed, still dominates in the Russian research of scientists studying the problem of colonic eubiosis and dysbiosis [1, 16, 29, 35]. Opponents of the research method claim, furthermore, that it reflects only the state microbiocenosis of distal parts of the gut and criticize it for detecting not more than 25 species of bacteria from 400-500 species colonizing the gut [6, 12, 18, 29], but these objections turn out to be untenable in an objective examination. From the physiology of the large gut it is known that fecal masses are formed throughout it. The epithelium of the gut is continuously updated (its complete replacement takes place every 2-4 days). Sloughed colonocytes with bacterial parietal microcolonies fixed on the surface are "dumped" into the cavity of the intestine (up to 220-250 g/day) and excreted in the feces, which are 35-55% consist of microbial cells [39, 49, 52]. Thus, microflora determined in feces, is an integral reflection of the parietal and intraluminal microflora of the large gut, rather than its distal parts, as claimed by some authors [4, 39, 41, 52].

The main microbial landscape of the large intestine in healthy forms 15-20 associations of the dominant anaerobic, aerobic and facultative aerobic bacteria species — representatives of the genera bacteroides, bifidobacteria, eubacteria, fusobacteria, proteus, clostridia, lactobacilli, bacilli, peptostreptococci, staphylococci, streptococci, enterococci, etc. Other bacterial species are rare and in small quantities. In this regard, there is no reason to detect each time the hundreds of species of

bacteria, as it is sufficient to establish the presence of 18-20 dominant species. In addition, many of them are not cultivated at all [8, 48].

However, all researchers studying the microbial composition of feces aiming to obtain objective results should strictly follow the rules of microbiological research. Key rules: using a sterile instrument, 0.2-1 g of feces are placed in sterile, hermetical seals vessels; to isolate anaerobes, feces are collected into tubes with a well stoppered rubber plugs, which are filled with a mixture gas of a certain composition (carbon dioxide, propane, hydrogen, nitrogen); sample for the study is collected from the middle or the last portion of feces; material is thoroughly homogenized using a sterile glass stick, bacteriological snare or glass beads; multiple dilutions are made (10-fold or more), and a sterile pipette transfers 0.5 ml to the tube; seeding is carried on special nutrient media (Endo, Simmonds, Saburo, 5% blood agar, and others) [3, 8].

Criticizing the informative value of microbiological examination of faeces, it is usually opposed with the gold standard technique of seeding for bacterial medium of jejunal aspirate obtained through a special enteric sterile probe [18, 26, 34]. But here comes the obvious substitution of concepts: study of the microbial composition of faecal determines the species composition of bacteria colonizing the large intestine, while studying the aspirate jejunum reflects microbial composition of the small intestine. Asserting that the microbiological examination of feces does not provide information on the composition of the parietal microflora of the large gut, it is considered that studies of aspirate obtained from the lumen of the jejunum reflect not only the composition of intraluminal, but also its parietal microflora. It is impossible to agree with it.

There is another direct method of studying the microbiocenosis of the large and small intestine, wherein greater certainty is observed: polymerase chain reaction, based on the amplification (multiple copies of DNA fragments of the microorganisms by DNA-polymerase enzyme [18]). K. Mullis, who developed the method, was awarded the Nobel Prize in Chemistry. This highly informative and accurate method, but it can be used to determine only a limited number of microorganisms, and the method itself is not available to everyone.

A number of indirect methods for studying the composition of the microbiota of the large and small intestine were elaborated, based on the determination of the metabolites of the intestinal microflora — indican, phenol, ammonia, and others. They are simple, accessible, but their specificity and sensitivity are not sufficient (50-90% and 25-90%, respectively).

Hydrogen breath test is rather widespread, especially the modification with lactulose load. The method is based on the fact that upon intestinal dysbiosis basic hydrogen concentration in the expired air after administration of 10 g of lactulose is increased (more than 20 ppm). The study lasts for 3 hours with the determination of hydrogen content every 15 minutes. The appearance of "early peak" in the hydrogen content in the exhaled air (in 1.5 hours) indicates intestinal dysbiosis, while the appearance of the "late peak" (3 hours) indicates colonic dysbiosis [4, 18, 30].

Method for determining the content of SCFA in the small intestine aspirate (butyric acid, propionic acid, hexanoic, etc.) is positively evaluated, which characterizes mainly the anaerobic spectrum of microorganisms. Method of gas-liquid chromatography is used in combination with mass spectrometry, which determines the metabolic activity of the microflora on the spectra and levels of SCFA. This method allows during 30-40 min to state integral metabolic activity and metabolic imbalance of predominantly anaerobic microflora, and the total number of bacterial metabolites [1, 4, 18, 22]. The disadvantage of this method is called the "loss" of 15-20% of the metabolites in the sample preparation [22].

In general, preference should be given to direct methods of diagnostics of intestinal dysbiosis, although they have their shortcomings too [41]. Justifying this thesis, let's present an example. As you know, there are direct and indirect methods of identifying *Hp*: direct determination of *Hp* in gastric biopsy specimens and determination by setting their urease activity, but urease activity, as it turned out, is not unique to *Hp*, another M-microflora of the stomach has it, actively producing the urease, therefore, urease test can not be considered a reliable method for diagnostics of *Hp* infection.

Myth 3: "There are certain diseases and syndromes, which are often mistakenly (?) treated as clinical manifestations of dysbiosis, bacterial overgrowth syndrome, antibiotic-associated diarrhea, traveler's diarrhea, irritable bowel syndrome, and others" [51]. This statement is incorrect on the substance, as bacterial overgrowth syndrome, and antibiotic-associated diarrhea (AAD), including its most formidable clinical form of pseudomembranous colitis (PMC), travelers' diarrhea, and, as it has been recently believed, a postinfectious form of irritable bowel syndrome, are being developed as a result of the qualitative and quantitative changes in microbiocenosis of the small and large intestine, being clinically manifest forms of intestinal dysbiosis [4, 11, 19, 31, 34, 38, 74].

The primary cause of the syndrome of bacterial overgrowth in the small intestine (enteric dysbiosis) is increased "occupation" of the small intestine by fecal microflora [4, 19, 30, 38, 39, 77], and the etiological factor of AAD and PMC — high degree of colonic dysbiosis after irrational antibiotic therapy [30, 38]. This is clearly evidenced by the term "antibiotic-associated diarrhea." The authoritative Therapeutic Reference Book of Washington University, having more than 30 editions, states: "Antibiotics is a common cause of diarrhea. They inhibit the normal gut flora, leading to dysbiosis. The most severe form is a pseudomembranous colitis" [31].

Myth 4: "The main representatives of the microflora of the gut are anaerobic gram-positive bacilli, bifidobacteria and lactobacilli [15, 18, 34, 36, 51]. This statement belongs mainly to clinicians, at the same time microbiologists are well known that strict anaerobes are bifidobacteria, while lactobacilli are the facultative aerobes [8, 22]. Therefore, bifidobacteria in healthy individuals primarily colonize only the large gut dominated by anaerobic microflora, while lactobacilli habitat is the digestive tract, beginning from the mouth and the stomach, where only aerobes can exist, and ending in the large gut dominated by anaerobes [8, 40].

Treatment of intestinal dysbiosis. The main diseases and syndromes, in the development of which colonic dysbiosis plays a leading role, are: AAD, a mild form of which somehow is unsuccessfully called idiopathic (idiopathicus — primary, of

unknown origin), because AAD is being developed as a secondary, and its cause is known (the irrational use of antibiotics); severe form of the AMA — PMC, which is caused by clostridial dysbiosis, as well as travelers' diarrhea, the development of which in 75% of cases is associated with enterotoxigenic *E. coli*, and irritable bowel syndrome (postinfectious variant).

The most frequent clinical forms of enteric dysbiosis are functional diarrhea (secretory and osmotic), maldigestion syndrome, and malabsorption [19, 26, 34, 38, 42, 50, 74].

Correction of intestinal dysbiosis needs integrated approach. The main objectives of therapeutic measures are:

- adequate treatment of the main disease that caused the development of intestinal dysbiosis;
- restoration of disturbed functions of the intestine;
- increase of general resistance macroorganism due to the stimulation of its immune and non-specific protection;
- correction of dysbiosis of the large and small intestine itself using functional nutrition, pre-, pro- and synbiotics, and (upon strict prescriptions) intestinal antiseptics, antibiotics and other antibacterial and antiparasitic agents.

At the initial (I and II) stages of intestinal dysbiosis occurring without obvious clinical symptoms, functional nutrition is prescribed (FN) that means regular use of natural products that are able to regulate and normalize the functions and biochemical reactions of microorganism [47]. FN presupposes the products of plant, animal and microbial origin containing dietary fiber, lactic acid bacteria and bifidobacteria, natural antioxidants (soy milk, pectins, proteins, vitamins, minerals, etc.), that are figuratively referred to as nutritional drugs. With their help one can often recover eubiosis of the large gut in a short time without having received pharmacological agents.

An important element of the FN are the dietary fibers (DF). They stimulate the passage of food chyme through the intestine, are a source of SCFA, membrane

phospholipids and amino acids (arginine, glutamine), affect the absorption of water and sodium bicarbonate secretion, trophic and proliferation of colonocytes, gluconeogenesis and lipogenesis, cholesterol metabolism. Furthermore, DF (wheat bran, flax seed, agar-agar, macrocrystalline cellulose, psyllium seed, etc.) possess anabolic, immunostimulatory and energetic potential (due to ATPase energy). It is important to emphasize that the DF help restore eubiosis of the large gut, acting as a "matrix" for fixing obligate bacteria, thereby increasing the colonization resistance of the human body (the daily dose of DF added to ready meals is 25-35 g).

Valuable aid in the treatment of primary (I and II) stages of colonic dysbiosis may serve mukofalk (psyllium) obtained from the shells of psyllium (*Plantago ovata*). It ensures the growth of the normal microflora, increases the levels of SCFA, the recovery of intestinal motility. The dose — 5 g per cup of cold water, the course of 3-4 weeks.

In the diet of patients with intestinal dysbiosis it is recommended to add, furthermore, cultured milk foods (yogurt, curdled milk, yoghurt, etc.) enriched by bifidus.

Besides FN, prebiotics may be useful for patients with mild forms of colonic dysbiosis — agents of non-microbial origin, recovering eubiosis by selective growth regulation of the main representatives of obligate microflora (bifidobacteria and lactobacilli) of healthy person.

Lactulose is widely used as a prebiotic (dufalac, normase) — a synthetic non-absorbable disaccharide (galactose + fructose), which forms SCFA in the large gut, which serve as a substrate for the growth of saccharolytic bacteria (bifidobacteria and lactobacilli, enterococci). The dose — 20-45 ml 1 time per day [9].

Another valuable prebiotic — hilak forte which contains metabolic products of the normal microflora of the large gut. Hilak forte helps to restore normal microflora in the gut by biological way, contains biosynthetic lactic acid and its buffer salts, hindering the development of opportunistic bacteria, as well as SCFA that restore obligate microflora of the large gut, stimulate an immune response. The dose — 40-60 drops 3 times a day for 10-15 days.

In case of insufficient effectiveness, treatment is supplemented by probiotic microorganisms (eubiotics) that contain living microorganisms, which are the part of the normal microflora of the large gut, especially bifidobacteria, lactobacilli and enterococci (fecal streptococci), sometimes E. coli. It is reasonable to use synbiotics containing both pro- and prebiotics.

Biform and linex (in capsules) are the most commonly used probiotics, which are specially coated, resistant to the action of enzymes, digestive juices (stomach, pancreas and small intestine). They have antibiotic resistance, antagonism towards pathogenic microflora of the large gut, and also have immunomodulatory effects (2 capsules 2 times a day for 3-4 weeks). The combined synbiotic (fly's) is of considerable interest, which contains living freeze-dried bifidobacteria and lactobacilli, the prebiotic inulin and (optionally) the various inclusions (4 variants): DF or complex of natural antioxidants, vitamins or toning plant extracts (adaptogens). Preservation of obligate microflora in the stomach and small intestine is provided by their adsorption on special media containing lactose. Another combined probiotic — bioflor — contains biologically active food additives (extract of propolis, mint, parsley, cabbage, etc.) in combination with a complete E. coli.

Useful biological preparations that contain microorganisms of extraintestinal origin and inhibit opportunistic bacteria: enterol, baktisubtil, flonivin BS, baktistatin) [15].

At the III-IV stages of colonic dysbiosis antibacterial agents to suppress the dominant opportunistic and pathogenic organisms are prescribed. Therapy usually begins with intestinal antiseptics, having selective effect on pathogenic microorganisms: intetriks (2 capsules 2 times a day), enterosediv (1-2 tablets 3 times a day), dependal-M (1 tablet 2-3 times a day) for 5-7 days. Antibiotic rifaximin, that is not absorbed in the gut, has been recognized (200-400 mg 2-3 times a day for 5-7 days).

Upon the lack of effectiveness of intestinal antiseptics and clinically difficult intestinal dysbiosis, it becomes necessary to prescribe resorptive broad-spectrum antibiotics. We give preference to fluoroquinolones (ciprofloxacin, levofloxacin,

ofloxacin), which are prescribed for 5-7 days, while the use of tetracycline, ampicillin, cephalixin we consider undesirable because of their severe side effects. Upon life-threatening PMC, treatment should begin immediately. Vancomycin (125-500 mg 4 times a day for 7-10 days) or metronidazole (250-500 mg 4 times a day for 7-10 days) are prescribed. As a reserve antibiotic, complex antibiotic bacitracin is used (125000 ME 4 times a day for 7-10 days), and for the prevention of recurrence of PMC — enterol (therapeutic yeast containing *Saccharomyces boulardii* — 500-1000 mg/day for 3-4 weeks). In such cases, immunomodulators could be useful (imunofan, teaktivin, galavit, etc.) to increase the overall resistance of the macroorganism.

For relief of the clinical manifestations of intestinal dysbiosis symptomatic therapy is applied: motility regulators (debridat) myotropic antispasmodics (ditsetel, spazmomen), enteric sorbates (smekta, neosmektin, enterosgel, enterodez, etc.). To combat flatulence defoamer (espumizan) and combined drug (meteospazmil) are used. Sometimes there is a need for infusion therapy [1, 2, 5, 6, 9, 15, 18, 19, 20, 25, 28, 29, 30, 38, 39, 42, 43, 50, 53, 54, 57, 59, 64, 74].

The basic principles of treatment of intestinal dysbiosis are complexity and individual approach.

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Eubiosis and dysbiosis of gastrointestinal tract: myths and reality

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Key words: eubiosis and dysbiosis of gastrointestinal tract, diagnostics, treatment, terminology, debatable problems

Current data on eubiosis and dysbiosis of gastrointestinal tract are discussed along with the role of its microflora in human body under normal and pathological conditions. Certain debatable problems are discussed. Classification of colonic dysbiosis is presented with reference to its stages, functions of normal flora, «myths» related to the science of eubiosis and dysbiosis, the authors views of the problem. Diagnostic methods and their informative value are described. The main diseases and syndromes associated with intestinal dysbiosis are discussed in conjunction with approaches to its correction.