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## THE ELIMINATION OF INTESTINAL DYSBIOSIS AND FORMATION OF THE IMMUNE SYSTEM BY BACTERIA SYMBIOTIC (Literature review)

**Abstract.** *Being HIV-infected the change qualitative and quantitative composition of the intestine microflora, from the one side deepens disturbance body's protection mechanism but from the other side the cause disturbances of intestinal microflora. According to the date of the literature representatives of normal microflora present in human body, as fixed to certain receptors of microcolonies located in biofilm which covers mucous membranes. The elimination of the intestine dysbiosis allows to return to the conditions which are necessary for the immune system formation on the account symbiotic bacteria. That why probiotics therapy is the basic of the complex treatment for those patients. Nowadays the most modern is the probiotics prescriptions which are made on the basic yeast yeasts family Saccharomyces especially "Enterol-250".*

**Key words:** *intestine dysbiosis, immunity, HIV-infection, probiotics*

Every day HIV-infection diagnosis is made to almost 60 Ukrainians. During the whole period of the epidemiological surveillance 22607 people died from the diseases caused by AIDS [1, 2].

Nowadays HIV-infection epidemic situation in Ukraine is characterized by growing numbers of morbidity and mortality from AIDS activation of the sexual way infecting HIV-infection, involving reproductive-aged women into the epidemic process. [3]. We are still leaders in Europe in spreading rate of HIV-infection, according to the UNAIDS experts evaluation 1.1% population in Ukraine is HIV-infected. According to the international experts predictions the number of children who lost both parents due to the HIV/AIDS epidemic can reach 42000 till 2014.

HIV-infection prevalence equals to 0.9%, that shows that the HIV/AIDS epidemic in our country is the biggest among European countries. It is known that in the evolution process ecosystems were created, they are based on symbiotic relations between a human and different microorganisms that found their place in a human body.

According to the modern opinions person's modern microflora is determined as a complex of many microbiocenosis which are characterized by

certain completion and take a certain biotope in human's body [4].

According to the researches definition "Regular microflora is an open biocenosis of the microorganisms which is detected in health people and animals" [5].

Obligate anaerobic bacteria are the basic of normal microflora of person. Even on a skin and in its deep layers the number of anaerobic bacteria exceeds 3-10 times the number of aerobic bacteria in the oral cavity. In the colon this ratio may increase to 1000:1 and more [4].

There are 4 types of the colon microflora differentiated: with domination of bacterioides, bifidobacteria, lactobacilli and with mixed flora [6]. A lot of types of enterobacteria, fecal streptococcus, clostridia and others belong to the cavity flora. The composition of mucosa microflora of the colon was studied not so much. General number of mucous flora is less than cavital and is about  $10^6$  cells. Bifidobacteria, lactobacteria, peptococci are dominated.

Data of different authors about species composition and quantitative ratio of the microorganisms are not always the same, but as it was said above everybody admits the domination of anaerobic flora before aerobic one.

So, during the examination of 50 healthy people there were defined microorganisms of 12 classes and 13 species, among them classes Bifidobacterium, Enterococcus, Escherichia – in 100%, Staphylococcus – in 96%, Candida – in 82%, Clostridium – in 72%, Pseudomonas – in 46%; Citrobacterium, Proteus, Klebsiella were less defined. From the species were more defined E. coli (96%), S. epidermidis (48%), P. aeruginosa (46%), more rarely – K. ozaenae, E. aerogenes, E. cloacae and others [7].

Representatives of normal microflora present in human body as fixed to certain receptors of microcolonies located on biofilm which covers mucous membranes. Biofilm consists of exopolysaccharides of the microbic origin, microcolonies of morphologically identical cells and produced by goblet cells mucin [8].

Endoecological system is useful for macroorganism due to antagonistic properties of the symbiotic microorganisms relatively to pathogenic and opportunistic microflora because they prevent from penetrating this flora into the areas of their resettlement. The bacteria's choice of the ecological recess depends of opportunity to produce attractants and repellents, which help many representatives of the microflora even if they are not able to move actively, to compete with other types [9]. To their number belongs as simple metabolites (fatty acids, lactic acids), as more complicated – bacteriocins, antibiotics, microcins, pyocins. Natural antagonism between endosymbiotic bacterias and viruses is also very important. Produced by this bacteria non-nuclear enzymes DNase and RNase dissolve viruses nucleic acid and decrease their activity which lose the ability to persist continuously in the human body.

The most complicated microbiocenosis of the biotope is the colon microflora. The microflora which populate a person and animals is extremely complicated, for example in 1 gram of cecum content there are more than 2 billion microorganisms representatives 17 different families, 45 types and above 400 species. [10]. In the whole colon a lot of types of microorganisms coexist on the principles of synergism and antagonism. Such a big number of the microflora types can be explained mostly by contacting multicomponent organic substances in the colon (starch, glycogen, raffinose, lactulose, sorbitol, xylitol, mucopolysaccharides, proteins, peptides); they're splitting to glucose to aminoacids happens

under the influence of bacteria enzymes. [11].

Bacteria flora in different parts of colon has its own specialty and it is rather permanent in the result of complicated interaction of the components of colon immune protection with the influence of non-specific factors. The mechanism which controls quantitative and qualitative content of conditionally pathogenic microflora and keeps dynamic balance between internal intestinal microflora and coming-inside microflora is marked as "colonization resistance" [12]. Among different functions which are done by normal microflora one of the most important is providing of the colonization resistance.

So, given data shows that the colon colonization resistance of the intestine which identify adults resistance to colonization of opportunistic microorganisms is provided by optimum content of Bifidobacteria.

Useful microorganisms are especially important in the process of digestion metabolism. They produce a big amount of enzymes and other necessary ingredients, also activate intestine enzymes, delay reproduction of pathogenic microflora, eliminate meteorism, normalize motor function of the intestine [13].

Normal intestinal microflora provides immunomodulated, adjuvans, mitogen and immunogenic [14].

In the modern sociality-economical conditions there is a full set of reasons which cause acute and chronic dysbiosis, ecological vulnerability, increasing stressful affects, common uncontrolled usage of antibiotics and chemotherapy drugs, increase radiation background and poor nutrition [15]. Whidespreading of the dysbiosis is the one of the most important factors which cause increasing of the frequency severity of the acute and chronic diseases. Microflora changes peculiar to dysbiosis, appear with reconstruction of the ecological ratio between different groups of microbes. Sharply decreased the number of Bifidobacteria among obligate microbes. On the background of these content of E. coli with hemolytic properties, enterococci and other cocci forms of bacteria are noticeably decreased. According to the quantitative content aerobic bacteria become the main flora. The most expressed changes happen in the remained group of microbes (opportunistic flora) which become permanent habitants of intestine. They are various in their species composition (Proteus, Candida, E. Coli, Clostridia, etc.) [16].

As researchers admit normal microbiocenosis [17] provides physiological activity of a persons and animals organism. A condition of normal microflora can serve as a health sensitive indicator changing with different diseases and “pre-clinical” violation of homeostasis and it is an integral feature of the functional usefulness of the antimicrobial defends mechanism. The connection between intestinal microflora and immunity is known for a long time. The microflora has an etiological role in pathogenesis of dysbiotic and immunological violation, although mutual influences of the dysbiotic and immunological shifts are variated [18].

In various infectious, autoimmune, and oncological diseases a change of qualitative and quantitative composition of the intestinal microflora on the one side violates defending mechanism of the organism and other side, oncological contribute to a violation of intestine microecology [19, 20].

Immunodeficiency contributes to the appearing of the dysbiosis [21]. As researchers point endogen intestinal microflora has the most important meaning in the mechanism of the immune formation and other non-specific reactions of the organism. The usage of radiation, antibiotics, chemotherapy and surgery depends on immunosuppression and dysbiosis.

In the immune status of the patients with intestinal dysbiosis with different origin is characterized by decreasing the activity of a T-cells, element of the immunity pathogenic function of the neutrophils.

Immune reactions which provide organism with dependence start polysaccharides, lipopolysaccharides, proteins of bacterial microflora with a basic stimulants of the protective reactions. The microbial agents' persistence in the organism provides the functioning of the immune system. Antigens which are permanent stimulus of the immune system have the endosymbiotic microorganisms which don't have any negative influence on a person's health. On the other side immune mechanisms provides a protection of the organism from the other bacteria. True symbiosis is directed to protect master for keeping symbiotic population. If a person loses symbiotic bacteria, the viruses which penetrate from the outside do not meet the resistance. It leads to settling viruses in the human's body, particularly HIV [22].

Viruses get the ability to persist continuously

causing different forms of viral diseases, the most dangerous is a slow infection, for e.g. HIV, which can cause fatal syndrome of AIDS. Significant decreasing CD4+ T-cells in HIV-infection enhances the process of microbial translocation [23]. HIV violates the integrity of mucous membrane, causing the conditions for the development of the colonal dysbiosis. According to the Shenderov's B. A. [4]. data most of population of post soviet area more or less suffers from dysbiosis which tells about the global social and ecological importance of the problem. Being widely spreaded dysbiosis the most frequently forms (and appears) in an intestine.

Intestinal dysbiosis is a clinic laboratory syndrome which occurs in a number of diseases and clinical situations, which is characterized by the change of qualitative and quantitative composition of the normal flora, metabolic and immune violations, in some patients it is accompanied by clinical symptoms of the intestine violations. Various factors which cause intestine dysbiosis are pointed in numerous sources of the literature: helminth invasion, chemical poisoning, stress and immunodeficiency. [7,13]. Sharp changes of the intestine microflora develop with salmonellosis, foodborne diseases, shigellosis etc, nutritional disorders while excessive protein, carbohydrate loads, when consuming a big number of refined foods.

Intestine dysbiosis is characterized by disorders of inner micro ratio due to decreasing the number of Bifidobacteria, E. Coli with reduction their antagonist fermentative activity, extremely breeding of facultative microorganisms, appearing E. coli which provide hemolysis on blood agar, increasing the number of opportunistic and pathogenic bacteria and yeasts representatives. While dysbiosis not only qualitative and quantitative disorder of the intestinal microflora occurs but also the change of their habitat [24]. The proximal part of the small intestine is colonized by the colon microflora. Normal peristaltic activity is an effective protective mechanism against excessive colonization of the small intestine. Any slowing down of the intestinal passage causes great increasing of the microorganisms [25].

Dysbiosis of the intestine can be symptomless but can cause bacteria with dyspepsia, body allergization, immunity oppression, development of different diseases, including sepsis [4].

To exit from ecological unfriendly state of the

body it is necessary to revive normal microbiocenosis. It allows to return to the conditions which are necessary to form an immune system in account symbiotic bacteria persistent in a lymphatic system. That's why the basic of the complex treatment intestine dysbiosis is a probiotic therapy. There are means which help to revive normal microflora. They influence a lot of settings of the intestine biocenosis, in particular the growth of the oppress opportunistic microbes and leads to their displacement.

First of all, drugs made of microorganisms which are the most of them met in the colon, have been started to use.

One of the first probiotics "colibacterinum" has been taken into the practice, it contains alive culture of the *E. coli*. Then drugs with Bifidobacteria, lactobacteria, Enterococci etc. appeared. Now they are widely known as "Bifidobacterinum" and "Lactobacterinum". To the first generation of probiotics belong the classical monocomponent drugs which contain normal microflora. The second generation consists of drugs which have competitive actions displacing pathogenic bacteria and which don't colonize the intestine: Bactisubtile, Biosporine, Sporobacterine, Enterolum. Then third generation of the probiotics appeared – multicomponent drugs of normal microflora which contain a combination of the bacteria. Modern probiotics can contain from 1 (Bifidobacterinum, Lactobacterinum, Bifilinum, Probioforum, Narine etc.) too 4 (Bificolum, Bifilongum, Bififormum, Acelactum, Linex etc.) and even 14-24 (Simbiter) strains alive microorganisms. The fourth generation of probiotics are combined drugs with optimized basis. Vitamins, lysozyme, plant extracts, propolis and micronutrients are added into alive bacterial drugs to increase the activity [26].

Probiotics prescriptions not only improve a microflora state of the colon but also influence the duration of the pathogen selection. According to the data of the researchers repetitive pathogens selection after probiotics treatment isn't fixed, meanwhile 7% patients which didn't get mentioned drugs the control bacteria exams were positive in the same terms. After finishing treatment erosions and ulcers epithelization in a colon is noted more than 90% patients who got probiotics and only 67% patients who didn't take them [27].

The main indications for prescribing antibiotics

are: subclinical form, erased, lightweight, protracted, protracted course of the disease; long form intestine violation and repetitive selection of bacteria in stage of reconvalescence; intolerance of chemotherapy drugs; the chronic diseases of the digestive tract, treatment and prevention of intestine dysbiosis [28].

Probiotics have a good effect not only on the intestine microbiocenosis but there are some instructions for stimulating effect on the Bifidobacterinum and Acelactum on depressed immunity [29].

Savchenko Z. I. and others used antibiotics "Bioflorum" for HIV-infected patients with late stage of disease in the presence of a sharp decline immunoregulatory index due to T-helper cells and functions of neutrophils, since the restoration of modified intestine microflora must provide immunocorrecting effect [30]. Immediately after 25 day course of "Bioflorum" treatment all 20 patients had normalization of neutrophils and B-lymphocytes function. In 30 HIV-infected of the test group there was established further declining of indicators IRI and neutrophils function by the end of observation period. (55 days)

During intestine dysbiosis of different origins the drug "Bioflorum" showed not only the direct antidysbiotic effect but also immunostimulatory which depended on the severity of dysbiosis and was its maximum at the first stage [31]. The authors explain immunostimulate action of "Bioflorum" by desintoxication as a result of oppression synthesis of enzymes and toxins of pathogenic opportunistic bacteria. Besides, normalization of antigenic structure of intestine microflora promotes the synthesis of normal antibodies which provide immune reactivity of the organism. Selective decontamination is used for the correction of the microbiocenosis violations through the usage of the specific bacteriophages and drugs which contain microbes antagonists of the pathogenic and opportunistic microorganisms "Biobactonum", "Bifacide", "Flonivine" and "Enterolum" [32].

However, if using bacterial probiotics there may be some side effects. In particular it is necessary to mention a violation removals and metabolic acidosis. The usage of milk with *L. acidophilus* culture by people with lactase deficiency accompanied with the same violation as usage of normal milk [31].

The violation of intestine flora when such gram-positive bacteria as Lactobacilli and

Bifidobacteria grown faster than gram-negative bacteria can increase D-lactate [32]. acidosis as a result of bacteria carbohydrate metabolism. The reason of enhanced growth of gram-positive bacteria can be surgical intervention, which leads to anatomical and functional intestine shortening and associated with it deepening D-lactate acidosis or antibiotic therapy, which causes increased resistant D-lactate producing bacteria growth, or oral *L. acidophilus* pills injection [33, 34]. The literature data suggest that *Lactobacilli*, *Enterococci*, *Bacillus cereus* and *Bifidobacteria* are not resistant to such antibiotics as amoxicillin, doxycycline, fluoroquinolone and cephalosporin.

The usage of these microorganisms in vivo during  $\beta$ -lactam, tetracycline, quinolone antibiotic therapy even in case of their intravenous injection may cause fast inactivation of microorganisms in small intestine [35]. So it was suggested to use antibiotic resistant bacteria as probiotics. But in this case there is a probability of antibiotic resistance transfer by plasmids to pathogenic bacteria [36].

Experimentally was demonstrated plasmid transfer from *Lactobacillus reuteri* to *Enterococcus faecium* and from *E. faecium* to *E. faecalis*. *E. faecium* infection is very dangerous because a lot of strains of this bacteria have plasmids, coded to resistance to various antibiotics including vancomycin [36].

Unfortunately, not enough effectivity of bacterial drugs based on alive microorganisms mostly caused restrictions, connected with fast bacteria strains elimination which were injected to unfriendly environment [37].

It should be mentioned, that usage of bacterial drugs often does not lead to the expected effect because of free space deficiency on the intestine wall which is occupied by pathogenic and opportunistic flora. Then probiotic microorganisms do not reach colonization advantage so cannot reach effective adhesion [37].

As a rule, drugs of bacteria strains in a human body do not survive because representatives of own microflora, in contrast from free living bacteria, can fix only on severely definite receptors of mucosa. Bacteria adhesion activity is one of mechanisms which provides their fixation and continuously persistence on a mucosa. In connection with the fact that intestinal content moving speed exceeds bacteria reproduction speed, microorganisms can stay fixed

continuously during a long time only in case of their adhesion on the mucosa. Immune system is tolerant to own microflora, but heterogeneous strains usually fast eliminate and do not cause clinical effect.

But very perspective is prescription of probiotics, which are produced using *Saccharomyces* yeasts. Using of these drugs is possible with antibiotic therapy. The yeasts' genetic distinction prevents possibility of the plasmids transfer with antibiotic resistance factor to pathogenic bacteria [36, 38]. Besides, they have significant antagonistic influence on pathogenic and opportunistic flora, based on natural yeasts properties.

One of these probiotics is "Enterolum-250" – a drug of biological origin, appropriated from yeasts; contains *Saccharomyces boulardii* [39]. *Saccharomyces* start active reproduction, when enter the digestive tract, because 37°C is an optimal temperature for their growth. The gastric acids do not affect on *S. boulardii*, so they save vital activity in all the digestive tract. Meanwhile yeasts do not colonize intestine so it can free in few days after treatment [39, 40].

Yeasts have straight antimicrobial property because of antagonistic to pathogenic and opportunistic bacteria effect. The drug increases local immunity because of IgA and other immunoglobulins production. The antisecretory effect with help of specific influence in intestinal receptors provides antitoxic action of "Enterol", especially for the *Clostridium difficile* toxins and enterotoxins. The antitoxine mechanism function of *S. boulardii* can be connected with protease production, which can disintegrate enterotoxins, proteins synthesis, which affect to membrane receptors, adhesion to enterocytes, decreasing production cAMP with next decreasing of water secretion [41]. The drug increases action of small intestine disaccharidases (lactase, maltase), has trophic function to intestinal mucosa. Indications for the drugs prescription – recurrent diseases, caused by *C. difficile* and colitis and diarrhea connected with usage of antibiotics [42].

In the West Europe *S. boulardii* is used during a long time, because it is relatively safe: during 10 years of active usage there only 7 cases of side effects were registered. *S. boulardii* treatment shows a good results in AIDS patients who tolerate these yeasts [43].

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