Probiotics and prebiotics in clinical practice

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PROBIOTICS

For the first time the term "probiotics" was introduced in 1954. F. Vergio, who in his monograph "Anti- und Probiotika" compared different compounds with both antimicrobial and positive effects on the intestinal microflora. Subsequently DM Lilly and RH Stilvell (1965), the term "probiotics" proposed understood as "substances produced by one microorganism to growth stimulation of other" [27], but now using a more precise definition: "Probiotics are live microorganisms which when administered adequate amounts have a beneficial effect on the health of the macroorganism by changing the properties of normal microflora " [57]. In 1989. Roy Fuller stressed the need for probiotic viability and put forward the idea of their positive actions for patients.

Probiotics are live microorganisms that can be incorporated into various types of food products, including pharmaceuticals and food additives. The most commonly used probiotics are strains of lactobacilli and bifidobacteria. Also for this role can serve yeast Saccharomyces cerevisiae and some strains of Escherichia coli. Lactic acid bacteria, including strains of lactobacilli, which have been used for thousands of years for food fermentation, have a dual effect as enzymatic agents and, in addition, a potential health-improving effect. The term "probiotic" should be reserved for live microbes, showed in controlled studies, the benefit to human health. At an international congress of gastroenterologists (Montreal, 2005), probiotics were determined as preparations on the basis of intestinal commensals, capable of performing biological control in the body and possessing regulatory, trigger properties [50].

The main probiotics are microorganisms: producers of lactic acid (bifidobacteria and lactobacilli), belonging to the most typical representatives of normal human microfloraLactobacilli are facultative anaerobes, bifidobacteria are obligate anaerobes. Yeast fungi Saccharomyces boulardii, used in the production of beer and wine, for which antibacterial drugs have no activity, which can be used as an advantage in creating probiotics [43]. Also Probiotics include Bacillus subtilis and Bacillus cereus — saprophytic spore forming anaerobes, probiotic activity in the application of spores of which is not exactly established [57].

The main strains of probiotics:

Lactobacillus — *L. acidophilus, L. casei, L. crispatum, L. delbruecki i subtype bulgaricus, L. fermentum, L. gasseri, L Johnsonii, L. paracasei, L. plantarum, L. lactis, L.reuteri, L. rhamnosus, L. salivarius.*

Bifidobacterium — *B. bifidum, B. breve, B. infantis, B. lactis, B. longum, B. A dolescentis*.

Other microorganisms — *Esche richia coli Nissle, Enterococcus faecium, E. Faecalis, Saccharomyces boulardii, Saccharomyces cerevisiae, Streptococcus thermophilus *, S. salivarius S., cremoris, S. lactis, S. diaacetylactis, S. intermedius, Bacillus subtilis *, Bacillus cereus *, Propionibacterium acnes., Lactococcus spp. cremonis, L. lactis spp. Lactis, Clostridium butiricum* (* — the probiotic activity of the microorganism is not exactly established) [1].

Studies of probiotics suggest that they have many positive effects on human health. Nevertheless, a specific effect can be attributed only to the strain under investigation (strains), but not to the species and not to a whole group of probiotics. The meaning of strain-specific effects is as follows [50] :

1. On the specific strain before entering eating products on sale, there must be documentation of its health benefits.

2. Research results and review articles on specific strains can not be used as evidence of the effectiveness of unexplored strains.

3. Studies showed efficacy in a certain strain of a particular dose can not serve as proof of its efficacy at a lower dosage.

The probiotic strain is classified by class, species and alpha- numerological name. In the scientific community there is an agreed nomenclature of microorganisms — for example, *Lactobacillus casei DN-114 001 or Lactobacillus rhamnosus GG*.

Probiotics are a heterogeneous group of non-pathogenic bacteria. In accordance with the definition of the WHO working group they include living microorganisms, which when applied in adequate amounts cause an improvement in the health of the host organism. Modern e probiotic and must meet the following criteria [18] :

- contain microorganisms, the probiotic effect of which has been proven in randomized controlled trials;
- have stable clinical efficacy;
- be phenotypic and genotypically classified;
- remain alive;
- be non-pathogenic and non-toxic, do not cause side effects with prolonged use;
- have a positive effect on the host organism (eg, increase resistance to infections);
- have the colonization potential, i.e. remain in the digestive tract until the maximum positive effect is reached (be resistant to high acidity, organic and bile acids, antimicrobial toxins and enzymes produced by pathogenic microflora);
- to be acid-resistant or enclosed in the acid capsule;
- be stable and retain viable bacteria with long shelf life [15, 32].

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

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

The classification of probiotics is based on the number of microorganisms entering the preparation, their generic accessory or the presence of additional components in the formulation. Probiotics are divided into monocomponent (monoprobiotics), monocomponent sorbed, polycomponent (polyprobiotics), combined (synbiotics); by composition — on bifidosoderzhaschie, laktosoderzhaschie, kolosoderzhaschie and consisting of spore bacteria and saccharomycete (self-eliminating antagonists) [12].

Currently, all probiotics are divided into 3 groups:

- drugs,
- dietary supplements, (parapharmaceuticals or nutraceuticals),
- Functional food products containing live probiotic microbes.

In Russia registered (Handbook of drugs "P USSIAN drugs» 2011 g.) as medicinal products of 34 pro- and synbiotic, as well as 16 prebiotic agents. In the section "Supplements — Probiotics and Prebiotics" are registered 229 funds available e 127 Trade name first. The most common strains of lactobacilli and bifidobacteria used in Russia for the production of probiotics and functional foods:

Lactobacillus acidophilus 100au; NK1; K3III24; Ep317 / 402
Lactobacillus fermentum 90- TC -4
La ctobacillus plantarum 8 RA -3
Bifidobacterium bifidum 1; 791; LVA-3
Bifidobacterium longum B 379 M
Bifidobacterium breve 79119; 79-88
Bifidobacterium infantis G 73-15; 79-43
Bifidobacterium adolescentis 7513; MC-42; Г013

There are 4 generations of probiotics [10]. By the first generation include monocomponent drugs (Colibacterin, Bifidumbacterin, Lactobacterin) containing 1 strain of bacteria.

Preparations of the second generation (Bactisubtil, Biosporin and Sporobacterin) are based on microorganisms that are not specific for humans and are self-exemptingantagonists. They can be used to treat severe forms of dysbacteriosis, but necessarily in combination with bifidus — and lactose-containing probiotics required for the normalization of the intestinal microbiocenosis.

Preparations of the third generation include polycomponent probiotics containing several symbiotic strains of bacteria of one species (Acilact, Acipol) or different species(Linex, Bifiform), with mutually reinforcing action. From

preparations of the first generation, they differ in a more balanced composition and are a new milestone in the treatment of dysbacteriosis. Particularly the advantages of third-generation drugs appear in patients with sub — and decompensated dysbacteriosis of the intestine [10].

TO IV generation include preparations immobilized on the sorbent of bifidobacterial probiotics (Bifidumbacterin forte, Probifor). Sorbed Bifidobacteria effectively colonize the intestinal mucosa, exerting a more protective effect than not sorbed analogues.

There are metabolic probiotics (Hilak-forte) [11].

In connection with a more balanced action at present Time advantage is recommended to give to combined probiotics of the third generation. Among them, the most widespread application was Linex®, which satisfies practically all the criteria listed above [14].

Probiotics affect the gastrointestinal ecosystem by stimulating the immune mechanisms of the mucosa and non-immune mechanisms through antagonism / rivalry with potential pathogens. The symbiosis between the microflora and the host can be optimized with the help of pharmacological or dietary interventions in the intestinal microbial ecosystem using probiotics.

Immunological effects of probiotics :

– and the activation of local macrophages to increase the presentation of antigens to B lymphocytes and increase the production of secretory immunoglobulin A (IgA) locally and systemically ;
– m odulirovanie cytokine profiles;
– Recalling the giperotveta in for food ALL e rgeny.

Non-immunological effects of probiotics :

– digestion of food and competition for nutrients with pathogens;
– and changing the local pH to create an unprofitable local environment for the development of pathogens ;
– the production of bacteriocins for the suppression of pathogens ;
– the wandering of superoxide radicals ;
– with the production of epithelial mucin ;
– Silenus in intestinal barrier function;
– competition with pathogens for adhesion ;
– modification of pathogenic toxins.

The action of probiotics is not limited to the simple colonization of the intestine, as is often the case. Their influence is more complex and multifaceted. This is a competition with pathogenic and opportunistic microflora; adhesion to the intestinal mucosa and interaction with epithelial cells; immunomodulating effect [9].

The mechanism of action of probiotics at the molecular level is actively studied. Virtually all microorganisms interact with cells of the macroorganism through so-called Toll-like receptors (TLR) — a family of membrane glycoproteins present on macrophages, neutrophils and dendritic cells. There are 10 types of TLR. The structure of TLR is quite simple: there is a cytoplasmic

domain and a domain that is located on the outer membrane of the cell and directly interacts with antigens. The cytoplasmic TLR domain consists of 200 amino acids, the homologous regions of which are 3 separate regions necessary for signal transmission inside the cell (signal transduction).

It is believed that all probiotics interact with TLR located on the membrane. The activation of TLR, and then through a complicated system of various intracellular factors (protein 88 myeloid differentiation — MyD88, the family of IL-1 receptor-associated kinase — TRAF6 — IRAK, associated with receptors factor 6) nuclear factor kappa B (NF-kB) is activated, which induces genes that determine the antimicrobial and pro-inflammatory response, in particular the production of pro-inflammatory cytokines (TNF-a, IL-1b, IL-6, IL-8). Probiotics "unblock" the function of TLR-4, which, when activated by peroxisome proliferator (PPAR-g) receptors, leads to cessation of NF-kB effects and, accordingly, to the lack of synthesis of pro-inflammatory cytokines [13].

The most important property of probitics is their ability to adhere to the intestinal epithelium. They attach to the epithelium through glycoconjugate receptors, thereby ensuring colonial resistance and preventing adhesion and invasion of pathogens. In the culture of the Colonocytes Sa-so-2 [28], it was shown that living probiotic strains adhere to the epithelium and thereby cause: strengthening of the cytoskeleton of intestinal epithelium cells (increased expression of tropomyosin TM-5, synthesis of actin and occlusin);decreased permeability (increased protein phosphorylation of intercellular compounds); increased synthesis of mucin (stimulation of the gene MUC-3); stimulation of synthesis and activation of the receptor of epithelial growth factor (EGF); an increase in the synthesis of polyamines, which are hormone-like substances that enhance the processes of epithelial regeneration. All these mechanisms ultimately contribute to increasing the resistance of the epithelium, enhancing its barrier functions and protection. The ability to adhere in vitro differs in different representatives of probiotics, it is proved in L. acidophilus and Bifidobacteriae [38].

It has been proved that probiotics take part in the formation of free amino acids, organic acids, oligosaccharides, short chain fatty acids, bioactive peptides, bacteriocin, reduce cholesterol levels, competitively interact with adhesion molecules for pathogenic bacteria, antioxidant, immunostimulating effect, neutralize food carcinogens, affect the synthesis of vitamins (biotin, vitamin K, etc.). In addition, a number of probable positive effects of probiotics are actively studied: anticarcinogenic (reducing the risk of cancer of the intestine, breast, etc.), antidiabetic, antiallergic, anti-inflammatory (in Crohn's disease, ulcerative colitis), etc. [54].

The conclusion about the safety of probiotics is based on the relevant production conditions, the results of clinical studies and application in real practice. The likelihood that they can cause infectious complications, unfavorable metabolic activity, excessive stimulation of immunity, transfer of genes, is very small. There are several cases of systemic infections in their use, although this connection is disputed [5 6].

Indications for the administration of probiotics are quite extensive [18] : diseases associated with Helicobacter pylori infection, chronic diffuse liver diseases, irritable bowel syndrome, diarrhea syndrome, constipation syndrome, treatment and prevention of antibiotic — associated diarrhea, helminthiases, vaginosis, colpitis, endocervicitis and others urogenital diseases, dermatoallergosis, premature and newborn children at risk.

Subject of probiotics in clinical practice is now so urgent, above all, because the amount devoted to various aspects of the problem of scientific work is rapidly increasing.At the same time, more and more studies are being carried out that meet the high requirements of evidence-based medicine — randomized controlled trials (RCTs), meta-analyzes and systematic reviews. So, if in the period from 1996 to 2005 in the database MEDLINE there were 2,748 works aimed at studying probiotics (MB De Morais, CM Abe Jacob, 2006), for two years (2006 — 2008) their number has already exceeded 2 thousand, and in 2010. — more than 1,5 thousand. And these scientific researches bring their tangible results: today there are more than 15 proven probiotic effects. The clinician should remember that a number of drugs that affect microbiocenosis are medicines in Russia and their purpose should be justified by specific indications developed in accordance with the principles of evidence-based medicine. Analysis of the efficacy of probiotics [30], which used the levels of evidence in the field of therapy / prevention, developed by the Oxford Center for Evidence-Based Medicine, determined the current state of knowledge on the use of probiotics by clinical studies:

Level of Evidence 1a:

Treatment of acute infectious diarrhea in children;

Prevention of nosocomial and community-acquired diarrhea in children ;

Prevention of antibiotic-associated diarrhea ;

Treatment of lactose malabsorption.

Level of Evidence 1 b:

Prevention of sponging (inflammation of the surgically created intestinal reservoir after resection of the large intestine) and maintenance of remission;

Prevention of postoperative infections;

Prevention and treatment of atopic diseases in children.

Level of Evidence 2 b:

Prevention of travelers' diarrhea;

Prevention of septic conditions in acute pancreatitis;

Maintenance of remission of ulcerative colitis;

Diseases associated with Helicobacter pylori (HP) infection ;

Lowering blood cholesterol.

In a number of studies, it has been shown that the addition of probiotics to standard anti-Helicobacter therapy regimens slightly improved the incidence of eradication of HP, but also significantly reduced the incidence of side effects and increased adherence of patients to treatment. In addition to the protective effect on the development of the syndrome of intestinal dyspepsia, probiotics also have an additive effect with preparations of the eradicationscheme. Culture or preparations made from cultures of lactobacilli and a number of other microorganisms

inhabiting the human digestive tract can suppress the vital activity of HP, probiotics can prevent the adhesion of HP to cell membranes and multiplication of HP [16, 34, 53].

When choosing a probiotic drug, several problem questions arise, the first of which is survival. As indicated above, probiotic properties are possessed only by living microbes. Moreover, a number of studies have shown that a dose of at least 107 CFU [55] can be considered as a minimally sufficient dose capable of effecting a significant effect.

The survival of bacteria depends on the technology of production and the storage conditions of the drug. For example, the addition of bifidobacteria to kefir does not guarantee their safety and ability to vegetation; the viability of microflora, both in liquid and in simple dry forms of drugs, can be lost before the official deadline. For mostprobiotics, especially for liquid dosage forms, special storage conditions are required, for example, temperature. It is necessary to take into account the destructive effect of gastric juice on unprotected flora. It is proved that only a small number of strains of lactobacilli (L. reuteri, L. plantarum NCIB8826, S. boulardii, L. acidophilus, L. casei Shirota) and bifidobacteria have acid resistance, most microbes perish in the stomach. Therefore, probiotics in an acid-fast capsule are preferred. According to Bezkorovainy A. [24], only 20-40% of selective strains survive in the stomach. Pochart D. [44] demonstrated that out of 108 CFU lactobacilli taken in an acid-fast capsule, 107 are found in the intestine, after receiving the same amount in yogurt — 104 cfu, and after taking the same dose in an open form as a powder, microbes in the intestine are not detected at all.

In the small intestine, probiotics are exposed to bile acids and pancreatic enzymes. As a consequence, many microbes, for example, L. fermentum KLD, L. lactis MG1363 almost completely die. This can be explained by the increased permeability of the bacterial cell membrane, which occurs in response to the effects of bile acids. The survival of most bacteria depends on how they are taken: in a protective capsule, in the form of yogurt, with milk or without any protection. Thus, according to Kailasapathy K. [38], many strains, for example, lactobacillus from fermented milk products either do not reach the intestine, or survive only a few days. These data call into question the effectiveness ofunprotected and acid-proof probiotics.

These properties are only a few drugs. An example of a probiotic preparation that meets modern requirements is Linex®. It consists of L. acidophilus, B. infantis, Ent.faecium, the content of which is not less than 107 microbial bodies. The microorganisms included in the preparation are enclosed in a capsule, which is opened in the stomach.However, due to the high acid resistance of all components of the drug, the bacterium does not break down in the stomach, and the drug is able to exert probiotic action at all levels of the gastrointestinal tract. The combination of lactobacilli and bifidobacteria with proven probiotic properties in the preparation provides a symbiotic effect in colonization of the large intestine, and the presence of an aerobic microorganism — enterococcus, promotes the active immunomodulating and bactericidal action of the drug at the level of the stomach and small intestine. The microbes included in Linex® are resistant to most

antibiotics, which makes it possible to use the drug against the background of antibacterial therapy. The resistance of the obtained strains is preserved by repeated inoculation for 30 generations and in vivo. In Linex® studies, it has been shown that there is no transfer of resistance to other microorganisms [20]. If necessary, Linex® can be used simultaneously with antibacterial and chemotherapeutic agents.

The effectiveness of the components of Linex®, their combinations and the preparation itself is proved in clinical studies with various gastrointestinal diseases [3, 6, 7,14, 17, 19].

The advantage of Linex® is its high safety. At a wide long-term use of the drug, side effects are not registered. Linex® does not have a teratogenic effect. Its safety and good tolerability make it possible to apply the drug to patients at risk — pregnant and breast-feeding women, including newborns, the elderly, etc. The quality of Linex® is alsoensured by the technology of its production that meets all the requirements for the production of probiotics.

Unfortunately, probiotic strains, despite numerous beneficial effects, are not equivalent to their own indigenous microflora and are not able to reproduce in the intestine.One of the reasons for this may be bio-compatibility with resident host bacteria [5]. Even the most effective probiotics work only during the course of treatment and are detected in the stool only for 3-7 days after its termination [8].

Therefore, in order to achieve a sustainable therapeutic effect, first, a long or even a constant reception is necessary, which is almost impossible. Secondly, it is desirable that the probiotic preparation be a normobiotic strain that is as compatible as possible with resident strains and the local immune system [9].

PREBIOTICS

Despite the fact that the term " prebiotics " entered the medical terminology in the mid-90's. XX century, this important and fruitful direction of scientific research has been around for almost 50 years, and its origins lie with the Austrian pediatrician F. Petuely. It was he who for the first time in 1957 described the properties of lactulose as a prebiotic, i.e. a disaccharide with a pronounced bifidogenic effect. In the study conducted by F. Petuely, it was shown that if the children fed on infant formula received a milk mixture with a content of 1.2 g / 100 kcal of lactulose, then a practically pure culture of bifidobacteria was formed in the intestine, and the microbiocenosis of the children of the artificialanimals was practically not different from the intestinal biocoenosis of children who are breastfeeding [47, 48].

Among prebiotics, the most popular are i- and oligofructans, soy oligosaccharides, galactooligosaccharides isolated from natural sources or obtained by biotechnological or synthetic methods. For the first time, the definition of prebiotics was given by G. R. Gibson [30] — he proposed to understand an indigestible food ingredient that could improve a person's health by selectively stimulating the growth and / or activity of one or a limited number of bacterial species in the large intestine. Further, M. B. Roberfroid (2007) defined the concept of prebiotics as food ingredients that are selectively fermented by intestinal

microorganisms, specifically changing the composition and / or activity of the microflora, which leads to improved health and human health [52].

By 2010, the world production of such prebiotics reached hundreds of thousands of tons. They are realized independently, in the form of enriching additives to a variety of food products, and also in combination with probiotic microorganisms (synbiotics) [18, 35, 36, 42, 45, 58].

In addition to those listed as prebiotic substances, various adhesion blockers and growth inhibitors of pathogenic and opportunistic microorganisms (lectins, antiadhesins, modulators of synthesis of secretory immunoglobulins, defensins of various types, structural components of probiotic microorganisms, their metabolites, etc.) are also used asprebiotic substances.

To strict prebiotic requirements are strict requirements: they should not be hydrolyzed by human digestive enzymes, should not be absorbed in the upper parts of the digestive tract, should selectively stimulate one species or a certain group of microorganisms resident for the large intestine [2].

The main types of prebiotic compounds are:

Monosaccharides, alcohols (*xylitol, melibiose, xylobiose, raffinose, sorbitol, etc.*);

O ligosaharidy *(lactulose, latsitol, soy oligosaccharide latitololigosaharid, fructooligosaccharide, galactooligosaccharide, isomaltooligosaccharides, diksilooligosaharid et al.);*

Polysaccharides (*pectins, pullulan, dextrin, inulin, chitosan, etc.*);

Enzymes (*b-microbial galactosidases, proteases of saccharomycetes, etc.*);

Peptides (*soy, milk, etc.*);

Amino acids (*valine, arginine, glutamic acid, etc.*);

Antioxidants (*vitamins A, C, E, a -, b-carotene, other carotenoids, glutathione, ubiquinol, selenium salts, etc.*);

Unsaturated fatty acids (*eicosapentaenoic acid, etc.*);

Organic acids (*propionic, acetic, citric, etc.*);

Plant and microbial extracts (*carrot, potato, corn, rice, pumpkin, garlic, yeast, etc.*);

Others (*lecithin, paraaminomethylbenzoic acid, lysozyme, lactoferrin, gluconic acid, starch syrup, etc.*).

Lactulose is a synthetic disaccharide, used as a drug in the treatment of constipation and hepatic encephalopathy. Prebiotic oligofructose (OP) is naturally present in many food products, for example, in wheat, onions, bananas, honey, garlic and leek. RP can also be isolated from the root of chicory or enzymatically synthesized from sucrose.Enzyme fermentation in the large intestine causes a variety of physiological effects, including:

– increase in the number of bifidobacteria ;
– increased absorption of calcium;
– increased fecal mass;
– decrease transit transit time through the gastrointestinal tract;
– probably a decrease in the level of lipids in the blood.

Based on his research, F.Petuely called lactulose " bifidus factor " (Der Bifidusfactor) and devoted almost 30 years to the study of this compound [48, 49]. The term "bifidus factor " has become widely used to denote nutrients that promote the growth of bifidobacteria and the normalization of the composition of the intestinal microflora. The chemical structure and method of synthesis of this compound were described in 1929. E. Montgomery and CS Hadson under the name " lactoketosis ". Lactulose is a disaccharide consisting of galactose and fructose (4-0-in-D-galactopyranosyl-D-fructose).

The prebiotic effect of lactulose has been demonstrated in numerous studies [21, 22, 23, 46]. In a randomized, double-blind, controlled study in 16 healthy volunteers (10 g / day of lactulose for 6 weeks), a significant increase in the number of bifidobacteria in the large intestine was demonstrated [40].

An increase in the production of short-chain fatty acids by intestinal bacteria normalizes trophic epithelium of the large intestine (due to the production of butyrate), improves its microcirculation (propionate effect), providing effective motor activity, absorption of water, magnesium and calcium. As part of medicines (Dufalac®), lactulosecan be effectively used in functional constipation, both in adults and in children. The frequency of side effects of lactulose is much lower compared to other laxatives and does not exceed 5%, and in most cases they can be considered insignificant. Safety of lactulose determines the possibility of its use even in premature infants, proven in clinical trials [4].With the same purpose, lactulose can be introduced into the mixtures for feeding children of the first year of life.

Short -chain fatty acids (SCLC), formed as a result of the metabolism of the saccharolytic microflora, lower the pH in the lumen of the intestine, which leads to a decrease in the concentration of secondary bile acids and their salts. In addition, the resulting SCFA are utilized by the macroorganism, which is accompanied by water absorption and a decrease in colonic contents [26]. Proceeding from this, it can be argued that the laxative effect of lactulose is primarily associated with its prebiotic ability and is due to an increase in the bacterial mass, as well as the positive effect of products of microbial metabolism on the intestinal wall.

The prebiotic effect of lactulose has significant metabolic effects. The decrease in pH in the colon lumen increases colonization the resistance of the entire microbial community, and also promotes the ionization of ammonia and its elimination in the form of ammonium ions. The last effect of lactulose has long been used in clinical practice for the purpose of detoxification in liver failure (hepatic encephalopathy). The growth of bifidobacteria — and lactobacilli in patients receiving lactulose reduces the activity of urease,which converts urea to ammonia. The activity of urease is also suppressed by a decrease in pH, because the optimum pH for β- glucuronidase is 7, and for nitro- and azo reductase it is 7.8. In a placebo-controlled study, a significant decrease in the fecal concentrations of phenol, cresol, indole and scatol was shown against the background of lactulose [23].

Lactulose reduces the alcohol-dehydrogenase activity of the intestinal microflora, significantly reducing the acetaldehyde concentration in the large intestine, which is believed to have carcinogenic activity [41].

Lactulose, stimulating the growth of normal intestinal microflora, promotes the maintenance of anti-infection protection of the macroorganism against shigella, salmonella,Yersinia and rotaviruses [29].

In 1960, the Dutch company Philips-Duphar BV started the production of lactulose syrup called Dufalac®. Since 1964 Dufalac ® has become widely used in the Netherlands, and from 1967 to the present time it is effectively used by doctors of many countries of the world. The drug Dufalac ® contains 66.7 g / 100 ml of lactulose and has wide indications including. treatment of constipation and hepatic encephalopathy. Relatively rare side effects may be the development of flatulence, manifestations of which in most cases are eliminated by reducing the dose, and in some children, it goes through several days of taking the drug itself as the "intestinal microflora" adapts to it.Contraindications to the use of lactulose is galactosemia, intestinal obstruction and individual intolerance of the drug components.

The current state of knowledge on the use of lactulose by clinical research results is determined [25, 33, 37, 39]:

Level of Evidence A

Constipation of various etiologies

Hepatic encephalopathy

Thus, lactulose (Dufalac®) is one of the most potent effects on bacterial metabolism of prebiotics, as evidenced by many years of experience in its use for the treatment of hepatic encephalopathy. It is in this condition requires a strong stimulation of growth of bifido — and lactobacilli that ammonia is used for constructing the cell wall, and stimulated the growth rate is sufficient for the effective relief of hepatic encephalopathy.

Thanks to not only its effectiveness, but also high safety and good tolerability, Dufalac ® is a drug that can be prescribed to children of young and middle age. In many countries, lactulose is added to milk for infants in order to increase the level of bifidoflora. Often, the first reception of solid food creates problems associated with constipation.In such cases, lactulose, prescribed even in very low doses, prevents the development of constipation.

Lactulose received more than one million pregnant women. At the same time, no data were available that would talk about the need to limit the use of lactulose during pregnancy (or in the lactation period). In this regard, lactulose is a laxative, most commonly used during pregnancy.

Dufalac ® is widely used to restore impaired motor activity in constipation, metabolized by the intestinal microflora to monosaccharides (fructose and galactose), and then to short-chain fatty acids, which restore the motor function of the intestine. Short-chain fatty acids increase the osmotic pressure in the lumen of the intestine and lower the pH, which stimulates the intestinal peristalsis. Thus, Dufalac ® is a physiological and safe regulator of motor function of the intestine.

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Probiotics and prebiotics in clinical practice

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Key words: probiotics, Bifidobacterium, Lactobacillus, prebiotics, Lactulose

Data on modern probiotics, definition, classification, medical and preventive effects, release forms, methods of application are provided in article. The review of prebiotic forms is also submitted, their similarity and distinctions, indications for application are described. The Lactulose as the main prebiotic medicine is described in detail.