MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
ACADEMIC AND RESEARCH MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

116, Kharkivska st., Sumy 40007, Ukraine eumj.med.sumdu.edu.ua
e-mail: eumj@med.sumdu.edu.ua ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite / Як цитувати статтю: Hryn VH, Ustenko RL, Svintsytska NL, Piliuhin AV, Fedorchenko IL, Tarasenko YaA, Lytovka VV. Analysis of data about the digestive tract microflora of the humans and white rats. *East Ukr Med J*. 2025;13(1):28-38

DOI: https://doi.org/10.21272/eumj.2025;13(1):28-38

ABSTRACT

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ANALYSIS OF DATA ABOUT THE DIGESTIVE TRACT MICROFLORA OF THE HUMANS AND WHITE RATS

Introduction. Issues related to the understanding of the mechanisms of development of functional disorders of the small and large intestine, which are widely known as dysbacteriosis (or dysbiosis), are still relevant problems in medicine. The causes of its development include all kinds of exogenous, endogenous and alimentary factors, as well as stressful states of the body. A special place is occupied by dysbacteriosis of iatrogenic origin, that arise as a result of the action of various drugs on the body.

Methods. Bibliographic analysis is based on published articles, books, textbooks and monographs. The search for sources was carried out in the scientific and metric databases of Google Scholar, Web of Science, PubMed, the National Medical Library and the electronic library of the Poltava State Medical University.

Results and their discussion. According to the literature, the largest number of bacteria (about 100 trillion) and more than 1,200 types of viruses live in the human gastrointestinal tract. Currently, its microflora is divided into obligate (principal, resident, autochthonous), facultative (saprophytic, conditionally pathogenic) and transient. Microorganisms that are present in the digestive tract from birth, making up about 95% of the entire microbiota, are called obligate microorganisms. Obligate microflora is not the source of any pathological processes. The facultative microflora includes many microorganisms, but its species and quantitative composition is not constant. Facultative microorganisms can cause various pathological conditions in cases where they begin to reproduce strongly. By localization in the small and large intestine, parietal and cavity microflora are distinguished. In addition, according to functional activity, the entire microflora of the digestive tract is divided into neutral, potentially pathogenic and probiotics. The modern concept of biofilms allows us to clarify the

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peculiarities of the interaction between obligate and facultative microorganisms. The results of these studies made it possible to divide all antimicrobial drugs into two main groups − those that penetrate biofilms well and poorly. All of the above refers to the microflora of the human gastrointestinal tract, a detailed investigation of which is quite difficult. On the other hand, it is known about the close similarity of the digestive tract structure of white rats and humans. This concerns the absence of significant species differences in the morphofunctional organization of lymphoid formations of the gastrointestinal tract and the division of the microflora of the gastrointestinal tract of white rats into parietal and cavity.

Conclusions. The entire microflora of the digestive tract is divided into two communities − parietal and cavity microbiota. The main mass of parietal microflora (about 95%) consists of obligate microorganisms, many of which belong to probiotics, which contribute to the maintenance of a favorable state of the digestive tract. The quantitative concentration of parietal microflora microorganisms in the digestive tract gradually increases in the caudal direction. Modern ideas about the effect of antibiotics indicate that none of them can completely destroy the formed biofilms. The clinical effect of antibiotics is largely related to the cessation of the settlement of biofilms and decreation in the biological activity of pathogenic microorganisms.

Key words: gastrointestinal tract, parietal microflora, cavity microflora, obligate and facultative microflora, biofilm.

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АНАЛІЗ ДАНИХ ПРО МІКРОФЛОРУ ТРАВНОГО ТРАКТУ ЛЮДИНИ І БІЛИХ ЩУРІВ

Вступ. Важливими задачами охорони здоров'я дотепер залишаються питання, пов'язані з вивченням та розумінням причин і механізмів розвитку функціональних порушень тонкої і товстої кишок, які, в основному, описуються під назвою дисбіози або дисбактеріози. Причинами їх виникнення вважають різноманітні екзогенні, ендогенні, аліментарні фактори та стресові стани організму. Важливу роль серед них відіграють дисбактеріози ятрогенного походження, тобто ті, що розвиваються під впливом на організм різних лікарських речовин.

Методи. Бібліографічний аналіз було проведено на основі опублікованих статей, книг, навчальних посібників, монографій, клінічних настанов. Для пошуку джерел використовувалися науково-метричні бази Google Scholar, Web of Science, PubMed, Національної медичної бібліотеки та електронної бібліотеки Полтавського державного медичного університету.

Результати та їх обговорення. Згідно літературних джерел шлунково-кишковий тракт людини містить величезну кількість бактерій (близько 100 трлн) та вірусів (більше 1200 видів). Натепер його мікрофлору ділять на облігатну, факультативну та транзиторну. Облігатна мікрофлора також описується як головна, резидентна або автохтонна, а факультативна мікрофлора – як сапрофітна або умовно-патогенна. Облігатні – це мікроорганізми,

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які на момент народження вже присутні в травній системі і складають близько 95% усієї мікробіоти. Така мікрофлора не призводить до розвитку будь-яких патологічних процесів. Факультативна мікрофлора включає багато мікроорганізмів, але її кількісний та видовий склад є мінливим. Факультативні мікроорганізми у випадку різкого збільшення їх кількісного складу можуть спричиняти розвиток різних захворювань. За локалізацією в тонкій і товстій кишці виділяють пристінкову й порожнинну мікрофлору. Крім того, за функціональною активністю вся мікрофлора травного тракту поділяється на нейтральну, потенційно патогенну та пробіотики. Сучасна концепція про біоплівки дозволяє з'ясувати особливості взаємодії між облігатними та факультативними мікроорганізмами. За результатами ряду досліджень всі антибактеріальні лікарські засоби було розподілено на дві великі групи, а саме, ті, що добре проникають у структуру біоплівок, та ті, що проникають погано. Всі ці наукові дані екстраполюються і на мікрофлору травного тракту людини, досконале дослідження якої на сьогодні залишається надто складним завданням. Натомість, високий ступінь подібності будови шлунково-кишкового тракту людини і щурів наразі є загальновідомим фактом. Як відомо, нема суттєвих відмінностей у морфологічній та функціональній організації лімфоїдних структур травного тракту людини та білих щурів та поділі його мікрофлори на пристінкову та порожнинну.

Висновки. Всю мікрофлору травного тракту розподіляють на дві групи – пристінкову і порожнинну. Близько 95% пристінкової мікрофлори утворені облігатними мікроорганізмами, багато з яких є пробіотиками, які забезпечують підтримку нормального функціонального стану травної системи. Концентрація мікроорганізмів які належать до пристінкової мікрофлори плавно збільшується вздовж шлунково-кишкового тракту. Сучасні відомості про чутливість біоплівок до антибактеріальних лікарських засобів говорять, що жодним з них неможливо досягнути повної ерадикації біоплівок. Клінічно наявний ефект від антибіотикотерапії зумовлений в основному зниженням біологічної активності патогенної мікрофлори та зупинкою поширення біоплівок.

Ключові слова: шлунково-кишковий тракт, пристінкова мікрофлора, порожнинна мікрофлора, облігатна та факультативна мікрофлора, біоплівка.

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INTRODUCTION / ВСТУП

Issues related to the understanding of the mechanisms of development of functional disorders of the small and large intestines, which are widely known as dysbiosis (or dysbacteriosis), are still relevant problems in medicine [1, 2, 3]. This heading is absent in the international classification of diseases, therefore, this name is usually used to describe various etiological disorders of the gastrointestinal tract microbiocenosis, including "bacterial overgrowth syndrome" [4, 5, 6].

The causes of its development include all kinds of exogenous, endogenous and alimentary factors, as well as stressful states of the organism. A special place is occupied by dysbacteriosis of iatrogenic origin, which

occurs as a result of the action of antibacterial drugs on the body. In this case we talk about dysbacteriosis associated with antibiotics [7, 8, 9]. Numerous scientific works allow us to divide antibacterial drugs into two groups: favorable and unfavorable. Favorable ones include amoxicillin, cefprozil, ceftibuten, levofloxacin, clarithromycin, cefotaxime, vancomycin, telavancin, and unfavorable ones include ampicillin, cefuroxime, cefditoren, norfloxacin, moxifloxacin, ezithromycin, ceftriaxone, teicoplanin, dalbavancin [10].

The digestive tract is an important microecological niche of both human and rats, which is formed by numerous populations of various groups of microorganisms (Fig. 1), (Table 1) [11, 12].

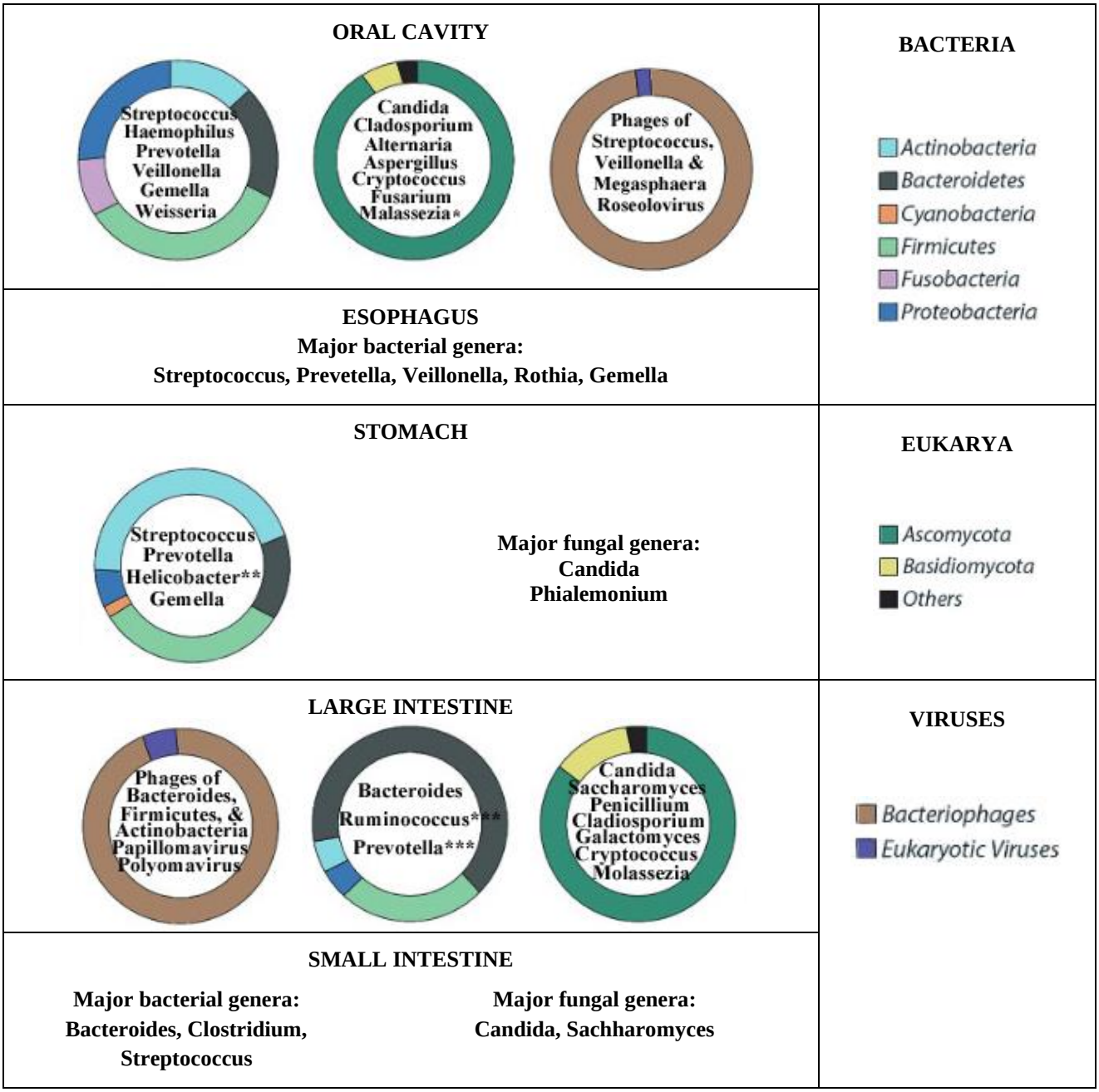

Figure 1 – Microbiome composition of Bacteria, Eukarya, and Viruses among the physiological niches of the human gastrointestinal tract. Phylum level compositional data are presented where available along with the most common genera in each gastrointestinal tract location. The colors on the doughnut plots correspond to the legend.

**Malassezia was very abundant in one study and was not detected in another study.*

*** The abundance of Helicobacter may vary greatly between individuals.*

**** Proportions of these and other colon genera vary with age, diet, and geographical location*

Table 1 – Major taxa of the gut microbiota in humans and rats

	Bacteria	**Archaea**	**Eukarya**	**Viruses**
HUMAN	Firmicutes Bacteroidetes Actinobacteria Proteobacteria	Methanobrevibacter Nitrososphaera	Candida Cladosporium Malassezia Saccharomyces	Adenoviridae Herpesviridae Papillomaviridae Polyomaviridae
RAT	Firmicutes Bacteroidetes	Methanobrevibacter	Ascomycota Basidiomycota Chytridiomycota Zygomycota	Variable

Since the intestinal microbiocenosis carries a large functional load, any changes in the microbiota create a background for the development of many diseases. Microbs the primary mediators of body homeostasis, impacting various physiological activities, such as metabolism, barrier homeostasis, inflammation, and hematopoiesis. The gut microbiota has recently been classified as a "vital organ" because of its multidirectional and communicational connection or axis with other organs through neural, endocrine, humoral, immunological, and metabolic pathways. Microbiota plays a key role in modulating immunity, weight gain or loss, energy homeostasis, obesity-related disorders, modulation of host immune response, and induction of chronic inflammation, fermentation of food, vitamin, amino acids and lipids production, energy and nutrient extraction from food. Human microbiota not only protects the host from external pathogens by producing antimicrobial substances but also serves as a significant component in the development of intestinal mucosa and immune system. Today it`s known that microbiocenosis influences development for development cardiovascular diseases (hypertension, atherosclerosis), cancer (lung cancer, colorectal cancer, pancreatic cancer, oral cancer), respiratory disease (asthma, bronchitis), diabetes (type1, type2, gestational), brain disorders (Parkinson`s disease, Alzheimer`s disease, depression), chronic kidney disease, liver disease (cirrhosis, hepatitis), inflamattory bowel disease (Crohn`s disease, ulcerative colitis). [13, 14, 15].

Purpose of the study was to investigate the state of the microflora of the human digestive tract and the influence of biofilms on it, as well as the microflora of the digestive tract of white rats using the method of bibliographic analysis.

MATERIAL AND METHODS

This bibliographic analysis is based on published articles, books, textbooks, and monographs. The search was carried out on the Internet in the scientific and metric databases of Google Scholar, Web of Science, PubMed, the National Medical Library and the electronic library of the Poltava State Medical University.

RESULTS AND DISCUSSION

It has long been known that the epithelial covering of the human digestive tract with an area about 400 m^2 constantly interacts with various types of microorganisms and comes into contact with food products that have antigenic properties, which determines the development of the corresponding immune system formations in it, in the form of individual and group lymphoid nodules. It is known that the animals which were grown in sterile conditions (gnotobionts) these formations are absent [16, 17, 18].

Intestinal microflora is a highly organized complex biocenotic system that reflects the state of the organism in various conditions of life, which has developed evolutionarily. According to the literature, the largest number of bacteria (about 100 trillion) and more than 1200 types of viruses live in the human gastrointestinal tract. In the digestive tract the number and diversity of microorganisms increases in the caudal direction; the maximum number of them is present in the large intestine. Under normal conditions this microbiota is generally in a balanced state with the host's body. Currently, it is divided into obligate (main, resident, autochthonous), facultative (saprophytic and opportunistic) and transitory [19, 20, 21].

Microorganisms that are always (from the moment of birth) present in the digestive tract, making up about 95% of the entire microbiota, are called obligate (obligatory) microorganisms. Due to the peculiarities of vital activity these microbes participate in digestion processes, partially stimulate the work of the intestines and perform other important functions. It should be noted that as a result of the interaction of this microflora with elements of the lymphoid tissue in the process of ontogenesis, tolerance of the immune system of the mucous membranes of the gastrointestinal tract is produced to it. That's why obligate microflora is not the source of any pathological processes. On the contrary, it

prevents the reproduction of disease-causing bacteria based on the principle of competition [22, 23, 24]. And it should be borne in mind, that a decreasing of its number becomes the cause of dysfunction of the gastrointestinal tract. The species and quantitative composition of obligate microflora is relatively constant. Its part periodically released naturally during defecation, but is compensated by the reproduction of the remaining microorganisms. The obligate group of intestinal bacteria is represented by anaerobes (propionibacteria, peptostreptococci) and aerobes (lactobacteria, enterococci, and escherichia) [23, 25].

Facultative microflora also includes many microorganisms. However, its specific and quantitative composition is not constant, depending on the way of life and nutrition, the region of residence of a person. This partly explains a number of symptoms that occur in humans with dysbiosis. Facultative microflora makes up only a few percent of the total number of microorganisms of the digestive tract and does not perform useful functions that are characteristic of obligate microflora. It is represented by saprophytes (bacteroids, peptococci, staphylococci, bacilli and yeast fungi), as well as aerobic and anaerobic bacilli. Among them are conditionally pathogenic microorganisms, such as klebsiella, protea, cytobacteria and enterobacteria [8, 26, 27, 28, 29].

In the organs of the digestive tract microorganisms are distributed accordingly.

Oral cavity. This department is in contact with the environment most often and the number of bacteria here is normally up to 10 billion in 1 ml of liquid. The specific and quantitative composition is determined by the bactericidal effect of saliva and its biochemical properties. The most typical are neisseria, streptococci, staphylococci, micrococci, lactobacilli, diphtheroids, etc. [30, 31, 32].

Stomach. Here the microflora is relatively poor due to an extremely acidic environment (normal pH is 1.5-2.0), in which most of the bacteria die that enter from the oral cavity. However, some microorganisms survive in these conditions, the so-called extremophiles. Normally, from 100 to 10 million microorganisms can be released from 1 ml of liquid in the stomach. The most typical for the stomach are lactobacilli and bifidobacteria in small quantities and also fungi, bacteroides. Also, the common pathogenic (disease-causing) bacterium Helicobacter pylori multiplies well in the acidic environment of the stomach [33, 34].

Duodenum. The alkaline environment of this part of the small intestine is better for bacteria. The number of microorganisms varies a lot here even during the day (it changes depending on the food). On average, it ranges from 10 to 100 thousand microorganisms per 1 ml. The most characteristic are lactobacilli and bifidobacteria, fecal streptococcus, yeast [34, 35, 36].

Small intestine. The number of microorganisms can vary widely in it - from 1000 to 100 million in 1 ml or more. Not so many opportunistic species live in the small intestine (they are more characteristic for the large intestine). Enterobacteriaceae, streptococci, clostridia, and staphylococci are most typical in this part of the gastrointestinal tract. There are also large numbers of lactobacilli and bifidobacteria [34, 37, 38].

Colon. The microflora is the richest in this part of the digestive tract. The number of microorganisms per 1 ml is more than 100 billion and their variety is very wide. Anaerobic microbes dominate, which don`t need oxygen for reproduction. A large number of conditionally pathogenic species live here. The most typical representatives in a healthy person are lactobacilli and bifidobacteria, peptococci, clostridia, escherichia coli, enterobacteria, etc. [34, 39].

By the localization in the small and large intestine parietal and cavity microflora are distinguished. Histaadhesiveness - the property of fixing and colonizing tissues - determines the transitory or indigenous nature of bacteria. Together with belonging to the group of pathogenic or opportunistic microorganisms, this ability of the intestinal microflora largely determines the nature of the interaction of microorganisms with the macroorganism. The species composition and number of the mucous membrane microflora of the different intestine parts, the intestine lumen and fecal masses is different. Cavity microflora is variable in its composition and concentration, parietal microflora is relatively stable. According to the research results the composition of the intestinal microflora is influenced by genetic factors more than the nature of nutrition. As you approach the large intestine distal parts, the partial pressure of oxygen decreases and the pH of the environment increases, which causes a certain arrangement of bacteria along the length of the intestine - aerobes, facultative anaerobes, strict (obligate) anaerobes [40, 41].

Thus, to sum it up, according to the literature, the entire microflora of the digestive tract can be divided into three groups according to their functional activity: 1) neutral microorganisms (for example, Escherichia coli); 2) potentially pathogenic microorganisms (bacteroids); 3) probiotics that contribute to the maintenance of the macroorganism health (certain strains of lactobacilli, bifidobacteria, and Escherichia coli).

But still some questions remain unspecified, especially what is the nutrient substrate for parietal microflora through which competition between obligate and facultative microorganisms occurs?

The modern concept of so-called biofilms, which was formulated at the end of the 20th century, will help clarify this. It draws attention to the special form of the microflora organization that covers the mucous membranes, skin and tooth enamel [38, 42, 43].

According to the literature, the bacteria themselves make up only 5-35% of the biofilm mass; its other part is the intercellular matrix, which most often consists of exopolysaccharide of microbial origin. It`s permeated with tubules, through which nutrients, waste products of microorganisms, enzymes, metabolites and oxygen circulate. It`s important to note, that at the same time the biofilm of the gastrointestinal tract contains mucin, which is produced by goblet cells. This statement allows us to think that the biofilm directly belongs to the mucus layer that lies on the surface of the glycocalyx of the gastrointestinal tract epithelial covering.

An especially important moment is the understanding that the biofilm is reliably fixed to the epithelial covering of the mucous membranes with the help of obligate ("beneficial") microorganisms, which have special "anchor" molecules that connect them to the apical plasma membrane of epithelial cells [43]. Obviously, this contact zone belongs to the glycocalyx, which was discussed in the previous subsection. By the way, the literature doesn`t address the issue of whether the glycocalyx belongs to the biofilm or separates it from the epithelial surface. It follows that facultative microorganisms (conditionally pathogenic and pathogenic) in the biofilm are deprived of direct contact with the epithelial covering of the gastrointestinal tract. Based on this it can be assumed, that the "anchor" molecules of the obligate microflora are histocompatible with the cells of the macroorganism and therefore its immune system is tolerant only to it [44, 45].

Parietal microflora associated in the biofilm has increased resistance to the action of various antibacterial drugs. After establishing the fact that bacteria can survive in biofilms in the presence of high concentrations of antibiotics, it became obvious that new studies of all antimicrobial drugs and a reevaluation of the results of their action on known pathogenic microorganisms are needed to choose effective therapy regimens [46, 47]. Studies have shown that many drugs that penetrate biofilms don`t lead to the complete death of bacteria, although their number decreases and the achieved effect is dose-dependent [48, 49]. The results of these studies made it possible to divide all antimicrobial drugs into two main groups - those that penetrate biofilms well and poorly. The first group of antibiotics includes tetracyclines, macrolides, fluoroquinolones, rifampicin, chloramphenicol, sulfonamides. It is believed, that their clinical effect is related to the fact that they prevent biofilms from maintaining their vital activity and settling. In such conditions pathogenic microorganisms obviously can not be stored in the body for a long time. Probably, it can be assumed, that at the same time they become the target of a successful attack by representatives of the normal microflora and factors of the body's immune defense [50, 51].

Penicillins, cephalosporins, monobactams, carbapenems, as well as aminoglycosides and fosfomycin turned out to be antibiotics that do not penetrate biofilms well. There is evidence that their failure is due to their stimulating effect on the variability of bacteria, which leads to the accelerated formation of their resistance. And this can contribute to the chronicity of the process and the formation of persistent infections with a recurrent course. [52, 53].

But all of the above refers to the microflora of the human gastrointestinal tract, the detailed study of which is considerably complicated by the scale of the organism and, most importantly, by the impossibility of reproducing certain physiological and pathological states in experimental conditions. In particular, the nature of the parietal microflora of the human gastrointestinal tract and its role in the development of dysbacteriosis has not been fully studied. At the same time, there are a number of other questions that can only be solved in an experiment on laboratory animals, namely white rats. In favor of this choice, data from the literature testify to the close similarity of the digestive tract structure of the white rats and humans (Fig. 3) [54, 55, 56]. This especially applies to the absence of any significant species differences in the morphofunctional organization of the gastrointestinal tract lymphoid formations [57, 58]. If we take into account that the motivating factor for their development is the process of its colonization by microorganisms, then it is logical to predict that their microflora will not differ significantly, except for some features of its zonal distribution. Indeed, according to the literature, in the gastrointestinal tract of white rats, as well as in humans, it is divided into parietal and cavity [37, 59, 60]. At the same time parietal microflora of white rats also consists of obligate and facultative microorganisms (Fig. 3.).

And finally, the most active vital activity of microorganisms in them, like in humans, takes place in the cecum, where anaerobes carry out fermentation processes, the substrate of which is mainly cellulose.

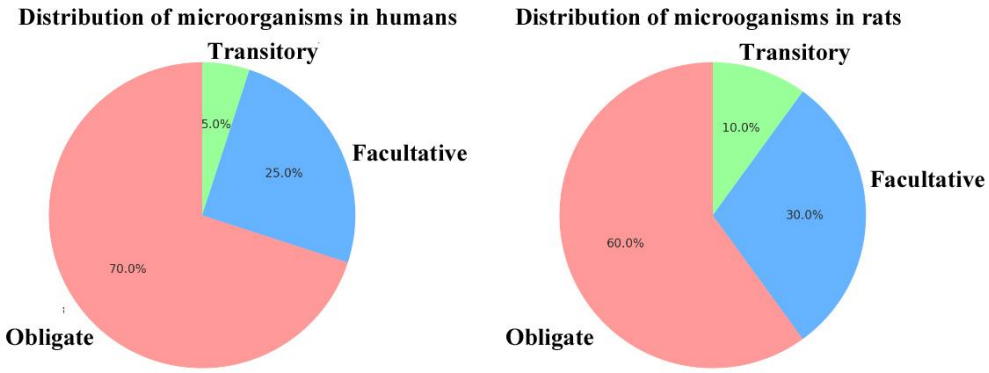

Figure 3 – Distribution of microorganisms in humans and rats

CONCLUSIONS

1. The entire microflora of the digestive tract, both in humans and in white rats, changing zonally in its respective departments, is divided into parietal microbiota and cavity microbiota. Apparently, the cavity microbiota is considered transient.

2. The main mass of parietal microflora (about 95%) consists of obligate microorganisms, which contribute to maintaining a favorable state of the digestive tract. Another part of parietal microflora is a facultative microbiota, among which there are conditionally pathogenic and disease-causing microorganisms.

3. In percentage terms, the quantitative concentration of certain microorganisms of the parietal, obligate, and facultative microflora in the digestive tract of humans and white rats is different, but insignificant.

4. Obligate microorganisms in the surface mucous layer in symbiosis with pathogenic microflora form biofilms, which, on the one hand, participate in the formation of protective mechanisms, and on the other hand, can contribute to increasing the biological activity of pathogenic microorganisms.

5. Modern antibacterial drugs can't completely destroy formed biofilms. Antibiotics that don't penetrate biofilms act only on those bacteria, that haven't become part of the biofilms or have left them for resettlement.

6. The clinical effect of antibiotics is largely related to the cessation of the biofilms spread and a decrease in the biological activity of pathogenic microorganisms. But at the same time, the obligate (normal) microflora also often suffers, which leads to the development of dysbiosis, which should be understood as a fundamental violation of the biofilm structure of the large intestine mucous membrane.

7. The protective function of normal microflora consists in competitive suppression of the pathogenic microorganisms activity. This protective mechanism can be conditionally called (using the term accepted in the literature) mucosal immunity of the mucous membranes.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

In the future it`s planned to investigate the neogenesis of lymph nodes of the gastrointestinal tract under the influence of broad-spectrum antibacterial agents.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

None.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

ARTIFICIAL INTELLIGENCE DISCLOSURE / ВИКОРИСТАННЯ ШТУЧНОГО ІНТЕЛЕКТУ

The authors confirm that no artificial intelligence-based technologies were utilized in the writing or editing of the manuscript.

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Received 31.10.2024
Accepted 14.03.2025

Одержано 31.10.2024
Затверджено до друку 14.03.2025

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