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CHARACTERISTIC OF COLON MICROBIOTA AT PULMONARY TUBERCULOSIS AND THE INFLUENCE OF DYSBACTERIOSIS ON THE RELAPSE OF TUBERCULOSIS

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OUTLINE

INTRODUCTION

Relevance of the topic. Today, tuberculosis (TB) continues to be an unresolved problem of modern medicine [1, 9, 11]. Despite of decrease indicators in TB incidence and prevalence, in Ukraine there is an annual increase in the number of relapse cases of the disease. Special attention is paid to early and late relapse causes of TB (RTB) in Ukraine, where the effectiveness of treatment reaches 74 %. A dangerous fact is that one-third of the relapse cases pass on to the 4-th category, due to the development of resistance of mycobacterium tuberculosis (MBT) to antituberculosis drugs (anti-TB drugs) [11, 13].

Treatment efficiency of RTB depends on a number of social and medical factors, among which an important place is occupied with concomitant diseases and conditions, in particular, colon dysbiosis (CD), that for today is poorly studied concomitant pathology at tuberculosis [10].

Microbiota of the colon is a collection of normal bacteria in the human intestine and performs a number of important physiological functions of the body. At TB are important functions of microflora such as digestive, immunogen, detoxification and synthetic. Obligatory bacteria promote the maturation of the immune system. They perform antigen stimulation of immune cells; participate in the synthesis of a number of vitamins and essential amino acids. Also they promote the digestion of dietary fiber and the elimination of toxic substances that are formed in the body in the process of life [6, 8, 15].

Numerous external and internal organism factors can negatively influence on composition and metabolic activity of intestinal microflora [2, 3, 7, 14]. In particular, the presence of extra-intestinal diseases [14]. The tuberculosis process and concomitant diseases can be predictors of CD. One of the factors that often accompany TB and, at the same time, adversely affect microbiocenosis of intestine is poor nutrition. It is proved that poor nutrition, particularly protein deficiency, has a pronounced negative effect on the intestinal microbiota [15]. In addition, changes in microbial landscape of the colon may result from prolonged TB intoxication, consumption of antibiotics at the stage of differential diagnosis of TB, alcohol,

etc. [5, 12, 14]. Moreover, prolonged use of anti-TB drugs may have a direct or indirect negative effect on the microflora of gastrointestinal tract (GIT) [4, 7, 12].

Today's studies prove the negative interference of CD and inflammatory diseases of different focalization [5]. The relationships connection between the composition of microflora of the large intestine and respiratory diseases are not fully understood and only partially studied, but the results of some studies have shown that inflammation in the lung tissue and inflammation of the intestine are related, which leads to progression of chronic lung diseases [14, 15].

The problem of CD in patients with RTB has been studied only little to date: the influence of dysbiosis on the clinical course and efficiency of treatment of TB has yet to be defined, which determines the relevance of the research.

The aim of the study. To establish the features of the course of pulmonary tuberculosis relapse with concomitant colon dysbacteriosis.

Objectives of the study.

1. Analyzing of the microbiota of the colon and the clinical course of tuberculosis relapse with concomitant colon dysbiosis.

2. To analyze the expression of endogenous intoxication in patients with relapse of pulmonary tuberculosis and concomitant colon dysbiosis.

3. To evaluate the impact of colon dysbiosis on the effectiveness of treatment of pulmonary tuberculosis relapse.

CHAPTER 1
MATERIALS AND METHODS OF RESEARCH

1.1. General characteristics of patients

In order to achieve the aim of the study, 43 patients were examined for RTB. Studies were conducted at the Regional Clinical TB Dispensary during the second half of 2016-2017.

The criteria for inclusion in the study were: confirmed diagnosis of RTB; retained sensitivity of MBT to isoniazid, rifampicin, ethambutol and pyrazinamide; negative result for the human immunodeficiency virus (HIV) infection; informed consent to participate in research signed by a patient. The criteria for inclusion from the study were: fibro-cavernous, cirrhotic tuberculosis; MBT's resistance to isoniazid, rifampicin, ethambutol, pyrazinamide; HIV-positive status.

Prior to forming groups of study, patients sick with RTB were subjected to bacteriological analysis of the contents of the colon, from which became the basis for forming of 2 groups: the main group 1 (G1), consisting of 27 patients diagnosed with RTB of lungs and concomitant CD, and control group 2 (G2), which was formed of 16 patients sick with RTB of lungs not accompanied with CD.

The average age of patients of G1 was 43,2±5,6 years old (minimum – 25 y.o., maximum – 49 y.o.), the average age of patients of G2 was 41,4±4,3 years old (minimum – 26 y.o., maximum – 52 y.o.). Both groups were dominated by the people of elderly age ($p < 0,05$).

By gender distribution criterion, both groups were dominated by males: in G1 men comprised 88,9% (24 persons), women – 11,1% (3 persons), while in G2, men and women comprised 81,3% (13 persons) and 18,8% (3 persons) respectively.

The treatment of patients of G1 and G2 was conducted under unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care "Tuberculosis in Adults" (order №620 The Ministry of Healthcare of Ukraine from 04.09.2014).

1.2. Survey methods

The complex examination of patients was conducted at the time of their hospitalization and included:

1. General clinical examination: collection of complaints and anamnesis of disease and life, epidemiological anamnesis; physical examination of patients (inspection, percussion, palpation, auscultation).

2. Laboratory examination: the mandatory set of general clinical analyses; analysis of serum for antibodies to HIV; double sputum microscopy with the use of Ziehl–Neelsen stain method; culture sputum for dense nutrient medium of Lowenstein-Jensen (1 sample) and liquid culture medium BACTEC (1 sample); molecular genetic studies of sputum (The Xpert MTB/RIF).

To study the quantitative and qualitative composition of microflora of the colon, the bacteriological studies of contents of the colon were performed. The stool of patients was being brought to the laboratory within 2 hours after collection. In sterile conditions, the selection of precise amount of 0,5-1,0 g of feces was conducted. The selected feces were then put in sterile tubes, where isotonic sodium chloride solution was added (1:10), and thoroughly stirred with a glass rod to homogeneity. From the given mass of samples, a set of serial ten-fold dilutions (from 10^{-2} to 10^{-9}) was prepared, after which there was a culture of 0,1 ml of solution out of every test tube of titration row for selective nutrient medium.

For culturing and isolating bifidobacterium in 1 ml dilutions, the latter were plated onto the surface regenerated Blaurock environment, while for lactobacilli the environment MRS-1 was used. Evaluation of the results was performed in 48 hours. The cultures were used to prepare stained smears according to Gram's method identify the presence of gram-positive lakto- and bifidobacterium.

The bacteria of Enterobacteria family were isolated in Endo and Ploskiryev growth media and bismuth-sulfite agar. Colonies were shot with the help of bacteriological loop and cultured in a combined environment for initial identification. The cultures were used to prepare smears, which then were stained according to Gram.

In order to determine lactose-negative Escherichia coli (E. coli), lactose fermentation assessment was carried out based on colour change of the skewed part of combined lactose-glucose environment.

To identify microorganisms and Enterobacterium of coccal groups with hemolytic properties, the culture of material on 5% blood agar was additionally conducted.

Enterococci were isolated by culturing the dilutions 10^{-3}, 10^{-5}, 10^{-7} in differential diagnostic medium for enterococci (milk-inhibitory environment with crystal violet and potassium tellurite).

To identify staphylococci, 0,1 ml of solutions with dilution 10^{-2}, 10^{-4}, 10^{-6} were cultured in gall-plated salt agar.

To isolate anaerobic spore-forming microorganisms, the medium of Kitt-Tarozzi was used.

The cultures were incubated at 37°C for 24-48 hours.

To isolate the fungi of the genus of Candida, culturing of 0,1 ml stool was conducted in dilution 10^{-3} in Saburo medium with added antibiotics (penicillin and streptomycin, 500 IU) for inhibiting the growth of nonspecific microflora. The cultures were incubated at 37±1 °C for 24 hours and then at 22±1 °C up to 5 days. The selection of pure culture was carried out by replanting the colonies in skewed Saburo agar and subsequent identification after 72 hours of growth in an incubator. Enzymatic properties of cultures have been studied in peptone water with 1-2% carbohydrate (glucose, lactose, sucrose and maltose) with the use of indicator (ph 6,0-6,5).

The amount of organisms was counted per 1 g of feces with regard to the number and breeding of material. The absolute number of microorganisms was expressed in decimal logarithm of colony-formed units per 1 g of feces (lg CFU/g).

3. X-ray examination: X-ray of the chest in frontal and side projections, linear tomography, computed tomography (if medically necessary).

1.3. Statistical analysis methods

Analysis of the data was performed in computer program "STATISTICA 10" (StatSoft Inc., USA) on a PC-using parametric and nonparametric methods of calculation.

1.4. Maintenance of bioethics requirements

The survey was conducted in compliance with the main provisions of GCP (1996), the European Convention on Human Rights and Biomedicine (from 04.04.1997), Helsinki Declaration of the World Medical Association on ethical principles of scientific medical research involving human subjects (1964-2013), the Order of The Ministry of Healthcare of Ukraine № 690 from 23.09.2009, № 616 from 03.08.2012.

CHAPTER 2
CHARACTERISTIC OF COLON MICROBIOTA AT PULMONARY TUBERCULOSIS AND THE CLINICAL COURSE OF TUBERCULOSIS RELAPSE WITH CONCOMITANT DYSBIOSIS OF THE LARGE INTESTINE

The results of bacteriological studies of colon content in patients of G1 showed a significant deficit of representatives of obligate microflora (Fig. 2.1) and increase in the number of conditionally pathogenic microorganisms.

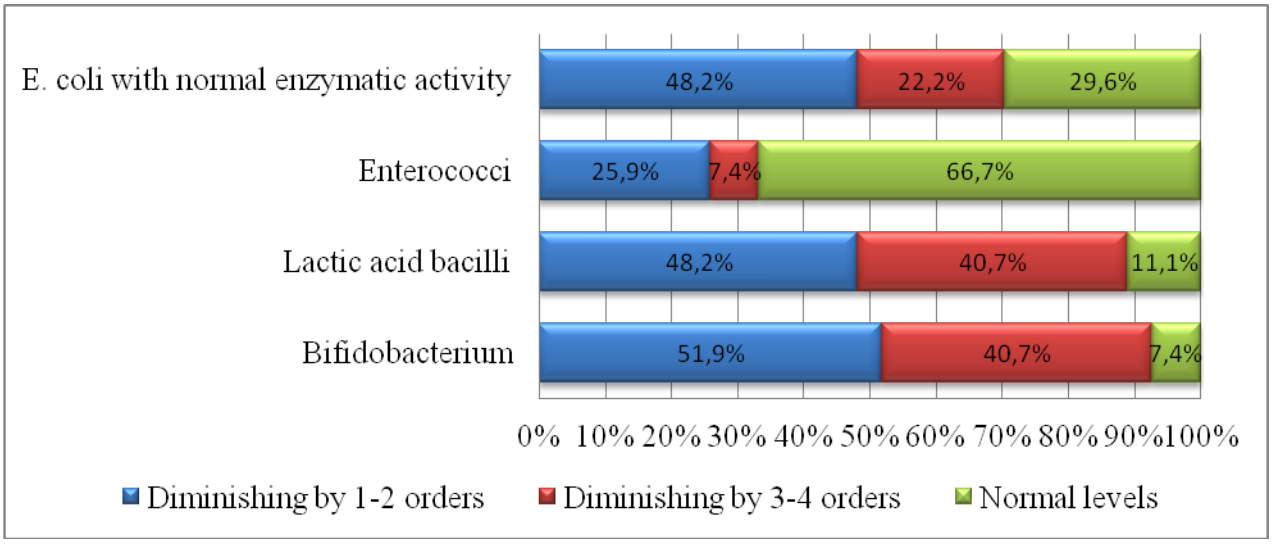

Fig. 2.1. The percentage of quantitative changes of obligate microflora of the colon in patients with newly diagnosed pulmonary tuberculosis before treatment.

The most pronounced changes were by bifidobacterium, lactic acid bacilli and Escherichia with normal enzymatic activity. The content of bifidobacterium in feces of patients of G1 was normal only in 7,4% of cases, lactic acid bacilli – in 11,1% of patients, enzymatically full of E. coli – in 29,6% of cases, and, in most cases, there was a decrease in their number ($p < 0,05$). In 51,9% of cases, the reduction of bifidobacterium by 1-2 orders was recorded, in 40,7% – by 3-4 orders. The level of lactic acid bacterium was reduced by 1-2 orders compared to normal value in 48,2% of patients in G1 and by 3-4 – in 40,7% of cases. 48,2% of patients experienced a reduction of E. coli by 1-2 orders , and 22,2% – by 3-4 orders , marked by a slight decrease in the number of E. coli, which means shortage of Escherichia ($p<0,05$).

The least changes were reported with regard to enterococci, the population of which was reduced by 1-2 orders in 25,9% of patients and by 3-4 orders – in 7,4% of patients.

Against a background of reducing number of aerobic and anaerobic microorganisms in patients with RTB in G1, the appearance of conditionally pathogenic microflora was observed in the feces. Among conditionally pathogenic microflora the fungi of the genus Candida were dominant, which were isolated in 44,4% of patients (clinically significant amounts – in 33, 3 %). The content of the fungi of the genus Candida within 10^{4-5} was observed in 22,2 % of cases and in amount 10^{6} and more – in 11,1% of patients. By the results of bacteriological examination of excrement, the patients in G1 CD was diagnosed with different levels (Fig. 2.2).

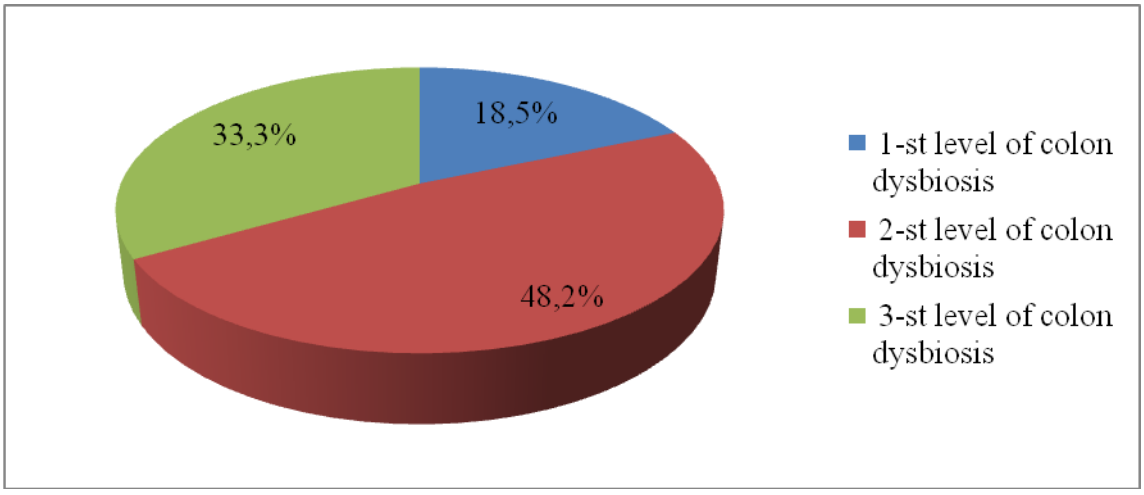

Fig. 2.2. The degrees of colon dysbiosis in patients with relapse of tuberculosis.

As shown in the figure, the patients with RTB are likely to experience more severe degrees of CD ($p < 0,05$). So, CD of the first degree was observed in 18,5% of patients, CD of the II-nd and III-rd degrees – in 48,2% and 33,3% of cases respectively.

A detailed survey of RTB patients was carried out about the availability of periodic or constant complaints from the GIT related to dysbiotic displays. It was established that patients of G1 had periodic complaints in 92,6% of cases (Fig. 2.3), of which 59,2% of patients had constant complaints.

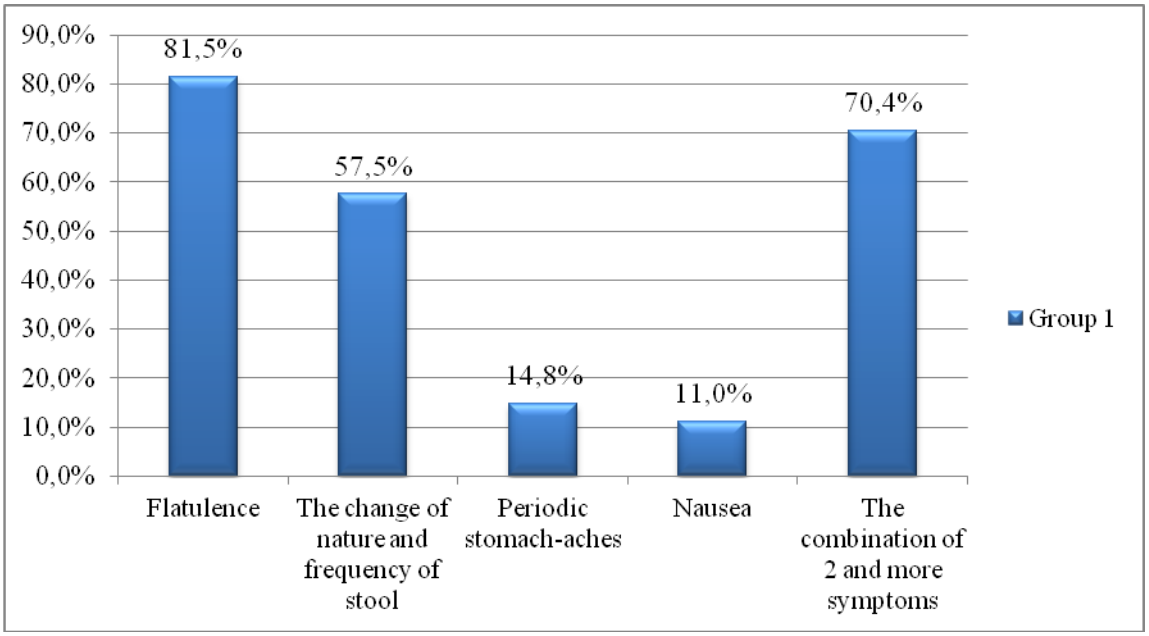

Fig. 2.3.The complaints from the gastrointestinal tract of patients with relapse of tuberculosis and concomitant colon dysbiosis.

As shown in fig. 2.3, in G1, the leading type of gastrointestinal complaints were because of flatulence, which 81,5% of patients noted, while the changes in nature and frequency of stool were experiences by 57,5% of patients. Constipation and stool dilution were observed almost with similar frequency ($p > 0,05$), the part of the patients noted the rotation of these disorders. Persons who complained of flatulence noted the abdominal discomfort that was manifested by collywobbles, feeling of bloating and abdominal overflow. 14,8% of patients periodically disturbed nature prickly pain in the stomach and 11% of people regularly had nausea. In the majority of patients (70,4%) 2 and more symptoms were observed simultaneously.

To determine the severity of intoxication and bronchopulmonary syndromes (IS and BPS) in patients with RTB, with and without CD, the complaints related to the major disease were collected and systematized with the use of specifically designed scales (Table 2.1 and 2.2), which allowed to characterize each complaint quantitatively. To assess IS, we considered symptoms such as low-grade fever or febrile body temperature, weight loss, sweating and weakness, and to assess BPS, we considered dry cough or sputum, chest pain associated with breathing, hemoptysis, pulmonary bleeding.

Table 2.1

Scale assessment of severity of intoxication syndrome.

Points	Characteristics of intoxication syndrome			
	Body temperature °C	Weight loss,% of initial body weight during the last 6 months	Increased sweating	General weakness
1 point	37,1-38	to 5	Slight increase	Minor fatigue
2 points	38,1-39	5-10	Moderate increase	Limitations of mobility
3 points	39,1 and above	More than 10	Profuse sweats	Lying position, shortness of active movements

The assessment of severity of intoxication implied the evaluation of each symptom on a scale from 1 to 3 points. IS was considered as mild with the amount of 1-4 points , moderate – with the amount of 5-8 points, heavy – with the amount of 9-12 points.

Table 2.2

Scale assessment of severity of bronchopulmonary syndrome.

Scores	Description of bronchopulmonary syndrome			
	Cough	Shortness of breath	Chest pain (associated with pulmonary process)	Hemoptysis / pulmonary bleeding
1 point	Periodic minor cough or cough that does not affect the quality of life and does not affect sleeping	During considerable exertion	Minor pain that occurs when coughing, moving etc.	Hemoptysis
2 points	Constant moderate cough that affect the quality of life and disturb at night	With slight physical activity, walking	Moderate, constant pain, which intensifies when coughing, moving, etc.	Pulmonary bleeding of mild severity
3 points	Constant coughing, intense, affects the quality of life and sleeping state.	Resting, while speaking	Distinct, regular pain	Pulmonary bleeding of moderate and heavy severity

While assessing the BPS on a scale for its severity, we took into account the main, the most frequent symptoms – cough, shortness of breath and chest pain, and hemoptysis / pulmonary bleeding regarded as additional symptoms. That's why the BPS was estimated as easy with the amount of points from 1 to 3 as moderate – in the amount of 4-6 points and grave condition – more than 7 points.

Table 2.3

Comparative characteristics of severity of intoxication syndrome in patients with relapse of tuberculosis with concomitant colon dysbiosis

Severity of intoxication syndrome	**Group 1 (n=27)**	**Group 2 (n=16)**	**p**
Missing, %	0	12,5	<0,05
Mild, %	25,9	37,5	<0,05
Moderate, %	33,3	31,2	>0,05
Heavy, %	40,8	18,8	<0,05
Average body temperature, °C	37,8±0,86	37,2±0,5	<0,05
Average scores	6,4±1,8	3,2±2,3	<0,05

It was determined that in patients with RTB with concomitant CD observed significantly more pronounced intoxication, in comparison with persons without CD: patients of G1 light IS was observed in 25,9% of patients and it was significantly less than in G2 ($p < 0,05$), moderate IS was found in 33,3% of patients in G1 vs. 31,2% of cases in G2 ($p > 0,05$) and heavy – in 40,8% of patients surveyed in G1 vs. 18,8% of patients of G2 ($p > 0,05$). The average body temperature in patients of G1 (37,8 ± 0,86 °C) was significantly higher ($p < 0,05$) than in patients of G2 (37,2±0,5 °C). The average number of points that characterized the IS, was calculated by a scale of severity assessment of IS, in patients of G1 was 6,4 ± 1,8 points, which was 2 times higher than in G2 – 3,2 ± 2,3 points.

Table 2.4

Comparative characteristics of severity of bronchopulmonary syndrome in patients with relapse of tuberculosis with concomitant colon dysbiosis.

Severity of bronchopulmonary syndrome	**Group 1 (n=27)**	**Group 2 (n=16)**	**p**
Mild, %	29,6	31,3	>0,05
Moderate, %	37,1	37,4	>0,05
Heavy, %	33,3	31,3	>0,05
Average scores	2,5±1,7	2,6±1,9	>0,05

When comparing the severity of BPS patients in both groups was found that the average number of points that characterized the BPS severity, in patients with RTB with concomitant CD in comparison with G2 did not differ significantly ($p > 0,05$) – 2,5± 1,7 points in G1 vs. 2,6± 1,9 points in G2. The frequency and severity of various BPS did not differ significantly between the groups ($p > 0,05$).

As a result of analysis by Spearman correlation, a weak positive correlation contact was found between the degree of CD patients in G2 and severity of IS ($r = -0,24$, $p < 0,05$).

Thus, in patients with tuberculosis relapse probably more severe degrees of dysbiosis are dominated ($p < 0,05$), accompanied by corresponding clinical symptoms. In patients with RTB with concomitant CD significantly more pronounced intoxication was observed in comparison with persons without CD, depending on the degree of microbiota violation ($p < 0,05$).

CHAPTER 3
THE EVALUATION OF THE SEVERITY OF ENDOGENOUS INTOXICATION IN RELAPSES OF TUBERCULOSIS WITH CONCOMITANT DYSBACTERIOSIS OF THE LARGE INTESTINE

The results of some studies have shown that the CD promotes the permanent source of intoxication in the large intestine due to the breeding of pathogenic microflora and reducing the detoxification function of normobiota [7, 8, 14, 15]. This is confirmed by preliminary results of our research, which showed the presence of more severe toxicity in RTB patients with concomitant CD. So, the next task of our research was to study the objective indicators of endogenous intoxication with indices of endogenous intoxication (IEI). The results are shown in Table 3.1.

Table 3.1

The indices of endogenous intoxication in patients with relapse of tuberculosis and concomitant colon dysbiosis.

Indicator	Normal Values	G1 n=27	G2 n=16	p
IK	1,8±0,46	3,49±1,68	2,63±1,01	<0,05
MLII	1-1,6 ± 0,5	2,60±1,19	1,99±0,74	<0,05
CID	–	0,35±0,14	0,29±0,12	<0,05
RRN	10,6 ± 2,1	23,84±4,62	10,72±4,8	<0,05
LESRR	1,87 ± 0,76	2,10±0,34	1,60±0,33	<0,05
LI	0,41 ± 0,03	0,34±0,14	0,42±0,13	>0,05
NLR	2,47 ± 0,65	3,49±1,57	2,64±1,01	<0,05
NMR	11,83 ± 1,31	15,72±5,31	12,97±6,5	<0,05
LMR	5,34 ± 0,59	4,96±2,23	5,19±1,74	>0,05

Notes: IK – index of Krebs; MLII – modified leucocidal index of intoxication; CID – core index of Dashtayants H.D.; RRN – reactive response of neutrophils; LESRR – leukocytes to erythrocyte sedimentation reaction (ESR) ratio; LI – leukocyte index; NLR – neutrophils to lymphocytes ratio; NMR – neutrophil to monocyte ratio; LMR – lymphocyte to monocyte ratio.

The results of research showed that patients with concomitant CD experienced significantly more pronounced rejection of the majority of indicators of endogenous intoxication from reference values compared with RTB patients without concomitant CD. Thus, IK, which objectively reflects the level of intoxication in G1 was 3,49 ± 1,68, that is, 2 times higher than the reference values and was exceeding the control value of G2 by 0,86 ($p < 0,05$). The value of IK for G1 was indicative of the presence of intoxication of medium severity, while in the value for G2 showed the mild degree of intoxication.

MLII in G1 was 2,60 ± 1,19 against 1,99 ± 0,74 in G2 ($p < 0,05$), which also shows the average severity of intoxication in G2. CID in G1was 0,35 ± 0,14 against 0,29 ± 0,12 in G2 ($p < 0,05$), indicating that the average severity of patients of the main group.

In G1 the changes of RRN indicator were the most pronounced, which is more than 2 times higher than the performance standards and rate of control group – 23,84 ± 4,62 in G1 against 10,72 ± 4,8 in G2 ($p < 0,05$). The indicator of RRN reflects the activity of neutrophils, a level of nonspecific immunity in response to stimulation by antigens. Since neutrophils do not play a significant role in TB immunity, the indicator of RRN in the control group did not exceed the reference values and was significantly higher in the study G1, where patients had concomitant CD. This indicates the activation of neutrophils in response to the growing number of antigens in large intestine due to reproduction of conditionally pathogenic microorganisms. A high indicator of RRN indicates subcompensation of endogenous intoxication and the need for its correction.

Deviation from the normal value of LESRR was observed only in G1, where the given indicator was 2,10 ± 0,34 against 1,60 ± 0,33 in G2 ($p < 0,05$). For this indicator, you can assess the presence of intoxication connected with infectious process (lower index) or autoimmune process (increasing index). As a result, the index in G2 was below than the reference value ($p < 0,05$), but in G1 it exceeded the norms and values of the control group. It is possible that this result may indicate the stimulation of autoimmune reactions by changing of microbiocenosis composition of the colon.

LI as an indicator that reflects the value of humoral and cellular levels of immune response was significantly lower in G1 and amounted to 0,34 ± 0,14 against 0,42 ± 0,13 in G2 ($p < 0,05$), indicating a lack of humoral response in patients with concomitant CD. This may be sharp deficit of normal microflora and the violation of its immunogenic function.

NLR as the indicator of RRN showed the activation of non-specific the immune response by neutrophils, and amounted to 3,49 ± 1,57 G1 against 2,64 ± 1,01 in G2 ($p < 0,05$). A similar trend was from NMR, which amounted to 15,72 ± 5,31 in G1 against 12,97 ± 6,5 in G2 ($p < 0,05$).

LMR, which reflects the ratio affector and effector parts of the immune response, showed more pronounced deficit of affector component in the main group, but it was not significantly different between G1 and G2, but was slightly lower in the main group – 4,96 ± 2,23 in G1 against 5,19 ± 1,74 in G2 ($p > 0,05$).

Thus, the results had demonstrated a significantly more pronounced endogenous intoxication in patients with concomitant CD, activation of non-specific immune response on the background of deficit of humoral immunity component.

CHAPTER 4
THE INFLUENCE OF LARGE INTESTINE DYSBIOSIS ON THE EFFECTIVENESS OF TREATMENT OF PULMONARY TUBERCULOSIS RELAPSE

To establish the impact of CD on the course and dynamics of tuberculosis relapse treatment, we analyzed the indicators of endogenous intoxication, the results of bacterioscopic researches of sputum and X-ray data obtained at the end of the intensive phase of chemotherapy.

The evolution of endogenous intoxication is presented in Table 4.1.

Table 4.1

The indices of endogenous intoxication in patients with relapse of tuberculosis with concomitant colon dysbiosis at the end of the intensive phase.

Indicator	G1 before treatment n=27	G1 at the end of intensive phase n=27	G2 before treatment n=16	G2 at the end of intensive phase n=16
IK	3,49±1,68	2,53±1,14	2,63±1,01	2,12±0,27
MLII	2,60±1,19	2,16±0,92	1,99±0,74	1,52±0,14
CID	0,35±0,14	0,27±0,09	0,29±0,12	0,17±0,08
RRN	23,84±4,62	18,32±2,67	10,72±4,8	10,62±2,6
LESRR	2,10±0,34	1,67±0,24	1,60±0,33	1,71±0,3
LI	0,34±0,14	0,37±0,12	0,42±0,13	0,38±0,11
NLR	3,49±1,57	2,89±0,86	2,64±1,01	2,56±0,09
NMR	15,72±5,31	12,24±4,26	12,97±6,5	11,95±2,45
LMR	4,96±2,23	5,13±1,46	5,19±1,74	5,22±0,54

Notes: IK – index of Krebs; MLII – modified leucocidal index of intoxication; CID – core index of Dashtayants H.D.; RRN – reactive response of neutrophils; LESRR – leukocytes to erythrocyte sedimentation reaction (ESR) ratio; LI – leukocyte index; NLR – neutrophils to lymphocytes ratio; NMR – neutrophils to monocytes ratio; LMR –lymphocytes to monocytes ratio.

By the end of the intensive phase, the values of indices of endogenous intoxication showed by group of RTB patients were maximally close to normal

values. Unlike in the case of G2, in G1, the positive dynamics of the IEI was observed; however, their value exceeded the standard value and indicators of G2 in dynamics, indicating a more prolonged maintenance of toxicity in given patients. IK decreased by 0,96 and totaled 2,53 ± 1,14 at the end of intensive phase, while for G2 in dynamics it amounted to 2,12 ± 0,27 ($p < 0,05$). MLII decreased from 2,60 ± 1,19 to 2,16 ± 0,92, that is, a change by 0,44; in G2 this index decreased by 0,47 and amounted to 1,52 ± 0,14 in the dynamics of treatment, which was significantly less than in G1 ($p < 0,05$). CID in G1 to the end of intensive phase decreased to 0,27 ± 0,09, that is corresponding to mild intoxication. RRN in G1 decreased to 5,52, but remained at a high level (18,32 ± 2,67) due to further stimulation of nonspecific immunity by opportunistic bacterium and toxins from the colon.

Dynamics of LESRR, LI, NLR, NMR and LMR was more pronounced with comparison of other indicators - these indicators as much as possible approached to that of the reference values.

Table 4.2 presents the main indicators of the effectiveness of tuberculosis treatment.

Table 4.2

The effectiveness of treatment of patients with tuberculosis relapse with concomitant colon dysbiosis at the end of the intensive phase.

Performance Indicator treatment, %	**Group 1 n=27**	**Group 2 n=16**	**p**
Positive clinical dynamics	81,5	93,8	<0,05
The suspension of bacteria	44,4	56,3	<0,05
Positive X-ray dynamics in a full or partial closing of cavities	29,6	43,8	<0,05

As shown in the table, RTB patients with concomitant CD showed significantly slower dynamics of treatment compared with patients with normal microbiocenosis state. The positive clinical dynamics during the intensive phase of treatment was observed in 81,5% of cases in G1 vs. 93,8% of cases in G2 ($p < 0,05$). After finishing of intensive phase of chemotherapy, sputum by smear was stopped in

44,4% of patients in the main group, which is 11,9% less than in the control group ($p < 0,05$). The positive X-ray dynamics in a reduction and closing of antrum of breaking also was observed significantly less frequently in G1 than G2: in 29,6% and 43,8% of cases respectively ($p < 0,05$).

As a result, relapse of pulmonary tuberculosis in patients with concomitant CD is characterized by more prolonged intoxication and slower dynamics of treatment as compared with patients with normal levels of microflora of the large intestine.

CONCLUSION

1. Dysbacteriosis of colon in patients with tuberculosis relapse is characterized by a deficit of bifidobacterium, lactic acid bacilli and Escherichium with normal enzymatic activity and the increase of conditionally pathogenic bacterium in the abdominal content of the colon, which are dominated by fungi of the genus Candida. Patients with relapse of tuberculosis presumably experience more severe levels of dysbiosis ($p < 0,05$): the 1^{st} level of dysbiosis was observed in 18,5% of patients, the 2^{nd} and 3^{rd} levels - in 48,2% and 33,3% of cases respectively.

2. 92,6% of patients suffering from relapse of tuberculosis with concomitant colon dysbiosis periodically have complaints about their gastrointestinal tract organs. It was determined that patients diagnosed with tuberculosis relapse accompanied by colon dysbiosis experience more pronounced intoxication syndrome compared with those without colon dysbiosis ($p < 0,05$).

3. Significantly more severe endogenous intoxication is observed in patients diagnosed with concomitant colon dysbiosis compared with relapse of tuberculosis patients without colon dysbiosis ($p < 0,05$), as confirmed by higher values of indices of endogenous intoxication. In patients with dysbiotic violation reliable increasing of reactive response of neutrophils was observed ($23,84 \pm 4,62$ in the main group vs. $10,72 \pm 4,8$ in the control group ($p < 0,05$), indicating that the activity of neutrophils as level of nonspecific immunity in response to the growing number of antigens in the large intestine due to reproduction of conditionally pathogenic microorganisms.

4. The observations show that patients with relapse of tuberculosis accompanied by colon dysbiosis have significantly slower treatment dynamics when compared with patients with normal microbiota: positive clinical dynamics during the intensive phase of treatment were observed in 81,5% of the main group vs. 93,8% of the cases in control group ($p<0,05$); suspension of bacteria – in 44,4% of patients in the main group vs. 56,3% in the control group ($p < 0,05$); closing of cavities – in 29,6% of cases vs. 43,8% of cases respectively ($p < 0,05$).

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