

## Clinical features of the drug susceptible, multi drug resistant and HIV-associated pulmonary tuberculosis depending on the degree of colon dysbiosis

L. D. Todoriko, O.V. Pidverbetska

HSEI “Bukovinian State Medical University”, Chernivtsi, Ukraine

\*Corresponding author. E-mail: pulmonology@bsmu.edu.ua

Paper received ; Accepted for publication .

**Abstract.** The article describes the results of the investigation of colon dysbiosis impact on the clinical course of pulmonary tuberculosis depending on the resistance of MBT and HIV-status. It's established that colon dysbiosis affects adversely on the course of pulmonary tuberculosis, in particular, contributes to strengthening the manifestations of intoxication syndrome and, in a case of severe dysbacteriosis - to strengthening the bronchopulmonary syndrome. Dysbiosis of the II-III degrees contributes to a prolonged duration of the tuberculous inflammation and is one of the factors of reducing the effectiveness of treatment.

**Keywords:** colon dysbiosis, lung tuberculosis, clinical features.

**Introduction.** The imbalance of immune response in pulmonary tuberculosis (TB), which leads to the disruption of adaptation of the organism and reduces the effectiveness of the safety mechanisms and systems, long intoxication syndrome due to continuous release of toxins into the bloodstream, general exhaustion lead to disturbances in the colon microbiota system, which microflora has the most functional load in the organism [1, 3]. The presence of such aggravating factors as prolonged drinking, smoking or using drugs, insufficient and low quality food, malnutrition, in a significant proportion of TB patients intensify the development of dysbiotic violations in the large intestine. Whereas colon dysbacteriosis (CD) violates a number of important microflora functions, including the maintenance of cytokine balance and regulation of immune processes of the body through the antigen-stimulating effect of the colon microbiota representatives [5].

Dysbiotic violation contributes to longer maintenance of inflammation in the lung tissue and other organs that can reduce the effectiveness of treatment of pulmonary tuberculosis [2]. Clinical symptoms of colon dysbiosis reduce the quality of patients' life because of the emergence of uncomfortable manifestations of this disease and reduce the adherence of patients to etiotropic treatment. Some literature data [1, 2, 4] indicate that a violation of colon microbiota can influence the clinical course of respiratory diseases.

**The aim** of this study was to investigate the clinical features of pulmonary TB in patients with preserved sensitivity of mycobacteria tuberculosis to anti-TB drugs (ATBD), multi drug resistant tuberculosis (MDR-TB) and

co-infection HIV/tuberculosis (HIV/TB) depending on the condition of the colon microbiota.

**Materials and methods.** The study included 60 patients with newly diagnosed pulmonary tuberculosis (NDTB) with preserved susceptibility of Mycobacterium tuberculosis to ATBD (group 1), 60 patients with pulmonary MDR-TB (group 2) and 30 patients with co-infection HIV/TB (group 3).

The state of intestinal microbiota was determined by bacteriological analysis of the colon cavity contents. Stool sample was removed for analysis in the morning before the start of ATBD taking. The material was delivered to the laboratory within 2 hours after collection. The number of organisms was counted per 1 g of feces and according to the amount and dilution of the material. The degree of dysbiosis was determined by I. B. Kuvaeva and K. S. Ladodo classification, 1991 [2, 4].

We used the program STATISTICA, version 10.0.228.8 (StatSoft, Inc.) for statistical analysis of data. Data samples were tested for normality by the Shapiro-Wilk test. Normally distributed data were presented as the mean and standard deviation (M±SD) and were analyzed using the Student's t test. The difference was considered statistically significant when p-value was less than 0,05. Correlation analysis was performed by Spearman.

**Results and its discussion.** The clinical course of TB was evaluated by intoxication (IS) and bronchopulmonary syndromes (BPS). To estimate the significance of the intoxication and bronchopulmonary syndromes, we collected the complaints of the patients and classified them according to the following criteria (Tables 1 and 2), that allowed us to describe every complaint on a quantifying level.

**Table 1.** Rating scale of the significance of the intoxication syndrome in TB patients

Points	Characteristics of the intoxication syndrome			
	Body temperature, °C	Weight loss, % from the initial body weight within the last 6 months	Hyperhidrosis	General weakness
1 point	37,1-38	up to 5	Negligible	Insignificant fatigability
2 points	38,1-39	5-10	Moderate	Limited excursion
3 points	39,1 and higher	more than 10	colliquative /profuse sweat	Recumbency, difficulty of active moves

The rating scale of the significance of the intoxication syndrome has a grade for each symptom from 1 to 3 points. The intoxication syndrome was considered as mild

when the sum of points was from 1 up to 4, moderate – with the sum 5-8 points, severe – with the sum 9-12 points.

**Table 2.** Rating scale of the significance of the bronchial-pulmonary syndrome in TB patients

Points	Characteristics of the bronchial-pulmonary syndrome			
	Cough	Dyspnea	Chest pain (connected with the pulmonary process)	Expectoration of blood / pulmonary hemorrhage
1 point	Periodic insignificant coughing or tussiculation, that does not make the quality of life and sleep worse	During considerable physical activity	Insignificant, that happens while coughing, walking, etc.	Hemorrhage
2 points	Constant coughing, moderately present, that can slightly affect the quality of life and bother at night	During the insignificant physical activity, while walking	Moderate, constant, get worse while coughing, walking, etc.	Pulmonary hemorrhage of a light level of complexity
3 points	Constant coughing, intensive, affect the quality of life and sleep	While at peace, while talking	Significant, constant	Pulmonary hemorrhage of a medium and complicated level of complexity

When defining the bronchial-pulmonary syndrome, using the rating scale of its significance, we looked at the main and most frequent symptoms – coughing, dyspnea and pain in the chest, and expectoration of blood/pulmonary hemorrhage considered as additional symptoms. That is why the bronchial-pulmonary

syndrome was considered to be light with the sum of points from 1 up to 3, as moderate – with the sum 4-6 points and significant – more than 7 points.

The analysis showed that IS grew with the growth of dysbiotic violations in the large intestine in patients with pulmonary TB (Table 3).

**Table 3.** Characteristics of the severity of intoxication syndrome in patients first diagnosed drug susceptible, MDR and HIV-associated tuberculosis, depending on the degree of dysbiosis colon

CD degree	Group 1 n=60	Group 2 n=60	Group 3 n=40	p
	Intoxication syndrome (scores)			
absent	3,12±0,49	–	–	–
I degree	4,27±0,72	4,39±0,65	5,13±0,52	p <sub>1,3</sub> <0,05 p <sub>2</sub> >0,05
II degree	6,39±1,14	7,18±1,11	8,22±0,76	p <sub>1,3</sub> <0,05 p <sub>2</sub> >0,05
III degree	8,40±1,03	9,84±1,21	10,24±1,07	p <sub>1</sub> <0,05 p <sub>2,3</sub> >0,05
IV degree	–	–	11,20±3,36	–

**Notices.** p<sub>1</sub> – statistical difference between group 1 and group 2; p<sub>2</sub> – statistical difference between group 1 and group 3; p<sub>3</sub> – statistical difference between group 2 and group 3.

It is established that severity of BPS in group 1 was 1,4 times higher in patients with CD of the I degree than in those without CD (p<0,05) and 1,5 times lower than in patients with CD of the II degree (p<0,05). Patients of group 1 with dysbiosis of the III degree had the highest score of IS, which exceeded the score in patients with CD of the II degree by 1,3 times and in patients with CD of I degree by 1,97 times (p<0,05 in both cases).

In MDR-TB patients the most severe manifestations of IS were at CD of the III degree – the average score of IS was 27% higher than the score of patients with CD of the II degree (p<0,05) and 55,4% higher than at CD of the I stage (p<0,05). As in the case of sensitive NDPT, the lightest IS manifestations in group 2 were observed in patients with minimal changes of the colon microbiota. Thus, IS in patients with CD of the I stage was 1,3 times less pronounced than in patients with CD of the II degree and 2,2 times – compared to CD of the III degree (p<0,05 in both cases).

HIV-associated TB is characterized by the most severe symptoms of intoxication among all groups of patients, however, in the case of co-infection the same trend of

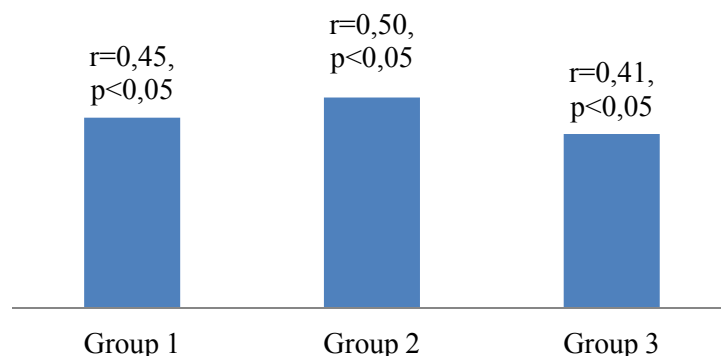
increasing the severity of IS manifestations deepening on dysbiosis was noticed. The highest points of the IS in group 3 were observed in patients with CD of the III and the IV degrees. It should be noticed that CD of the IV degree was found only in these patients. The index of IS severity in patients with CD of the IV degree was only 8,6% higher than the comparable indicator in patients with CD of the III degree (p>0,05), 26,6% higher compared to CD of the II degree (p<0,05) and 54,2% – compared to CD of the I degree (p<0,05). The difference between the IS in patients with CD of the II and the III degrees was 19,7% (p<0,05), between CD of the I and the III degrees – 49,9% (p<0,05). The least severe manifestations of IS were in patients with minimal dysbiotic changes (CD of the I stage) (p<0,05).

Thus, the analysis of the study results showed that dysbiotic violations in the colon have a negative effect on the clinical course of tuberculosis. Some researchers believe [4] that the reproduction of opportunistic bacterial species of colon microflora contributes to the accumulation of toxic compounds, which are soaked into the bloodstream and contribute to the increasing of

endogenous intoxication. However, obligate microorganisms are one of the components of the detoxification mechanism, so their elimination weakens the detoxification function of intestinal microflora. This is confirmed by our results - tends to IS increasing in

patients with pulmonary tuberculosis in response to the dysbiosis increasing.

Correlation analysis showed the dependence of IS severity on the severity of dysbiotic violations of colon in patients with pulmonary TB in all groups (Fig. 1).



**Fig. 1.** The correlation between the degree of colon dysbiosis and severity of clinical manifestations of intoxication syndrome in patients with newly diagnosed sensitive, MDR and HIV-associated tuberculosis.

As it's shown in Fig. 1, positive correlation of moderate strength was found in group 1 and group 3, strong positive correlation – in group 2. In our view, the increasing number of pathogenic microorganisms in the colon contributes to the creation of additional foci of infection, and leads to the loss or reduction of detoxification function of obligate microflora that causes the growth of toxins in the blood.

It was found that dependence of the IS on the severity of CD is significantly lower in HIV-positive patients than in HIV-negative patients ( $p < 0,05$ ) due to the presence of a significant number of factors (deep immunosuppression, opportunistic infections, viral load etc.), which have a significant effect on the severity of intoxication.

Our results of analysis of the IS severity dependence on the MBT sensitivity showed that IS was significantly more pronounced in patients with MDR-TB compared to patients with susceptible NDTB at CD of the II degree

(difference was 11%,  $p < 0,05$ ) and at CD of the III degree (difference was 14,6%,  $p < 0,05$ ).

The indicators that characterized the IS in co-infection HIV/TB were higher at all degrees of CD than in groups of HIV-negative patients. The average score of IS in patients of group 3 with CD of the I degree consistent with moderate intoxication and exceeded the average score of group 1 and group 2 by 16,8% ( $p < 0,05$ ) and 14,4% ( $p < 0,05$ ), respectively.

CD of the II degree in group 3 was characterized by more severe IS compared to group 1 and group 2 – the average score of IS was 22,2% and 12,7% higher, respectively ( $p < 0,05$  in both cases). The intensity of the IS in HIV/TB patients with CD of the III degree exceeded the same indicator in patients of group 1 by 18% ( $p < 0,05$ ) and in patients of group 2 – only by 4% ( $p > 0,05$ ).

The results showed that bronchopulmonary syndrome was less dependent on the degree of dysbiotic violations than the IS in all groups (Table 4).

**Table 4.** Characteristics of the severity of bronchopulmonary syndrome in patients with newly diagnosed drug susceptible, multi drug resistant and HIV-associated tuberculosis depending on the degree of colon dysbiosis

CD degree	Group 1 n=60	Group 2 n=60	Group 3 n=40	p
	Bronchopulmonary syndrome (scores)			
absent	2,95±0,38	–	–	–
I degree	3,26±0,32	3,37±0,46	2,16±0,83	$p_{1>0,05}$ $p_{2,3}<0,05$
II degree	3,19±0,74	3,42±0,81	2,62±0,86	$p_{1>0,05}$ $p_{2,3}<0,05$
III degree	4,41±0,89	4,54±0,96	3,13±0,92	$p_{1>0,05}$ $p_{2,3}<0,05$
IV degree	–	–	3,24±0,71	–

**Notices.**  $p_1$  – statistical difference between group 1 and group 2;  $p_2$  – statistical difference between group 1 and group 3;  $p_3$  – statistical difference between group 2 and group 3.

As it's shown in the table, the significant difference between the severity of BPS in patients with the I and the II degrees of CD was not found in both sensitive NDTB and MDR-TB ( $p > 0,05$ ). However, in both groups BLS was accompanied by more severe symptoms in patients

with III degree of CD compared to the patients with the I and the II degrees of CD.

BPS in group 1 was on 27,7% more severe at than III degree of CD than at the II degree of CD and on 26% – than at the I degree of CD ( $p < 0,05$  in both cases).

The average score of BPS severity in CD of the III degree was reliably higher than in CD of the I and II degrees on 25,8% and 24,7%, respectively ( $r < 0,05$ ). The analysis showed that high score of BPS in patients with CD of the III degree was mainly associated with more severe cough with sputum. There are researches today [4] which show that patients with severe dysbiotic disorders of the colon more likely than individuals without dysbiosis develop the contamination of upper respiratory tract with pathogenic microflora with further chronic inflammatory response development that increases the expression of BPS.

The most pronounced symptoms of BPS in patients with co-infection were observed at CD of IV degree ( $p < 0,05$ ) and less pronounced – at CD of the I degree ( $p < 0,05$ ). There was no significant difference in the severity of BPS between patients with CD of the II and the III degrees ( $p > 0,05$ ).

Special attention should be given the fact that BPS in patients co-infected with HIV-infection at dysbiosis of different degrees was significantly lower than in group 1 and group 2: at CD of the I degree – 1,5 times lower than in group 1 and 1,6 times lower than in group 2; at CD of the II degree – 1,2 times less than in group 1 and 1,3 times less than in group 2; at CD of the III degree – 1,4

times less compared to group 1 and 1,5 times – compared to group 2 ( $p < 0,05$  in all cases).

Correlation analysis showed that dysbiotic violation of the colon has minimal impact on the intensity of bronchopulmonary syndrome: in group 1 –  $r = 0,18$ ,  $p < 0,05$ ; in group 2 –  $r = 0,19$ ,  $p < 0,05$ ; in group 3 –  $r = 0,16$ ,  $p > 0,05$ .

**Conclusions.** 1. It is established that violation of the qualitative and quantitative composition of the microflora of the large intestine has a negative effect on the clinical course of tuberculosis. Colon dysbiosis mostly affects the intensity of the manifestations of intoxication syndrome.

2. According to the correlation analysis, the most pronounced dependency of the intoxication syndrome intensity on the degrees of colon dysbiosis was in patients with MDR tuberculosis ( $r = 0,50$ ,  $p < 0,05$ ).

3. It is proved by correlation analysis that dysbiotic violation of the colon has minimal impact on the manifestation of bronchopulmonary syndrome. The significant role of the colon microbiota violations in the intensity of BPS was proved only at colon dysbiosis of the III degree in patients with newly diagnosed drug susceptible TB and MDR-TB and at colon dysbiosis of the III-IV degrees in patients with HIV/TB.

#### REFERENCES

1. Clinical and bacteriological manifestations of intestine dysbacteriosis in patients with pulmonary tuberculosis, complicated with accompanying pathology of the gastrointestinal tract / Z.E. Lyneva, N.A. Hulyaeva, M.V. Romanov [et al.] // *Mezhdunarodnyi zhurnal prikladnykh fundamentalnykh issledovaniy.* – 2013. – №11. – P. 88-93.
2. Pavlova E.S. Efficiency of treatment of primary diagnosed patients with destructive lung tuberculosis and pathology of the gastrointestinal tract: Author. dis .. PhD. : Special 14.00.26 "Phthisiology" / E.S. Pavlova. – M., 2005. – 115 p.
3. Ryhlitska K.V. Pathogenic substantiation of differential treatment of chronic obstructive pulmonary disease with concomitant atherosclerosis of mesenteric vessels and intestinal dysbiosis: Author. dis .. PhD. : Special: 14.01.02 / K.V. Ryhlitska; BSMU. – K., 2010. – 16 p.
4. Todoriko L.D. Peculiarities of comorbidity of tuberculosis and respiratory diseases / L.D. Todoriko, O.V. Pidverbetska // *Materials of the conference "Actual problems of pulmonology."* – 2013. – P. 25-29.
5. Stephen M. Collins. A role for the gut microbiota in IBS / Stephen M. Collins // *Gastroenterology & Hepatology.* – 2014. – V. 11. – P. 497-505.
6. The role of intestinal microbiota and the immune system / F. Purchiaroni, A. Tortora, M. Gabrielli [et al.] // *European Review for Medical and Pharmacological Sciences.* – 2013. – P.323-333.

#### **Клинические особенности течения лекарственно-чувствительного, мультирезистентного и ВИЧ-ассоциированного туберкулеза легких в зависимости от степени дисбиоза толстой кишки**

**Л. Д. Тодорико, Е. В. Подвербецкая**

**Аннотация.** В статье приведены результаты исследования влияния дисбактериоза толстого кишечника на клиническое течение туберкулеза легких в зависимости от спектра резистентности МБТ и при коморбидности ВИЧ/туберкулез. Установлено, что дисбиотические нарушения толстого кишечника негативно влияют на течение туберкулеза легких, в частности способствуют усилению проявлений интоксикационного синдрома и, при тяжелом дисбактериозе, – и бронхолегочного синдрома. Дисбиоз толстой кишки II-III степеней способствует более длительному течению туберкулезного воспаления и является одним из факторов снижения эффективности этиотропного лечения.

**Ключевые слова:** дисбактериоз толстого кишечника, туберкулез легких, клинические особенности.