

# Management of pulmonary tuberculosis on the background of intestinal malabsorption syndrome

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Conflict of interest: none

**OBJECTIVE.** To investigate the frequency of malabsorption in newly diagnosed sensitive pulmonary tuberculosis (TB) and to establish the effectiveness of treatment correction in these patients.

**MATERIALS AND METHODS.** In the first stage of the study, 73 patients with new drug-susceptible TB underwent lactulose-mannitol test. Individuals with intestinal permeability index  $<3$  were selected and divided into main group which received injectable forms of isoniazid, rifampicin, ethambutol and oral pyrazinamide and control group which received standard treatment orally.

**RESULTS.** Bacterial excretion stopped in 88.2 % of patients in the main group and in only 61.5 % of patients in the control group. In 46.1 % of cases in the control group treatment failure was diagnosed. The frequency of positive radiological dynamics at the end of the intensive phase of treatment was 64.7 % in the main group versus 30.8 % in the control group. The total efficacy of treatment at the end of the main course of chemotherapy was 88.2 % in the main group against 53.9 % in the control group ( $p < 0.05$ ).

**CONCLUSIONS.** Malabsorption, which requires correction of treatment, occurs in about one-fifth of patients with new TB. Usage of injectable anti-TB drugs in such patients increases the effectiveness of treatment by 34 % ( $p < 0.05$ ).

**KEY WORDS:** tuberculosis, malabsorption, injectable anti-tuberculosis drugs.

## Лікування туберкульозу легень на тлі синдрому кишкової мальабсорбції

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Конфлікт інтересів: відсутній

**МЕТА.** Дослідити частоту мальабсорбції при вперше діагностованому чутливому туберкульозі (ТБ) легень і встановити ефективність корекції лікування в цих хворих.

**МАТЕРІАЛИ ТА МЕТОДИ.** На першому етапі дослідження 73 пацієнтам зі вперше діагностованим чутливим ТБ було проведено лактулозно-манітоловий тест. Особи з індексом кишкової проникності  $<3$  були відібрані та розподілені на основну групу, яка отримувала ін'єкційні форми ізоніазиду, рифампіцину, етамбутолу та пероральний піразинамід, і контрольну групу, яка отримувала стандартне лікування перорально.

**РЕЗУЛЬТАТИ.** Припинення бактеріовиділення спостерігалось у 88,2 % пацієнтів основної групи та лише в 61,5 % пацієнтів контрольної групи. У 46,1 % випадків у контрольній групі встановлено неефективність лікування. Частота позитивної рентгенологічної динаміки наприкінці інтенсивної фази лікування становила 64,7 % в основній групі проти 30,8 % у контрольній групі. Загальна ефективність лікування наприкінці основного курсу хіміотерапії становила 88,2 % в основній групі проти 53,9 % у контрольній групі ( $p < 0,05$ ).

**ВИСНОВКИ.** Мальабсорбція, що потребує корекції лікування, спостерігається приблизно в п'ятій частини хворих із новими випадками ТБ. Застосування ін'єкційних протитуберкульозних препаратів у таких пацієнтів підвищує ефективність лікування на 34 % ( $p < 0,05$ ).

**КЛЮЧОВІ СЛОВА:** туберкульоз, мальабсорбція, ін'єкційні протитуберкульозні препарати.

# Лечение туберкулеза легких на фоне синдрома кишечной мальабсорбции

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**ЦЕЛЬ.** Исследовать частоту мальабсорбции при впервые диагностированном чувствительном туберкулезе (ТБ) легких и установить эффективность коррекции лечения у данных больных.

**МАТЕРИАЛЫ И МЕТОДЫ.** На первом этапе исследования 73 пациентам с впервые диагностированным чувствительным ТБ был проведен лактулозного-манитоловый тест. Лица с индексом кишечной проницаемости  $<3$  были отобраны и распределены на основную группу, которая получала инъекционные формы изониазида, рифампицина, этамбутола и пероральный пиразинамид, и контрольную группу, которая получала стандартное лечение перорально.

**РЕЗУЛЬТАТЫ.** Прекращение бактериовыделения наблюдалось у 88,2 % пациентов основной группы и только у 61,5 % пациентов контрольной группы. В 46,1 % случаев в контрольной группе установлено неэффективность лечения. Частота положительной рентгенологической динамики к концу интенсивной фазы лечения составила 64,7 % в основной группе против 30,8 % в контрольной группе. Общая эффективность лечения к концу основного курса химиотерапии составила 88,2 % в основной группе против 53,9 % в контрольной группе ( $p < 0,05$ ).

**ВЫВОДЫ.** Мальабсорбция, которая требует коррекции лечения, наблюдается примерно у пятой части больных с новыми случаями ТБ. Применение инъекционных противотуберкулезных препаратов у таких пациентов повышает эффективность лечения на 34 % ( $p < 0,05$ ).

**КЛЮЧЕВЫЕ СЛОВА:** туберкулез, мальабсорбция, инъекционные противотуберкулезные препараты.

### Introduction

The main method of treatment of pulmonary tuberculosis (TB) is etiotropic antimycobacterial therapy, which aims to destroy the TB pathogen and reduce its ability to reproduce [1]. Treatment of drug susceptible forms of TB requires the use of the first-line anti-TB drugs.

The preference is given to the oral administration of medicines, which is more convenient for the patient and easier to reproduce, including in an outpatient setting [1]. Oral administration of anti-TB drugs in patients with a high adherence to the treatment, compliance with the continuity and controllability of treatment usually provides high efficiency of therapy [2].

However, there is some another obligatory condition for effective treatment with standard chemotherapy regimens – the normal absorptive capacity of the patient's small intestine [3]. Effective treatment of TB is possible only in the case of a sufficient concentration of anti-TB drugs in the blood and the focus of specific inflammation [4].

Reducing the peak concentration of anti-TB drugs in the body leads to a decrease in the effectiveness of treatment, slowing down the positive dynamics of the process and the development of resistance of *Mycobacterium tuberculosis* to anti-TB drugs.

This situation occurs in the case of slow absorption of drugs or incomplete absorption of drugs. The causes of malabsorption in TB are currently unknown. However, factors that lead to impaired epithelial cell function may include prolonged intoxication, nutrient deficiencies, alcohol and drug use, vitamin deficiencies, congenital anomalies, long-term use of enterotoxic drugs etc. [4].

The frequency of malabsorption in the small intestine is currently unknown. Therefore, the assessment of the

state of absorption function of the small intestine in TB is an important part of examination of a TB patient, the result of which should be the basis for choosing the route of administration of anti-TB drugs.

### Materials and methods

The study was conducted in 2 stages: in the first stage the study included 73 patients with new drug-susceptible TB cases.

Prior to treatment, these patients underwent lactulose-mannitol test to determine the state of absorption of the small intestine. The degree of malabsorption was determined by the rate of intestinal permeability index, which was calculated according to the results of the ratio of extinctions of lactulose and mannitol excreted in the urine.

In this way, individuals who needed to switch to injectable anti-TB drugs (individuals with intestinal permeability index  $<3$ ) were selected. These patients entered the second phase of the study, which aimed to establish the effectiveness of the proposed correction of treatment.

Patients with intestinal permeability  $<3$  were divided into main and control groups. The main group included 17 patients who received injectable forms of isoniazid, rifampicin and ethambutol along with oral pyrazinamide in standard doses. The control group included 13 people who received standard treatment for sensitive tuberculosis orally.

The effectiveness of TB treatment in patients of the main and control groups was evaluated according to generally accepted criteria: the dynamics of clinical manifestations of TB; dynamics of cessation of bacterial excretion; dynamics of radiological changes.

## ОРИГІНАЛЬНЕ ДОСЛІДЖЕННЯ

### Results

The first stage of the study revealed that the average rate of intestinal permeability in patients with new pulmonary TB was 7.78/3.86-12.53.

In 41.1 % of patients the intestinal permeability index was >11, in 17.8 % of patients this indicator was in the range of 6.1-10.9, in 21.9 % of persons – in the range of 3.1-6 and in 19.2 % of patients with intestinal permeability was <3.

Evaluation of clinical manifestations of pulmonary TB in the dynamics of the proposed treatment during the intensive phase in patients with intestinal permeability index (main and control groups) is shown in table 1.

Analyzing the dynamics of clinical manifestations of TB and the general condition of patients, we found that in the main group before the completion of intensive phase of treatment the general condition was satisfactory in 94.1 % of patients, which was 9.5 % higher than the control group ( $p>0.05$ ).

The main indicators that reflect the effectiveness of treatment of the TB process are the dynamics of cessation of bacterial excretion and radiological dynamics (table 2).

As it is shown in table 2, bacterial excretion in the main group stopped in 1.8 times more often at the end of the intensive phase of chemotherapy (60 doses) than in the control group ( $p<0.05$ ).

The intensive phase was prolonged to 90 doses in 17.6 % of patients in the main group and in 23.1 % of patients in the control group ( $p<0.05$ ). At the end of 3 months of chemotherapy bacterial excretion stopped in 17.6 % of patients in the main group, which was 1.4 times more than in the

control group ( $p>0.05$ ). After 90 doses of treatment 1 patient in the control group was diagnosed with treatment failure.

Thus, by the end of the intensive phase, bacterial excretion stopped in 88.2 % of patients in the main group and in only 61.5 % patients in the control group. In 46.1 % of cases in the control group treatment failure was diagnosed. The average time of cessation of bacterial excretion was on 0.22 months shorter in the main group comparing with the control group ( $p>0.05$ ).

The tendency of radiological dynamics coincided with the tendency of dynamics of cessation of bacterial excretion. The radiological dynamics was assessed by reduction of the size and number of foci, infiltrative changes, decay cavities, increasing the intensity of foci. The frequency of positive radiological dynamics at the end of the intensive phase of treatment was 64.7 % in the main group versus 30.8 % in the control group. After completion of 90 doses of chemotherapy the frequency of positive X-ray dynamics was 82.3 % in the main group, which was 1.5 times higher than in the control group ( $p<0.05$ ).

The total efficacy of treatment at the end of the main course of chemotherapy was 88.2 % in the main group against 53.9 % in the control group ( $p<0.05$ ).

### Discussion

The results suggest that about 20 % of patients with new pulmonary TB may have a significant reduction in small intestinal absorption and treatment correction.

Decreased adsorption capacity of the small intestine, as already mentioned, leads to incomplete or prolonged

**Table 1.** Clinical manifestations of pulmonary TB in the dynamics during the intensive phase of treatment

Criterion	Main group (n=17)	Control group (n=13)
Normalization of the general condition	94.1 %	84.6 %
Disappearance of intoxication syndrome	94.1 %	84.6 %
Disappearance/significant reduction of bronchopulmonary syndrome	88.2 %	76.9 %
The average period of disappearance of intoxication syndrome, weeks	2.14±0.63*	3.19±0.75
The average period of disappearance of bronchopulmonary syndrome, weeks	4.32±0.69*	5.87±0.71

Notes: \*  $p<0.05$ .

**Table 2.** Dynamics of bacterial excretion in patients with new pulmonary TB during the intensive phase of treatment

Criterion		Main group (n=17)	Control group (n=13)
Terms of cessation of bacterial excretion	2 months	70.6 %*	38.5 %
	3 months	17.6 %	15.4 %
	4 months	–	7.7 %
The percentage of sputum smear conversion	88.2 %*	61.5 %	
The average conversion time of a sputum smear, months	2.18±0.39	2.4±0.79	
Bacterial excretion has not stopped (ineffective treatment)	11.8 %*	38.5 %	

Notes: \*  $p<0.05$ .

## ОРИГІНАЛЬНЕ ДОСЛІДЖЕННЯ

absorption of anti-TB drugs, that, according to M. Gurusurthy and co-authors [4], is accompanied by a decrease in peak drug concentrations in the blood and foci of specific inflammation. From the above we can conclude that the optimization of etiotropic treatment in patients with impaired absorption should be aimed at increasing the concentration of antimycobacterial drugs in the blood and foci of specific inflammation.

Domestic and foreign researchers in the field of TB have proposed and investigated various methods of increasing the concentration of anti-TB drugs in areas affected by the TB process [5]. One of such scientific directions was the study of treatment regimens with the use of high doses of drugs. Isoniazid has been most widely studied in this aspect, as this drug has been used in the past depending on the rate of acetylation and was prescribed even at a dose of 900 mg [6]. However, this method of treatment is accompanied by an increase in the frequency of toxic effects of isoniazid [7].

A. Diacon, R. Patientia, A. Venter [8] and co-authors investigated the use of rifampicin at a dose of 20 mg/kg and showed that this dosing regimen can increase the bactericidal activity of the drug in both blood and sputum patients. Similarly, a study led by R. Ruslami in the Netherlands the same year showed higher bacteriostatic blood activity with rifampicin at a dose of 13 mg/kg compared to a standard dose of 10 mg/kg [9]. However, the positive effects of such high doses of this drug are offset by an increase in the frequency of side effects, in particular hepatotoxic reactions of mild to moderate severity, nausea and other dyspeptic disorders.

Another research branch aimed at increasing the concentration of anti-TB drugs in the area of inflammation is the use of different methods of delivery. One of the variations of alternative methods of drug administration is lymphotropic endolymphatic therapy. Different variations of this method were used by A.V. Zakharov, B.S. Kibrik, L.V. Pidubna, A.V. Yelkin [10], demonstrating the positive results of the method in the form of accelerating the disappearance of clinical symptoms, reducing the time of cessation of bacterial excretion and closure of decay cavities. This method allows to increase the concentration of anti-TB drugs directly in the area of specific inflammation, which can give positive results in patients with malabsorption syndrome. However, the negative factor is that this technique is invasive and requires daily endolymphatic intervention, which is often complicated by lymphostasis and related secondary complications, which significantly limits the use of this technique [10].

Inhalation of anti-TB drugs through a nebulizer allows them to be delivered directly to the lung tissue [11]. However, the duration of maintaining the proper concentration of drugs in the blood is significantly shorter compared to oral administration, so we believe that this method can not be used alone.

S.S. Gavriliev and co-authors [12] present in their works patented methods of rectal administration of anti-TB drugs, which allows to ensure their rapid absorption with the creation of high concentrations. At the same time, the use of such treatment regimens is limited to a very narrow selection of anti-TB drugs in the form of rectal suppositories. In addition, the partial leakage of the candle, which may be observed periodically, reduces the dose of the drug.

Given the analyzed data from the literature, in our opinion, the most optimal method of administration of anti-TB drugs in patients with pulmonary TB with reduced absorptive capacity of the mucous membrane of the small intestine is the intravenous route, which allows to achieve 100 % bioavailability of drugs and create high maximum peak concentrations of drugs in the blood and in all tissues of the body [13-15].

According to the results of this study, the use of injectable forms of anti-TB drugs in a case of violation of absorption in the small intestine can significantly accelerate the positive dynamics of the disease in the form of increasing the frequency and shortening the duration of bacterial excretion, positive radiological and clinical dynamics. Ultimately, this correction of treatment leads to high efficiency of TB treatment.

This effect is due to high levels of bacteriostatic activity of the blood when injecting anti-TB drugs. Authors [13], studying the concentration of anti-TB drugs and bacteriostatic activity of blood depending on the form of anti-TB drugs administration, found that the average value of the maximum concentration of rifamycin sodium salt after intravenous administration at a dose of 450-600 mg probably exceeds the concentration of rifampicin in capsules 2.6 times, and the inhibitory concentration of injectable rifampicin is 10 times less than that of rifampicin in capsules.

### Conclusions

Syndrome of malabsorption in the small intestine, which requires correction of treatment, occurs in about one-fifth of patients with new TB.

Management of patients with malabsorption syndrome requires the use of injectable anti-TB drugs. The regimen of treatment of drug-susceptible TB that include injectable isoniazid, rifampicin and ethambutol in combination with pyrazinamide tablets reduces the disappearance of intoxication syndrome by 1.5 times, bronchopulmonary syndrome by 1.4 times, increases the frequency of cessation of bacterial excretion by 1.8 times and the frequency of positive X-ray dynamics by 1.5 times during the intensive phase of treatment ( $p < 0.05$  in all cases). The effectiveness of treatment with this treatment scheme increases by 34 % ( $p < 0.05$ ).

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