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THE COURSE OF RESISTANT PULMONARY TUBERCULOSIS COMBINED WITH HIV-INFECTION AMONG ADULTS

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Summary.

The researched group was 1.5 times dominated by male patients (42: 68.8%), over female (19: 31.2%), while the majority of people were aged 31 to 50 years. 9.8% (6) of patients with chemoresistant pulmonary TB were hospitalized in serious condition. The average number of bed-days in hospital was (61.7 ± 4.5) . 16 (26.2%) patients with chemoresistant TB died in the hospital.

Our research shows that among patients with CR-PTB/HIV, rifampicin (R) resistance was 2 times more common than resistance to combination HRZE and Pre-XDR (32.8% vs. 16.4%, $P < 0.05$). Resistance to combination HRZ was the least common (1.4%). In some cases, they showed resistance to new anti-TB drugs (Bdg and Dlm). Disseminated PTB was 2.4 times more often diagnosed than miliary TB, and infiltrative PTB was 4.0 times more likely among CR-PTB/HIV.

Keywords: HIV/AIDS/TB, chemoresistant pulmonary tuberculosis.

Rezumat. Evoluția tuberculozei pulmonare rezistente combinată cu infecția cu HIV la adulți.

Lotul de studiu a fost dominat de 1,5 ori de pacienții de sex masculin (42: 68,8%), față de feminin (19: 31,2%), în timp ce majoritatea persoanelor aveau vârsta cuprinsă între 31 și 50 de ani. Dintre pacienții cu tuberculoză pulmonară chimiorezistentă 9,8% (6) au fost spitalizați în stare gravă. Numărul mediu de zile-pat în spital a fost de $(61,7 \pm 4,5)$. 16 (26,2%) pacienți cu tuberculoză chimiorezistentă au decedat în spital. Cercetarea noastră demonstrează că, printre pacienții cu CR-PTB/HIV, rezistența la rifampicină (R) a fost de 2 ori mai frecventă decât rezistența la combinația HRZE și Pre-XDR (32,8% vs. 16,4%, $P < 0,05$). Rezistența la combinația HRZ a fost cea mai puțin frecventă (1,4%). În unele cazuri, aceștia au prezentat rezistență la noile medicamente antituberculoase (Bdg și Dlm). PTB diseminată a fost diagnosticată de 2,4 ori mai des decât tuberculoza miliară, iar PTB infiltrativă a fost de 4,0 ori mai probabilă în rândul PTB-CR/HIV.

Cuvinte cheie: HIV/SIDA/TB, tuberculoză pulmonară chimiorezistentă.

Резюме. Течение резистентного туберкулеза легких в сочетании с ВИЧ-инфекцией у взрослых.

В исследуемой группе больных мужчин было в 1,5 раза больше (42:68,8%), чем женщин (19:31,2%), при этом большинство людей были в возрасте от 31 до 50 лет. 9,8% (6) больных химиорезистентным туберкулезом (ХР-ТБ) легких были госпитализированы в тяжелом состоянии. Среднее количество койко-дней в стационаре составило $(61,7 \pm 4,5)$. В стационаре умерло 16 (26,2%) больных химиорезистентным туберкулезом.

Среди пациентов с ХР-ТБ/HIV резистентность к рифампицину (R) встречалась в 2 раза чаще, чем резистентность к комбинации HRZE и Pre-XDR (32,8% против 16,4%, $P < 0,05$). Наименее распространенной оказалась резистентность к комбинированному HRZ (1,4%). В некоторых случаях они показали резистентность к новым противотуберкулезным препаратам (Bdg и Dlm). Диссеминированный ТБ диагностировался в 2,4 раза чаще, чем милиарный ТБ, а инфильтративный ТБ был в 4,0 раза чаще среди больных ХР-ТБ/HIV.

Ключевые слова: ВИЧ/СПИД/ТБ, химиорезистентный туберкулез легких.

Introduction.

Tuberculosis (TB) remains one of the leading causes of ill health and mortality in the World, and the current rate of decline in the epidemiological burden of TB is not fast enough, despite progress in treatment and prevention.

According to the European Centre for Disease Prevention and Control (ECDC) [4, 10-12, 14-16] Ukraine is one of the TB problem countries in the European Region and one of the nine countries in the

World with a high burden of rifampicin-resistant TB (Rif-TB) or multi-drug-resistant TB (MDR-TB) [3].

Starting from 2020 there is a tendency to increase the incidence of chemoresistant (CR) TB in Ukraine. In recent years, the clinical structure of MDR-TB has increased the frequency of disseminated and fibrous-cavernous TB. Almost all patients show destruction with bacterial excretion. A significant role in the deterioration of the epidemiological situation in Ukraine was influenced by the Coronavirus disease

(COVID-19) and the terrible war that is taking place in our time [2, 14 -16].

Due to the pathomorphosis of CR-TB over the past 13 years, a clear upward trend in primary resistance to fluoroquinolones (in particular, extended resistance) from the minimum frequency in 2006 is determined among adult patients (0%) to almost 30.0% in 2019, with a decrease in MDR-TB without resistance to fluoroquinolones (from 60.0% to 40.0%). An unfavorable trend has been observed since 2017, when the number of patients with MDR-TB and TB with extended resistance (XDR-TB) is almost equal. 1.3 TB deaths were reported despite continuous improvement in diagnosis and treatment of the specific process in 2021. The COVID-19 epidemic played a significant role [2, 3, 6].

The terrible consequences for Ukraine are the war unleashed by Russia. In regions covered by active hostilities, people suffer from food shortages, chronic stress, do not have access to basic medical services. People are forced to stay in temporary shelters that are overcrowded and poorly ventilated. A significant number of TB patients are unable to continue treatment due to difficulties in visiting a medical institution, change of location or restrictions in the work of the anti-TB service. Interruption of treatment in these patients leads to disease progression and restoration of their contagiousness. Difficulties in obtaining medical care in all regions of Ukraine are due to the lack of medical workers due to their mobilization or departure, overload of the health care system in places of mass stay, interruptions in the provision of health care facilities with medicines and medical supplies, general deterioration of the health of the population [4].

TB has now become the most common opportunistic disease (OD) in HIV/AIDS and the leading cause of death in patients with human immunodeficiency virus (HIV) [9]. The spread of the TB/HIV epidemic is an objective threat on a national scale and continues to negatively affect the working and reproductive potentials of the population of many countries of the World. The studies of Matsegora N.A. et al. [7] confirm that only 10-15% of HIV-negative persons fall ill after contact with the bacterioexcretor, and 40-50% of HIV-positive persons fall ill. It is also known that the combination of TB and HIV-infection is a risk factor for chemoresistant forms: only 27.3% of patients with isolated TB have resistant forms, and among patients with co-infection TB/HIV/AIDS 60.0%.

In patients with deep immunodeficiency, extrapulmonary localization of the tuberculous process, in particular in combination with lung

damage, is likely to be detected more often than pulmonary (70.1% vs. 62.9%). Among the researched patients with co-infection HIV/AIDS/TB, 30% had isolated pulmonary TB, 33% – combined pulmonary/extrapulmonary TB, and the largest proportion was extrapulmonary TB without lung damage [8].

The emergence of strains of *Mycobacterium tuberculosis* (MBT) with multi-resistant and extended resistance, double co-infection TB/HIV, inferiority of medical care, which is associated with the introduction of strict quarantine restrictions on the spread of COVID-19, led to an increase in the mortality rate from TB. According to estimates, every year 10 million people suffer from TB, which is the most common opportunistic infection in HIV-positive patients, and in the later stages of HIV-infection, TB has a progressive course, which leads to the generalization of infection with the development of extrapulmonary forms. It was established that 75% of TB patients with MDR-TB do not receive proper treatment. Several main risk factors for worsening the course and results of TB treatment have been established, in particular, the resistance of MBT, concomitant conditions – human immunodeficiency virus (HIV), diabetes mellitus, coronavirus disease (COVID-19), war, etc. [2, 4, 5].

One of the reasons for the low effectiveness of treatment in patients with MDR-TB is its untimely diagnosis due to the duration of cultural methods for isolating the TB pathogen and obtaining the results of the drug sensitivity test (DST). It is established that the delay in the diagnosis of new cases of MDR-TB on the background of HIV-infection reduces the effectiveness of treatment by 29,2–37,5% [6,8].

A special problem in connection with the difficulties of timely diagnosis is TB of extrapulmonary localization, which today in AIDS patients in 90-95% of cases is detected only at autopsy. This is due to the fact that with the deepening of immunosuppression, traditional methods of TB diagnosis, such as fluoro- and radiography, sputum microscopy on MBT become uninformative due to the peculiarities of inflammation pathomorphology, frequent extrapulmonary localization of the tuberculous process in HIV-infected [8].

Thus, in modern languages the problem of timely diagnosis and treatment of opportunistic infection (HIV/AIDS/TB) remains relevant according to the analysis of medical literature.

Objective.

To study the course of resistant pulmonary tuberculosis combined with HIV/AIDS infection among adults.

Materials and methods.

61 medical records files of patients with co-infection HIV/AIDS/CR-TB were analyzed for the period 2020-2024. All patients were treated in the departments of the Lviv Regional Phthisiopulmonological Clinical and Diagnostic Center (Pulmonary Health Center). In the examined patients, resistant strains of MBT to antimycobacterial drugs (AMBDs) were found. All of them were assigned to the group of patients who had chemoresistant pulmonary TB (CR-PTB/HIV).

Microbiological study included: detection of MBT in sputum by smear microscopy, inoculation of material on Levenstein-Jensen medium, typing of isolated mycobacteria on BACTEC MGIT 960, determination of DST of MBT strains to first and second-line AMBDs, as well as molecular genetic sputum study, in particular by GeneXpert MBT/RIF and linear probe analysis, which included determining the sensitivity of MBT to AMBDs of the 1st line (to isoniazid and rifampicin) using GenoType MBTDRplus mutation kits. Sensitivity/resistance to II-line drugs (fluoroquinolones and aminoglycosides) was determined using the GenoType MBTDRsl mutation kit [1]. All patients were screened for HIV-infection with an express test and a polymerase chain reaction (PCR).

Results and discussion.

In the researched group 1.5 times (42: 68.8%), over female (19: 31.2%), while the majority of people were aged 31 to 50 years (88.5%). Up to 30 years was not at all (Fig. 1).

The changes in the lungs in the majority (81.3%) of patients were detected when contacting a family doctor. At the same time, the condition was of moderate severity in 38 (62.3%) and severe – in 21 (34.4%), and one patient was extremely severe during hospitalization. Most often, the diagnosis was established in 2-3 months (52.5%) after the appearance of manifestations of the disease, but there were patients whose diagnosis was established in six months and a year (47,5%). The specific process in most patients developed gradually (44: 72.1%), and acutely – in 17 (27,9%) patients with CR-PTB/HIV. In 16 (26,2%) patients, the disease ended in mortality.

Figure 2 shows the duration of stay of patients with TB combined with HIV-infection.

All patients with CR-PTB received urgent inpatient treatment. Most of them were in hospital for more than 10 days (83.6%). The average hospital stay was (61.7 ± 4.5) days.

Fig. 3 shows the structure of resistance of pathogen strains in patients with pulmonary TB. Our studies suggest that patients with CR-PTB/HIV were 2 times more likely to show rifampicin (R) resistance than those with combination resistance HRZE and pre- extended resistance (Pre-XDR-TB) (39.3% vs. 16.5%, P < 0.05). Resistance of strains to HRZ combination (1.4%) was least noted. It should be noted that in some cases they showed resistance to bedaquiline (BDQ – 3.3%) and to delamanide (Dlm - 3.3%). Thus, 2 (3.3%) patients showed extended resistance (XDR-TB) to new anti-TB drugs.

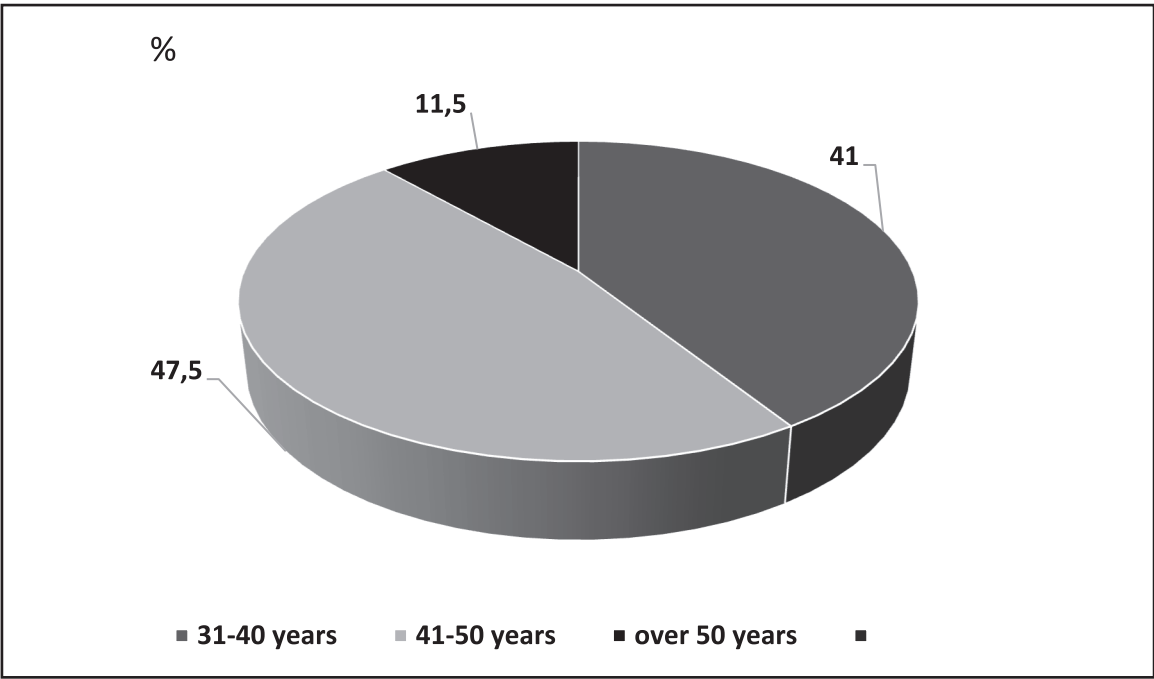


Figura 1. Age structure of CR-PTB patients combined with HIV/AIDS-infection (%).

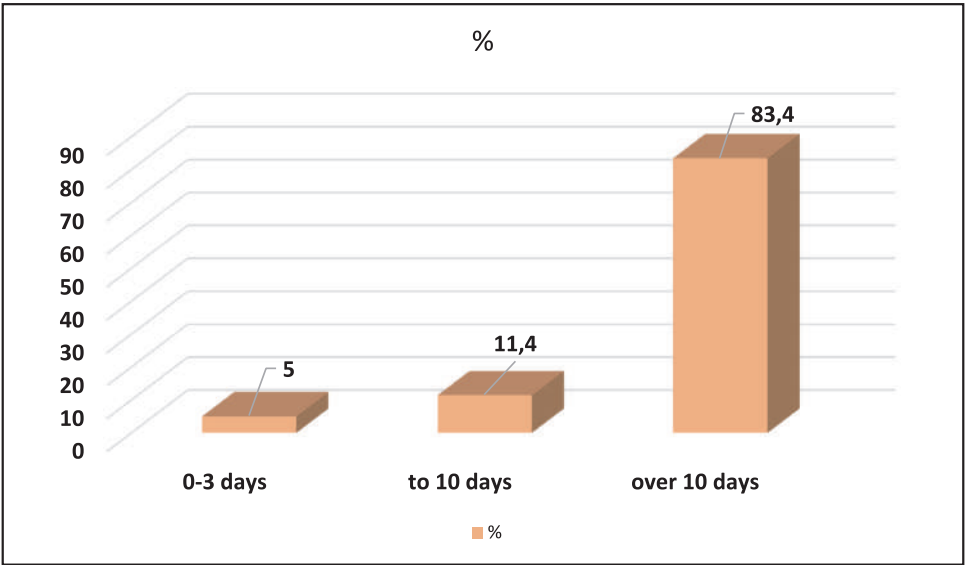


Figura 2. Duration of stay of patients with TB combined with HIV-infection in hospital, %

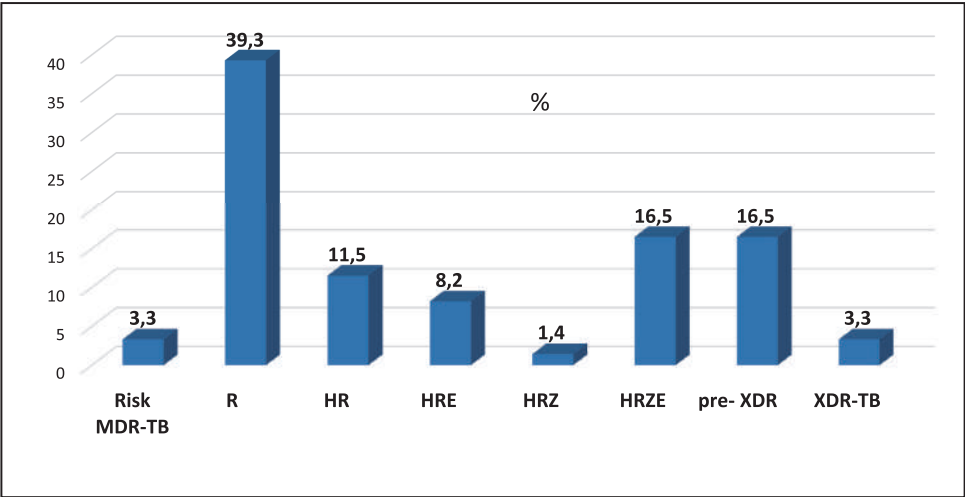


Figura 3. Structure of resistance of MBT strains to AMBDs in patients with CR-PTB/HIV, %

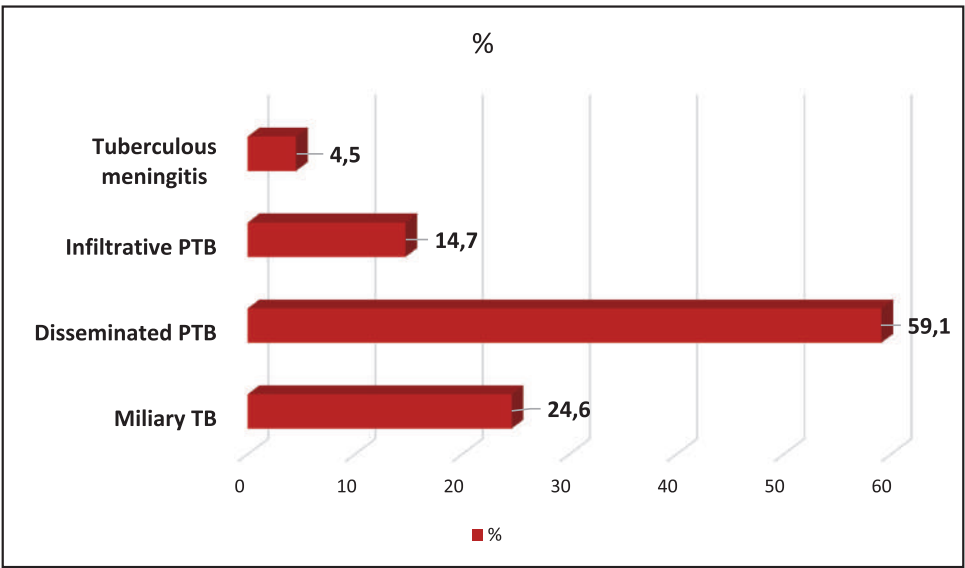


Figura 4. Frequency of clinical forms of HIV-associated CR-PTB, %

Patients with CR-PTB with HIV-infection were most often diagnosed with disseminated PTB (36: 59.1%), as well as miliary TB (15: 24.6%), but infiltrative PTB was noted in 9 (14.7%) and tuberculous meningitis was much less common (1: 1.6%).

In the future, we analyzed the frequency of damage to individual organs and systems in patients with CR-PTB/HIV. Our researches indicate that the majority of patients with severe intoxication and cachexia (54.1%) had iron deficiency anemia (55.7%), pleurisy (8.2%), and hemoptysis (8.2%), as well as spontaneous pneumothorax (16.4%). Sepsis (6.5%) and pericarditis (4.9%) were diagnosed with almost the same frequency. So, in patients with CR-PTB/HIV on the background of HIV-infection, probably more often developed severe intoxication and cachexia than other complications.

Research have shown that nonspecific lesions of the respiratory system were detected on average in $(67.3 \pm 2.5\%)$ patients with CR-PTB/HIV. In particular, the following complications were noted: respiratory failure (90.2%), pneumonia (19.7%), chronic obstructive bronchitis (44.3%).

The general condition of the patient significantly worsened due to liver damage in the form of chronic hepatitis C (48.3%), cirrhosis (34.4%), ascites (18.1%) and toxic liver damage (21.3%) and chronic hepatitis B (21.3%). In this case, liver damage and its consequences were observed on average in $(28.7 \pm 2.8\%)$ patients with CR-PTB/HIV.

We have analyzed the frequency of nervous system damage in patients with CR-TB/HIV. It is proved that in patients with CR-PTB/HIV, the nervous system is often affected, spastic paraplegia (29.6%), spastic tetraplegia (16.4%) and encephalopathy (23.0%) were observed. On average, damage to the nervous system was ascertained in $(34.5 \pm 2.3\%)$ cases [9].

In patients with CR-TB on the background of HIV-infection, visual lesions were observed, which was manifested by background retinopathy (13.1%), retinal lesions (11.4%), astigmatism (9.8%). On average, the pathology of the organs of vision was noted in $(17.2 \pm 2.7\%)$ of patients with HR-TB/HIV.

Patients with HR-PTB/HIV were more likely to be diagnosed with oral candidiasis (96.7%) than cerebral cryptococcosis (32.8%), toxoplasmosis (29.5%). On average, fungal-parasitic diseases were observed in almost $(79.5 \pm 4.3\%)$ of patients.

Conclusion: in patients with chemoresistant tuberculosis combined with HIV infection, a multi-organ lesion is observed in the form of pathology of the respiratory system (67.3%), nervous system

(34.5%), liver (28.7%), visual organ (17.2%) and fungal-parasitic lesions, which in total contributes to the development of severe intoxication and cachexia (79.5%). At the same time, due to the progression of tuberculosis and HIV/AIDS-infection, the process ended in mortality in 16 (26.2%) patients.

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