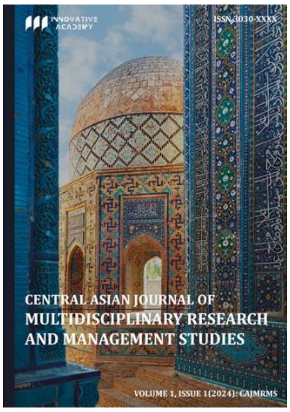

MODERN VIEW TO THE DIAGNOSIS AND TREATMENT OF RESISTANT FORMS OF PULMONARY TUBERCULOSIS

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ABSTRACT

Numerous scientific studies are being conducted around the world to study the effectiveness of treatment. Numerous studies by domestic and foreign authors have been devoted to the issue of drug resistance of Mycobacterium tuberculosis.

The spread of multidrug-resistant tuberculosis (MDR-TB) throughout the world is a major obstacle to tuberculosis control and achievement of the targets set by the World Health Assembly and included in one of the United Nations Sustainable Development Goals [1; pages. 161-171, 178; p., 2; pages. 57-66.].

According to WHO experts, drug-resistant tuberculosis is; a case of pulmonary tuberculosis with the isolation of MBT resistant to one or more anti-tuberculosis drugs [3; pages. 6-15.].

Epidemiological features. Globally, multidrug-resistant mycobacterial tuberculosis is estimated to occur in 3.3% of new tuberculosis cases and 20% of previously treated tuberculosis cases, a level that has changed little in recent years [4; 133-140, 5; pages. 448, 6; pages. 372-376.].

Of particular concern is the steady increase in the number of patients with primary MDR MBT [20; pages. 40-49.]. In patients with newly diagnosed and relapsed pulmonary tuberculosis, there is a high level of primary and secondary MDR MBT not only to the main, but also to reserve anti-tuberculosis drugs (ATDs). Patients with chronic forms of pulmonary tuberculosis are a high-risk group for developing MDR, the next stage of which is the formation of extensive drug resistance (XDR) - a combination of drug resistance to main and reserve anti-TB drugs [7, p. 67-72.].

The continued rise in the prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) in the era of human immunodeficiency virus (HIV) infection poses a serious threat to effective TB control. Drug resistance in Mycobacterium tuberculosis occurs due to low-frequency spontaneous chromosomal mutations. The clinical form of drug-resistant TB occurs mainly as a result of anthropogenic selection during the treatment of the disease of these genetic rearrangements due to indiscriminate drug supply, doctors' prescription of suboptimal treatment regimens and unsatisfactory treatment adherence on the part of patients [8; pages. 7-19.].

In 2014, according to various estimates, MDR-TB killed 190,000 people. More TB patients were tested for drug resistance in 2014 than ever before [4, 5]. Globally, 58% of previously treated patients and 12% of newly diagnosed patients were tested, which represents a corresponding increase from the existing rates of 17% and 8.5% in 2013 [6, 7].

According to WHO estimates, the Russian Federation, together with China and India, accounts for more than half of the world's MDR-TB cases [139 p.]. In Russia for the period 2004–2014. against the backdrop of a decrease in incidence (from 83.3 to 59.5 cases per 100 thousand population) and TB prevalence (from 218.3 to 137.3 cases per 100 thousand population), the prevalence of MDR TB over the same period increased almost by 2 times (from 14.2 to 24.8 per 100 thousand population) [9; pages. 25-34, 10; pages. 11; pages. 280.].

Another significant point was the negative pathomorphosis of tuberculosis, which was expressed in the appearance of a large number of unfavorably current forms of the disease, characterized by a significant prevalence of the lesion and insufficient effectiveness of treatment [20; pp.3-5, 12; pages. 174, 13; pages. 24-25, 14; pages. 171, 15; pages. 242, 16; pages. 47.]. Among these, the proportion of pulmonary tuberculosis with drug-resistant Mycobacterium tuberculosis (MBT) is high [59; pages. 5-13, 101; pages. 130, 12; pages. 81-85.]. All this suggests that the disease will continue to have a high level of spread [9; pages. 10-11, 21; 3-5, 11; pages. 152.]. In addition, it is reported that the maximum incidence is recorded in men aged 25–45 years and in women aged 25–34 years, respectively, i.e. in the young, most economically active period of life. Consequently, the problem of tuberculosis requires special attention in this age category [19; pages. 160-164.].

Currently, much attention is paid to the study of multidrug-resistant tuberculosis (MDR), when Mycobacterium tuberculosis (MBT) is resistant to at least isoniazid and rifampicin. High levels of MDR tuberculosis have a significant impact on the spread of tuberculosis through the accumulation of sources of infection due to the low effectiveness of treatment. The prevalence of MDR tuberculosis has increased 5.9 times over the past 14 years [5; pages. 23-25.].

WHO estimates that globally in 2013, MDR-TB was detected in 3.5% of new and 20.5% of previously treated TB cases. Thus, in 2013, the development of MDR-TB was detected in approximately 480 thousand people. On average, approximately 9.0% of patients with MDR-TB were diagnosed with XDR-TB.

A study of the structure of MBT DR in young patients showed a decrease in monoresistance by 1.8 times, an increase in MDR by 1.7 times, and multiresistance did not change significantly. Among the main drugs are DR significantly increased for isoniazid and rifampicin, and decreased significantly for ethambutol. Among reserve drugs, there was a significant increase in resistance to prothionamide [3; pages. 39-41.].

Drug-resistant TB is not a new phenomenon. Strains of M. tuberculosis that were resistant to streptomycin (SM) appeared shortly after its introduction into TB treatment in 1944. Genetic resistance to one or another anti-tuberculosis drug is manifested as a result of spontaneous chromosomal mutations that occur at a frequency of 10-6 to 10-8 replications of mycobacteria. Mobile genetic elements such as plasmids and transposons, known for their role as mediators of drug resistance in various bacterial species, behave differently in M. tuberculosis. Since the mutations that cause drug resistance are not related to each other, the probability of bacilli developing resistance to three simultaneously taken drugs is in the probability range from 10-18 to 10-20. Therefore, theoretically, the chances of developing drug resistance are virtually eliminated during treatment with three effective drugs as part of a combination therapy for TB.

Amplification of the above-mentioned genetic mutation due to human errors leads to the emergence of the clinical form of drug-resistant TB. Errors of this kind include "monotherapy" due to irregular drug supply, inappropriate medical prescriptions and, most importantly, due to unsatisfactory compliance by patients with the prescribed course of treatment [8; pages. 7-19.]. Further transmission of resistant strains of M. tuberculosis from the primary source of infection to others exacerbates this problem. The cause of the MDR/XDR phenotype is the sequential accumulation of mutations in different genes involved in the formation of drug resistance at the individual level.

Diagnostics. In the last decade, there has been an increase in the incidence of both nonspecific inflammatory pulmonary diseases, tuberculosis, and lung cancer [4; pages. 134, 16; pages. 12-18, 6; 7-17.]. To prevent the spread of pulmonary tuberculosis, timely and reliable diagnosis of this disease is of great importance [6; pages. 23-28.].

The main reasons for the increase in DR-TB, from a clinical point of view, are late diagnosis of drug resistance of the pathogen, inadequate or incomplete previous treatment, the use of low-quality anti-TB drugs, as well as interruptions in treatment, temporary withdrawal of a particular drug and non-compliance with the timing of chemotherapy [15; pages. 72., 6; pages. 25-34].

The main methods of diagnosing and monitoring pulmonary tuberculosis currently used are general clinical, radiation, laboratory, microbiological, molecular genetic, and histological. Each of these methods has its own disadvantages and cannot be considered absolute [5; pages. 46-47, 7; pages. 7-17.]. The clinical symptoms of infectious pulmonary diseases are determined by the presence of intoxication and pulmonary syndromes, which do not have specific characteristic features and therefore cannot be used as a reliable diagnosis of pulmonary tuberculosis.

Since the discovery of X-rays by V. Roentgen, the X-ray method has been one of the main ones in the diagnosis of respiratory tuberculosis. Improvements in X-ray technology have recently made it possible to more accurately diagnose pulmonary tuberculosis, as well as effectively monitor its treatment [4; pages. 27.]. However, according to some authors, due to the clinical pathomorphosis of pulmonary tuberculosis, a frequent cause of diagnostic errors and treatment difficulties is the erasure of differences in the clinical and radiological manifestations of respiratory diseases [20; pages. 16-23]. Accordingly, the role of such modern high-resolution X-ray diagnostic methods as digital tomosynthesis and multi-slice computed tomography, which significantly increase the information content of detected changes in the lungs, is increasing.

The emergence and active implementation of X-ray examination methods at the beginning of the 20th century, which made it possible to visualize structural changes in the lungs affected by a specific process, opened a new era in the diagnosis of tuberculosis [6; pages. 7-17.]. Over the past hundred years, detailed symptoms of tuberculous lung disease have been developed and are constantly being improved, depending on the form and course of the disease, and differential diagnostic algorithms have been developed [4; pages. 99.]. Modern X-ray methods make it possible to identify and detail structural changes in the affected organ, establish the localization, extent, and complications of the tuberculosis process [20; pages. 31-35.]. The use of computer programs for converting images obtained during radiation studies is promising. However, detectable radiological signs cannot be pathological only for pulmonary tuberculosis.

Based on radiological data, it is impossible to make a final conclusion about the genesis of morphological changes [5; pages. 27-31.]. As a result, radiological techniques need to be confirmed by other methods.

Indirect diagnostic methods. Indirect methods for determining the presence of MBT in the patient's body are based mainly on the detection of specific antibodies. Historically, the first method is tuberculin diagnostics, which consists of identifying antibodies fixed on cells (lymphocytes, monocytes) when they interact with tuberculin. Currently, intradermal testing (Mantoux test) is widely used. This test has retained its diagnostic value only among patients of childhood and adolescence, when its result is one of the diagnostic criteria [7; pages. 81-85.]. In addition, tests with subcutaneous injection of tuberculin, when guided by a characteristic general, local and focal reaction (Koch test), have some auxiliary value in the diagnosis of tuberculosis. "Diaskintest" is a new method for diagnosing tuberculosis disease and the state of infection, which is based on determining the response of the examined person's body to specific proteins that are found only in virulent strains of Mycobacterium tuberculosis [15; pages. 52-56.]. A positive Mantoux test result means that the person being examined has either been in contact with a tuberculosis infection, or has recently received BCG vaccination, or is infected with non-pathogenic mycobacteria that cannot cause disease and do not require any treatment [11; pages. 9-13.]. Unlike the Mantoux test, a positive result of the Diaskintest indicates with a high degree of accuracy that the person being examined is either currently infected with tuberculosis or is already sick with it [7; pages. 7-17.].

Recently, a new method for diagnosing latent tuberculosis has appeared - QuantiFERON TB-2G, which does not have the disadvantages of a skin test [13; pages. 21-26.]. It is based on the in vitro detection of interferon gamma production by the patient's blood lymphocytes. ESAT-6 and CFP-10 M. tuberculosis antigens are used as inducers of interferon synthesis during its implementation. These antigens are expressed by M. tuberculosis, M. bovis, M. africanum, but they are absent in the BCG vaccine strain and most non-tuberculous mycobacteria, including M. avium, M. intracellulare. Thus, high specificity of the test indications is achieved [20; pages. 29-32.]. Increasing the sensitivity of the test and the objectivity of its readings is achieved by automating the detection of interferon. Tests conducted by Japanese specialists from the Tuberculosis Research Institute showed that the specificity and sensitivity of the QuantiFERON TB-2G test are 98.1 and 89.0%, respectively. Immunological diagnosis of tuberculosis is very promising [9; pages. 41-44.]. However, to date, no serological test has been developed that is so sensitive that it could replace the currently used methods for diagnosing tuberculosis [1; pages. 47-55].

Bacteriological and histological verification of diagnosis

The development and implementation of promising technologies for the accelerated diagnosis of TB and the determination of the pathogen's LC is extremely important for providing highly effective treatment based on the selection of personalized chemotherapy regimens. One of the most promising and sought-after areas in the development of laboratory diagnosis of TB, which is supported by WHO, the Global Laboratory Initiative and the European Laboratory Initiative, is the use of molecular genetic methods (MGM) [17; pages. 101.].

More than a century of experience of phthisiatricians around the world has proven that the "golden" standard for diagnosing tuberculosis is the classic combination of microscopic and cultural methods for studying MBT, which remain relevant today, despite the emergence of a large number of alternative methods. Bacterioscopic examination is the most accessible, fastest and cheapest method for identifying acid-fast mycobacteria [8; pages. 445.]. However, the limits of the method, even when using the most advanced microscopic technology, including luminescent technology, make it possible to detect acid-fast mycobacteria when they contain at least 10,000 microbial bodies in 1 ml of material. This amount of mycobacteria is contained in the sputum only in patients with common, progressive forms of the tuberculosis process [3; pages. 81.]. When the severity of the tuberculosis process in the lungs is insignificant, only in 34% of patients it is possible to detect the pathogen by bacterioscopy of a sputum smear, even after multiple repeated studies. If there are no visible changes on radiographs, detection of mycobacteria in a sputum smear is unlikely. The disadvantages of the bacterioscopic method include:

1. Negative results if in patients the amount of mycobacteria they secrete is below the sensitivity of microscopic examination or there is no bacterial excretion.
2. Microscopic detection of acid-fast mycobacteria does not allow differentiating mycobacteria of the M. tuberculosis complex (the causative agent of tuberculosis) from non-tuberculous (atypical) mycobacteria that cause mycobacteriosis.
3. Does not allow determining the viability of mycobacteria.

A nanoimmunofluorescence method has been developed for rapid detection of tuberculosis bacteria in pathological material [7; pages. 20-22.]. It is carried out using silicone nanoparticles with covalently immobilized protein A. In terms of sensitivity, it is significantly superior to the fluorescent method for diagnosing tuberculosis. The use of an epifluorescent filter makes it easier to record test results and reduces the time required for this [16; pages. 89].

The seeding method, or cultural method for detecting mycobacteria, is more sensitive and has a number of advantages over the microscopy method [14; pages. 55-59.]. It allows you to identify MBT if there are several dozen viable pathogens in the pathological material being studied. A very important advantage of the method is the ability to obtain a culture of the pathogen, which can be examined in detail, identified and studied in relation to drug sensitivity, virulence and other biological properties. There are real opportunities to increase the effectiveness of classical methods of microbiological research by improving methods of material preparation, using new dyes, modifying cultivation systems and recording the growth of mycobacteria, for example, the use of automated systems such as BACTEC MGIT 960 [7; pages. 89.]. Reproduction of tuberculous mycobacteria in liquid nutrient media occurs much faster than in solid media.

The use of the PCR method for diagnosing tuberculosis makes it possible to establish the presence of MBT DNA in the diagnostic material within 1 working day (2–3 hours). Preference is given to test systems with real-time result detection, which almost completely eliminate the risk of sample contamination with amplification products [11; pages. 46.].

The most promising method for determining genotypic lymph nodes is multiplex real-time PCR. The advantage of this method over the technologies described above is the absence of a hybridization step and evaluation of the results in real time, which reduces the possibility of contamination. An example of such test systems is GeneXpert MTB/RIF (Ceiphid, USA). However, this test system determines resistance only to rifampicin (90% specificity [17]) and is characterized by a very high cost of analysis. Among the Russian PCR test systems for determining MDR, one can note “Amplitub-MDR-RV” produced by Syntol CJSC (specificity for rifampicin and isoniazid is about 94%) [19; pages. 38-44.].

Current state of treatment. Standard controlled chemotherapy for tuberculosis is highly effective in treating tuberculosis caused by susceptible pathogens [20; pages. 44-49, 13; pages. 10-13.].

Numerous studies by domestic and foreign authors are devoted to the issue of drug resistance of Mycobacterium tuberculosis [7; pages. 19-21]. The meaning of the concept of “drug-resistant strain” has changed as knowledge about the mechanisms of drug resistance has accumulated. At the stage of introduction of anti-tuberculosis drugs, it was proposed to designate a strain as resistant if it was isolated from a patient in whom treatment did not provide improvement. This approach lost its significance after the complete abandonment of monotherapy [3; pages. 6-15, 5; pages. 23-25.].

Conducting a microbiological study of the drug sensitivity of MBT to the main and reserve anti-tuberculosis drugs is necessary in each case of isolating an MBT culture. After obtaining data from a microbiological study of the drug sensitivity of MBT, correction of chemotherapy and the prescription of individualized treatment regimens are mandatory.

Drug resistance of MBT has not only clinical and epidemiological, but also economic significance, since the treatment of such patients is more expensive than patients with MBT who are sensitive to the main anti-TB drugs. pages the introduction into practice of rapid methods for diagnosing drug resistance of Mycobacterium tuberculosis, it became possible to timely prescribe a chemotherapy regimen with reserve anti-inflammatory drugs to patients with primary MDR Mycobacterium tuberculosis [2]. The development of standards for the treatment of drug-resistant tuberculosis is one of the priorities of modern phthisiology.

Thus, the course of pulmonary tuberculosis with multiple and extensively drug-resistant mycobacteria is accompanied by the development of a systemic inflammatory response, the severity of which depends on the drug resistance profile [10; pages. 31-36.].

References:

1. Pranger A. D. et al. The role of fluoroquinolones in the treatment of tuberculosis in 2019 // Drugs. Springer International Publishing. – 2019. – Vol. 79, № 2. – P. 161-171.
2. Русских А. Е., Кутузова Д. М., Ловачева О. В., Самойлова А. Г., Васильева И. А. Краткосрочные схемы лечения больных туберкулезом с множественной лекарственной устойчивостью. Современная ситуация и дальнейшие перспективы // Туберкулёз и болезни лёгких. – 2020. – Т. 98, № 12. – С. 57-66.
3. Пунга В.В., Русакова Л.И., Пузанов В.А. и соавт.. Распространенность туберкулеза с лекарственной устойчивостью //Туберкулез и болезни легких. –2011. – № 10. – С. 6–15.
4. Яблонский П.К. и др.. Лекарственная устойчивость Mycobacterium tuberculosis при различных локализациях заболевания / Инфекция и иммунитет. – 2016.– Т. 6, № 2. – С. 133–140.
5. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis /World Health Organization; 2014. – 448 p.
6. Yablonskii P. et al.. Tuberculosis in Russia its history and its status today/American Jornal of Respiratory and Clinical Care Medicine.-2015.-Vol.191.-№4.-P.372-376.
7. Кононец А.С., Сафонова С.Г., Сидорова С.В., Хорошилова Н.Е. и др. Клинические проявления и эффективность лечения больных деструктивным туберкулезом с

множественной лекарственной устойчивостью микобактерий в противотуберкулезных учреждениях ФСИН России // Пульмонология. – 2008. – № 3. – С. 67–72.

8. Zhang Y., Yew W.W.. Механизмы развития лекарственной устойчивости у Mycobacterium tuberculosis//Международный журнал «Туберкулез и легочные заболевания». Том-2, №1, 2011.-С.7-19.

9. Черноусова Л.Н., Андреевская С.Н., Смирнова Т.Г., Ларионова Е.Е., Ивахненко О.И., Новоселова Е.А., Шевкун Н.А.. Лекарственно-устойчивый туберкулез: перспективы ускоренной диагностики и химиотерапии. Бактериология. 2017; 2(1): 25–34.

10. Эпидемическая ситуация по туберкулезу в России. Противотуберкулезные Мероприятия. Федеральный Центр мониторинга противодействия распространению туберкулеза. Доступно по: http://www.mednet.ru/images/stories/ files/CMT/tb2015.pdf.

11. Туберкулез в Российской Федерации 2011 г. Аналитический обзор статистических показателей, используемых в Российской Федерации и в мире. М., 2013, 280 с.

12. Дрыга О.П. Непосредственные и отдаленные результаты комплексного лечения прогрессирующего и остропрогрессирующего туберкулеза легких : дис. ... канд. мед. наук. –2004. – 174 с.

13. Калюк А.Н., Туркина Л.А.. Эпидемиологические аспекты медикосоциальной проблемы туберкулеза // Туберкулез в России. Год 2007: Материалы VIII Российского съезда фтизиатров. – М.: Идея, 2007. – С. 24–25.

14. Кузьмин А.Н.. Особенности клинического течения и эффективность лечения больных остро прогрессирующими формами туберкулеза легких : дис. ... канд. мед. наук. – М., 2002.– 171 с.

15. Васильева И.А., Аксенова В.А., Эргешов А.Э., Марьяндышев А.О., Самойлова А.Г., Багдасарян Т.Р., и др. Федеральные клинические рекомендации по диагностике и лечению туберкулеза органов дыхания с множественной и широкой лекарственной устойчивостью возбудителя. М., Тверь: ООО «Издательство «Триада», 2014, 72 с.

16. Виноградова Л.В. Особенности эмоциональной сферы больных туберкулезом легких с различной динамикой заболевания / Туб. и болезни легких. - 2011. - № 4. - С. 85-86.

17. Винокурова М.К., Яковлева Л.П., Кравченко А.Ф.. Значение определения региональной устойчивости микобактерий туберкулёза для выбора оптимальных режимов химиотерапии/ Бюллетень ВСНЦ СО РАМН, 2011, 2 (78). С.19-21.

18. Владимирский М. А., Шипина Л.К., Левченко М.В.. Эффективность обнаружения микобактерий туберкулеза методом полимеразно цепной реакции/Проблемы туберкулеза и болезней легких. – 2003. – № 12. – С. 28–30.

19. Владимирский М.А., Шульгина М.В., Варламов Д.А, Аляпкина Ю.С., Шипина Л.К., Домотенко Л.В., и др. Применение метода ПЦР в реальном времени для определения и контроля за распространением лекарственно-устойчивых штаммов микобактерий туберкулеза. Проблемы туберкулеза. 2008; 4:38-44.

20. Власова Н.А., Никишова Е.И., Миронюк О.М., Марьяндышев А.О. Результаты лечения 100 больных туберкулезом с множественной лекарственной устойчивостью, получивших лекарственные препараты по одобрению комитета «Зеленый Свет» Всемирной организации здравоохранения в 2005 году, в Архангельской области// Туберкулез и болезни легких. – 2010. – № 8. –С. 44–49.