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MODERN STATUS OF DRUG-RESISTANT FORMS OF PULMONARY TUBERCULOSIS

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ABOUT ARTICLE

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Abstract: The worldwide spread of MDR pulmonary tuberculosis is an obstacle to achieving the goals set by the UN and the World Health Assembly - tuberculosis control, positive epidemiological indicators [82] .

According to the experts of the World Health Organization, drug-resistant tuberculosis is a pulmonary tuberculosis disease that isolates Mycobacterium tuberculosis, resistant to one or more anti-tuberculosis drugs [78].

INTRODUCTION

According to modern recommendations, the following are the existing forms of TMB sensitivity to drugs:

1) drug-sensitive tuberculosis - sensitive to all anti -tuberculosis drugs;
2) monoresistance - resistance to one drug, including isoniazid or pyrazinamide or ethambutol, which is included in the first-line anti-tuberculosis drugs except rifampicin;
3) polyresistance - resistance to two or more other anti -tuberculosis drugs , except resistance to isoniazid and rifampicin at the same time;
4) Multi-drug resistance (MDR) - simultaneous resistance to isoniazid and rifampicin , regardless of resistance to other anti -tuberculosis drugs ;
5) extensive prior drug resistance - established resistance to isoniazid and rifampicin, fluoroquinolones, and only one second-line injectable drug (kanamycin, amikacin, or capreomycin);
6) extensive drug resistance (XDR) - isoniazid and rifampicin, fluoroquinolones, and two or more second-line injectable drugs (kanamycin, amikacin, or capreomycin);
7) total drug resistance - all anti-tuberculosis drugs

resistance to the means is determined [5].

Epidemiological features. Currently, the spread of tuberculosis caused by multidrug-resistant mycobacteria remains a serious problem for the health care system [20,81].

resistance globally , occurring in 3.3% of newly diagnosed TB patients and 20.0% of previously treated patients, and this rate has been increasing in recent years.

Of particular concern is the ever-increasing number of patients with primary MDR-TB [20]. Primary and secondary resistance of TMB in patients with newly detected and relapsing pulmonary tuberculosis remains high, not only to the main anti-tuberculosis drugs, but also to the reserve drugs. Especially in patients with chronic forms of pulmonary tuberculosis, there is a high risk of developing MDR tuberculosis, the next stage of which is the formation of extensive drug resistance (XDR), that is, the emergence of resistance to the main and reserve anti-tuberculosis drugs [47] .

By the 70s and 80s of the 20th century, the incidence rate of tuberculosis, which gradually decreased (34 cases per 100,000 population), was replaced by a significant increase (2.7 times) in 1991-2000, and in the Russian Federation it was 90 per 100,000 population. It was 7 cases. In general, according to the literature of recent years, the negative epidemiological stability of tuberculosis disease is reflected in the world. Thus , the incidence rate in the last decade remains high and is in the range of 82-85 per 100,000 population. [9].

The continuous increase in the incidence of MDR and XDR tuberculosis in the world and the increase in the incidence of human immunodeficiency virus infection pose a serious threat to the effective fight against tuberculosis. Drug resistance in Mycobacterium tuberculosis is caused by low-frequency spontaneous chromosomal mutations. The clinical appearance of drug-resistant tuberculosis is mainly due to inadequate treatment procedures prescribed by the doctor, insufficient compliance of patients with the treatment procedure , and irregular supply of drugs , as a result of genetic restructuring - anthropogenic selection in tuberculosis mycobacterium. occurs .

According to the data provided, in 2014, MDR tuberculosis killed 190,000 people. This year, more drug resistance tests were conducted in patients with tuberculosis than in previous years [4]. Globally, this year, drug resistance was tested in 58% of previously treated patients and 12% of first-time patients. As a result of the investigation, it was found that the disease increased by 17% and 8.5%, respectively, compared to 2013 [6].

According to BJSST, more than half of the total number of MDR tuberculosis cases in the world are made up of patients in the Russian Federation, China and India.

During 2004-2014, the incidence in Russia decreased from 83.3 to 59.5 per 100,000 population, and the prevalence of the disease decreased from 218.3 to 137.3 per 100,000 population. it was observed that it increased from 14.2 to 24.8 per population .

According to the World Health Organization, in 2017, 600,000 patients with MDR-TB were registered worldwide , resistance to isoniazid and rifampicin was detected in 490,000 cases, and resistance to rifampicin itself in 110,000 cases. In the Russian Federation, 37,925 cases of MDR-TB were registered in 2016 [65].

The negative pathomorphosis of tuberculosis is one of the important aspects, which has led to the emergence of numerous, bad forms of the disease and is characterized by a significant spread of the disease and insufficient effectiveness of treatment methods [21, 33, 42, 51, 57]. Among them, the proportion of MDR pulmonary tuberculosis was observed [59].

All of the above allows us to assume that the epidemiological indicators of the spread of the disease continue at a high level [9, 21]. In addition, the highest incidence is recorded in men aged 25-45 and women aged 25-34, that is, in the young, most socially active period of a person's life. Therefore, the problem of the spread of tuberculosis in this age group requires special attention [64].

In five years - from 2006 to 2011, the number of patients with MDR-TB in the Republic of Belarus increased by 4 times, and with XDR-TB by 10 times [45]. Such a situation is observed in other regions of the world, including some countries of Eastern Europe and the Russian Federation [22].

At present, much attention is being paid to the study of Mycobacterium tuberculosis, which is resistant only to isoniazid and rifampicin. High rates of MDR-tuberculosis have a significant impact on the spread of tuberculosis due to the accumulation of sources of infection due to the decrease in the effectiveness of treatment. Over the past 14 years, the prevalence of MDR-tuberculosis has increased by 5.9 times [5].

BJ SST, in 2013, 3.5% of MDR-TB patients were diagnosed for the first time and 20.5% of previously treated TB patients worldwide, and about 480 thousand people were diagnosed with MDR-TB in 2013. On average, about 9.0% of patients with MDR-TB develop XDR-TB.

The problem of tuberculosis remains one of the urgent and priority problems in the Russian Federation. In 2011-2012, the rate of morbidity recorded among permanent residents was 58.6-55.1 per 100,000 population, and stabilization of the indicator was observed. The high incidence rate of tuberculosis also poses a danger to society. A more serious problem for modern phthisiology is the drug resistance of the causative agent of tuberculosis , which is one of the main factors that reduce the effectiveness of treatment methods. Since 1999, when statistics on MDR-TB in patients with tuberculosis were recorded, the incidence rate of MDR-TB in the Russian Federation increased 2.4 times - by 2012, it was 1.7 to 4.1 per 100,000 population. Among all registered patients, the number of patients with MDR-TV increased from 1.9% to 16.3%, and the incidence rate increased by 8.6 times. These indicators significantly reduce the results of treatment and cause an increase in mortality [81].

The study of the structure of resistance to TMB anti-tuberculosis drugs in patients showed a 1.8-fold decrease in monoresistance, a 1.7-fold increase in MDR, and no significant change was observed in XDR paralysis . Resistance to isoniazid and rifampicin is among the main drugs significantly increased, but significantly decreased to ethambutol. Resistance to prothionamide among reserve drugs significantly increased [63].

The concept of the formation of a drug-resistant type of mycobacteria. Drug-resistant tuberculosis is not a new phenomenon, but after the introduction of streptomycin in the treatment of tuberculosis in 1944 , streptomycin-resistant strains of M. tuberculosis appeared soon after. Genetic resistance to one or another anti-tuberculosis drug is manifested due to spontaneous chromosomal mutations that occur at a replication frequency of 10 6 to 10 8 of mycobacteria. Mobile genetic elements such as plasmids

and transposons mediate the development of drug resistance in various bacterial species . Since the mutations that cause drug resistance are not related to each other, the probability that the bacillus will develop resistance to three drugs taken at the same time is reduced in the probability range from 10 18 to 10 20 . Therefore, theoretically, the possibility of developing drug resistance during treatment with three effective drugs in combined therapy for tuberculosis is almost eliminated.

The aggravation of the aforementioned genetic mutation due to human error leads to the appearance of the clinical manifestation of drug-resistant tuberculosis. Such types of errors include irregular supply of drugs, incorrect medical instructions, and most importantly, "Monotherapy" that occurs due to improper adherence of patients to the prescribed course of treatment [18].

Transmission of resistant strains of M. tuberculosis from the primary reservoir of infection to others exacerbates this problem. The sequential accumulation of mutations in various genes involved in the formation of drug resistance at the individual level is the main reason for the appearance of the MDR/XDR phenotype.

Although the definitions of "acquired" and "primary" drug resistance are conceptually relatively clear, in practice they are often misclassified because information on prior treatment is not readily available. Therefore, to cover acquired resistance to drugs of "unknown" or "unexplained" origin, the term "primary" drug resistance is often preferred over the term "primary" drug resistance . This issue has now been further simplified by categorizing drug resistance into categories of first-identified and previously treated TB patients. The previously treated category refers to patients whose treatment lasted at least 1 month [18].

The development of MDR-tuberculosis is primarily caused by violation of the antibacterial therapy regimen, social adaptation factors and concomitant diseases [22].

Specific features of the clinical course. The incidence is 1.6 times higher in men among first-diagnosed patients aged 18-34, and significantly higher in women aged 18-24. The disease often occurs significantly more among men in unsatisfactory financial and household conditions, who are unmarried, who are constantly in contact with patients with tuberculosis, who have not undergone fluorography examination for more than 5 years, and who have harmful habits. Disseminated pulmonary tuberculosis is more common in men and infiltrative pulmonary tuberculosis in women when men and women seek medical examination [63].

Clinically, a more severe course of the disease was observed. The process in the lungs spreads into 2 or more parts and is accompanied by the formation of many caverns of average size of 2-4 cm. Bacterial separation is often massive and can even be detected with a microscope. Drug-resistant tuberculosis often occurs among young people who do not have a permanent job, have harmful habits, and have concomitant diseases, and complications of tuberculosis have been observed. Thus, pulmonary tuberculosis diagnosed for the first time in young patients with a drug-resistant type of TMB depends on the social status of the patient, taking into account the severity of the clinical and radiological course, further treatment and rehabilitation measures should be applied. [64].

When the incidence was analyzed by social status, unemployed persons of working age had the largest share. In the composition of clinical forms, infiltrative, disseminated pulmonary tuberculosis prevailed, and caseous pneumonia, tuberculoma, miliary and fibro-cavernous tuberculosis were observed in less cases, respectively. Disintegration of lung tissue was found in patients. The disease is often detected when patients apply.

The clinical course of the disease in patients suffering from the drug-resistant form of mycobacterium tuberculosis is severe with symptoms such as severe intoxication, febrile fever and shortness of breath even at rest. In the objective examination, reduction of percussion sound, bronchial breathing, combination of dry and moist wheezing was found in most patients. Radiographically disseminated tuberculosis, caseous pneumonia and fibro-cavernous pulmonary tuberculosis prevailed. The process in the lungs spreads into 2 or more parts, and in most cases it is accompanied by the formation of several cavities up to 2-4 cm. Bacterial separation is often massive and can be detected even with a microscope. Polyresistant form of TMB was found in almost 1/2 of patients, monoresistance - 37.9%, and MDR in 13.9% [64].

Various reactions occur, forming a state of systemic inflammation, which determines an adequate protective response corresponding to the level of damage and embodies the complex interaction of different systems. The diversity of the pathological process in pulmonary tuberculosis determines the need to take into account many factors, including the biological characteristics of the microorganism and the specificity of the body's response to infection [10].

the research showed that in patients with QD 1 type, MDR pulmonary tuberculosis was observed more often in patients aged 18 to 39 years. The main form of tuberculosis in patients of this category was infiltrative pulmonary tuberculosis with obvious tuberculosis intoxication and small erosion spaces (up to 2 cm). In patients with type 2 diabetes, MDR pulmonary tuberculosis was observed more often among those over 40 years of age. In this category of patients, fibro-cavernous pulmonary tuberculosis with symptoms of moderate intoxication is often found [46].

Diagnosis of MDR pulmonary tuberculosis. In the last decade, there was an increase in the incidence of tuberculosis and lung cancer, along with nonspecific inflammatory lung diseases [4, 26]. Timely and reliable diagnosis of this disease is of great importance to prevent the spread of pulmonary tuberculosis [53].

From a clinical point of view, the main reasons for the increase of drug-resistant tuberculosis include late detection of drug resistance of mycobacteria, insufficient or incomplete previous treatment, use of low-quality anti-tuberculosis drugs, as well as interruptions in treatment, temporary cancellation of one or another drug in treatment, and non-compliance with chemotherapy [53].

In modern conditions, the main methods of diagnosis and control of pulmonary tuberculosis are general clinical, radiological, laboratory, microbiological, molecular-genetic and histological examinations. Each of these methods has shortcomings and advantages, and they cannot be recognized as an absolute verification method [58]. In infectious diseases of the lungs, the clinical presentation is determined by the presence of intoxication and lung syndromes that do not have specific characteristics, so we cannot use clinical symptoms in the final diagnosis of pulmonary tuberculosis [31].

diagnosis. Since the discovery of X-rays by Wilhelm Roentgen, X-ray examination method is one of the main methods in the diagnosis of respiratory tuberculosis. Recent improvements in X-ray technology have made it possible to more accurately diagnose pulmonary tuberculosis, as well as to monitor the effectiveness of its treatment [71]. Nevertheless, according to some authors, due to differences in the clinical and radiological manifestations of respiratory diseases, which are related to the clinical pathomorphosis of pulmonary tuberculosis, errors in diagnosis and difficulties in treatment arise [35, 76]. Therefore, the role of modern high-level x-ray diagnostic methods is increasing to a certain extent, methods such as digital tomography and multispiral computer tomography provide information on all changes in the lungs [67, 68].

At the beginning of the 20th century, the emergence and active application of X-ray examination methods made it possible to imagine the origin of structural changes in the lungs under the influence of a specific process, and opened a new era in the diagnosis of tuberculosis [82].

Over the past hundred years, depending on the type of pulmonary tuberculosis, the clinical course and symptoms of the disease have been studied, algorithms for differential diagnosis have been developed and perfected [50]. Modern x-ray methods make it possible to identify changes in the structural structure of the affected organ one by one, while showing the localization, duration and complications of the tuberculosis disease process [25]. The use of computer-programmed X-ray methods in research is becoming increasingly important in creating image transformations [75, 80]. However, the X-ray signs that can be determined cannot be attributed only to the patho-anatomical characteristics of pulmonary tuberculosis . Depending on radiological data, it is not possible to make a final conclusion about the genesis of morphological changes [49]. Therefore, it is necessary to confirm the obtained results by other reliable methods along with X-ray methods.

Indirect (indirect) methods of diagnosis. Indirect methods of determining the presence of TMB in the patient's body are mainly based on the detection of specific antibodies. Historically, the first method is tuberculin diagnostics, which involves the detection of antibodies that interact with tuberculin antigens and are fixed on the cell (lymphocytes, monocytes) membrane. Currently, intradermal test (Mantu) is widely used. Although the result of this test is one of the diagnostic criteria, it retains its diagnostic value only in children and adolescents. [77]. In addition to these, tuberculosis in the diagnosis of tuberculin subcutaneous test - Koch test sometimes has an auxiliary value, and attention is paid to general, local and focal changes. "Diaskintest" method - tuberculosis It is a new diagnostic method that shows the presence of infection. Based on this method, the reaction of specific proteins in the examined human organism shows that a positive result occurs in the presence of only virulent strains of Mycobacterium tuberculosis [55]. A positive Mantoux test can also be observed when communicating with patients with tuberculosis or recently vaccinated with the TB vaccine, or when infected with non-pathogenic mycobacteria that do not cause tuberculosis and do not require any treatment [11]. A positive result of "Diaskintest" has a very high level of accuracy compared to the Mantoux test, and indicates that the examined patient is infected with tuberculosis infection or has been suffering from this disease for a long time [80].

Recently, Quantiferon TB 2G method of detection of latent tuberculosis disease by a new diagnostic method without skin test was created [13]. This is based on determining the in vitro derivative of

gamma-interferon with lymphocytes in the patient's blood. In performing this test, M.tuberculosis ESAT-6 and SPF-10 antigens are used as interferon synthesis inducers. These antigens M. tuberculosis, M. bovis, M. africanum, but they are produced in the BTsJ vaccine strain and mycobacteria that do not cause tuberculosis disease , as well as M.avium, M. not found in intracellulare. Accordingly, it is noted that the test has a high level of specificity [29]. An increase in the sensitivity of the test and the objectivity of its indicators are achieved through the automatic determination of the amount of interferon. In tests conducted by Japanese scientists at the Institute of Tuberculosis Research, the specificity of the Quantiferon TB 2G test was 98.1 and the sensitivity was 89.0%. Immunological diagnosis of tuberculosis is very promising. However, until now, no serological test with high sensitivity has been developed, therefore, it is not possible to replace the currently used diagnostic methods of tuberculosis with another one [1, 80].

A central place in systemic inflammation is a wide range of proteins developed by the liver - the acute reactant phase (ORF), the changes in concentration of which increase to varying degrees. A significant ((SRO) - S-reactive protein), partial (haptoglobin (GP), α 1-acid, glycoprotein (AGP), α 1-protease inhibitor (α 1-PI), fibrinogen) increase or normal increase to the limit (ceruloplasmin (TsP), α 2-macroglobulin (α 2-MG)) and some indicators can be observed to decrease (albumin, transferrin), requiring individual assessment. The complexity of the analysis is that multi-functionality is characteristic for these indicators, all proteins can be changed in other inflammatory processes, and GP, AGP and TsP have antioxidant properties.

TsP and hemopexins, which bind copper and iron, have a direct antibacterial effect, respectively. α 1-PI, α 2-MG and AGP have antiprotease activity. Their important function is to inhibit the activity of elastase and chymotrypsin-like proteinases, which enter inflammatory exudates from granulocytes and cause secondary tissue damage. A regulator of the inflammatory response is elastase (E1), which can be used as both a pro-inflammatory and anti-inflammatory agent in various situations. An important modulating component of the systemic inflammatory response is adenosine, whose accumulation outside the cell leads to a decrease in the activity of immune cells and protection of tissues from damage. One possible way to study this relationship between adenosine and the functional status of immune cells is to study the activity of adenosine deaminase, which regulates adenosine levels and converts it to inosine [10,13].

In conclusion, it can be said that it is necessary to develop a short-term treatment regimen in the drug-resistant form of tuberculosis . Despite the progress made in the development of practical applications , none of them are considered ideal, so research in this area should not be stopped. A convenient and effective short-term treatment regimen can be the key to a successful fight against the epidemic of drug-resistant tuberculosis [82].

The occurrence of multi-drug-resistant types of pulmonary tuberculosis is accompanied by the systemic development of inflammation in the body, and the degree of its manifestation depends on the form of drug resistance of mycobacteria.

Thus, in the world literature , there are many scientific works devoted to the problems of drug resistance of pulmonary tuberculosis , but mycobacterium tuberculosis is not lagging behind science , but is changing its nature and composition, at the same time, the region, environmental factors,

continent and people's way of life affect the disease. plays a special role in the development or spread of Mycobacterium Koch. The problem is urgent and requires the implementation of new research, including modern adequate methods of diagnosis and treatment.

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