



MAIN DIRECTIONS OF TUBERCULOSIS RESEARCH ON PREVENTION, DIAGNOSIS AND TREATMENT

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Summary

This review article is devoted to the most topical issues of epidemiology, diagnosis and treatment of tuberculosis.

Keywords: tuberculosis, diagnosis, treatment, drug resistance of mycobacteria .

ОСНОВНЫЕ НАПРАВЛЕНИЯ ИССЛЕДОВАНИЙ ТУБЕРКУЛЁЗА ПО ПРОФИЛАКТИКЕ, ДИАГНОСТИКЕ И ЛЕЧЕНИЮ.

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Резюме

Обзорная статья посвящен наиболее актуальным вопросам эпидемиологии, диагностики и лечения туберкулеза.

Ключевые слова: туберкулез, диагностика, лечение, лекарственная устойчивость микобактерий.

Today, the problem of tuberculosis is given priority at the global level. worldwide : to reduce the absolute number of deaths from TB by 90%, to reduce the incidence of TB by 80% (new cases per 100,000 people per year) compared with 2015 [27,44, 53]. The UN High Level Meeting was initiated and prepared by the First Global Ministerial Conference on Ending TB . According to world statistics, despite the measures taken, since 2010 the number of new cases of the disease has increased to 10.42 million and by 2017 has decreased slightly - to 10.0 million cases (Fig. 1) [54, 55, 56] . A very insignificant trend in the decline in mortality from tuberculosis has been observed in recent years [54–56]. According to statistics, most of the tuberculosis patients now live in the regions of South Africa (26.21 %), Southeast Asia (45.6%), much less in the countries of the Eastern Mediterranean (7.2%), European (3.11%) and Americas regions. According to WHO documents, tuberculosis is one of the 10 leading causes of death in the world, ahead of both HIV infection and malaria





in importance. In 2016, 1.78 million people died from this disease (including 0.4 million people with HIV infection) [26,29,42]. Starting from 2016, according to the WHO global strategy, the goal was set to stop the tuberculosis epidemic. This strategy, adopted by the World Health Assembly in May 2014, determines the introduction of new methods for early diagnosis of tuberculosis, support for people living with HIV infection and patients with drug-resistant tuberculosis , the development of new methods of preventing the disease, which may reduce 2030, the mortality rate from tuberculosis (compared to the level of 2015) by 9 1.0% and reduce the number of new cases of the disease by 80.0% [8,28]. The decline in TB morbidity and mortality from TB occurs against the backdrop of an increase in the coverage of the population with preventive examinations for tuberculosis, development and implementation of modern clinical protocols, procedures and standards of medical care, taking into account international experience, and as a result, a decrease in the number of advanced forms of tuberculosis among newly diagnosed patients [26]. Against the background of the improvement of the epidemic situation, the increase in the incidence of tuberculosis with drug resistance of the pathogen is of particular concern, so from 2009 (36.91%) to 2016 (46.61 %) the number of such patients increased by 10%. By 2016, there has been an increase in the incidence of multidrug-resistant tuberculosis from 4.0 per 100,000 population in 2009 to 5.6 per 100,000 population [4–6,8,29]. Another problem is presented by patients with a combination of tuberculosis and HIV infection. Mortality from tuberculosis in this group of patients continues to grow catastrophically, which is due not only to the low level of early diagnosis of tuberculosis in HIV-positive individuals, but also to the high prevalence of tuberculosis in general. According to WHO data, by 2015, 500,564 people had HIV-positive status, of which 15% were patients with tuberculosis . About 400 thousand people in 2017 died from tuberculosis infection [42]. Although some researchers point to a relatively favorable epidemiological situation in tuberculosis, the rate of decline in the incidence should be recognized as insufficient, since they will not allow achieving the targets by 2020. As the authors specify, at least two more circumstances do not allow talking about the epidemiological well-being of tuberculosis . Firstly, the coverage of the adult population with preventive fluorographic (FLG) examinations remains low . Secondly, the risk of infection with mycobacteria remains at a fairly high level, which indicates a tense epidemic process supported by a large number of bacterial excretors . At the same time, according to the latest data, Beijing strains were isolated in 85% of cases in the North-West region, which in 38% of cases belonged to the B o /W148 cluster. The expansion of the spectrum of drug resistance of mycobacteria, especially the Beijing strain , significantly reduces the effectiveness of





tuberculosis chemotherapy and contributes to the formation of a qualitatively new reservoir of the pathogen [9,41,47].

The issues of drug resistance of mycobacteria and the characteristics of the macroorganism are directly related to the conduct of etiotropic therapy in patients with tuberculosis. The middle of the 20th century was marked by the discovery of effective antibacterial drugs for the treatment of tuberculosis. Until that time, only sanatorium treatment was carried out, which included rest, fresh air and enhanced nutrition. Despite some benefit from such treatment, long-term results have been disappointing. More than 60% of discharged patients died of tuberculosis within six years [28]. The treatment of tuberculosis has been slightly improved by the introduction into practice of surgical methods, such as artificial pneumothorax and thoracoplasty, which cause collapse of the affected lung segments and activation of pulmonary macrophages under the influence of increased processes of active lipodieresis in the collapsed lung [39,40]. However, a real breakthrough in treatment was obtained after the discovery of streptomycin in 1944 by American scientists Waksman, Shats and Budzhi, who isolated *Streptomyces griseus* and received a powerful anti-tuberculosis antibiotic. With the discovery of streptomycin, highly effective anti-tuberculosis chemotherapy originates, for which Z. Waksman was awarded the Nobel Prize in 1952 [35]. At present, it has become obvious that the cause of the formation of multidrug resistance of mycobacteria strains to drugs was chemotherapy itself [10]. Recent advances in the development of new drugs and regimens give hope that new drugs will be effective and well tolerated, and will help reduce the duration of TB treatment. In 2012–2013, two new anti-tuberculosis drugs were introduced to the world: bedaquiline and delamanid [42,56]. Bedaquiline (a group of diarylquinolines) was approved based on the results of clinical trials, which confirmed the effectiveness and safety of the drug. The results obtained served as the basis for recommending the inclusion of bedaquiline in the chemotherapy regimen for multidrug-resistant tuberculosis of mycobacteria [55]. Research started back in the late 80s of the XX century by the staff of the Laboratory of Experimental TB S and Petersburg Research Institute of Phthisiopulmonology under the direction of T.I. Vinogradova (1994, 1999) made it possible to develop and bring to market a new domestic anti-tuberculosis drug thioureidoiminomethylpyridinium perchlorate (Tpp or Perchlozon ®), which was registered in 2012 (LP-001899 dated 09.11.2012) [11,35]. Today, it has been proven that Perchlozone ®, being a new generation thiosemicarbazone, has a bacteriostatic effect on mycobacterium tuberculosis, has a pronounced anti-tuberculosis effect on both drug-susceptible and drug-resistant strains of mycobacteria. Over the past few years, studies have been conducted to





study the effectiveness of the treatment of patients with pulmonary tuberculosis with multiple and extensively drug-resistant mycobacteria, where the spectrum of adverse reactions was studied during the use of the drug, and recommendations for their correction were developed [25,27,52]. Studies are underway on the targeted delivery of the drug to the foci of infection using nanoparticles, targeted immunoglobulins and macrophages [53]. Surgical treatment has been one of the stages in the complex treatment of patients with tuberculosis for many decades. In recent years, Russia has developed and implemented not only the world's first surgical classification of pulmonary tuberculosis, but also methods for performing simultaneous-sequential bilateral lung resections, transpleural reamputation of the stump of the main bronchus in pulmonary-bronchial fistulas, pneumonectomy in conditions of pleural empyema, the tactics of surgical treatment of patients with aggravated and complicated forms of pulmonary tuberculosis: amyloidosis, aspergillosis, respiratory failure, cardiovascular diseases, etc. [2]. Due to the spread of drug-resistant tuberculosis, the importance of the surgical stage of tuberculosis treatment has increased significantly. In 2014, at the initiative of the chief freelance specialist in thoracic surgery, Professor P.K. Yablonsky, an International Consensus was created on the use of surgical methods in the complex treatment of pulmonary tuberculosis, supported by WHO [48], which was based on the richest experience of the Russian phthiology school, founded by Professor Yu.M. Repin. The results of a literature review published in 2016 also indicate the relevance of the surgical method, especially in cases of unilateral pulmonary tuberculosis, when a combined approach can increase the overall effectiveness of treatment up to 75–98% [45]. The spread of tuberculosis with multiple and extensive drug resistance of the pathogen has led to the need for the introduction of new surgical methods for the treatment of patients with different distribution of the pulmonary process [20]. The use of minimally invasive technologies is associated with technical features that have never been used in phthiology before [18,3]. In recent years, the possibilities of using robotic technologies in the treatment of respiratory tuberculosis have been studied [36, 48]. Previously, studies were conducted that showed the advantages of robot - assisted operations over videothoracoscopy in patients with lung cancer, but the effectiveness and safety of this technology in conditions of infectious pathology of the respiratory system has not been proven [45]. The introduction of robot- assisted operations can reduce the number of complications in the postoperative period, shorten the recovery period and increase the effectiveness of treatment. The results of the analysis of the effectiveness and safety of robot-assisted lobectomy indicate the possibility of their use in local pulmonary tuberculosis. The presence of pleural adhesions is not a





contraindication for this technology: on the contrary, robotic access makes it possible to successfully deal with them, even if the pleural cavity is completely obliterated [40]. The analysis of the long-term results of treatment of patients with bilateral fibrocavernous pulmonary tuberculosis with multidrug and extensive drug resistance, who underwent various types of surgical interventions, taking into account the prevalence of a specific process, showed that due to the chosen tactics, it was possible to increase the effectiveness of treatment up to 80% [45]. According to WHO recommendations, detection of the pathogen in appropriate biological samples is necessary to confirm tuberculosis. New WHO-approved methods for the detection of various forms of mycobacteria (molecular and non-molecular, liquid culture and fluorescence microscopy) in developing countries are inferior to traditional methods such as sputum microscopy, solid cultures due to higher cost and the need for expertise to implement new techniques.

Thus, the problem of tuberculosis is still relevant and attracts the attention of the most advanced areas of biomedicine. Despite the measures taken, the number of new cases of the disease is decreasing slightly, as well as the share of the disease in the structure of mortality. The increase in the frequency of combination with HIV infection and comorbidity in patients with tuberculosis creates even greater difficulties for both treatment and diagnosis of the disease. The spread of drug-resistant tuberculosis, especially the Beijing strain, leads to the development of severe forms of the disease, which require the use of new and highly effective technologies for their cure. In this connection, the need to develop and introduce new anti-tuberculosis drugs, means of their targeted delivery and theranostics remains relevant, and the use of surgical methods for the treatment and diagnosis of the disease is still in demand. At In this regard, a change in approaches in the early diagnosis of TB with the use of immunological tests in risk groups and screening in children, along with a change in the approach in the use of fluorography, are key points in controlling the spread of infection.

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