SCHOLASTIC:
Journal of Natural and Medical Education
Volume 2 Issue 4, Year 2023 ISSN: 2835-303X
https://univerpubl.com/index.php/scholastic

Immunological Features of Pulmonary Tuberculosis in Patients with Drug Resistance

Rustamova Saodat Abdullaevna, Muazzamov Bakhodir Rakhmanovich
Bukhara state medical institute, department of phthisiology and pulmonology

Article Information

Received: February 05, 2022
Accepted: March 06, 2023
Published: April 07, 2023

Keywords: *tuberculosis, newly diagnosed case, immunity, TNF-α, VEGF, ADA.*

ABSTRACT

Currently, the main threat to the effectiveness of measures aimed at improving the epidemic situation is the spread of tuberculosis caused by drug-resistant mycobacteria (MBT). Tuberculosis with multidrug-resistant MBT (MDR-tuberculosis), when resistance to the most effective first-line anti-TB drugs - rifampicin and isoniazid, is detected, has been registered in almost all countries. These data indicate that at present there are a number of obstacles to the effective fight against tuberculosis, where drug resistance (DR) of MBT to anti-tuberculosis drugs, as well as the state of the immunobiological forces of the body is the main ones.

Under these conditions, the problem of increasing the effectiveness of treatment of patients with pulmonary tuberculosis, taking into account the characteristics of immunobiological properties in various variants of the course of tuberculosis in newly diagnosed patients, becomes highly relevant. Understanding the pathogenetic mechanisms of the development of the inflammatory response in different variants of the course of tuberculosis is a necessary prerequisite for improving the effectiveness of the treatment of patients with tuberculosis by targeting these mechanisms. The literature provides data on certain aspects of the systemic inflammatory response in the human body in pulmonary tuberculosis. However, a comprehensive study of immunobiological properties in newly diagnosed patients with pulmonary tuberculosis in the intensive phase of treatment has not yet been carried out. This knowledge is important in the development of schemes and methods of pathogenetic therapy aimed at improving the effectiveness of treatment of patients with pulmonary tuberculosis. All of the above was the basis for the present study.

The epidemiological situation of tuberculosis at the present stage.Tuberculosis continues to be one of the most common infections in the world and poses a huge threat to public health. The disease is still a complex socio-economic and biomedical problem (23). Tuberculosis is becoming both a national and a global health problem (48). According to WHO data, in 2011 there were 8.7 million cases of tuberculosis, which is equal to 125 cases per 100,000 population worldwide. According to the WHO, 2006 rin in the world there were 9.24, in 2007 г. - 9.27, in 2008 - 9.4 million new cases of tuberculosis (2010). At the same time, in 2008, 440,000 cases of multidrug-resistant tuberculosis (MDR) MBT were registered in the world. According to WHO estimates, 1.3 million HIV-negative patients worldwide died of tuberculosis in 2008y.

The current epidemiological situation in many countries, including Uzbekistan, is characterized by deterioration in the main indicators of tuberculosis (morbidity, mortality, disability) (Mukhtarov D.Z. 2005). Tuberculosis at the present stage is characterized by the identification of common and acute progressive forms with extensive destructive processes, massive bacterial excretion against the background of various concomitant diseases.

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

Tuberculosis remains an important national problem in Uzbekistan, despite the complex of ongoing large-scale anti-tuberculosis measures, the epidemiological situation with tuberculosis remains tense (Parpieva N.N., 2014).

In the early 1990s, the first reports appeared about the deterioration of the epidemiological situation of tuberculosis in Uzbekistan, especially in those regions where the negative impact of environmental and socio-economic factors is great and the level of anti-tuberculosis measures has been reduced [Khamraev A.K., 2011] .

Among the reasons explaining this process, the leading role is played by the presence of a significant reservoir of tuberculosis infection, a significant number of patients excreting multiresistant forms of Mycobacterium tuberculosis [Mukhtarov D.Z. et al . 2005; 18.].

The weakening of the work of the fluorographic service in the Republic contributed to the late detection of tuberculosis and the formation of a significant reservoir of tuberculosis infection. Every third TB patient excretes MBT and is dangerous for others, every fifth TB patient becomes disabled [Babadzhanov A.S. et al., 2003].

Tuberculosis often affects the most productive age of the population and causes economic damage to society [Golyanova et al., 2000; Mukhamedov K.S., Dzhurabaeva M.Kh., 2014].

insufficiently effective treatment, concomitant diseases play an important role , i.e. they aggravate the course of tuberculosis and cause its unfavorable dynamics [Nazirov FG, 2000; Karimov U.A., 2000; Saidova Sh.M., 2001; Parpieva N.N., 2002; Asadov D.A., Vafakulova U.B., 2003.].

Thus, despite the complex of ongoing large-scale anti-tuberculosis measures, the epidemiological situation of tuberculosis in Uzbekistan remains tense (Tillyashaikhov M.N., Parpieva N.N., 2014). The course of tuberculous inflammation in recent years has undergone pathomorphosis induced by many factors, the clinic of tuberculosis has changed, progressive forms of the disease have appeared that are difficult to treat (Mukhtarov D.Z., 2005).

The problem of recurrence of the tuberculosis process in the lungs at the present time. The problem of recurrence of the tuberculosis process in the lungs is currently very acute, since the contingents of anti-tuberculosis dispensaries are replenished annually, as the main source of the formation of chronic destructive forms of tuberculosis, the spread of Mycobacterium tuberculosis (Litvinov V.I. 2003; 104; 97; Parpieva N.N. ., et al., 2011; Plieva S. L., Seltsovsky P. P. 2011; Mironyuk O. M., et al. , 2014;). In the general structure of the incidence of pulmonary tuberculosis, there is an increase in the proportion of relapses, which are characterized by a more severe course, the complexity of therapy and epidemiological features. According to the TsNIIOIZ of the Russian Federation, in recent years there has been an increase in the rate of recurrence of tuberculosis from 7.8 per 100 thousand of the population in 2004 to 12.0 per 100 thousand of the population in 2009 (Rukosueva O.V., 2010). Considering the historically close structure of the anti-tuberculosis service in our country and the Russian Federation, it can be assumed that the situation with relapses of tuberculosis in the Republic of Uzbekistan is similar to that in the Russian Federation.

Relapses of pulmonary tuberculosis are much more severe, more often turn into a chronic course and lead to higher mortality compared to the newly diagnosed process (Komisarova O.G., 2005; Vyazkova N.N., 2008; Rukosueva O.V., 2010). Treatment of this category of persons turns out to be longer, more expensive and less effective (Mishkinis K. et al ., 2000; Zakoska M., 2004; Ilyina T. Ya et al ., 2004; Vyazkova N.N., 2008).

The best prevention of the spread of tuberculosis is the timely detection and effective treatment of all patients (Espinal M.A., 2002; Levashev Yu.N., Repin Yu.M., 2008). The effectiveness of

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

treatment of newly diagnosed patients with bacterial excretion reaches 85% and 70% in the European region (Shilova M.V., 2008; WHO, 2009; Mishin V.Yu. et al., 2010).

The causes of relapse remain poorly understood. The views of different researchers regarding the influence of certain factors on the development of relapse differ. A number of authors prioritize concomitant diseases in the reactivation of tuberculosis (Krasnov V.A., 2000; Maksimova O.M., 2004), others prefer the presence of large residual changes in the lungs (Kovalev G.K., 1994; Eisaev B.A. et al ., 1995). And, finally, many clinicians pay attention to the inferiority of the main course of chemotherapy for the first disease (42; Komisarova O.G., 2005; Ilyina T.A. et al ., 2005; Vyazkova N.N., et al ., 2007).

Relapses of tuberculosis of the respiratory organs occur approximately equally often against an unchanged X-ray background, against the background of small and against the background of large residual tuberculous changes (Alekseeva T.V. 2001; Shikhaliev Y.Sh. 2001; Andreeva T.N., Kirilov M.N., 2003 Gomez JE, Mc Kinney JD, 2004; Mishin V.Yu., Zhestovskikh S.N., 2005).

The predominance of destructive forms of tuberculosis, the prevalence of the process and the resistance of mycobacteria to anti-tuberculosis drugs make it difficult to treat patients with relapses of respiratory tuberculosis. Despite the costs, the effectiveness of the treatment of patients with recurrent tuberculosis remains low (42; Komisarova O.G., 2005; Vyazkova N.N., et al ., 2007;).

The indicator of the frequency of early recurrences reflects the presence of defects in the treatment and quality of examination when transferring TB patients to inactive dispensary groups. The indicator of the frequency of late relapses indicates the prevalence of tuberculosis infection, unfavorable medical, biological and social factors (Alekseeva G.I., 1993; Krasnov V.A., Alekseeva T.V. 2002; Maksimova O.M.. 2004).

Most publications are aimed at studying the structure of relapses of respiratory tuberculosis, the social composition of patients, the factors that determine the late registration of relapses and the causes of death from them, the timing of early and late relapses, the impact of relapses of tuberculosis on the epidemic situation of tuberculosis, the causes of death from relapses of tuberculosis (Elyshn A.V., 2000; Arefieva E.V., 2009). A number of authors (Tonchkina T.V., Nizovtseva N.I., Maryandyshev A.O. 2003; Cox H., Kebede Y., Allamuratova S., Ismailov G., Davletmuratova Z., et al . 2006) pay attention to the algorithm preventive and health-improving measures in anti-tuberculosis institutions and the general medical network; criteria for assessing the quality of work of the district phthisiatrician serving the adult and children's population in the prevention of relapses of respiratory tuberculosis.

According to Arefieva E.V. (2009), among registered patients with relapses of respiratory tuberculosis, patients with early relapses accounted for 40.7% of cases, with late relapses - 59.3% of people. The author notes that in 23.8% of cases, the diagnosis of recurrence was established posthumously, 41.2% died in the first year after diagnosis, 35.0% were observed before their death from tuberculosis for more than one year.

In clinical practice, tuberculosis recurrence is often differentiated from nonspecific inflammatory processes that occur against the background of post-tuberculous residual changes. The relevance of early diagnosis of tuberculosis recurrence is determined by the low level of solution of this problem. Due to the complexity of the differential diagnostic process at the outpatient stage, a certain proportion of patients are hospitalized in anti-tuberculosis institutions for periods exceeding 3 months. from the beginning of detection of reactivation, often with complications of a specific process, secondary infection. The detection and diagnosis of disease relapses is significantly delayed and creates a real "hidden reservoir" of infection, which requires the

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

development of new evidence-based approaches to solving this problem (Alekseeva T.V., 2001; Ilyina T.Ya. et al., 2008) .

Among the factors contributing to the development of relapses, an important place is occupied by social factors, which include: unsatisfactory living and working conditions, low income that does not provide a living wage, malnutrition, occupational hazards, stay in the penitentiary system of the Federal Penitentiary Service, etc. (Vyazkova N.N. et al ., 2007; Nechaeva O.B. et al ., 2007; Skachkova E.I. et al ., 2008; Arefieva E.V., 2009)

According to Russian authors (Skachkova E.I. et al ., 2008; Shilova M.V., 2010; Plieva S.L., Seltsovsky P.P., 2011), the relevance of the issue of tuberculosis recurrence is determined by the fact that since 2005 their number is increasing in persons with residual post-tuberculosis changes, who are removed from the register of anti-tuberculosis institutions, in accordance with the Order of the Ministry of Health of the Russian Federation No. 109 dated March 21, 2003, and transferred to the supervision of primary health care institutions.

It should be noted that the currently used standard chemotherapy regimen in patients with relapses of pulmonary tuberculosis consists of a combination of the main anti-tuberculosis drugs: isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin is mainly focused on patients with a low level of MBT drug resistance to anti-tuberculosis drugs. According to A.A. Adzhemyan (2011), with the introduction of the DOTS program into practice, the contingent of patients in need of re-treatment has expanded. The author notes that the study of the clinical course of pulmonary tuberculosis in a contingent of patients in need of re-treatment, as a holistic category, since therapeutic and preventive measures for the individual components of this group are the same. At the same time, a number of authors, in addition to the concept of “relapse”, refer to WHO experts who introduced such formulations of indications for repeated treatment as “unfavorable outcome of the previous treatment”, “violation of the previous course of treatment” and “others” (43).

In this regard, it seems interesting to study the clinical course of pulmonary tuberculosis in a contingent of patients in need of repeated treatment as an integral category, since therapeutic and preventive measures for the individual components of this group are the same.

The development of relapses of pulmonary tuberculosis is largely determined by the state of nonspecific reactivity of the patient's body. Among the humoral systems involved in the formation of nonspecific reactivity of the body, an important role belongs to the functional status of circulating blood phagocytes, which are able to synthesize various biologically active substances (Kaminskaya G.O., Abdullaev R.Yu., 2002; Erokhin V.V., Zemskova 3 .S., 2003; Petrova L.Yu., 2005).

In addition to the bacterial factor, an important role in the course and outcomes of the tuberculosis process is played by the immunobiological state and reactivity of the human body, which determine its response to the introduction and subsequent reproduction of MBT (Puzik V.I., 1973; Averbakh M.M., 1976). The body's defensive response to any infection, including MBT, manifests itself in the form of a systemic inflammatory response syndrome, which is currently under the scrutiny of many researchers around the world. The balances of the complex of its constituent reactions or, on the contrary, the violation of their physiological control determine the development and nature of the course of tuberculous inflammation (the predominance of an exudative or productive tissue reaction) (Morozova T.I., 1996; Kaminskaya G.O. 1997; Erokhin V.V., 2009).

The low efficiency of chemotherapy, which, according to a number of authors (Mishin V.Yu., 2003; Philips M., 2004; Shilova M.V., 2005) is in the range of 60-70%, is associated with an increase in the proportion of destructive forms of tuberculosis among cases, an increase in cases

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

of primary and secondary resistance of Mycobacterium tuberculosis to chemotherapy drugs, a high proportion of comorbidities (Raviglione MC, 2001; Zhuk N.A., 2003; Skornyakov S.N., 2003; Svistunova A.S., 2005;), forced breaks due to side effects of drugs, the level of energy and plastic processes in the body, and the functional state of the hypothalamic-pituitary-adrenal system, which determines homeostasis and reactivity of the body (Brazhenko N.A., 1998; Trofimov V.N. et al ., 2003). The latter is provided by a complex combination of simultaneous and sequential reactions from many humoral and cellular systems of the body (Kryzhanovsky G.N. et al ., 2002; Agadzhanyan N.A. et al ., 2006).

Understanding the pathogenetic mechanisms of the development of the systemic inflammatory response syndrome in different variants of the course of tuberculosis is a necessary prerequisite for improving the effectiveness of the treatment of patients with DR tuberculosis by targeting these mechanisms. The literature provides data on certain aspects of the systemic inflammatory response in the human body with pulmonary tuberculosis (Kaminskaya G.O. et al., 1986; Kazenny B.Ya. 2004; Gando S. 2004; Breen RA et al ., 2008). However, a comprehensive study of various aspects of the systemic inflammatory response, including the metabolic function of the vascular endothelium (VEGF), the state of the hemostasis system and the degree of protein and energy supply of the body in patients with relapse of pulmonary tuberculosis before and during treatment has not yet been carried out. This knowledge is important in the development of schemes and methods of pathogenetic therapy aimed at improving the effectiveness of treatment of patients with pulmonary tuberculosis, including MBT with MDR and XDR.

Detection and identification of the causative agent of tuberculosis is the main task of medical microbiology. The "gold" standard for diagnosing tuberculosis is a combination of microscopic and cultural methods of research (Order of the Ministry of Health of the Republic of Uzbekistan No. 160 of April 3, 2003).

Bacterioscopic examination is the fastest method for detecting acid-fast bacteria. However, the method allows detecting mycobacteria when the content of more than 5000-10000 microbial bodies in 1 ml of material (according to WHO data), and such an amount of mycobacteria is found in the sputum of a patient with advanced progressive forms of tuberculosis (Golyshevsky V.I., et al . 2001) . In addition, microscopic examination of acid-fast mycobacteria does not allow differentiation of MBT from non-tuberculous mycobacteria. The expediency of emergency microscopy for MBT in patients with suspected tuberculosis in the emergency department of a multidisciplinary hospital has been proven (Prostakishina Yu.M., et al. , 2005).

The seeding method, or the cultural method for detecting mycobacteria, is more sensitive and allows not only to isolate the pathogen, but also to study its biological properties. It is possible to increase the effectiveness of classical methods of microbiological research by improving the methods of preparing the material, using new dyes, modifying the cultivation systems and recording the growth of mycobacteria (for example, the use of automated systems such as BACTEC MGIT 960, MB/BACT, etc.) (Freiman G.E. , et al. 2007).

The use of the PCR method makes it possible to reduce the time for confirming the diagnosis of tuberculosis (Skryagina E.M., et al., 2001; Chernousova L.N., et al., 2001). This method is especially relevant in patients with oligobacillary forms of tuberculosis (Salina T.Yu. 2006). The source material for this study can be obtained from any tissue or biological fluid, as well as biopsy material.

Known diagnostic methods based on the use of the results of histological and bacteriological studies are laborious and time consuming (Ungerer J.PJ., et.al. 1994; Mitchison DA, 2005). The well-known method for the biochemical diagnosis of active tuberculosis did not indicate the sensitivity and specificity of the test, which does not allow us to judge its true diagnostic value, especially in the absence of MBT in the sputum and with a dubious x-ray picture (Valdés L., et

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

al ., 1996; Dickenson O., et al ., 2002 Zhestovskikh S. N., 2002; Khudushina T. A., Voloshina E. P., 2003; Ilyina T. Ya, Zhangiriev A. A., Sidorenko O. A., 2004; Boshoff HI, Barry CE, 2005; Taganovich A.D. , et al. , 2008). In order to reduce the time for diagnosing active tuberculosis, as an auxiliary method for determining the level of adenosine deaminase (ADA) activity in the blood serum, the value of which is compared with the threshold value and, if the latter is exceeded, active tuberculosis is diagnosed.

In recent years for Express diagnosis of tuberculosis uses a polymerase chain reaction (PCR), which makes it possible to detect DNA sequences specific to MBT within a few hours. In terms of its sensitivity (34.6%), PCR surpasses both bacterioscopic and cultural methods for detecting MBT (Vishnevsky B.I. et al., 2000). A. de-Lassence et al (1992) concluded that the determination of the gene code by PCR only with a sensitivity of the method of 40% is important in determining the etiology of the disease.

The clinical course of recurrence of tuberculosis of the respiratory organs is much more severe, more often becomes chronic and leads to higher mortality compared to the newly diagnosed process.

Often a recurrence of the disease is detected late, and the treatment of this category of people is lengthy, expensive and not effective enough. In recent years, problems have arisen in the organization of treatment of patients with tuberculosis, which require a scientifically based solution. In this regard, it is relevant to create a unified approach to assessing the result of the main course of treatment, to find out the reasons for its low effectiveness and the occurrence of relapses in the context of modernizing treatment and meeting the standards of treatment for patients, and conducting bacteriological monitoring through a detailed study of MBT drug resistance.

Thus, the causes of recurrence remain poorly understood. The influence of various unfavorable factors of the external and internal environment on the development of recurrent tuberculosis of the respiratory organs is described in a few studies. In this case, priority is given to concomitant diseases.

Immunological characteristics in patients with pulmonary tuberculosis.The study of the immune status in tuberculosis, its individual characteristics in patients at various stages of treatment is of great importance for deciding on rational therapy, choosing the direction of therapeutic action, as well as for assessing the course and predicting the tuberculosis process. (Dranik G.I. et al ., 1994; Knoring B.E., 1996; Nesterova N.V., 2000; Kozlov V.K. et al ., 2001; Mayansky A.N., 2001; Simonov A. V., 2002; Sukhovey Yu.G. et al., 2004; 18, Kostromtsov S. V., 2012).

The main goal of immunological studies in tuberculosis is to assess the condition and identify possible changes in the immune system that can be used for differential diagnosis. Considering the multicomponent and complexity of the structure of the immune response, to evaluate it, it is necessary to use a set of tests that reflect the intensity of both cellular and humoral immunity [Vasilyeva E.V. et al. 2012].

Despite the key role of mycobacteria and their biological properties in determining the nature of the course of tuberculosis, the mechanisms of immune dysregulation are also of no small importance in the development of the disease (Mayansky A.N., 2002; 42). Proved today is the fact that the degree of violations of immunological reactivity closely correlates with the clinical and radiological manifestations of tuberculosis infection, reflects the severity of the disease. Moreover, changes in the immune status of patients with pulmonary tuberculosis are associated with a decrease in the effectiveness of therapeutic measures (Gegert V.Ya. et al ., 1995; 42). It is possible that the appearance, or rather the multiplication of drug-resistant forms of MBT in the

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

process of standard chemotherapy, is a consequence of the weakening of the body's immune surveillance.

According to modern concepts, the key role in the elimination of the pathogen and the formation of anti-tuberculosis immunity is played by the cooperation of mononuclear phagocytes and polymorphonuclear leukocytes, which ensure the functioning of a single phagocytic cell domain and various subpopulations of T-cells (Mayansky D.N., 1991; Freidlin I.S., 1995). At the same time, the outcome of the interaction between macrophages and mycobacteria depends on the balance of antimicrobial activity of phagocytic cells and the resistance of mycobacteria to their bactericidal effect (Khonina N.A. et al ., 2000).

Despite the fact that at present a generalized idea of the immunophagocytic system of peripheral blood has already been formed, the process of nonspecific resistance in tuberculosis, given its complexity, remains not fully understood. Meanwhile, a comprehensive study of the functional and metabolic properties of phagocytic blood cells in drug-resistant pulmonary tuberculosis can be used to assess immune response disorders, their clinical significance, predict the course and outcomes of the disease, and also serve as the basis for creating effective methods for immunocorrection of the disease (23) .

V. Yu. Mishin (1995) believes that the severe course of tuberculosis is due to various metabolic disorders and the functional activity of peripheral blood lymphocytes and monocytes. These data fit into the concept of K.S. Kazakov (1975) that the leading link in the pathogenesis of tuberculosis is a violation of tissue respiration.

The reason for the slow regression of specific changes and the preservation of the morphological activity of the tuberculosis process is a decrease in the immunological reactivity of the body. Clinically, TB in immunocompromised individuals is difficult to treat. (Batyan A.N., 1995; Zhdanova E.A., 2002).

Immunological studies in the clinic for tuberculosis are used not only to detect violations of the immune system and, accordingly, the prognosis of the disease. They, in particular, serve to determine the effectiveness of treatment to restore immunological reactivity (along with an improvement in clinical status) [Khomenko A.G. et al., 1976, 1982; Arshinova S.S. 2002]. In addition, the results of such studies serve as the basis for the appointment of immunocorrective agents.

However, research results are conflicting. The severity of deviations in the parameters of the protective systems is determined by the duration of the disease, the presence of concomitant pathology and complications, the intensity of the exudative component in the overall picture of inflammation, manifestations of tuberculosis intoxication, the prevalence of lesions, the clinical form and phases of the process, the number and size of decay cavities in the lung tissue (Morozova T.I. ,1996).

According to Vaneeva T.V. (2002), the presence of significant changes in the main nonspecific indicators of cellular immunity is not typical for newly diagnosed patients with tuberculosis. At the same time, patients with chronic forms of tuberculosis without signs of drug resistance to anti-tuberculosis drugs are characterized by an imbalance in the subpopulation composition of T-cells, primarily due to a further increase in T-helpers and a decrease in cytotoxic lymphocytes, which, first of all, is reflected in a significant increase in immunoregulatory index. It should be emphasized that, essentially, none of the patients showed signs of an immunodeficiency state, but there was a change in the ratio of effector cells, which reflects a significant restructuring of the main components responsible for the immunological reactivity of patients with tuberculosis. Whereas, in patients with drug resistance, both imbalance and suppression of the main indicators of cellular immunity are noted.

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

However, in patients with acute progressive forms of pulmonary tuberculosis, there is a sharp decrease in immunity (Khomenko A.G., 1996; Krasnov V.A., 1998; Morozova T.I. et al., 1999 ; Chelnokova O.G., 2004; 43 ; Sukhovey Yu.G. et al., 2004; 18).

According to Averchenkov V.M. et al . (1998) the immune deficiency mentioned above is due to the toxic effect of specific microflora on immunocompetent cells and the immunosuppressive effect of chemotherapeutic agents. Immune deficiency has a combined character. In addition to a decrease in a number of quantitative indicators, there is a deep deficiency in the functional activity of lymphocytes and cells of the macrophage -monocyte link.

Vasiliev A.V. et al . (1990) revealed a decrease in the number and functional activity of T-lymphocytes in 92% of patients suffering from fibrous-cavernous pulmonary tuberculosis. There was a combination of a negative specific cellular response (according to RBTL with PPD) and hyperproduction of specific antibodies (according to RNHA and RSK). Such a ratio of cellular and humoral immunity factors indicates its deep violations. This, as a rule, contributed to the difficult course of the process with massive bacterial excretion .

The course of drug-resistant and drug-susceptible pulmonary tuberculosis is accompanied by unidirectional disorders of the metabolic and functional state of monocytes and neutrophilic granulocytes of peripheral blood, the severity of which is determined by the variant of the course and the clinical form of the disease.

Dysregulation of the nonspecific link of immunity in multidrug-resistant pulmonary tuberculosis is due to inhibition of the anti-infective potential of neutrophils (decrease in the number of active phagocytes, completeness of phagocytosis and reserve NBT-reactivity), and a decrease in the receptor- expressing function of monocytes and neutrophils, their metabolic depletion, expressed in a decrease in glucose depot and lipid content against the background of increased absorption capacity, activity of serum lysozyme, lysosomal enzymes and the content of non-enzymatic cationic proteins in neutrophils (23).

Patients with MDR-TB are at significant risk of adverse disease course and death. After analyzing the lethal outcomes of MDR-TB patients, F. Drobniewski [Narvskaya O.V., 2003; Sapozhnikova N.V., 2003; Drobniewski F. et al ., 2005; Kondakova M.N., 2005; Park YK and al ., 2005] et al . cites the following risk factors for mortality: immunodeficiency (the probability of death is 9 times higher), the impossibility of obtaining the results of a microbiological study within 30 days or prescribing three or more drugs to which sensitivity is preserved, age (for every 10 years of life, the risk doubles).

In addition, a clear relationship was found between MBT drug resistance and impaired immunity: in patients excreting DR MBT, low levels of T-cell immunity are significantly more common than in patients with preserved MBT sensitivity [Korneev A.A. et al., 1999; Krasnov D.V. et al., 2003] .

Thus, a decrease in T-lymphocyte colonies, a change in their subpopulation composition and a decrease in functional activity were noted in 86.8% of patients with DR-TB and in 37.9% of patients with drug – susceptible tuberculosis [Chukanov V.I. et al., 1996; Krivonos P.S. and co-authors, 2003].

A specific immunopathological sign of tuberculosis infection is a decrease in the activity of alkaline phosphatase in neutrophils, a decrease in the basal production of nitric oxide by blood mononuclear leukocytes, which increase in chronic obstructive pulmonary disease in the acute stage. (23)

In patients with acutely progressive forms of drug-resistant tuberculosis, pronounced immunological disorders are detected in 100% of cases [Kibrik B.S. 2000; 18] .

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

Alenova et al. (2002) found that in patients with acquired MDR MBT, disorders of immune homeostasis are more pronounced than in patients with primary MDR MBT. N.V. comes to the same conclusion. Kuzmina, who determined profound immune disorders in 52.17% of patients with secondary resistance and in 20% with primary DR MBT.

Consentration of adenosine deaminase (ADA) in the blood and pleural fluid can serve as one of the possible markers of pleural effusion of tuberculous etiology. It has been established that ADA plays an important role in the development and functioning of blood cells. Individuals deficient in this enzyme have a dysfunctional immune response due to inadequate metabolism of adenosine and deoxyadenosine (Gorguner M. , Cerci M. , Gorguner I ., 2000).

Known diagnostic methods based on the use of the results of histological and bacteriological studies are laborious and time consuming (Ungerer J. _ P. _ J. , et . al.1994 ; Mitchison D. _ A. , 2005). The well-known method for the biochemical diagnosis of active tuberculosis did not indicate the sensitivity and specificity of the test, which does not allow us to judge its true diagnostic value, especially in the absence of MBT in the sputum and with a dubious x-ray picture (Vald é s L. , et . al ., 1996; Dickenson al ., 2002; Zhestovskikh S. N., 2002; Khudushina T. A., Voloshina E. P., 2003; Ilyina T. Ya, Zhangiriev A. A., Sidorenko O. A., 2004; Boshoff H. I ., Barry C. E. , 2005; Taganovich A.D. , et al. , 2008;). In order to reduce the time for diagnosing active tuberculosis, as an auxiliary method for determining the level of adenosine deaminase (ADA) activity in the blood serum, the value of which is compared with the threshold value and, if the latter is exceeded, active tuberculosis is diagnosed.

According to Vasiliev E. V. and co-authors (2012), a comprehensive determination of the presence of antibodies in diagnostic dilution and quantitative determination of gamma-interferon before and after stimulation of immunocompetent blood cells with specific mitogens will make it possible to more confidently diagnose tuberculosis and, possibly, predict its severity and curability.

Thus, in the pathogenesis of extensive cheesy necrosis of the lung tissue, a fundamental role is played by severe immune deficiency, which is characterized by profound structural and metabolic changes and apoptosis of immunocompetent cells, especially cells of the mononuclear phagocytic system. Such cells in the zone of specific inflammation cannot withstand the excessive microbial load and, being functionally inactive and non-viable, are quickly and in large numbers destroyed. Their cytolysis leads to the release of lysosome enzymes, interleukins , tumor necrosis factor, prostaglandins , fibrinolysis activators and other inflammatory mediators, which contribute to the rapid development of caseous-necrotic changes, and thereby creates conditions for rapid and massive reproduction of MBT (Mishin V.Yu., 1995; Khomenko A.G., 1996).

The role of cytokines during pulmonary tuberculosis. TNF-α refers to pro-inflammatory cytokines, consists of long elongated β-chains. Molecular weight 17 kDa. TNF-α exhibits selective cytotoxicity against certain tumor cells; activates granulocytes, macrophages, endothelial cells, hepatocytes (production of acute phase proteins), osteoclasts and chondrocytes (resorption of bone and cartilage tissue), transcription of other pro-inflammatory cytokines; stimulates the proliferation and differentiation of neutrophils, fibroblasts, endothelial cells (angiogenesis), hematopoietic cells, T- and B -lymphocytes; enhances the flow of neutrophils from the bone marrow into the blood; has antitumor and antiviral activity *in vivo* and *in vitro* .

TNF-α, like other cytokines, is an important low-molecular mediator of intercellular interactions. Quantitative determination of the level of TNF-α is of great importance in assessing the immune status of the organism.

VEGF (Vascular endothelial growth factor) vascular endothelial growth factor, is a group of

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

dimerized glycoproteins with a molecular weight of 34-42 kDa . The method is intended for the determination of representatives of the VEGF - A family (VEGF 121 and VEGF 165) circulating in natural body fluids .

VEGF is the leading angiogenase factor and blocks apoptosis of endothelial cells of blood vessels, induces proteinases that remodel the intercellular substance, enhances vascular permeability and vasodilation, and inhibits antigen- presenting dendritic cells.

Normally, VEGF is produced by activated macrophages, keratinocytes, cells of the visceral epithelium of the renal glomeruli and mesangial cells of the kidneys, hepatocytes. smooth muscle cells, Leydig cells , embryonic bronchial fibroblasts, and choroid plexus epithelium. Platelet α-granules are believed to be the main source of serum VEGF. Platelet aggregation is accompanied by the release of this growth factor, and therefore the reference values for VEGF concentration may depend on the method of obtaining serum. In citrated blood plasma in healthy people, VEGF is practically not detected. VEGF expression is upregulated by a variety of pro-angiogenic factors, including hypoxia, various growth factors (epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, etc.), as well as TNF-α, estrogens, and androgens.

VEGF stimulates the secretion of von Willebrand factor by endothelial cells and induces the expression of tissue factors by endothelial cells and monocytes. Also, VEGF is characterized by chemotaxis of monocytes and osteoblasts. VEGF is extremely important for the formation of the vascular system during embryogenesis and in the early postnatal period; however, in adults, its physiological activity is limited to tissue regeneration and regulation of the female reproductive system.

It is also an important factor in the development of a number of pathological processes, such as rheumatoid arthritis (elevated concentrations of VEGF have been reported in the synovial fluid), diabetic proliferative retinopathy (high levels of VEGF in the vitreous body) and psoriasis.

VEGF is expressed by cancer cells in human lung adenocarcinoma, bladder cancer, breast cancer, fibrosarcoma , and others. The level of circulating VEGF concentration is an important marker of malignancy status. An increase in the concentration of VEGF in cancer patients is associated with an increase in the risk of metastasis, with tumor growth and, as a result, with an unfavorable clinical prognosis, i.e. failure to respond to chemotherapy and reduced survival.

Measurement of the concentration of C-reactive protein (CRP) in blood serum is used to monitor and control the effectiveness of the treatment of bacterial and viral infections, chronic diseases, complications during surgical interventions, in the post-traumatic and post-burn periods, in gynecology and oncology.

With any damage to the body, a cascade of physiological reactions (local and systemic) develops aimed at restoring functions, which is called the “acute phase of inflammation”. This phase includes fever, leukocytosis, increased immunoreactivity, including radical changes in the biosynthesis of liver proteins. The group of acute phase proteins (APP) includes up to 30 plasma proteins, their features include non-specificity and a high correlation of blood concentrations with disease activity and the stage of the process. The latter favorably distinguishes BOF from other indicators of inflammation, such as ESR or a shift in the leukocyte count.

A unique marker of the acute phase of inflammation is C-reactive protein (CRP), as it is a very sensitive indicator of damage (the concentration in the blood increases 20-100 times, sometimes 1000 times!) and the fastest (the first 6-10 hours). This α2 is a plasma globulin belonging to the pentraxin family, consists of 5 identical, non-covalently linked subunits (each with a mol . mass 21-23 kDa). Its content in the blood of an adult is up to 8 mg/l, in newborns up to 0.5 mg/l. The synthesis of CRP is carried out in hepatocytes and is regulated by the interleukins IL -1 and IL-6.

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

CRP is a multifunctional acute phase protein that plays an important role in defense against foreign agents and in autoimmune processes. It is included in the nonspecific immune response immediately after the penetration of the antigen into the body and acts through the stimulation of phagocytosis of neutrophils and cells of the monocyte-macrophage series. The products of CRP proteolysis cause an increase in the production of the O^{2-} anion , increase the activity of myeloperoxidase , act as x e - moattractants and regulate the proliferation of T- and B-lymphocytes. Complexes of CRP and a ligand component of the membranes of microorganisms and/or damaged cells) activate the complement system via the classical or alternative pathway. In addition, CRP promotes the removal of substances formed during cell destruction.

The degree of CRP elevation varies depending on the cause of the inflammation. The level of CRP concentration reaches 10-30 mg/l in viral infections, tumor metastasis , chronic or systemic rheumatic diseases. In the case of bacterial infections, exacerbation of chronic diseases, tissue damage (surgical operations, acute myocardial infarction), the amount of CRP increases to 40-200 mg/l. Generalized infections, burns, sepsis are accompanied by the highest increase in the level of CRP - up to 300 mg/l or more.

With the introduction of highly sensitive (lower detection limit - 0.5 mg/l) methods for the detection of CRP into laboratory practice, its concentrations, previously considered "trace" or "background" (< 5-8 mg/l), began to be called "basic" and be used in cardiology as a prognostic indicator for cardiovascular diseases (CVD). The baseline CRP level is significantly significant for acute myocardial infarction and cerebral stroke, especially in combination with the determination of troponin , cholesterol, fibrinogen.

Treatment of pulmonary tuberculosis at the present stage. According to the WHO Global Tuberculosis Program (1996), intensive polychemotherapy is recommended for treatment - a combination of 4-5 anti-tuberculosis drugs (Voronina G.A., 1999; Chelnokova O.G., 2004).

Treatment of tuberculosis at the present stage is very difficult. On the one hand, this is due to significant changes in the characteristics of the microbe (mycobacterium tuberculosis is virulent multiresistant, the population is massive), a concomitant infection often joins, and on the other hand, the acutely progressive course of the tuberculosis process is provoked by changes in the macroorganism (immunodeficiency, regulation of the detoxification system, metabolic disorders). Therefore, treatment must necessarily be complex etiopathogenetic, based on clinical, laboratory and radiological data and providing for the features of each clinical form of pulmonary tuberculosis (G.S. Balasanyants , M.S. Greimer , 2003).

However, the use of intensive polychemotherapy against the background of impaired metabolism, a high incidence of concomitant diseases (Mamadbekov M.V., 1997; Gavriliev S.S. et al., 2001; Kobeleva G.V., 2001), hypovitaminosis and dysbacteriosis , environmental problems (Dzhunsunbekov A.D., 1997; Mukhtarov D.Z., 1999; Lineva Z.E., Tyaptirgyanova N.G., 2001), secondary immunodeficiency (Khomenko A.G., 1998; Morozova T.I. et al., 1999; Ryskulova B.A. et al ., 2002; Chelnokova O.G. 2003; 43), is often complicated by the development of adverse reactions and their relapses from anti-tuberculosis drugs, and in 7.7% of patients they become unrecoverable and require permanent discontinuation of the drug. Adverse reactions are provoked to a large extent by intoxication, as well as methods of administration of anti-tuberculosis drugs, respectively, pathogenetic therapy should include the prevention of adverse reactions and their rapid elimination (Balasanyants G.S. et al., 2000; Frolova I.A., 2004).

In order to correct concomitant pathological syndromes, it is preferable to prescribe pathogenetic therapy with infusions of saline, metabolic drugs (riboxin , potassium chloride, vitamins B and C, low-volume plasmapheresis or intravascular laser blood irradiation, using corticosteroid hormones, immunostimulants, antihypoxants , anticoagulants and vitamins. At the same time, the best results were obtained after the use of prednisolone in combination with T- activin,

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

cytochrome -C or water-soluble β- carotene (Gavriliev S.S. 1997; Voronina G.A., 1999., Petrenko T.I. et al. 2004).

According to Averchenkov V.M. et al. (1998), the use of myelopide has a stimulating effect on the humoral and cellular immunity, and according to Chelnokova O.G., Kibrik B.S., (2003) the use of isophon for 1.5-2 months leads to a change in the stereotype of the course of the disease and allows to achieve clinical and radiological involution of the process, including with previously ineffective treatment.

In addition, in the course of chemotherapy in patients with caseous pneumonia, the insular apparatus is depleted. A dynamic study of cortisol levels reveals hypocortisolemia as a possible manifestation of adrenal insufficiency. A sharp decrease in the level of cortisol in dynamics allows us to suggest hormone replacement therapy after 2-4 months of treatment (G.S. Balasanyants , 2000).

However, the authors note a high mortality rate in patients with advanced forms of pulmonary tuberculosis from 25-30% (Chelnokova O.G., Kibrik B.S., 2003) to 60-80% (Kibrik B.S., Chelnokova O.G., 2003). This is determined not only by the acutely progressive nature of the course of the disease against the background of the presence of concomitant pathology or a combination of HIV/TB, but also by the late start of anti-TB therapy, which causes treatment failure due to a significant amount of lung tissue damage and the development of severe multiple organ disorders. Therefore, the responsibility of the therapist and pulmonologist for every day of missing the diagnosis of pulmonary tuberculosis is extraordinary, since the possibility of not only therapeutic, but also, as a last resort, surgical treatment is lost (Balasanyants G.S., 2000; Kibrik B.S., Chelnokova O.G., 2003).

Economic difficulties in the era of epidemiological troubles, the growth of primary and secondary drug resistance, the development of removable and irremovable adverse reactions, the issue of the occurrence and course of acute progressive forms of pulmonary tuberculosis is extremely relevant and needs to be resolved today.

LITERATURE

1. Ахмедов Т.Г. Основные факторы риска заболевания туберкулезом //Медицинский журнал Узбекистана. – 2003. - № 2. – С. 16-17.
2. Кильдюшева Е.И., Кравченко М.А. Особенности течения туберкулёза у больных с множественной лекарственной устойчивостью. // IX Съезд фтизиатров России. / Туберкулез и болезни легких. 2011. - №4. - С. 188.
3. Кноринг Б. Е. Автореферат диссертации на соискание ученой степени доктора медицинских наук, Особенности иммунного статуса больных туберкулезом легких и его роль в диагностике, прогнозировании течения и иммунокоррекции терапии, Санкт-Петербург 1996
4. Комиссарова О. Г. Особенности течения процесса и эффективность лечения рецидивов туберкулеза легких у больных с различным уровнем генерации оксида азота в мононуклеарах и нейтрофилах крови. Автореферат дисс.канд.мед.наук. М.2005.
5. Мишин В.В., Ромодановский П.О., Финогеева М.А. и др. Качество медицинской помощи при выявлении туберкулеза учреждениями общей лечебной сети //Матер.8-го Рос. съезда фтизиатров. – М., 2007. 158 с.

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

6. Мишин В.Ю. Чуканов В.И., Васильева И.А. Эффективность лечения туберкулеза легких, вызванного микобактериями с множественной лекарственной устойчивостью // Пробл.туберкулеза- 2002. № 12.- С. 18-23.
7. Мишин В.Ю., Дейкина О.Н., Назарова Н.В. Дифференциальная диагностика туберкулеза легких и внебольничной пневмонии // Consilium Medicum. – 2004. – Т.6, №4. С. 232-238.
8. Мишин В.Ю. К вопросу об оптимизации химиотерапии больных с впервые выявленным туберкулезом легких. Лечение туберкулеза. Рекомендации для национальных программ. // Клиническая микробиология и антимикробная химиотерапия. 2002. - №4. - С. 414.
9. Мишин, В.Ю., Жестовских С.Н. Особенности диагностики рецидивов туберкулёза органов дыхания// Пробл. туб. -2005. №5. — С.39-43.
10. Некрасов С.П., Попов С.А., Панова А.Е., и др. Повышение эффективности режимов химиотерапии больных туберкулезом с лекарственной устойчивостью. // IX Съезд фтизиатров России / Туберкулез и болезни легких. 2011. - №5. - С. 71.
11. Орловский противотуберкулёзный диспансер “Об эпидемиологической ситуации по туберкулёзу в орловской области”,2014г
12. ВОЗ. Глобальная борьба с туберкулезом: эпиднадзор, планирование, финансирование. // Женева. Швейцария. 2008. - Ь.
13. Перельман М.И.; Ред. Фтизиатрия: Национальное руководство. – М.: ГЭОТАР–Мед, 2007. 367 с.
14. Салина Т.Ю., Морозова Т.И. Современные технологии лабораторной диагностики туберкулеза (эффективность использования в клинической практике) // Пробл. туб и бол. легких. – 2008. – №12. с. 42-44.
15. Скотникова О.И. Молекулярно-биологические методы по фтизиатрии (обзор литературы)// Пробл. туб. – 2005. – №8. с. 5-9.
16. Таганович А.Д. , Гуревич Л.,. Алинежад С.М, Захаревский Ф.И.Способ диагностики плеврита туберкулезной этиологии на основании определения активности аденозиндезаминазы в сыворотке крови и в плевральной полости. Инструкция по применению. Минск, 2008.
17. Таганович А.Д., Алинежад С.М. Диагностические характеристики АДА-теста у больных туберкулезным плевритом – жителей Белоруссии // Пробл. туб. – 2008. – №8. с. 38-42.
18. Титаренко О.Т., Потапенко Е.И., Хокканен В.М. и др. Аденозиндезаминаза в комплексной диагностике различных форм внеклеточного туберкулеза // Пробл. туб. – 2006. – №4. с. 14-18.
19. Титов В.Н. Диагностическое значение повышения уровня С-реактивного белка в «клиническом» и «субклиническом» интервалах. // Клиническая лабораторная диагностика. - 2004. - №6. - С.3–10.

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

20. Ткаченко А.С. Уровень VEGF и ФНО-α при хроническом каррагенан-индуцированном гастроэнтероколите. // Вісник проблем біології і медицини. – 2013. - №3 (103). – Т.2. – С.231-234.

21. Тончкина Т.В., Низовцева Н.И., Марьяндышев А.О. Эффективность лечения больных с рецидивами туберкулеза. Туберкулез сегодня: Материалы VII Рос.съезда фтизиатров. - М.: Изд-во Бином., 2003. - С. 264.

22. Убайдуллаев А.М., Хамракулов Р.Ш., Мамарасулова О.У. Динамика основных эпидемиологических показателей по туберкулезу в Республике Узбекистана за период 1990-2008 годы //Вестник ассоциации пульмонологов Центральной Азии. № 1-4, 2009, с.62-68.

23. ВОЗ. Четвертый глобальный отчет по борьбе с туберкулезом лекарственной устойчивости в мире. // Женева. Швейцария. 2008. - а.

24. Убайдуллаев А.М., Казаков К.С., Садыков А.С., Черник Р.Б., Саидова Ш.М.. Упка силининг кайталаниши прогнози ва даволаш Самара-дорлигини ошириш (методик кулланма) /– Т. – 1999. – 14б.

25. Хамраев А.К., Медицинский журнал Узбекистана. 2011. №5 с-43-44

26. Ширикина А.Е., Бурухина Л.В., Шуругин А.А., Милашина Е.Н. Диагностическая значимость коэффициента аденозинаминазы у больных туберкулезным экссудативным плевритом// Пробл. туб. – 2009. – №4. – С. 49-52

27. (WHO/HTM/TB-2008.393; WHO/HTM/TB-2008.394; WHO/ HTM/TB - 2009.411; WHO/HTM/TB - 2010.3)

28. Farah M.G., Rygh J.H., Steen T.W., Selmer R., Heldal E., Bjune G. BMC Infect Dis Patient and health care system delays in the start of tuberculosis treatment in Norway. // 2006, 6, 33.

29. Gunluoglu G., Yazar E.E., Veske N.S., Seyhan E.C., Altin S. Mean platelet volume as an inflammation marker in active pulmonary tuberculosis. // MultidiscipRespir Med. – 2014. - 9(1). – P.11-16.

30. Parsons L.M, Salfinger M, Clobridge A, et al. Phenotypic and molecular characterization of Mycobacterium tuberculosis isolates resistant to both isoniazid and ethambutol. // Antimicrob Agents Chemother. 2005, 49

31. Storla D.G., Yimer S., Bjune G.A. A systematic review of delay in the diagnosis and treatment of tuberculosis. // BMC Public Health. 2008, 8, 15.

32. Verver S, Warren RM, Beyers N, Richardson M, van der Spuy GD, et al. Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. Am J RespirCrit Care Med.,2005, 171: 1480-1485.

33. Zakoska M. Risk factors for relapses of tuberculosis // Eur. Resp. J. 2003. -V. 22. — suppl. 45. -P.2172.

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

34. Usmonov, Isomiddin, and Umrzok Shukurov. "Features of the Clinical Course, the State of Diagnosis and Treatment of Hiv-Associated Pulmonary Tuberculosis in Modern Conditions Literature Review." Annals of the Romanian Society for Cell Biology (2021): 1809-1828.
35. Kh, Usmonov I., Bahodir R. Muazzamov, and Muhtor F. Jumaev. "Features of diagnostics and treatment of drug-resistant forms of pulmonary tuberculosis." International journal of pharmaceutical research 13.1 (2021): 2484-2489.
36. Usmonov, Isomiddin Xaydarovich, and Nodir Yusufovich Kobilov. "Epidemiology, Clinical Course, Diagnosis and Treatment of Generalized Tuberculosis in Modern Circumstances Literature Review." Annals of the Romanian Society for Cell Biology (2021): 3806-3819.
37. Kh, Usmonov Isomiddin, and I. Bozorov Shukhrat. "Improvement of anterior extraperitoneal approaches in the surgical treatment of tuberculosis of the lumbar and lumbosacral spine." International journal of pharmaceutical research 13.1 (2021): 2476-2483.
38. Khaydarovich, Usmonov Isomiddin, and Nazirov Primkul Khodgamovich. "Technique of use of titanium mesh cylinder of exemplary cage tubercular spondylitis." European science review 9-10-2 (2018): 178-184.
39. Kh, Usmonov I. "Clinical Course and Modern Diagnosis of Resistant Forms of Pulmonary Tuberculosis." American journal of social and humanitarian research 3.2 (2022): 250-260.
40. Khaydarovich, Usmonov Isomiddin, and Shukurov Umrzoq Zarifboevich. "CHALLENGES OF DIAGNOSTICS AND FEATURES OF TREATMENT FOR LUNG TUBERCULOSIS IN HIV INFECTED PATIENTS." EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE 2.2 (2022): 92-97.
41. Aslonov, F. I., S. A. Rustamova, and K. M. Raxmonova. "Immunopatological aspects in patients with first detected pulmonary tuberculosis." World Bulletin of Public Health 4 (2021): 91-95.
42. Ismoilovich, Aslonov Farrukh. "Tuberculosis Diagnostics with Modern Solutions (Literature Review)." Central Asian Journal of Medical and Natural Science 3.3 (2022): 377-383.
43. Аслонов, Фаррух. "ЭПИДЕМИОЛОГИЧЕСКИЕ И КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ТУБЕРКУЛЕЗА МОЧЕВИДЕЛИТЕЛЬНОЙ СИСТЕМЫ." Eurasian Journal of Medical and Natural Sciences 2.10 (2022): 59-63.
44. Ismoilovich, A. F. "Modern Diagnostic Test for Tuberculosis." European Multidisciplinary Journal of Modern Science 4 (2022): 408-412.
45. Ulugbek o'gli A. M. Factors Predicting Mortality in Pulmonary Tuberculosis //Central Asian Journal of Medical and Natural Science. – 2022. – Т. 3. – №. 3. – С. 362-367.
46. Ulugbek o'gli A. M. Test for Procalcitonin as a Way to Predict Patients with Respiratory Tuberculosis //European Multidisciplinary Journal of Modern Science. – 2022. – Т. 4. – С. 486-491.
47. Ulugbekugli A. M. CLINICAL ASPECTS OF TUBERCULOSIS DISEASE //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 12. – С. 73-80.

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

48. Муаззамов Б. Р., Жумаев М. Ф. О преподавании фтизиатрии на лечебном и медико-педагогическом факультетах //Материалы VIII Съезда фтизиатров и пульмонологов Узбекистана. Тошкент. – 2018. – С. 109-110.
49. Муаззамов Б. Р., Муаззамов Б. Б., Медведева Н. В. ПРИМЕНЕНИЕ ИНТЕРАКТИВНЫХ ПЕДАГОГИЧЕСКИХ МЕТОДОВ ПРЕПОДАВАНИЯ ПРЕДМЕТА" ФТИЗИАТРИЯ" НА ПРИМЕРЕ ТЕМЫ" ДЕСТРУКТИВНЫЕ ФОРМЫ ТУБЕРКУЛЁЗА ЛЁГКИХ" //Новый день в медицине. – 2019. – №. 3. – С. 45-50.
50. Erkinova, Nigora. "OBSERVATION OF ALBUMINURIA IN CHRONIC HEART FAILURE AND SOME OF ITS CLINICAL FEATURES." Galaxy International Interdisciplinary Research Journal 9.05 (2021): 442-446.
51. Nigora, Erkinova, and Xuddieva Nargiza. "Observations, clinical features of albuminuria with renal changes in chronic heart failure." Academicia Globe: Inderscience Research 2.5 (2021): 1-5.
52. Erkinovna, Erkinova Nigora, and Olimova Aziza Ulugbekovna. "THE COURSE OF COMORBID CONDITIONS IN DIFFERENT FUNCTIONAL CLASSES OF CHRONIC HEART FAILURE." INTERNATIONAL CONFERENCE ON MULTIDISCIPLINARY RESEARCH AND INNOVATIVE TECHNOLOGIES. Vol. 1. 2021.
53. Erkinovna, Erkinova Nigora. "PRE-AND POST-TREATMENT INDICATIONS IN CHRONIC HEART FAILURE WITH VARIOUS COMORBID DISEASES." Galaxy International Interdisciplinary Research Journal 10.11 (2022): 302-308.
54. Erkinovna, Erkinova Nigora, and Kasimov Khurshid Ilhomovich. "The Role of Aldosterone in the Development of Chronic Heart Failure and the Effectiveness of Mineralocorticoid Receptor Antagonists in its Treatment." Research Journal of Trauma and Disability Studies 1.9 (2022): 136-140.
55. Erkinovna, Erkinova Nigora, and Kosimov Khurshid Ilkhomovich. "Comorbid Conditions in Different Functional Classes of Heart Failure." Research Journal of Trauma and Disability Studies 1.9 (2022): 93-99.
56. Алимова Г. С. Массовый Скрининг Для Выявления Туберкулезной Инфекции У Детей В Возрасте От 2 До 8 Лет //Central Asian Journal of Medical and Natural Science. – 2022. – Т. 3. – №. 3. – С. 368-376.
57. Salimovna A. G. Diagnosis of Tuberculosis Infection Activity by ELISA and Transcription Analysis Methods //European Multidisciplinary Journal of Modern Science. – 2022. – Т. 4. – С. 492-497.
58. Alimova G. DETECTION OF ADOLESCENT TUBERCULOSIS IN THE REGION OF BUKHARA WITH THE HELP OF THE DRUG" DIASKINTEST" //Eurasian Journal of Medical and Natural Sciences. – 2022. – Т. 2. – №. 10. – С. 46-51.
59. Рахмонова К. М. Разработка Методов Ранней Диагностики, Лечения И Профилактики Хронической Дыхательной Недостаточности При Туберкулёзе Легких (Обзорная Литературы) //Central Asian Journal of Medical and Natural Science. – 2022. – Т. 3. – №. 3. – С. 262-272.

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

60. Рахмонова К. М. Туберкулез Легких И Сопутствующие Заболевания //Central Asian Journal of Medical and Natural Science. – 2021. – Т. 2. – №. 6. – С. 137-144.
61. Mizrobovna R. K. Accompanying Diseases of the Respiratory System Pulmonary Tuberculosis //European Multidisciplinary Journal of Modern Science. – 2022. – Т. 4. – С. 244-250.
62. Muzrobovna R. K. Diagnosis and Treatment Patients with Pulmonary Tuberculosis with Concomitant Bronchoobstructive Syndrome //Research Journal of Trauma and Disability Studies. – 2022. – Т. 1. – №. 10. – С. 109-118.
63. Rakhmonova K. TUBERCULOSIS AND IRON-CONTAINING CHEMOTHERAPEUTIC DRUGS //Eurasian Journal of Medical and Natural Sciences. – 2022. – Т. 2. – №. 10. – С. 40-45.
64. Жумаев М. Ф. СЛОЖНОСТИ ДИАГНОСТИКИ И ЛЕЧЕНИЯ ЛЕКАРСТВЕННО-УСТОЙЧИВЫХ ФОРМ ТУБЕРКУЛЁЗА ЛЕГКИХ //Вопросы науки и образования. – 2021. – №. 15 (140). – С. 21-27.
65. Fatullayevich J. M. BIOLOGICAL CHARACTERISTICS OF THE CAUSATIVE AGENT OF TUBERCULOSIS IN PATIENTS WITH PULMONARY TUBERCULOSIS //World Bulletin of Public Health. – 2021. – Т. 5. – С. 27-32.
66. Жумаев М. Ф. ДИАГНОСТИКА ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТИ ПРИ ТУБЕРКУЛЕЗЕ ЛЕГКИХ У ПАЦИЕНТОВ МОЛОДОГО ВОЗРАСТА И ПРИЧИНЫ ЕЕ ФОРМИРОВАНИЯ //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 10. – С. 358-362.
67. Жумаев М. Ф. ХАРАКТЕРИСТИКА И НЕДОСТАТКИ КЛИНИЧЕСКОЙ И МЕДИЦИНСКОЙ ДИАГНОСТИКИ ТУБЕРКУЛЕЗА ЛЕГКИХ //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 10. – С. 367-372.
68. Жумаев М. Ф. ТРУДНОСТИ ДИАГНОСТИКИ САНИТАРНО-ГИГИЕНИЧЕСКАЯ ГРАМОТНОСТЬ БОЛЬНЫХ ЛЕКАРСТВЕННО-УСТОЙЧИВЫМИ ТИПЫ ТУБЕРКУЛЕЗА ЛЕГКИХ //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 10. – С. 346-350.
69. Fatullaevich J. M. CHARACTERISTICS AND DISADVANTAGES OF CLINICAL AND MEDICAL DIAGNOSTICS OF LUNG TUBERCULOSIS //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 12. – С. 25-30.
70. Fatullaevich J. M. DIAGNOSTICS OF DRUG RESISTANCE IN TUBERCULOSIS LUNG IN YOUNG PATIENTS AND CAUSES OF ITS FORMATIONS //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 12. – С. 19-24.
71. Fatullaevich J. M. DIFFICULTIES OF DIAGNOSTICS AND SANITARY AND HYGIENIC LITERACY OF PATIENTS WITH DRUG-RESISTANT FORMS

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).

PULMONARY TUBERCULOSIS //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2022. – Т. 2. – №. 12. – С. 31-35.

72. Jumayev M. INFLUENCE OF DIABETES MELLITUS COURSE AND RESULTS OF TUBERCULOSIS TREATMENT //Eurasian Journal of Medical and Natural Sciences. – 2022. – Т. 2. – №. 10. – С. 52-58.
73. Рустамова С. А. и др. Изучение причин и факторов, способствующих развитию рецидивов туберкулеза органов дыхания //Медицинский альянс. – 2015. – №. 1. – С. 115-115.
74. Рустамова С. А. и др. Спектр лекарственной устойчивости и эффективность лечения впервые выявленных больных туберкулезом легких //Медицинский альянс. – 2015. – №. 1. – С. 116-116.
75. Мухамедов К., Джурабаева М., Рустамова С. Частота встречаемости вирусных гепатитов среди впервые выявленных больных туберкулезом легких //Журнал проблемы биологии и медицины. – 2014. – №. 3 (79). – С. 132-133.
76. Davlatovna Y. T. MAIN DIRECTIONS OF TUBERCULOSIS RESEARCH ON PREVENTION, DIAGNOSIS AND TREATMENT //Web of Scientist: International Scientific Research Journal. – 2022. – Т. 3. – №. 10. – С. 389-396.
77. Yitmasova T. BASIC RESEARCH METHODS IN TUBERCULOSIS PREVENTION AND TREATMENT //Theoretical aspects in the formation of pedagogical sciences. – 2022. – Т. 1. – №. 5. – С. 55-56.
78. Davlatovna, Y. T. . (2022). Specific Characteristics of the Thyroid Gland Morphometric Parameters in Goit's Disease. Research Journal of Trauma and Disability Studies, 1(9), 221–227.
79. Воронкова О. В., Хасанова Р.Р., Урасова О.И., и др. Клинико-иммунологическая характеристика Beijing-туберкулеза в Томской области. // IX Съезд фтизиатров России / Туберкулез и болезни легких -2011.-№4.-С. 96.
80. Джурабаева М.Х. Особенности клинического течения и эффективность лечения острых прогрессирующих форм туберкулеза легких у женщин фертильного возраста: Автореф.дис. канд.мед.наук. Ташкент, 2005. – 33с.
81. Земляная Н. А. Клинико-иммунологические особенности туберкулеза легких с множественной лекарственной устойчивостью Автореферат диссертации на соискание ученой степени кандидата медицинских наук, Томск - 2007
82. Ильина Т. Я, Жангириев А.А., Сидоренко О.А. Абацилярные рецидивы туберкулеза органов дыхания. //Пробл. туб.- 2004.- № 2.- С.33-35.
83. Инструкция по применению набора реагентов для иммуноферментного определения концентрации фактора некроза опухолей-альфа // ЗАО «Вектор-Бест». Новосибирск,30.09.08. – 22 с.
84. Кибрик, Челнокова О.Г. Некоторые особенности лекарственной резистентности микобактерий туберкулёза у больных с остропрогрессирующими деструктивными формами туберкулёза лёгких лечении туберкулеза легких у больных с устойчивостью МБТ и непереносимостью химиопрепаратов // В кн. Химиотерапия туберкулеза. - М.2000,с-75

© 2023 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/).