OPTIMIZATION OF METHODS FOR ELIMINATING THE NEPHROTOXIC EFFECT OF ANTI-TUBERCULOSIS DRUGS IN PATIENTS WITH RESISTANT TUBERCULOSIS (LITERATURE REVIEW)

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The review analyzes publications devoted to the frequency of renal adverse reactions during tuberculosis chemotherapy. The most significantpathophysiological mechanisms causing development of drug-induced nephrotoxicity are presented. The article describes the specific features ofnephrotoxic effect of I line and II line of anti-tuberculosis drugs.

Key words:Multidrug resistant tuberculosis, acute kidney injury, anti-tuberculosis drugs, acute drug reactions, nephrotoxic side effects, adverse drug reactions, mycobacterium tuberculosis,molecular genetic methods

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Abstract

The problem of kidney damage on the background of long-term drug therapy is relevant and important for assessing the prognosis of patients' life. The study of drug-induced kidney damage in phthisiology is not given sufficient attention, perhaps because often small manifestations of drug-induced nephropathy can be veiled by more pronounced manifestations of drug intolerance. In the spectrum of adverse reactions in chemotherapy patients with tuberculosis, the frequency of nephrotoxic reactions varies from 5 to 16%.

Meanwhile, for the development of drug-induced nephrotoxicity in patients with tuberculosis, there are all the prerequisites: the presence of a severe infectious disease with intoxication syndrome and multiple organ damage to internal organs, long-term use of a large number (5-6 or more) of anti-tuberculosis drugs, the presence of concomitant pathology (chronic kidney disease, diabetes, hepatitis).

Increased concentration, altered chemical composition and physical properties of drugs and their metabolites can lead to various and varying degrees of damage to the renal structures and the occurrence of pathological conditions.

Epidemiological indicators of tuberculosis - susceptible and resistant forms of tuberculosis

Despite significant progress in the fight against tuberculosis, it is still the most deadly bacterial infectious disease worldwide. Every year up to 10 million people worldwide still die from tuberculosis. The World Health Assembly has set itself the goal of reducing TB deaths by 90% and new infections by 80% by 2030. Of particular importance are prevention and infection control measures in public health facilities and wherever there is a high risk of transmission of TB bacterium [93. Christof C, Nußbaumer-Streit B, Gartlehner G. P. 885-889].

Tuberculosis is an infectious bacterial disease caused by Mycobacterium tuberculosis (MTB), which is transmitted between people through the respiratory tract and most often affects the lungs, but can damage any tissue. Only about 10 percent of those infected with MTB progress to active TB disease during their lifetime; the rest of the infected successfully contain their infection. One problem with TB is that the pathogen remains dormant in many infected people for many years and can be reactivated to

cause disease. The risk of progression of TB disease after infection is highest shortly after the initial infection and increases dramatically for individuals co-infected with HIV/AIDS or other immunocompetent conditions. Treatment of tuberculosis disease requires several drugs for many months. These long-term drug regimens are challenging for both patients and health systems, especially in low- and middle-income countries (LMICs), where the disease burden often far exceeds local resources. Drug-resistant TB is on the rise in some areas, requiring even longer treatment regimens with drugs that are more expensive and difficult to tolerate.

Diagnosis in LMIC is predominantly made by microscopic examination of stained sputum smears from suspected patients; however, smear microscopy is only able to detect 50-60 percent of all cases (smear-positive). Recently, more sensitive methods for diagnosing tuberculosis and detecting drug resistance have become available, although more expensive. The time between the onset of the disease and the diagnosis and initiation of treatment is often prolonged, and such delays allow the transmission of the disease. Although Bacillus Calmette-Guerin (BCG) remains the most widely used vaccine in the world, its effectiveness varies geographically and is incomplete. Modeling suggests that more effective vaccines are likely to be needed to move TB towards elimination in high incidence settings. [92. Bloom BR, Atun R, Cohen T.]

Chemotherapy for tuberculosis is one of the most cost-effective of all health interventions. This evidence has played a central role in the global advancement of WHO and the Stop TB Partnership policy on directly observed therapy, a short-term strategy (DOTS), a package of best practices in the diagnosis and care of TB patients [UN General Assembly, year 2000]. The DOTS TB control strategy promotes standardized care with observation and patient support, which may include, but is much broader than, direct observation of therapy (DOT), where a healthcare worker personally observes a patient taking medication [122. WHO 2013a].

The new guidance aims to highlight the need for multisectoral, well-coordinated, comprehensive strategies to prevent TB infections in health care settings, as well as in high-risk community settings. As a first step, this guideline provides an overview of the general recommendations and proven practices that are necessary for the successful implementation of infection prevention and control. These core components of infection prevention and control are an integral part of WHO's strategy to prevent current and future threats. In addition, they are designed to strengthen health system resilience, prevent infections in health care settings, and combat antimicrobial resistance [120.WHO. 2019].

Two decades ago, the World Health Organization (WHO) initiated the Global Drug-Resistant Tuberculosis Surveillance Project, which aimed to control the epidemic with timely assessment and implementation of an adequate public health response. According to the WHO, drug-resistant TB continues to be a public health crisis. In 2016, more than 600,000 people worldwide developed TB resistant to rifampicin, the most effective first-line drug, and of these, 82% had multidrug-resistant TB (MDR-TB). A significant contribution to the problem of tuberculosis is made by the global epidemic of HIV infection [96. Floyd K., Glaziou P., Zumla A., Raviglione M. 299-314].

Fighting TB will require three new advances: the development of new point-of-care diagnostics, more effective treatment regimens to control drug-susceptible and drug-resistant TB, and more effective vaccines. As argued in this chapter, this requires new strategies and tools that include moving away from traditional passive case-finding for DOTS and moving towards more active case-finding in high-burden regions; provision of services targeted at the most vulnerable populations and integrated with other services, especially HIV/AIDS services; and care based on primary health care and the community level. Particularly in countries with a high TB burden, many people with TB are asymptomatic, so that the expectation that patients will get sick enough to seek medical care has not

been sufficient to markedly reduce transmission and incidence [Bates and others 2012; Mao and others 2014; Willingham and others, 2001; Wood and others 2007]. A more proactive and aggressive approach is needed to remove health system barriers to effective TB control.

The results of modeling the further development of the epidemic process of tuberculosis in several regions of the world, including the Uzbekistan, indicate an unfavorable prognosis in the spread of tuberculosis with multidrug and extensive drug resistance Mycobacterium tuberculosis. Pasechnik O. A., Stasenko V. L. [62. P. 58] consider the improvement of the system of epidemiological surveillance of tuberculosis caused by drug-resistant strains of MTB in modern conditions. To this end, scientists conducted an epidemiological analysis of the manifestations of tuberculosis infection in the Omsk region for the period 2006–2017, assessed the effectiveness of the existing system of epidemiological surveillance, and showed the need for its optimization. In the Omsk region, against the background of improving a number of indicators characterizing the epidemiological situation, reducing the incidence and mortality of the population from tuberculosis, there was a stable incidence of multidrug-resistant tuberculosis, a pronounced upward trend in the incidence and prevalence of extensively drug-resistant tuberculosis, as well as the incidence of tuberculosis in HIV-positive patients. The observed changes in the most important quantitative and qualitative characteristics of the epidemic process of tuberculosis demonstrate the insufficient effectiveness of anti-tuberculosis measures, determine the need to improve the system of epidemiological surveillance and control. Approaches to the implementation of epidemiological surveillance of tuberculosis infection in modern conditions are presented, criteria for assessing its quality and effectiveness are proposed.

A group of Chinese scientists [102.Liu Y, Zhang X, Zhang Y, Sun Y.2018. 658] characterize strains of Mycobacterium tuberculosis in Beijing, China: drug susceptibility phenotypes and genotype transmission of the Beijing genotype family. The most common strains of Mycobacterium tuberculosis (MTB) in Beijing belong to the Beijing genotype family. The influence of the prevalence of the Beijing genotype on the development of drug resistance and the association of infection with the Beijing MTB genotype with population characteristics in Beijing, however, is still unclear. Scientists conducted retrospective studies of 1189 isolates. Patients were subjected to drug susceptibility testing (DST) and molecular epidemiological analysis, and differences in the percentage of drug resistance between Beijing and non -Beijing strains of the genotype were compared. The relationship between the occurrence of drug resistance and the prevalence of the Beijing MTB genotype was analyzed using statistical methods. The Beijing genotype family was the dominant genotype (83.3%) among 1189 isolates MTB. Beijing strains of the MTB genotype were more likely to spread among males [p = 0.018, OR (95% CI): 1.127(1.004-1.264)] and people in the 45-64 age group [p = 0.016, OR (95% CI): 1.438 (1.027-2.015)]. In contrast, non-Beijing genotype MTBstrains were more common among over 65 [p=0.005, OR (95% CI): 0.653 (0.474-0.9)] and non-resident populations [p=0.035, OR (95 % CI): 1.185(0.985-1.427)]. The DST results showed that 849 (71.4%) strains were fully sensitive to first-line drugs, while 340 (28.6%) strains were resistant to at least one drug, and 9% (107/1189) were MDR-TB. The frequency of INH-resistance among Beijing genotype strains was significantly lower than among non-Beijing genotype strains (p = 0.032). In addition, clusters are easily formed in the Beijing family of genotypes. Thus, the results show that male and middle-aged people were more likely to be infected with the Beijing MTB genotype, older people and non-residents were more likely to be infected with the non- Beijing MTB genotype. The high percentage of INH resistance found in non-Beijing genotype strains suggests that non-Beijing genotype strains should receive much more attention in Beijing.

In another investigation by Chinese scientists [112.Qiu B, Tao B, Liu Q, Li Z. 2021. 368] shows a description of the cluster characteristics of Mycobacterium strains tuberculosis circulating in eastern China and determining the ratio of relapses to re-infections in relapsed patients. In August 2013 and

December 2015, scientists recruited sputum smear-positive pulmonary tuberculosis patients from five cities in Jiangsu Province, China. Patients were followed up for treatment outcomes and relapses based on a cohort design. MTBstrains were isolated and genotyped using the MIRU-VNTR 12 locus. The Beijing family was identified using an extended region of difference (RD) analysis. The Hunter-Gaston Discrimination Index (HGDI) was used to evaluate the resolution of the MIRU-VNTR. The odds ratio (OR) together with the 95% confidence interval (CI) was used to assess the strength of the association. We performed a cluster analysis of 2098 isolates MTBand classified them into 545 genotypes and five categories (I, 0.19%; II, 0.43%; III, 3.34%; IV - 77.46%; V, 18.59%). After adjusting for potential confusion, the Peking family genotype (OR = 118.63, 95% CI: 79.61-176.79, P = 0.001) was significantly associated with dominant strain infections. Patients infected with non-dominant strains had a higher risk of developing a lung cavity (OR = 1.39, 95% CI: 1.01-1.91, P = 0.046). Among 37 paired recurrent cases, 22 (59.46%) were identified as endogenous reactivation and 15 (40.54%) were exogenous reinfection. The type of MTB strains that are common in Jiangsu is relatively lonely. Beijing familial strains infection dominates in local cases of tuberculosis. Endogenous reactivation appears to be the main cause of recurrent tuberculosis in East China. This finding highlights the importance of follow - up and monitoring of cases after completion of anti - tuberculosis treatment.

Kazakh authors Akhmetova A, Bismilda V, Chingissova L, Kozhamkulov U. [87. 129-135] assess the biological diversity of MTB clinical isolates from different regions of Kazakhstan based on the analysis of MIRU-VNTR genotyping. The MIRU-VNTR method was used for the genotype of 134 clinical isolates of MTB isolated from new cases and recurrent cases of tuberculosis from different regions of Kazakhstan. Amplification was performed using 15 MIRU-VNTR loci. The number of tandem repeats in the corresponding locus was determined using the Quantity software. One v.4.4.0 (BioRad, USA). Reference strain H37Rv (NC_000962) was used as a positive control. Phylogenic the tree was built using the www.miru-vntr.org web resource based on the results of the MIRU-VNTR analysis. Peking family strains associated with drug resistance to anti-tuberculosis drugs were common among all MTB isolates circulating in Kazakhstan. Peking genotype strains were common in both new cases (65%) and recurrent cases (89.4%) of tuberculosis. The second significant genotype, which is common in Kazakhstan, is LAM, the prevalence rate is 7.3% in new cases and 4.5% in recurrent cases. Other MTB families such as Ural, Haarlem, CAS, NEW-1, S were found in less than 4% of cases. The prevalence of strains of the Beijing family among all isolates of MTB from different regions of Kazakhstan is shown. Strains of this family are common among young people. This genotype is responsible for the ongoing transmission of tuberculosis at the present time. This genotype is more virulent; therefore, the study of the epidemiology of the Beijing genotype plays a crucial role in the monitoring of tuberculosis. According to the results of genotyping, strains of the MTB family Beijing were found in 65.3% of cases. Of the 177 Beijing isolates (68.4%), 121 were drug-resistant. MDR-TB prevalence was found among drug-resistant Beijing (58.7% - 71/121) and LAM family isolates (50% - 10/20).

Japanese scientists [107.Mizukoshi F, Kobayashi N, Kirikae F 2021.6(4):e0097820] consider clinical isolates of drug-resistant (isoniazid and/or rifampicin -resistant) Mycobacterium tuberculosis were obtained from 254 patients diagnosed with drug-resistant tuberculosis in Japan from April 2015 to March 2017 in the hospitals of the National Hospital Organization. The 254 patients accounted for approximately 32% of all 795 patients diagnosed with culture-confirmed drug-resistant TB from 2015 to 2016 nationwide in Japan. The whole genome sequences of all isolates from 254 patients and the lines of these isolates were determined, and phylogenetic trees were built on the basis of concatemers single nucleotide polymorphism. Of these patients, 202 (79.5%) were born in Japan and 52 (20.5%) were born elsewhere. Of the 254 drug-resistant isolates, 54 (21.3%) were multidrug-resistant, being resistant to

both isoniazid and rifampicin. The percentage of multidrug-resistant isolates was significantly higher in patients of foreign origin (38.5% [20/52]) than in patients of Japanese origin (16.8% [34/202]). Of the 54 multidrug-resistant isolates, nine were extensively drug-resistant, which were obtained from patients of Japanese descent. Five extensively drug-resistant isolates were obtained from patients with budding tuberculosis. A significant number of multidrug-resistant strains of MTB have been isolated from foreign-born patients from Asian countries with a high burden of tuberculosis. Isolates of foreign origin affect the nationwide genetic diversity of drug-resistant MTB in Japan. Widely drug-resistant isolates of MTB were transmitted among the Japanese population. The incidence rate of tuberculosis (TB) in Japan was 11.5 per 100,000 population in 2019. Of TB patients in Japan, 61.1% were >70 years of age and 10.7% were born outside of Japan, mostly in Asian countries with a high burden of TB. Of the TB patients in the present study, 5.4% and 1.0% showed resistance to isoniazid and rifampicin, respectively, and 0.7% were multidrug resistant. The aim of this study was to clarify the molecular epidemiological properties of drug-resistant tuberculosis in Japan. Molecular epidemiology provides several clues for informing potential responses to drug-resistant TB in Japan.

Modern methods for diagnosing the nephrotoxic effect of anti-TB drugs

Timely diagnosis of acute drug reactions (ADR) and the rational use of corrective agents make it possible, by maneuvering prescriptions, to conduct continuous combined chemotherapy, up to the clinical cure of the patient.

Early diagnosis and effective treatment of patients with extensive drug resistance can significantly reduce the burden of TB infection. However, if the introduction of new technologies in the laboratory diagnostics of drug-resistant forms of tuberculosis (GeneXpert MTB/RIF) makes it possible to diagnose drug resistance relatively quickly, then ineffective treatment of patients with extensive drug resistance contributes to the chronicity of the disease, the accumulation of patients with extensively drug-resistant tuberculosis in the contingent, the implementation of high risk of transmission of extensively drug-resistant tuberculosis in the population.

Chotchaev R. M. [82.2019] recommends that in the diagnosis of urogenital tuberculosis from radiation methods, preference should be given to multispiral computed tomography of the kidneys with contrast, which, in comparison with excretory urography, has a higher resolution in identifying specific signs of the disease. Percutaneous puncture nephrostomy under ultrasound and/or X-ray control in patients with tuberculosis of the kidney and ureter should be performed at the late (III-IV) stages of hydroureteronephrosis, and at early (I-II) - with the failure of stenting. The obtained data on glomerular filtration make it possible to determine the feasibility of performing an organ- removing or reconstructive-restorative operation.

The development and implementation of promising technologies for the accelerated diagnosis of TB and the identification of non-resistant MTB of the pathogen are extremely important to ensure highly effective treatment based on the selection of personalized chemotherapy regimens. One of the most promising and demanded directions in the development of laboratory diagnostics of TB, which is supported by WHO, the Global Laboratory Initiative and the European Laboratory Initiative, is the use of molecular genetic methods (MGM). The use of the PCR method for the diagnosis of tuberculosis makes it possible to establish the presence of MBT DNA in the diagnostic material within 1 working day (2-3 hours). Preference is given to test systems with real-time result detection, which almost completely eliminate the risk of sample contamination with amplification products.

Sokova E.A. et al (73. 2020. 123-133), from14 to 26% of drugs used in clinical practice are potentially nephrotoxic, remaining a common cause of acute kidney injury and chronic kidney disease. Acute kidney injury in adults and children is associated with a high risk of readmissions, complications,

and death. Purpose of the work: analysis of scientific information on modern approaches to the assessment of drug-induced kidney injury. The pathogenetic mechanisms of kidney damage during the use of drugs, as well as the molecular mechanisms of drug-induced damage at the level of their transporters, are described. The risk factors for the development of drug-induced kidney damage are considered: age, gender, ethnicity, comorbid conditions (chronic kidney disease, diabetes mellitus, cardiovascular diseases, immune disorders, sepsis, etc.), dose and duration of therapy, pharmacokinetics of drugs, interaction potentially nephrotoxic drugs, genetic determinism of drug metabolism and transport, and others. It has been shown that traditional markers of nephrotoxicity - creatinine level and urine output - have low sensitivity in determining the early stage of kidney damage, so the search for new renal biomarkers for the diagnosis and monitoring of acute kidney damage in patients with various diseases continues. Some of these biomarkers are already used in the development of new drugs, in preclinical and clinical studies to assess and predict the safety of drugs. The analysis performed showed that none of the new renal biomarkers is universal for routine use in clinical practice. The development of new biomarkers for acute kidney injury is a long-term investment and essential for early diagnosis and successful treatment of drug-induced kidney injury.

Fan W, Ankawi G, Zhang J [95. 2019. 57(5):567-76] according to the scientific literature, a large number of new renal biomarkers have now been identified that are being tested as candidates biomarkers of safety in preclinical and clinical studies for the prediction and evaluation of AKI in various diseases.

In the work of T.C. Fuchs et al. [97. 5(6):763-79] presented in detail the main biomarkers of AKI and their localization. Today, AKI is usually assessed by serum creatinine and urine output, but this does not provide early detection of AKI. Therefore, for the early detection of AKI that occurs with the use of drugs, it is advisable to use additional markers. In 2018, the US Food and Drug Administration (Food and drug Administration, FDA) has qualified the first biological markers of renal safety. The panel included six renal biomarkers: clusterin (Clusterin, CLU), cystatin C (Cystatin -C, CysC), kidney damage molecule 1 (Kidney injury molecule-1, KIM-1), K-acetyl - glucosaminidase (N- acetyl - beta - (D) - glucosaminidase activity, NAG), neutrophil gelatinase -associated lipocalin, or lipocalin 2 (Neutrophil gelatinase-associated-ed lipocalin, NGAL), and osteopontin (Osteopontin, OPN). Reports from the FDA and the European Medicines Agency (European Medicines Agency, EMA) stated that a biomarker panel should always be used in conjunction with the traditional measures of nephrotoxicity, elevations in serum creatinine and blood urea nitrogen to detect renal tubular injury in phase I studies in healthy volunteers when it is tentatively assumed that the drug can cause damage to the renal tubules in humans. Because the biomarker qualification process is complex and financially demanding, efforts are supported by large consortiums (e.g., Predictive Safety testing Consortia, PSTC; Innovative Medicines Initiative, IMI), which are collaborating with the government, pharmaceutical industry representatives, and patient advocacy groups to use biomarkers in preclinical and clinical studies to accelerate the drug development process.

Clinical and laboratory studies confirm the presence of kidney lesions in pulmonary tuberculosis. Proteinuria and hematuria (usually microhematuria) are the most frequent and early clinical and laboratory signs of kidney damage in these patients. The morphological substrate of nonspecific kidney lesions in various clinical and anatomical forms of tuberculosis is a variety of combinations of damage to the glomeruli, tubules and interstitial tissue of the kidneys of varying severity: glomerulo- and tubulointerstitial nephritis, dystrophic and necrobiotic changes in the tubular epithelium, including necrotizing nephrosis and glomerulosclerosis. The polymorphism of clinical and morphological manifestations of nonspecific kidney lesions in tuberculosis is determined by the combined effect of many factors that cause damage to various structures of the kidneys: immunopathological, dyscirculatory, metabolic, exogenous intoxication, and others. The influence of these factors in various

clinical and anatomical forms of tuberculosis varies, leading to the predominance of immune -mediated changes in the glomeruli in primary and hematogenous disseminated tuberculosis and tubulointerstitial lesions of a dystrophic and inflammatory nature in post-primary forms.

To date, the prevention and diagnosis of AKI continue to be an unresolved medical problem. Clinical manifestations of AKI often go unnoticed, especially under conditions of short-term exposure to drugs, which makes it difficult to diagnose, assess the severity and long-term consequences of this condition. Recognition of AKI is complicated by the fact that the mechanisms of kidney damage and the period of time from the onset of exposure vary depending on the use of a particular drug. There is a consensus that in order to assess the ratio of the expected benefit to the possible risk of using drugs that can potentially be nephrotoxic, it is necessary to take into account the risk factors for the development of AKI: features of the pharmacokinetic and pharmacogenetic profile of the patient, his age, gender, ethnicity, comorbid conditions, etc. Therefore, a personalized approach is paramount for effective prevention, early diagnosis and treatment of AKI.

Epidemiological indicators of nephrotoxic side effects (NSE) of anti-tuberculosis drugs (ATD) (especially those of the reserve group) during the course of the disease and after chemotherapy

Gupta A, KumarV, NatarajanS. [99. 2020. 67(4 S): S 69- S 78]. Multiple drugs taken long-term in the treatment of TB, especially drug-resistant TB (DR-TB) can cause adverse drug reactions (ADRs). Although any anti-TB drug can cause ADR, they are more common with drugs used to treat DR-TB. However, most ADRs with these drugs are mild to moderate and can be managed if adequate surveillance and monitoring is in place. However, a few ADRs can be serious or potentially life-threatening and may require removal of the offending drug. Patients with TB who have comorbidities and are being treated for them may experience drug interactions with anti-TB drugs and may require dose modification or drug changes. For a good TB treatment outcome, patient compliance must be ensured, and adverse events and drug interactions must be properly considered by clinicians. The authors outline most of the possible ADRs for anti-TB drugs used for the management of DR-TB and their common drug interactions, with practical guidelines for identifying the possible drug(s), responsible and most adequate management in each situation.

Multidrug-resistant tuberculosis (MDR-TB), caused by M. A strain of tuberculosis that is resistant to both the main drugs, isoniazid, and rifampicin, remains a public health crisis and a health security threat. Treatment of MDR-TB and extensively drug-resistant TB (XDR-TB; MDR-TB with additional resistance to any fluoroquinolone and at least one of the three second-line injectables amikacin, capreomycin, or kanamycin) is challenging because it relies on drugs with lower efficacy and greater toxicity than those used for drug-susceptible tuberculosis (DS-TB) [116. Tiberi S, du Plessis N, Walzl G.2018. 18: e 183– e 198]

Lan Z, Ahmad N, Baghaei P, Barkane L, [101. 2020. 8(4):383-394]. Treatment of multidrug-resistant tuberculosis requires long-term therapy with a combination of several second-line drugs. These drugs are associated with numerous adverse events that can cause severe morbidity such as deafness and, in some cases, death. The authors provide estimates of the absolute and relative rates of adverse events associated with various anti-tuberculosis drugs to provide useful information for clinicians and TB programs in selecting optimal treatment regimens. According to the authors, the fluoroquinolones, clofazimine, and bedaquiline had the lowest frequency of adverse events leading to permanent drug discontinuation, while the second-line injectables, aminosalicylic acid, and linezolid had the highest frequency. These results suggest that careful monitoring of adverse events is important for patients undergoing treatment for multidrug-resistant TB. The results also highlight the urgent need for safer and

better tolerated drugs to reduce morbidity from the very treatment of patients with multidrug-resistant TB.

Sharma R, Battu P, Singla M. [114. 2019. 24(7):689-695] consider anti-tuberculosis drugs that induce nephrotoxicity. Isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) are part of the first-line anti-tuberculosis therapy used against mycobacterium infection. tuberculosis. However, these drugs are known to be potentially harmful as they are associated with numerous side effects, and when combined, their harmful results increase in a synergistic manner. The identification of a possible mechanism underlying RIF + INH + PZA induced nephrotoxicity may be helpful in developing strategies to prevent their toxic effects.

In the experimental study, rats were divided into two groups of six each: control (tap water) and toxicant (INH + RIF + PZA) at a dosage extrapolated from human dosage for 28 days once a day. The antioxidant activity and histology of the kidneys were studied. In addition, apoptosis was also studied using pro- and anti-apoptotic markers and TUNEL staining to test for nephrotoxicity. The results showed that the combined (INH, RIF and PZA) 28-day exposure in Wistar rats caused an increase in free radicals/reactive oxygen species which additionally induce changes in the levels of enzymatic antioxidants such as glutathione, superoxide dismutase, catalase and glutathione - s- transferase. Altered content of pro (BAD&BAX) and anti-apoptotic genes (BCL-2 & BCL2L1) genes, TUNEL positive cells and DNA fragmentation highlighted the involvement of apoptosis.This study concluded that nephrotoxicity is associated with combined anti-tuberculosis drug therapy.

Martin SJ, Sabina EP. [121. 2016. 38(7):1115-21] evaluate the improvement of anti-TB drug oxidative stress in the kidneys with Spirulina fusiformis in a rat model. Nephrotoxicity is a rare complication associated with anti-tuberculosis therapy caused by oxidative stress. cyanobacterium Spirulina fusiformis Voronikhin, belonging to the family Oscillatoriaceae, is traditionally used as a source of antioxidants against oxidative stress. The scientists aimed to investigate the effectiveness of S. fusiformis in modifying isoniazid (INH) and rifampicin (RIF) changes caused by changes in the kidneys of Wistar rats. Animals were divided into six groups: normal control rats; toxicological control (INH & RIF-50 mg/kg b.w./sd each; po.); INH & RIF + S. fusiformis (400 mg/kg bw/ day); INH & RIF + S. fusiformis (800 mg/kg bw/ day); S. fusiformis (800 mg/kg bw/ day) self treated rats; INH & RIF + silymarin (25mg/kg bw/ day). The duration of the study was 28 days, after which blood and kidneys were analyzed. We also studied the binding and interaction of the transcription factors Liver X receptor (LXR) and farnesoid X receptor (FXR) with INH, RIF, and representative active compounds of S. fusiformis by methods in silico. Treatment with INH & RIF caused a significant ($p<0.05$) decrease in antioxidant levels and a significant ($p<0.05$) increase in creatinine, urea, and uric acid levels, indicative of impaired renal function. Spirulina Fusiform moderated these effects in a dose dependent manner. Histological examination of the kidneys confirmed these findings. Analysis results in silico have shown that individual active components of S. fusiformis interact with LXR and FXR and may be a possible mechanism of action. S. fusiformis conferred protection against antituberculous drug oxidative stress in rat renal tissues.

Mozhokina G. N., Samoilova A. G. [52. 2020. 78-84]. In the spectrum of adverse reactions (AR) during chemotherapy of patients with tuberculosis, the frequency of nephrotoxic reactions varies from 5 to 16%. Meanwhile, for the development of drug-induced nephrotoxicity in patients with tuberculosis, there are all the prerequisites: the presence of a severe infectious disease with intoxication syndrome and multiple organ damage to internal organs, long-term use of a large number (5-6 or more) of anti-tuberculosis drugs (ATP), the presence of concomitant pathology (chronic kidney disease, diabetes, hepatitis). The kidneys play an important role in drug metabolism in the body. A significant part of drugs is excreted through the kidneys, and often their concentrations in urine and renal structures are higher than in blood plasma. Most of the drugs are excreted through glomerular filtration, tubular secretion,

excretion and reabsorption, with the participation of complex transfer enzyme systems. Along with the liver, the kidneys are involved in the oxidation, reduction, breakdown and binding of drugs. The role of the kidneys in maintaining water and electrolyte homeostasis in the body is important, which affects the activity and toxicity of drugs. With changes in diuresis, relative density and pH of urine, drug concentrations can increase significantly. Increased concentration, altered chemical composition and physical properties of drugs and their metabolites can lead to various and varying degrees of damage to the renal structures and the occurrence of pathological conditions. Among the most common pathophysiological mechanisms through which drug nephrotoxicity manifests itself, mention should be made of hemodynamic disturbances in the glomeruli, toxic effects on the tubular epithelium, inflammation, dysmetabolic disorders, rhabdomyolysis, and thrombotic microangiopathy. In order to recognize and prevent iatrogenic renal failure, it is important to know the mechanisms of the damaging effects of drugs on the kidneys [110. Olayinka ET, Ore A., Ola OS 385023].

According to Chinese scientists Chen D., Luo C., Tang Z., Zhou Y. et al. (2012) kidney damage may occur as a result of the direct toxic effects of drugs and their metabolites, may be secondary to nephrotuberculosis, or develop as a result of immunological processes such as delayed-type hypersensitivity involving T-lymphocytes. The cells of the renal tubules, especially the proximal ones, are sensitive to the toxic effects of drugs, since, being involved in the processes of reabsorption of glomerular filtrate and urine concentration, these structures come into contact with circulating toxins in high concentrations. The toxic effects of drugs on the glomerular epithelium are due to dysfunction of mitochondria, transport through the tubule wall, increased oxidative stress and the formation of free radicals.

Awdishu L., Mehta R. [106. 2017. 11(9):1–12] believes that the risk of nephrotoxicity associated with aminoglycosides increases with increasing drug concentration, when combined with thiazide or loop diuretics, non-steroidal anti-inflammatory drugs and depends on the age of the patient. Nephrotoxic reactions are relatively more common and more severe in children due to the still incomplete development of the organ, and among elderly patients, the frequency of drug-induced nephrotoxicity reaches 66%. Patients with kidney disease, diabetes mellitus, HIV infection are also at high risk of developing nephrotoxic reactions to the injectable drug.

However, kidney damage, ceteris paribus, does not develop in all patients. There are internal, genetically determined predisposition factors for nephrotoxic reactions to aminoglycosides. These include: the small diameter of the tubules and epithelial cells lining their lumen; high activity of lactate dehydrogenase, enzymopathy of succinate dehydrogenase and acid phosphatase, low content of ribonucleoproteins ; reduced respiratory capacity of mitochondria; activated system of lipid peroxidation (LPO), low antioxidant potential. The greatest contribution to the implementation of nephrotoxicity is made by a low level of reduced glutathione [10. Bushma K. M., Spas V. V., Chapel I. A 2009.157-162],

capreomycin, similar to aminoglycosides in terms of the mechanism of toxic action, causes a decrease in creatinine clearance and changes in urinary sediment. Rarely, as a result of toxic damage, renal tubular necrosis develops with the appearance of the clinical picture of AKI [117. Toktogonova A.A. 2017. 63-67].

Aminoglycosides, amphotericin, sulfonamides, first-generation cephalosporins, especially in combination with diuretics, have a direct toxic effect on the kidneys [108. Naughton CA 743-750].

Nephrotoxic reactions in patients with tuberculosis, associated with the intake of injectable anti-TB drugs, are characterized by a violation of the functional state of the kidneys, determined by the increase and growth in the dynamics of the content of creatinine in the blood serum, the rate of creatinine excretion. According to D. Yu.Shchegertsov et al. [84. 2018. 35-43], drug nephrotoxicity was

observed in 12.8% of patients. An increase in creatinine level of more than 133 μmol/l was recorded after an average of 4.8 months of treatment. Only one patient discontinued therapy with the exclusion of aminoglycosides.

According to A. Arnold et al. [89. 2017. R. e 02586-1] an increase in plasma creatinine up to one and a half times was observed in 25% of patients, in 3.5% of patients there was an increase in creatinine levels by more than 3 times. The creatinine concentration returned to baseline in 19 of 21 patients: in 16 before the end of treatment with injectable drugs, in 3 before the end of treatment for multidrug-resistant pulmonary tuberculosis (MDR-TB).

According to Japanese authors Inoue T., Ikeda N., Kurasawa T. et al [107. 6(4):e0097820] taking pyrazinamide and ethambutol can cause hyperuricemia due to impaired renal excretion of urine acid (UA). According to different authors, an increase in the level of UA in the blood when using pyrazinamide is observed in 43-100% of patients in the period from 2 to 8 weeks of the drug using. A decrease in the level of UA was observed only after the end of the pyrazinamide intake or its withdrawal.

According to Russian scientists Ivanov D. A., Borisov S. E [27. 2018. 47-54], hyperuricemia during chemotherapy was detected in 61.6% of patients. The median duration of treatment before the detection of hyperuricemia was 36 days. In most patients, the UA level was 677.4 ± 392.5 μmol/L. In patients with hyperuricemia over 720 μmol /l, there was a direct relationship between the level of blood UA and the frequency of nephrotoxic reactions, which indicates the role of uric acid nephropathy in the spectrum of causes of AKI. The main culprit of hyperuricemia in most patients was pyrazinamide; the drug was discontinued in 35.5% of cases of hyperuricemia.

However, in the study Ivanova D. A., Borisov S. E. [27. 2017. 47-54] showed that with long-term use of pyrazinamide (8 months) in the intensive phase of treatment of newly diagnosed pulmonary tuberculosis with MDR pathogen, an increase in the level of sUA had 2 peaks. The first peak is after 1-2 months from the start of treatment; the second peak - after 7-8 months of therapy. The results of the monthly determination of the level of sUA indicated a transient increase in the level of sUA against the background of long-term chemotherapy, including pyrazinamide, which generally does not cause significant clinical changes and does not require correction. Only 1 patient discontinued pyrazinamide due to severe joint pain. In most patients for 8 months treatment with pyrazinamide, the level of UA was within the normal range.

A group of scientists [72. Skryagina E. M. et al. 2018. 5-14] conducted an analysis of the efficacy and safety of 20 chemotherapy regimens for the treatment of patients with MDR/ XDR tuberculosis, consisting of 5-8 components, including bedaquiline and linezolid, which showed that renal dysfunction was included in the number of frequent adverse reactions. Impairments in the functional state of the kidneys in the form of an increase in serum creatinine (45.8%) and a decrease in GFR (34.6%) were predominantly mild and in 42 and 31.1% (respectively), the chemotherapy regimen did not contain aminoglycoside antibiotics. However, in cases of development of toxic nephropathy (in 3.7% of patients), the chemotherapy regimen contained kanamycin or capreomycin. There was no correlation between the severity of hypokalemia and the presence of an aminoglycoside antibiotic in the treatment regimen. The development of hypomagnesemia, which was recorded in 46.1% of patients, was not associated with aminoglycoside antibiotics in 45.3% of cases. However, in all cases of moderate, severe and life-threatening hypomagnesemia regimens contained kanamycin or capreomycin. Data for the nephrotoxicity of bedaquiline directly are not given by the authors.

In multicomponent chemotherapy regimens for tuberculosis, it is difficult to clearly identify the drug that is the “culprit” of adverse reactions. For some drugs (aminoglycosides, capreomycin, rifampicin, pyrazinamide, ethambutol), the mechanisms of nephrotoxic action are known and adverse

events are predictable. On the result The general safety profile of chemotherapy regimens with the inclusion of new and poorly studied drugs can have a significant impact on regular clinical and laboratory monitoring of safety parameters.

Belarusian scientists [4. Antonova N.P., Povelitsa G.E.2021. S.1552-1555] consider the problem of nephrotoxic reactions in phthisiology. It is well known that aminoglycosides and capreomycin are drugs with a high risk of developing nephrotoxic reactions. Kidney function was studied in groups of patients with the development of nephrotoxic reactions and without this side effect. Presence of renal failure prior to treatment was an exclusion criterion. Most often, nephrotoxic reactions developed by the 4th month of treatment. Statistically significant differences in GFR dynamics were observed between the groups after the 1st month of treatment. Most often, nephrotoxic reactions developed in patients in the age group over 55 years. In the group of patients with nephrotoxic reactions, a statistically significant decrease in GFR according to MDRD occurred after 1 month of therapy. Most often, nephrotoxic reactions developed after 3 months of chemotherapy. With the development of nephrotoxic reactions, the need to switch to an intermittent drug regimen was in 34.9% (n=8) of patients, in 65.2% (n=15) of cases, therapy was canceled.

Authors from Kazakhstan present the results of a study on the use of new anti-tuberculosis drugs in the treatment of patients with drug-resistant pathogens in Kazakhstan [46. Maretbaeva Sh. M., Rakisheva A. S. et al. 2018. P. 12-17]. The use of new anti-TB drugs - bedaquiline and delamanidau in MDR/XDR-TB patients can increase the effectiveness of complex therapy. Treatment of tuberculosis with the use of bedaquiline exceeds the cost of treating patients with forms sensitive to the main anti-tuberculosis drugs by 50 times or more. However, the first experience of using these drugs in Kazakhstan made it possible to introduce completely new schemes, as well as to extract the results of their combined use. It should be noted that the combined use of these drugs has not yet been studied. However, the combination of drugs was used in selected cases and represented one of the alternative options for clinicians in light of the shortcomings of the standard regimen [11. S. 11-16]. During the 2 years of the project to expand access to new anti-TB drugs, more than 400 patients with MDR/XDR-TB started treatment with new anti-TB drugs in Kazakhstan. The purpose of the study was to evaluate the effectiveness of treatment of patients with MDR/XDR-TB when new anti-TB drugs - bedaquiline and delamanid - are included in the treatment regimen. To achieve this goal, 471 patients taken for treatment using new anti-TB drugs in Kazakhstan were included in the treatment regimen: Bedaquiline - 249 (53%), Delamanid - 86 (18%), combined use of Bedaquiline + Delamanid (29%). For Kazakhstan, this is a great positive experience, combined with good intermediate results for improving the treatment of drug-resistant forms of tuberculosis. First of all, this made it possible to expand access to new anti-tuberculosis drugs, improve the tolerability of anti-tuberculosis therapy, shorten the treatment time for patients, thereby increasing the adherence and quality of life of patients.

Scientists of Minsk [V.V. Martinovich et al. 2020] believe that in order to increase the effectiveness of the treatment of tuberculosis with drug-resistant mycobacteria, attention should be paid to the biochemical mechanisms of action of drugs used in the complex. Pyrazinamide, capreomycin and amikacin inhibit protein synthesis in a bacterial cell, have a bacteriostatic effect. Kanamycin, binding to the 30S subunits of ribosomes, leads to the formation of inactive monosomes and disruption of protein synthesis. By inhibiting two vital microbial cell enzymes - DNA gyrase and topoisomerase-4. Fluoroquinolones disrupt DNA synthesis, which leads to the death of bacteria. In addition, antibacterial activity is due to the effect on the RNA of bacteria, the stability of their membranes, and the effect on other vital processes of bacterial cells. Ethionamide blocks enzymes (catalase, dehydrogenase, deoxyribonuclease, etc.) and disrupts the metabolic processes of mycobacteria. Cycloserine inhibits cell wall synthesis of Gram-positive and Gram-negative bacteria, including Mycobacterium tuberculosis.

Pathogenesis and pathomorphology of the nephrotoxic effect of drugs in the treatment of tuberculosis

The presence of clinical signs of kidney damage in pulmonary tuberculosis is noted by many researchers [52. Mozhokina G. N., Samoilova A. G. 2020. S. 78-84; 59. Pavlova M. V., Starshinova A. A. 2015.S.61-67]. Pathological data confirm the high frequency of these lesions: 70-100% of cases [103. Martin SJ, Sabina EP.2016. 38(7):1115-21]. Clinical manifestations of kidney involvement in pulmonary tuberculosis are extremely diverse and vary from obliterated, with the detection of renal changes only during post-mortem examination, to bright, with advanced nephrotic syndrome and/or renal failure.

According to the authors Dolgov I.B., Ariel B.M. [23. 2002.], morphological changes in nephrobiopsy were varied. Glomerular lesions in these patients were interpreted by the authors as glomerulonephritis, in 8 observations out of 12, the authors of which used not only light, but also immunofluorescent and electron microscopy, in addition to mononuclear infiltration of the glomeruli, there was an expansion of the mesangium and an increase in the number of mesangiocytes in 50 - 80% of the glomeruli of the studied samples, with the formation of crescents in 3 cases. Interstitial changes (edema, predominantly mononuclear infiltration, focal growths of the connective tissue) varied from mild to severe and were detected in 6 out of 12 cases, the diagnosis of interstitial nephritis associated with glomerulonephritis, and the cause of kidney pathology, according to the authors, was rifampicin therapy dystrophic changes in the epithelium of the tubules were noted in 3 cases. Only in a few cases vascular changes were found: swelling and wrinkling of endothelial cells, thickening of the capillary walls, necrosis of individual vascular loops of the glomeruli. Between 32 and 36% of the glomeruli in the samples were sclerosed. The authors identified changes in the glomeruli in 9 out of 12 randomly selected patients with pulmonary tuberculosis using only light-optical microscopy of nephrobiopsy specimens. Mononuclear infiltration of the glomeruli and thickening of the basement membrane of the capillaries of varying severity were characteristic of the changes found. The proportion of affected glomeruli ranged from 50 to 100% in each sample studied. The authors regarded the pathology of the kidneys as glomerulonephritis, resembling post-streptococcal and lupus, thus suggesting the presence of immune lesions of the kidney parenchyma.

It is extremely important to create patterns of drug prescriptions in the treatment of tuberculosis, HIV infection, viral hepatitis and concomitant infectious and non-infectious pathologies, which imply a large pharmacological burden. A feature of chronic infectious pathology is the duration of drug administration.

An ideal drug should have a wide "therapeutic corridor", maximum efficiency, preferably subjectively felt by the patient; minimally influence the patient's lifestyle and have a comfortable reception regimen; not cause an effect on basic physiological functions (appetite, physical activity, circadian rhythms, sexual function, weight gain and loss, including uneven - lipodystrophy); have a good drug interaction profile, controlled metabolism, optimal elimination rate. Risk of nephrotoxicity aminoglycosides depends on the dose and duration of administration. The intensity of monitoring of renal function and the need for dose adjustment of antiretroviral drugs is determined by the clinical situation. Co-administration may lead to an increase in the concentration of capreomycin and emtricitabine or lamivudine. The intensity of monitoring of kidney function is determined by the clinical situation.

The complexity and diversity of the mechanisms underlying TB/HIV infection dictates the need for a differentiated approach to their diagnosis and treatment of patients, taking into account the pathogenesis and clinical course of the disease in each specific case.

Improving Anti-TB Drug Oxidative Stress in the Kidney with Spirulina fusiformis in an experimental study by American scientists Martin SJ, Sabina EP. [103. 2016 38(7):1115-21].

Nephrotoxicity is a rare complication associated with anti-tuberculosis therapy caused by oxidative stress.Cyanobacterium Spirulina fusiformis Voronikhin, belonging to the family Oscillatoriaceae, is traditionally used as a source of antioxidants against oxidative stress. The authors aimed to investigate the efficacy of S. fusiformis in modifying isoniazid (INH) and rifampicin (RIF) changes caused by changes in the kidneys of Wistar rats. Animals were divided into six groups: normal control rats; toxicological control (INH & RIF-50 mg/kg b.w./sd each; po.); INH & RIF + S. fusiformis (400 mg/kg bw/day); INH & RIF + S. fusiformis (800 mg/kg bw/day); S. fusiformis (800 mg/kg bw/day) self treated rats; INH & RIF + silymarin (25mg/kg bw/day). The duration of the study was 28 days, after which blood and kidneys were analyzed. The authors also studied the binding and interaction of the Liver X receptor (LXR) and farnesoid X receptor (FXR) transcription factors with INH, RIF, and representative active compounds of S. fusiformis by methods in silico. Treatment with INH & RIF caused a significant ($p<0.05$) decrease in antioxidant levels and a significant ($p<0.05$) increase in creatinine, urea, and uric acid levels, indicative of impaired renal function. Spirulina fusiform moderated these effects in a dose-dependent manner. Histological examination of the kidneys confirmed these findings. Analysis results in silico have shown that individual active components of S. fusiformis interact with LXR and FXR and may be a possible mechanism of action. S. fusiformis conferred protection against antituberculous drug oxidative stress in rat renal tissues.

Signs, symptoms of manifestation of nephrotoxic action of anti-TB drugs - early - late

Features of pathogenesis determine the spectrum of adverse reactions during anti-tuberculosis chemotherapy. According to most authors, the "three" most frequent reactions during PTH in newly diagnosed patients include hepatotoxic reactions (up to 94.2% of all HP), symptoms of gastrointestinal tract damage (up to 63.2%) and allergic reactions (mainly skin rashes, up to 59.2%) [20. Danilov, A. N. 2015. P. 576–582, 59. Pavlova, M. V. 2015. P. 61-67]. In second place are neurotoxic reactions (up to 35.4%), joint damage with or without hyperuricemia (up to 29.8%), in third place are nephro- and cardiotoxic reactions (up to 5.5% and 11.2%, respectively).), oto- and vestibulotoxicity (up to 18.3% of all HP). All other NR fall into the category of "other reactions", occurring in less than 2% of cases. [27. Ivanova, D. A. 2018. pp. 47-54]

Nephrotoxic reactions may accompany treatment with polymyxin, amphotericin B, neomycin, monomycin, kanamycin, gentamicin, sisomycin, tobramycin, streptomycin, cephaloridine, griseofulvin, ristomycin, sulfonamides. Patients with impaired renal excretory function are especially susceptible to the nephrotoxic effect of drugs, which is associated with their cumulation and the creation of high concentrations in the blood due to impaired excretion. In violation of the excretory function of the kidneys, the nephrotoxicity of many drugs increases with the simultaneous spread of the toxic effect on the liver. In these cases, it is necessary to prescribe drugs with a less pronounced nephrotoxic effect, primarily penicillins and cephalosporins. In the occurrence and development of nephropathies caused by antibiotics, as well as many other drugs, allergic and toxic mechanisms and their combinations matter. The leading role is played by sensitization to drug antigens (immunocomplex, cellular or antibody damage to kidney tissue). The toxic effect is realized both directly at the level of the nephron, especially its tubular section, and indirectly - due to the primary violation of hemodynamics, microcirculation, homeostasis (dyselectrolithemia), metabolism, and the like.

Morphological changes in the kidneys depend on the nature of the pathological process caused by antibiotics. Acute interstitial nephritis is accompanied by edema and cellular infiltration (eosinophils, mononuclear cells, giant cells) of the interstitium, focal lesions of the tubules. Electron microscopy shows inclusions in the cytoplasm of mitochondrial degradation products. Changes in the permeability of cell membranes and their lipid composition are characteristic of lesions caused by polyene antibiotics.

In nephropathy, in the genesis of which changes in humoral and cellular immunity play a leading role, damage to the glomeruli is possible, from minor to severe, as in poststreptococcal or lupus GN. ARF characteristic tubular necrosis. In a chronic course, degenerative changes in the renal tubules (mainly proximal), proliferation of connective tissue elements, infiltration of the interstitium, plethora of glomeruli, vascular damage (manifestations of hemorrhagic vasculitis), and morphological signs characteristic of CRF are formed at the final stages of the development of chronic nephropathy.[44. EAT. Lukyanova 2002.S. 33-41].

In the doctoral dissertation of Ivanova D.A [29. 2018. S. 24-31] the issues of adverse reactions in the treatment of newly diagnosed patients with respiratory tuberculosis are considered. In the course of the study, the author concludes that the treatment of newly diagnosed patients with respiratory tuberculosis is accompanied by AR in 93.3% (95% CI 90.6-95.4%) of cases; the inclusion of reserve-line drugs in the treatment regimen leads to a significant increase in the incidence of AR (up to 96.0% compared to 89.6% against the background of taking only first-line drugs) and the associated withdrawal of anti-TB drugs. Severe AR (3-4 severity) develop in 54.3% (95% CI 49.6-58.9%) of patients, regardless of the therapy regimen; in 69.2% of patients (95% CI 64.7-73.3%), adverse events are accompanied by the withdrawal of at least one anti-tuberculosis drug in the regimen, which is associated with a significant prolongation of the intensive phase and length of stay in the hospital (on average by 34, 1 day). Independent risk factors for AR are: for hyperuricemia - serum creatinine before treatment more than 80 µmol /l (OR 1.99, 95% CI 1.11-3.57); for allergic reactions - blood eosinophilia more than 300 cells/ µl before treatment (OR 3.51, 95% CI 1.69-7.29), fungal co-infection (OR 2.09, 95% CI 1.28-3, 40), aggravated allergic history (for severe allergic reactions, OR 1.90, 95% CI 1.12-3.27); for gastrointestinal reactions - female (OR 2.14, 95% CI 1.38-3.32), concomitant pathology of the gastrointestinal tract (OR 1.73, 95% CI 1.04-2.89. Ivanova D.A recommends: With an asymptomatic increase in the level of uric acid in the blood up to 600 µmol/l, non-drug methods of correction are recommended (purine-restricted diet, alcohol exclusion, heavy drinking, correction of accompanying therapy) under the control of uric acid once every 2 weeks. Non-drug methods of correction are recommended, in the absence of contraindications, it is possible to prescribe allopurinol at a starting dose of 100 mg/day and/or switch to intermittent pyrazinamide with weekly control of uric acid.uric acid and blood creatinine.The abolition of pyrazinamide is indicated for hyperuricemia of more than 900 µmol /l, gouty arthritis, severe arthralgia, not stopped while taking non-steroidal anti-inflammatory drugs and reducing the dose of pyrazinamide.An analysis of the literature data suggests that the opinion of researchers on the impact of comorbidity on the incidence of ADR is generally unanimous.

Wolf S.B. [fourteen. 2016] anti-tuberculosis drugs, suppressing the vital activity of mycobacterium tuberculosis, also have an adverse effect on the macroorganism, which can manifest itself with certain clinical symptoms. This is primarily due to the fact that ATDS do not have absolute selectivity of action and can affect various organs and systems of the body, causing unwanted side effects and adverse reactions. The development of side effects of anti-tuberculosis drugs depends on a number of reasons. On the one hand, the type of drug, the form of its use, the dose and duration of treatment, and the combination with other drugs matter. On the other hand, the state of the patient's body plays a certain role - age, the functional state of a number of internal organs and systems, the nature of individual reactivity, allergic mood, etc. Polychemotherapy of tuberculosis, including various combinations of ATDS, has a negative effect on many of its organs and systems. Often, patients with tuberculosis during treatment experience dysfunctions of the respiratory organs, gastrointestinal tract, liver, kidneys, central and peripheral nervous system, immune system, cardiovascular system, hematopoietic system.

Literature Review Conclusion

A feature of the treatment of multidrug-drug tuberculosis (MDR-TB) is the use of injectable drugs in treatment regimens that have a nephrotoxic effect. The review presents an analysis of literature data on the frequency of adverse reactions from the kidneys during chemotherapy in patients with tuberculosis. The most significant pathophysiological mechanisms of development of drug nephrotoxicity are considered. The features of the nephrotoxic action of a number of drugs are shown. The conclusion was made about the need for regular clinical and laboratory monitoring of kidney function for the timely detection of nephrotoxic reactions.

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