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Features of the Course and Effectiveness of Treatment of Pulmonary Tuberculosis with Drug-Resistant Pathogen

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Abstract: The article describes the methods used at the present stage for the treatment of tuberculosis with multiple drug resistance. A clinical example of treatment of a patient with multidrug category 4 resistance, second-line drugs, the use of which made it possible to achieve clinical improvement, cessation of bacterial excretion and involution of specific changes in the lungs. Efficiency therapy is proven by achieving shorter stabilization of tuberculous inflammation.

Keywords: acquired resistance, multidrug resistance, confirmed, second-line drugs, regardless, treatment regimen.

After the introduction of INH for treatment of TB in the 1950s, resistance to INH emerged. Generally, "INH-resistant" TB refers to strain with resistance to INH and susceptibility to RIF confirmed *in vitro*, regardless of concurrent resistance to other anti-TB drugs. "INH mono-resistance" TB refer to resistance to a single first-line drug such as INH, and susceptibility to any other anti-TB drugs. Resistance to INH is usually due to a mutation in *katG* or *inhA*, and is less commonly due to mutations in other genes, such as the *ahpC32* gene. INH is a prodrug that must be activated by catalase-peroxidase, an enzyme regulated by *katG*, to be effective against TB. Mutations in *katG*, most commonly at Ser315Thr, can result in high-level resistance to INH. The *inhA* gene encodes an enoyl acyl carrier protein reductase involved in fatty acid synthesis in *M. tuberculosis*. Because these fatty acids are the targeted by the active derivative of INH, mutations in *inhA* or its promoter region block INH binding and result in low-level INH resistance. Isolates with an *inhA* mutation are also typically resistant to ethionamide and prothionamide.

In *Mycobacterium tuberculosis*, drug resistance develops through spontaneous genetic mutations. Thus, the development of acquired drug resistance usually occurs when there is a large bacterial population, such as in pulmonary cavities or when an inadequate drug combination or dosage is prescribed. Rarely, malabsorption of anti-TB drugs may account for acquired resistance. Risk factors for developing INH resistance have been reported, and most studies have found a strong correlation between a history of TB treatment and INH resistance. In an analysis of drug-resistant TB trends in the United States, a history of TB, foreign birth, and Asian or Pacific Islander ethnicity were found to be risk factors for INH resistance. Similarly, in Germany and Israel, a history of TB treatment was identified as a risk factor for INH resistance. The lack of rapid diagnosis of tuberculosis with pathogen resistance to isoniazid with preserved sensitivity to rifampicin (IR-TB) may be the reason for low effectiveness of therapy and lead to amplification of drug resistance, including the formation of multidrug resistance. The aim of the work was to determine the incidence of IR-TB in the modern population, to characterize the phenotypic sensitivity and genetic determinants of resistance to isoniazid in representatives of this group of

M. tuberculosis using representative material. We analyzed the results of drug susceptibility testing obtained from the study of M. tuberculosis isolates / M. tuberculosis DNA isolated from patients with pulmonary tuberculosis from the clinical departments of the Central Research Institute of Tuberculosis using molecular genetic and/or cultural methods for the period 2020–2023. The incidence of IR-TB was 10% of all detected cases of tuberculosis. M. tuberculosis with IR were both monoresistant to isoniazid (40%) and multiresistant (resistant to 3–5 antituberculosis drugs), and resistance to isoniazid was caused by mutations in the katG gene, leading to a high level of resistance.Based on an analysis of literature data and our own observations, the importance of the development and implementation of new simple molecular tests to determine resistance to both rifampicin and isoniazid is emphasized.

Compliance with ethical standards: a retrospective analysis of the results obtained during routine laboratory tests for patients undergoing treatment at the Central Research Institute of Tuberculosis was carried out; All patients signed voluntary informed consent for the study.Drug-resistant tuberculosis (TB) is a major public health problem. The main focus is currently on combating multidrug-resistant tuberculosis (MDR-TB), i.e. tuberculosis in a form in which the pathogen is simultaneously resistant to the two most effective anti-tuberculosis drugs (ATDs) - isoniazid and rifampicin. Russia ranks third in the world in terms of MDR-TB prevalence.

In 2022, the incidence and prevalence rates of MDR-TB in the Russian Federation stabilized and amounted to 1.1 and 21.4 per 200,00 people, respectively. At the same time, the proportion of patients with MDR-TB among bacterial isolates increased (from 24.2% in 2020 to 20.3% in 2020 among new TB cases and from 50.0% in 2020 to 55.3% in 2021 d. among all patients with respiratory TB secreting Mycobacterium tuberculosis).Against this background, insufficient attention is paid to other forms of resistance. One of these forms, identified by WHO as a separate group, is isoniazid-resistant tuberculosis (Hr-TB, IR-TB), which is characterized by pathogen resistance to isoniazid and sensitivity to rifampicin.

Isoniazid is a 1st-line drug that is highly effective for the treatment of active tuberculosis and has a bactericidal effect on M. tuberculosis. Phenotypic resistance to isoniazid is associated with mutations in a number of genes (katG, inhA, ahpC, etc.), the products of which are involved in the pharmacokinetics and pharmacodynamics of isoniazid in the bacterial cell.

Inadequate therapy for IR-TB creates a high risk of developing acquired drug resistance to other anti-TB drugs, including rifampicin, leading to the development of MDR. According to WHO, the prevalence of IR-TB is 5–11% depending on the region. There is insufficient information on the prevalence of IR-TB in Russia.

Purpose of the study: to characterize the frequency of occurrence of IR M. tuberculosis isolated from patients with pulmonary tuberculosis from the clinical departments of the Federal State Budgetary Institution "Central Scientific Research Institute of Infectious Diseases" for the period 2021–2023, to provide an expanded characteristic of phenotypic sensitivity and to describe the genetic determinants of resistance to isoniazid of this group of M. tuberculosis.

MATERIALS AND METHODS: We studied clinical isolates of M. tuberculosis and/or M. tuberculosis DNA isolated from diagnostic material obtained from each patient admitted to the consulting and clinical departments of the Federal State Budgetary Institution "Central Research Institute of IT" (for the period 2020–2023). All types of microbiological studies were carried out from one portion of diagnostic material.

Cultural diagnostics: Detection of M. tuberculosis was carried out using Middlebrook 7H9 liquid medium in the BACTEC MGIT 960 system (BD; USA) according to the manufacturer's standard protocol. Phenotypic drug sensitivity was determined by a modified method of proportions in the BACTEC MGIT 960 system (BD; USA) to eight anti-tuberculosis drugs at critical concentrations: isoniazid (H, 0.1 μg/ml), rifampicin (R, 1.0 μg/ml), ethambutol (E, 5.0 μg/ml), pyrazinamide (Z, 100.0 μg/ml), ethionamide (Eto, 5.0 μg/ml), amikacin (Am, 1.0

μg/ml), capreomycin (Cm 2.5 μg/ml) and levofloxacin (Lfx 1.0 μg/ml) according to standard procedures.

RESEARCH RESULTS: Cultural and molecular genetic studies of diagnostic material from 4056 patients with pulmonary tuberculosis were carried out. In 71 cases, neither M. tuberculosis DNA nor M. tuberculosis culture was isolated; these cases were excluded from the study. From the remaining 3985 samples of diagnostic material, DNA and/or cultures were isolated M. tuberculosis and determined phenotypic/genotypic sensitivity to anti-TB drugs. When obtaining results for clinical isolates of M. tuberculosis by both cultural and molecular genetic methods (MGM), in case of their discrepancy, priority was given to data obtained by culture. 38 strains for which, during the culture study, resistance to both isoniazid and rifampicin were determined, but mutations in rpoB, which determine resistance to rifampicin, were not determined, were classified as MDR, since the tests we used for the molecular genetic determination of DR detect only a limited number of mutations, so genetic determinants of rifampicin resistance may not have been identified in these cases. Conversely, 29 strains with identified mutations in rpoB, which did not have the phenotypic manifestation of resistance to rifampicin, were classified as IR.Since cultural methods for diagnosing tuberculosis are less sensitive than molecular genetic methods, some samples did not give culture growth M. tuberculosis on nutrient media. Therefore, phenotypic sensitivity to TTPs was determined for only 250 M. tuberculosis isolates with IR. When classifying M. tuberculosis isolates with IR according to the nature of drug resistance, we relied on the following definitions: monoresistance - resistance of Mycobacterium tuberculosis to only one of the anti-TB drugs; multiresistance - resistance of Mycobacterium tuberculosis to two or more anti-tuberculosis drugs, but not to a combination of isoniazid and rifampicin.

The frequency of occurrence of resistance to isoniazid with preserved sensitivity to rifampicin was studied in M. tuberculosis isolated from patients with pulmonary tuberculosis from the clinical departments of the Federal State Budgetary Institution "TsNIIT" for the period 2021–2023.

The frequency of occurrence of this form of TB and the dynamics of population spread in different regions of the world have their own specifics. Thus, when analyzing data on the drug sensitivity of the tuberculosis pathogen submitted to WHO for the period 1994–2009. From 131 TB facilities around the world, the highest incidence of IR-TB was reported in Eastern Europe (15%), lower in Western and Central Europe (11%), and in other WHO regions did not exceed 8%.

For a number of regions, these authors showed a trend towards a decrease in the prevalence of this form of tuberculosis, for others, on the contrary, an increase, but in most regions no clear linear dynamics of the indicator was established. The frequency of occurrence of IR described by us M. tuberculosis (11%) is similar to the indicators characteristic of Eastern Europe, and the dynamics of the indicator, as in most regions, was non-linear. In a systematic review on the relationship between primary resistance to isoniazid and the acquisition of resistance to other anti-drug medications, it was concluded that acquired resistance to any anti-drug (not only transition to MDR) in isoniazid-monoresistant strains occurs 5.1 times more often compared to drug-resistant strains. - sensitive strains. The high frequency of occurrence of multidrug-resistant strains shown in our study (55% of all IR), resistant except for isoniazid in addition to 1–5 anti-TB drugs, confirms the possibility of amplification of drug resistance in M. tuberculosis with IR.

In this regard, two clinical studies should be mentioned, the purpose of which was to establish the dependence of the effectiveness of therapy with high doses of isoniazid on IR forms of TB on mutations in the genome of the pathogen. It is known that mutations in katG (dominated in our study) lead to a high level of resistance to isoniazid, and mutations only in inhA lead to a low level of resistance. According to the results of clinical studies, isoniazid therapy was effective if the pathogen had mutations at the inhA level, and unfavorable treatment outcomes occurred with mutations at the katG level.

All of the above indicates that it is necessary to develop effective treatment regimens for IR-TB. In addition, it is important to pay attention to the rapid diagnosis of isoniazid DR. Rapid, specific and sensitive diagnosis of M. tuberculosis lymph nodes can only be provided by molecular genetic methods (1–2 days compared to several weeks of culture diagnostics), which also make it possible to obtain information about the mutation and the level of resistance to isoniazid of the pathogen. This makes MGM the most popular in diagnosing tuberculosis and determining the drug resistance of the pathogen.

CONCLUSIONS: Tuberculosis with IR pathogen can be considered as a potential precursor to MDR tuberculosis. It is therefore important to control the spread of primary isoniazid resistance and prevent amplification of resistance. Analysis of the frequency of occurrence of resistance to isoniazid with preserved sensitivity to rifampicin in M. tuberculosis isolated from patients with pulmonary tuberculosis showed a fairly high level of occurrence of IR-TB (more than 12% of all analyzed cases) - usually with mutations leading to a high level of resistance to isoniazid. The data obtained emphasize the importance of accelerated determination of the drug sensitivity of M. tuberculosis to both rifampicin and isoniazid using molecular genetic methods in laboratories at all levels. To ensure this possibility, it is necessary to develop new simple point-of-care tests that do not place high demands on laboratory infrastructure.

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