МНОГОМЕРНЫЕ СТРАТЕГИИ В БОРЬБЕ С ТУБЕРКУЛЕЗОМ С МНОЖЕСТВЕННОЙ ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТЬЮ: ГЛОБАЛЬНАЯ ПЕРСПЕКТИВА

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Аннотация. *В этой научной статье рассматривается острая проблема общественного здравоохранения, связанная с туберкулезом с множественной лекарственной устойчивостью (МЛУ-ТБ), и предлагается комплексный и надежный подход к борьбе с этой глобальной угрозой здоровью. В нем тщательно анализируются эволюция, эффективность и ограничения различных схем лечения, включая стратегию DOTS-Plus и индивидуальные планы лечения, основанные на чувствительности к лекарственным средствам, а также рассматривается ключевая роль хирургических вмешательств в определенных контекстах. В статье анализируются эпидемиологические тенденции МЛУ-ТБ, особое внимание уделяется регионам с высоким бременем и различиям в успехах программ. В ней подчеркивается необходимость раннего выявления, борьбы с резистентностью и приверженности пациентов к лечению для улучшения результатов лечения. Завершаясь призывом к активизации глобального сотрудничества, статья подчеркивает необходимость расширения научных исследований, совершенствования стратегий диагностики и лечения и усиления мер общественного здравоохранения для эффективного противодействия растущей проблеме МЛУ-ТБ.*

Ключевые слова*: Туберкулез с множественной лекарственной устойчивостью, МЛУ-ТБ, лекарственная чувствительность, ДОТС-Плюс, химиотерапия, эпидемиология, хирургическое вмешательство, глобальное здравоохранение, результаты лечения, стратегия общественного здравоохранения*

MULTIDIMENSIONAL STRATEGIES IN THE BATTLE AGAINST MULTIDRUG-RESISTANT TUBERCULOSIS: A GLOBAL PERSPECTIVE

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Annotation. *This scholarly article addresses the exigent public health challenge posed by multidrug-resistant tuberculosis (MDR-TB), advocating for an integrated and robust approach to combat this global health threat. It scrutinizes the evolution, effectiveness, and limitations of various treatment regimens, including the DOTS-Plus strategy and individualized drug sensitivity-based treatment plans, while also considering the pivotal*

role of surgical interventions in certain contexts. The article analyzes the epidemiological trends of MDR-TB, focusing on high-burden regions and the disparities in program successes. It highlights the imperative of early detection, resistance management, and patient adherence to improve treatment outcomes. Concluding with a call for intensified global cooperation, the article underscores the necessity for enhanced research, improved diagnostic and treatment strategies, and reinforced public health measures to effectively confront the escalating challenge of MDR-TB.

Keywords*: Multidrug-resistant tuberculosis, MDR-TB, drug sensitivity, DOTS-Plus, chemotherapy, epidemiology, surgical intervention, global health, treatment outcomes, public health strategy*

MULTIDORILARIGA CHIDAMLI SILGA QARSHI KURASHDA KO'P O'LCHOVLI STRATEGIYALAR: GLOBAL ISTIQBOL

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Annotatsiya. *Ushbu ilmiy maqola ko'p dori-darmonlarga chidamli sil kasalligi (MDR-TB) tomonidan sog'liqni saqlashning dolzarb muammolariga bag'ishlangan bo'lib, ushbu global sog'liq tahdidiga qarshi kurashish uchun kompleks va mustahkam yondashuvni qo'llab-quvvatlaydi. U turli xil davolash rejimlarining evolyutsiyasi, samaradorligi va cheklovlarini, shu jumladan DOTS-Plus strategiyasini va individual dori sezgirligiga asoslangan davolash rejalarini sinchkovlik bilan o'rganadi, shu bilan birga ma'lum kontekstlarda jarrohlik aralashuvlarning asosiy rolini hisobga oladi. Maqolada MDR-TB epidemiologik tendentsiyalari tahlil qilinib, yuqori yukli mintaqalar va dastur muvaffaqiyatlaridagi nomutanosibliklarga e'tibor qaratilgan. Bu davolash natijalarini yaxshilash uchun erta aniqlash, qarshilikni boshqarish va bemorga rioya qilish zarurligini ta'kidlaydi. Global hamkorlikni kuchaytirishga qaratilgan chaqiriq bilan yakunlanar ekan, maqolada MDR-sil kasalligining avj olayotgan muammolariga samarali qarshi turish uchun tadqiqotlarni takomillashtirish, diagnostika va davolash strategiyalarini takomillashtirish, sog'liqni saqlash choralarini kuchaytirish zarurligi ta'kidlangan.*

Kalit so'zlar: *ko'p dori-darmonlarga chidamli sil, MDR-TB, dori sezgirligi, DOTS-Plus, kimyoterapiya, epidemiologiya, jarrohlik aralashuvi, global salomatlik, davolash natijalari, sog'liqni saqlash strategiyasi*

Tuberculosis (TB), an infectious disease caused by Mycobacterium tuberculosis (MTB) and known to humanity since ancient times, remains a significant concern even in the 21st century. Primarily transmitted through airborne droplets and dust, the primary source of the infection in communities are the patients whose sputum smear, under simple microscopy, reveals the presence of the bacteria. The most effective method of halting the

spread of tuberculosis is through the treatment of these infectious patients, thereby cutting off the disease's transmission pathways. Comprehensive treatment primarily involves anti-tuberculosis chemotherapy, which, when applied correctly, facilitates the recovery of patients with infectious forms of TB and interrupts the transmission routes of the pathogen.

Currently, there is global concern over the rise of tuberculosis with multidrug-resistant Mycobacterium tuberculosis (MDR-TB). This disease, caused by strains of MTB resistant to at least two primary anti-tuberculosis drugs and potentially more, has been highlighted in studies conducted by WHO and the International Union Against Tuberculosis and Lung Disease between 1994 and 1997, which found that 2.2% of global TB cases were caused by MDR strains.

At the dawn of the 20th century, there were no pharmaceutical treatments for tuberculosis. Sanatorium treatment, which included rest, fresh air, and enhanced nutrition to boost the chances of spontaneous recovery, was the norm. Though many patients showed improvement with this therapy, the long-term results were disappointing, with over 60% of discharged patients dying from tuberculosis within six years. The outcomes slightly improved after the introduction of surgical interventions like artificial pneumothorax and thoracoplasty, which induced the collapse of the affected lung segments.

A significant breakthrough occurred in the 1940s, linked to the discovery of streptomycin by Waksman and Schatz and the synthesis of para-aminosalicylic acid (PAS) by Lehmann and Rosdahl. Notably, the issue of acquired (secondary) drug resistance emerged during the initial trials of these new drugs. Drug resistance was detected after four months of monotherapy in 90% of isolated MTB cultures, and the five-year survival rate of patients after streptomycin monotherapy was no higher than that with sanatorium treatment.

Subsequent research on the combined chemotherapy of streptomycin and PAS demonstrated that multi-drug therapy prevents the development of drug resistance and effectively cures tuberculosis. In the 1950s and 1960s, new anti-tuberculosis drugs were introduced, including isoniazid, pyrazinamide, cycloserine, ethionamide, kanamycin, capreomycin, rifampicin, and ethambutol. By the late 1980s, fluoroquinolone antibiotics, some active against MTB, were synthesized.

Anti-tuberculosis drugs are generally categorized into three groups: first-line (primary) drugs like isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin; second-line (reserve) drugs including cycloserine, ethionamide, prothionamide, kanamycin, capreomycin, amikacin, PAS, fluoroquinolones; and third-line (alternative) drugs such as clarithromycin, clofazimine, and amoxiclav.

Resistance to MTB was observed with each new anti-tuberculosis drug. Since the 1950s, polychemotherapy regimes and strategies to ensure maximum adherence by patients became the standard in TB treatment, as they were found to reduce the

frequency of drug resistance. It was demonstrated that using standardized polychemotherapy regimes with combinations of the most active and well-tolerated first-line drugs led to increased cure rates and reduced the duration of treatment from 18 to 6-8 months.

A series of clinical trials by the British Medical Research Council and other organizations from the 1970s to the 1990s helped assess and optimize regimes consisting of various combinations of anti-tuberculosis drugs. For patients with pulmonary tuberculosis, the most effective, well-tolerated, and shortest regime was found to be a combination of isoniazid, rifampicin, and pyrazinamide for two months, followed by isoniazid and rifampicin for four months. The American Thoracic Society and the Centers for Disease Control recommended short-course chemotherapy (SCC) with the inclusion of ethambutol and streptomycin in the initial intensive phase of treatment until drug sensitivity results were obtained.

The set of diagnostics, therapeutic, and organizational methods patented by WHO was named Directly Observed Treatment, Short Course (DOTS), suitable for effectively combating tuberculosis. The success of this strategy is determined by five components: 1) government commitment to a national tuberculosis control program; 2) detection of new cases through microscopic examination of the sputum of all patients suspected of having tuberculosis; 3) standard short-course chemotherapy under direct medical supervision; 4) continuous, uninterrupted provision of all necessary anti-tuberculosis drugs to participating medical institutions; 5) a monitoring system to oversee the program's implementation and evaluation. DOTS aims to cure at least 85% of new patients with infectious forms of pulmonary tuberculosis and detect at least 70% of infectious cases.

The application of DOTS can reduce morbidity, mortality, and the spread of infection through the successful treatment of all tuberculosis patients, primarily those excreting bacteria. Additionally, it reduces the formation of MDR-TB cases since each identified patient receives a controlled course of chemotherapy without breaks in treatment.

The outlook for further progress in the fight against tuberculosis is promising. According to WHO, most of the 22 countries bearing about 80% of the global TB burden are now implementing DOTS, at least in pilot areas, and plan to gradually expand and eventually cover the entire country over the next few years. Notable successes have been achieved in countries like Kenya, Peru, Vietnam, and Cambodia, where treatment success rates exceed 70% and detection rates are acceptable (over 50%).

A global project monitoring 35 regions has proven that DOTS can effectively prevent the emergence of drug-resistant mutants. As the majority of tuberculosis cases worldwide remain sensitive to these potent and well-tolerated first-line drugs, these treatment regimes can be successfully applied globally. Experience has shown that most cases of tuberculosis, resistant only to isoniazid or streptomycin, can be cured. Treatment failures are only 0-2%, with relapses observed in 11% of cases.

However, individuals already diagnosed with MDR-TB cannot be cured with SCC. Furthermore, the ratio of drug-resistant to drug-sensitive tuberculosis cases may increase in countries with well-organized DOTS programs because while drug-sensitive cases respond well to treatment, those suffering from drug-resistant forms remain untreated and become sources of infection. In Peru and Korea, according to recent publications, the treatment was only successful in 58% and 56% of MDR-TB cases, respectively, lower than for sensitive cases.

In Russia and other countries undergoing deep socio-political transformations, the high level of MDR-TB in the general population casts doubt on the ability of DOTS alone to control the disease. Although the overwhelming majority of TB cases in the world are currently caused by drug-sensitive strains, MDR-TB poses a threat to the global fight against this disease.

Studies from the 1930s showed that some tuberculosis patients (according to some sources, up to 50%) could live for 5 or more years without treatment. Due to this "chronicization" of the tuberculosis infection, MDR-TB patients with a positive smear, who are untreated and survive for five or more years, pose a real threat not only to their families but also to society at large, and cast doubt on the success of anti-tuberculosis programs. The occurrence of failures using DOTS therapy regimes in countries with high levels of MDR-TB, as well as in treating individual cases of MDR-TB, can discredit the otherwise successful DOTS program.

The cure rates for patients with MDR-TB undergoing chemotherapy regimens for previously treated tuberculosis patients (1 month - isoniazid, rifampicin, ethambutol, pyrazinamide; 3 months - isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin; 5 months - isoniazid, rifampicin, ethambutol) varied across different anti-tuberculosis programs, ranging from 0 to 36%. This is unsurprising since the concept of using standard chemotherapy regimens was conceived before MDR-TB became a recognized issue. Furthermore, there is a concern that in patients with MTB initially resistant to isoniazid and rifampicin, standard regimens of first-line drugs might select for strains with additional resistance to these drugs, a phenomenon known as the "amplification effect."

In response, the WHO deemed it necessary to develop approaches to the problem of MDR-TB, leading to the creation of a working group on MDR-TB and the emergence of the DOTS-plus strategy. Within this group's activity, DOTS-plus is defined as "a case management strategy designed to combat MDR-TB using second-line drugs within the DOTS strategy in low and middle-income countries."

Key issues in the treatment of MDR-TB include strengthening political commitments to tuberculosis treatment and securing long-term investments in personnel and resources. Coordinating efforts among the community, local authorities, and international organizations and establishing leadership that addresses all project aspects and defines the roles and responsibilities of participating organizations are also vital. Forming a specialized unit to manage MDR-TB patients, ensuring the availability of specialized laboratory

services, including reliable drug sensitivity testing, and developing an appropriate treatment strategy with second-line anti-tuberculosis drugs are crucial steps. Moreover, organizing a reliable supply of high-quality second-line drugs, creating conditions to help patients adhere to treatment, and organizing an information system to manage data correctly, monitor program execution, and evaluate activities are also important.

A specific feature of MDR-TB is that its treatment has not yet been standardized. The necessary second-line drugs are less effective and more toxic than first-line drugs, and the cost of treatment and diagnosis is high.

In line with the core principles of tuberculosis treatment in DOTS-plus, combined chemotherapy is employed. It's advised that treatment regimens for MDR-TB include at least three second-line anti-tuberculosis drugs not previously used by the patient (thus likely to be effective as the strains of MTB they harbor are probably sensitive to these drugs), and/or first-line anti-tuberculosis drugs that retain sensitivity. Treatment with second-line anti-tuberculosis drugs should be conducted under the strict supervision of medical personnel. Patients must take these drugs daily for no less than eighteen months.

An essential part of the therapy includes organizing the proper management of side effects that arise from taking second-line anti-tuberculosis drugs. Two primary models for managing MDR-TB cases have been proposed: individualized treatment regimens (ITR), based on the drug sensitivity testing of the entire set of first and second-line drugs, and a standardized regimen for treating tuberculosis with MDR. These approaches are designed to tailor the treatment to the specific needs and circumstances of the patient while ensuring the effectiveness of the therapy and managing the potential development of further drug resistance.

The advantages of individualized treatment regimens (ITR) include a higher likelihood of successful treatment because drug sensitivity testing allows clinicians to create regimens with a sufficient number of effective anti-tuberculosis drugs. There's also a reduced chance of unintentional amplification of drug resistance, as patients won't receive drugs to which their strains are resistant. Additionally, there's a lower probability of patients unnecessarily suffering from drug toxicity, as they won't receive drugs to which their infecting strain is resistant. ITR also offers greater flexibility in adjusting regimens based on the clinical course of individual patients.

Two approaches to implementing the standardized model for treating MDR-TB have been proposed. The first assumes that patients who fail treatment with empirical SCC regimens suffer from MDR-TB. The second approach considers local epidemiological data on resistance when developing treatment regimens for a specific area.

Standardized treatment models for MDR-TB have potential advantages and risks. Possible benefits include lower initial costs since drug sensitivity testing for each patient is not required and simplified case management, as all patients receive standard doses of the same anti-tuberculosis drugs. However, one possible drawback is that patients with strains sensitive to potent first-line drugs might not receive these drugs in the standardized

regimen. In addition to these significant disadvantages, the likelihood of treatment success is also lower because not all patients will receive three or more drugs to which their infecting strain is sensitive.

The Peruvian national anti-tuberculosis program trialed a standardized regimen for treating MDR-TB in the urban part of the metropolis Lima. This treatment was prescribed to all patients for whom a course of retreatment (category II according to DOTS) was ineffective, meaning that both the primary and the retreatment courses were unsuccessful. The standard treatment course involved 3 months of taking kanamycin, fluoroquinolone, ethionamide, pyrazinamide, ethambutol, and 15 months of kanamycin, ethionamide, pyrazinamide, ethambutol with daily (six days a week) intake of anti-tuberculosis drugs. Strict control of side effects and monthly microbiological sputum examination (smear and culture) and chest radiography every 3 months were integral. The cure rate using the standard regimen in Peru was 48%, with 28% treatment failure.

Individual treatment regimens for MDR-TB were used in 12 medical institutions in Denmark, the Netherlands, the USA, Canada, Hong Kong, South Korea, Peru, and Turkey. The percentage of cures for MDR-TB varied from 38 to 100. The best cure result was recorded in Denmark and the Netherlands - 95%, New York and Florida (USA) - 81 and 79% respectively, Turkey and Canada - 75, Peru - 73, Hong Kong - 73%. On average, MTB resistance was observed to four first-line drugs for oral administration. The results did not show a significant correlation between the number of drugs to which MTB patients were resistant and treatment failure. This lack of correlation is likely because some groups tested sensitivity to only 4 drugs, while others tested 5-11. However, it's proven that the loss of drug sensitivity to ethambutol and/or pyrazinamide, in addition to resistance to isoniazid and rifampicin, is associated with an unfavorable outcome, and the chances of cure drop equally for all patients. Studies demonstrated that the number of drugs used affects treatment outcome. Treatment conducted in inpatient settings was more effective compared to outpatient. One factor leading to a low cure rate was the high percentage of patients who stopped therapy or fell out of observation.

The treatment program for tuberculosis patients with MDR-TB, developed by Harvard Medical School and Partners in Health, is being implemented in three districts of the metropolis Lima (Peru). It involves conducting individualized treatment regimens (ITR) that include: a) the use of at least 4 (in some cases up to 8) anti-tuberculosis drugs to which the strains of MTB isolated from the patients have retained sensitivity; b) the prescription of maximum tolerable doses of drugs; c) prolonged treatment (from 18 to 24 months). Initially, patients receive empirical treatment, which is then adjusted based on the incoming results of the drug sensitivity testing of MTB, conducted in a reference laboratory (Boston, USA).

If the isolated MTB strains are sensitive to all anti-tuberculosis drugs, then usual standard treatment is resumed in accordance with DOTS principles. If MDR-TB is identified, the treatment regimen must be revised: drugs to which resistance has been established

are excluded, and those drugs not previously used in the regimen but to which sensitivity is retained are included. Thus, it must be proven that sensitivity to all used anti-tuberculosis drugs is retained. This approach ensures that the treatment is as targeted and effective as possible, reducing the likelihood of further drug resistance and maximizing the chances of successful treatment.

Treatment regimens developed by the Centers for Disease Control and Prevention (CDC&P, Atlanta, USA) are being utilized in the Ivanovo region of Russia. These regimens prefer fluoroquinolones (mainly ofloxacin), capreomycin, and cycloserine based on drug sensitivity testing of MTB in the region, as there has been no detected drug resistance to these in patients from Ivanovo. The idea is to implement a standard initial regimen for MDR-TB treatment with capreomycin, ofloxacin, cycloserine, ethambutol, pyrazinamide, and ethionamide, as estimates suggest that 90% of MTB strains will be resistant to at least two of these anti-tuberculosis drugs. Regimen modification is possible following drug sensitivity testing and considering treatment costs.

Treatment regimens designed by the Public Health Research Institute, the Medical Emergency Relief International (MERLIN), and the University of Alabama-Birmingham, USA, have been successfully applied in the Tomsk region of Russia. Based on drug sensitivity testing of MTB strains isolated from 102 patients in the region's penal institutions in 1998, 12 variants of drug resistance to 1—5 anti-tuberculosis drugs were identified. Treatment regimens for drug-resistant tuberculosis were proposed based on both empirical approaches and the results of microbiological research. The empirical regimen is prescribed to patients at high risk of MDR-TB: new cases identified in prisons with acid-fast bacteria in sputum and/or the presence of cavities, new civilian sector cases known to have contact with former inmates with MDR-TB, and all cases of retreatment due to disease relapse or ineffectiveness of the first course without drug sensitivity information. Treatment involves: isoniazid, rifampicin, ethambutol, pyrazinamide, capreomycin, fluoroquinolone, and PAS if available. PAS is recommended if the patient received fluoroquinolones within the 6 months prior to TB detection (indicating a risk of developed resistance). Following the results of drug sensitivity testing of MTB, the regimen is adjusted.

Aggressive, lengthy chemotherapy regimens using second-line drugs are less well-tolerated by patients, and side effects can lead to a high frequency of patients discontinuing drugs. However, if side effects are monitored and persistently managed, patients are likely to continue chemotherapy. According to literature, side effects encountered in MDR-TB treatment regimes include mental disorders (depression, anxiety, psychosis) in 3—13% of patients, peripheral neuropathy in 1%, hypothyroidism in 23%, headaches in 1.5—30%, hearing loss in 4—25%, arthralgias and arthritis up to 70%, renal failure in 9—13%, hepatitis in 0.5—30%, and significant gastrointestinal disorders in 1.5—35% of patients.

Given the possible high percentage of failure in MDR-TB drug therapy, the possibility of surgical treatment should be seriously considered. Planned surgical interventions should only be carried out when a certain positive clinical and radiological dynamic and stabilization of the process in the lungs have been achieved. If a patient with MTB resistance can only undergo weak chemotherapy from 2—3 anti-tuberculosis drugs to which MTB sensitivity is retained, the optimal time for planned surgical intervention is shown to be from 5 to 6 months from the start of treatment with reserve anti-tuberculosis drugs. After surgical intervention, the same chemotherapy regimen considering drug resistance of MTB should be used for at least 10—18 months.

An example of successful MDR-TB treatment using surgical methods can be seen in the experience of 205 patients treated at the National Jewish Medical and Research Center (Denver, Colorado, USA) from 1984 to 1998. The frequency of surgical treatment increased over the years: 44% of patients underwent surgery from 1984 to 1988, 63% from 1989 to 1993, and 83% from 1994 to 1998. Cure rates were 75%, 85%, and 94% respectively.

Calculations using a mathematical model show that to achieve a tenfold reduction in the incidence of primary MDR-TB over 20 years, anti-tuberculosis programs must achieve a cure rate of 85% and an annual case detection rate of 70%. However, even the best existing programs today do not achieve these results, and there is a significant gap between the best and the worst programs. Two conclusions can be drawn regarding the success in combating MDR-TB. First, programs curing less than 60% of MDR-TB cases likely do not fully utilize the potential of SCC with first-line drugs. Second, to bridge the gap between achievable (60%) and desired (85%) cure rates and reduce the average duration of contagiosity, a new strategy is needed. There are four ways to reduce the duration of contagiosity and increase the cure rate:

Active instead of passive detection of contagious cases.

Isolation of contagious patients.

Earlier drug resistance testing (before a patient with possible drug resistance and a positive smear shows treatment failure).

Prolonged use of a more expensive complex of second-line drugs (with possible surgical treatment).

The goal is to find a strategy that combines these four approaches to minimize the number of future cases and deaths from tuberculosis, including MDR-TB, within existing resources. Additionally, it's crucial to prevent the formation of extensively drug-resistant TB (XDR-TB) by using SCC for sensitive tuberculosis as effectively as possible.

However, prevention is the least complex part of the problem. Much more challenging is gaining control over already developing epidemics. Treating MDR-TB is an extremely complex task requiring significant organizational and material resources. Sufficient experience has not yet been accumulated, and all existing guidelines are merely advisory. Given the public health significance of tuberculosis and that MDR-TB poses an

additional threat to the global fight against it, it's necessary to develop and widely apply standardized approaches to managing patients with this pathology.

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