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TUBERCULOSIS IN THE 21st CENTURY – CHALLENGES, ENDEAVOURS AND RECOMMENDATIONS TO DOCTORS

TUBERKULOZA U XXI VEKU – IZAZOVI, STREMLJENJA I PREPORUKE LEKARIMA

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Summary – The magnitude of problem with tuberculosis lies in the fact that one third of the world population is infected by *Mycobacterium tuberculosis*. Even in the 21st century, tuberculosis kills more people than any other infective agent. Definition of case of resistance - the case of resistant tuberculosis is precisely defined by the recommendations of the World Health Organization as primary, initial, acquired multidrug resistant and extensively drug resistant tuberculosis. The development of resistance tuberculosis may result from the administration of mono-therapy or inadequate combinations of anti-tuberculosis drugs. A possible role of doctors in the development of multi drug-resistant tuberculosis is very important. Actually, multi drug-resistant tuberculosis is a direct consequence of mistakes in prescribing chemotherapy, provision of anti-tuberculosis drugs, surveillance of the patient and decision-making regarding further treatment as well as in a wrong way of administration of anti-tuberculosis drugs. The problem of extensively drug-resistant tuberculosis in the world has become very alarming. In South Africa, extensively drug resistant tuberculosis accounts for 24% of all tuberculosis case. It can be concluded that only adequate treatment according to directly supervised short regimen for correctly categorized cases of tuberculosis can stop the escalation of multidrug or extensively drug resistant tuberculosis, which is actually an incurable illness in the 21st century.

Key words: Tuberculosis; History, 21st Century; Tuberculosis Multidrug-Resistant; Extensively Drug-Resistant Tuberculosis; Antibiotics, Antitubercular; Antitubercular Agents; Medical Errors

The magnitude of tuberculosis problem worldwide

The essence of the tuberculosis control problem in the 21st century is the fact that one third of the total number of people in the world (close to two billion) is infected by *Mycobacterium tuberculosis*. In the 21st century, *M. tuberculosis* still kills more people than any other infective agent. The vast majority of tuberculosis cases, up to 95% of all the diseased and 98% of all who died of tuberculosis, come from developing countries. The special socio-economic significance lies in the fact that 75% of people with this disease are individuals from economically productive age group (15-50 years of age) [1-4].

Due to demographic factors, socio-economic changes, inadequate control of tuberculosis movements in many countries, outbreak of Human immunodeficiency virus (HIV) epidemic, we are facing a huge number of cases of directly positive pulmonary tuberculosis, which is frequently neither diagnosed nor treated. Unfortunately, even in a certain number of treated patients, inadequate administration of drugs and inappropriate supervision of the treatment outcome result in the increasing number of those patients who cough out tuberculosis bacilli resistant to anti-tuberculosis drugs.

A successful tuberculosis control requires proper and timely diagnosis as well as efficacious, cheap and simple therapy in standardized regimes applicable to a greater number of the diseased in every country.

Therefore, in 1991, the World Health Organization (WHO) adopted the *WHO Resolution 44.8* emphasizing successful treatment as the key intervention in con-

trolling tuberculosis epidemic. This resolution recommends strengthening of the national programs in fighting tuberculosis by introducing short-term chemotherapy regimes. Since 1992, the WHO has developed the General anti-tuberculosis program, a new DOTS strategy with the aim to prevent global tuberculosis. DOTS is the brand name recommended by the WHO, which means directly observed short-term tuberculosis treatment regime, which is considered the most useful in preventing tuberculosis epidemic [2].

Successful tuberculosis therapy includes four basic aims:

- healing of a patient,
- prevention of further spreading of tuberculosis infection,
- prevention of tuberculosis recurrence as well as the fatal outcome
- prevention of the development of the resistance to the applied standard anti-tuberculosis therapy [3-6].

In the countries where the DOTS strategy has been applied for more than 5 years, it is possible to achieve sputum conversion up to 90% of newly affected by tuberculosis, where the recurrences, even those unsuccessfully treated, are found in less than 10%, acquired resistance in approximately 2%, and multi-resistant tuberculosis in 0.5-1% of tuberculosis (TB) patients. Unfortunately, the DOTS strategy implementation is not even in the world. In many countries, where tuberculosis is a serious epidemiological problem, the absence of standardized regimes and control of treatment outcome represents the, so-called, "hot zones". The consequence is the increased number of those affected by tuberculo-

Abbreviations

HIV	– Human immunodeficiency virus
MDR TB	– multi drug-resistant tuberculosis
XDR TB	– extensively drug-resistant tuberculosis
WHO	– World Health Organization
TB	– tuberculosis

sis multi-resistant to the first line anti-tuberculosis drugs [5,6,8].

According to the WHO reports from 2001, there were over 50 million individuals infected by multi drug-resistant tuberculosis bacilli (MDR TB), and 273,000 of the diseased were treated [8].

Regardless of the extent to which the tuberculosis control national program implementation has come, the development of bacterial resistance in the newly diseased patients, who have never before been treated, i.e. primary resistance, is the consequence of the level of acquired resistance in the community.

The greater the number of patients coughing out resistant bacilli during or after the treatment the greater is the risk of transmitting the resistant bacilli to healthy individuals and appearing of new primary resistance cases. Primary and acquired resistances differ in prevalence and severity [8].

A special problem in the 21st century is the outbreak of extremely drug-resistant tuberculosis (XDR TB), recorded in 23 countries; however, it is believed to be present to a much greater extent [9–13].

Defining the antituberculous resistant cases

Tuberculosis resistant to drugs – these are patients with pulmonary tuberculosis, who throw out the bacilli resistant to one or more first line anti-tubercular drug.

Patients with resistant tuberculosis can be found in the category I of the newly diseased, that is, in patients who have never before been treated for tuberculosis, or were treated for less than a month. This is *primary resistance*. This case includes category I patients infected by *M. tuberculosis* of patients with acquired resistance.

If the clinical assessment does not provide reliable data regarding the patients on previous anti-tuberculosis therapy, the detected resistance is called *initial resistance*. The initial resistance is the mixture of primary and non-detected acquired resistance.

In the patients with previous treatment, bacterial resistance is called *acquired resistance*. Epidemiologically, the true reservoir of acquired first line anti-tuberculosis resistance are the patients from the category II of tuberculosis patients, i.e. those with tuberculosis relapse, unsuccessfully treated patients, patients treated after the cessation and patients with chronic tuberculosis.

The possibility of development of primary resistance in the newly found patients with tuberculosis is successfully overcome by standard first line drugs for the category I tuberculosis patients, in directly supervised short-term treatment regime according to the DOTS strategy, during 6-8 months, as recommended by the WHO.

In the greatest number of patients previously treated for more than a month (the category II patients), the risk

of development of acquired resistance decreases with the application of the standard regime according to the DOTS strategy, during 8 months, as recommended by the WHO.

MDR bacilli and MDR tuberculosis – MDR bacilli are resistant to isoniazid-H and rifampicin-R, which are the main bactericidal first line anti-tubercular drugs. MDR represents the most severe form of bacterial resistance. MDR tuberculosis is, therefore, a significant problem for tuberculosis control in many countries [2,8,10,11,15].

XDR tuberculosis is defined as pulmonary tuberculosis case resistant to bactericidal first line anti-tubercular drugs – isoniazid and rifampicin, resistant to quinolones and one or more than three parenteral second line anti-tuberculosis drugs – capreomycin, amikacin or kanamycin [12–14].

The WHO has clearly defined not only the categories of resistant tuberculosis but also the categories of TB patients, regimes and outcomes of their treatment, which should always be respected within the successful national program of tuberculosis control [8–10].

Repeated treatment failure is defined as a case of the patient with tuberculosis whose sputum is directly positive after 5-month treatment, or after the discontinuation of the 8-month treatment, during which the drugs are taken under the direct surveillance of medical personnel.

Repeated treatment regime includes three-month initial phase of clinical treatment under the direct surveillance, which consists of two-month administration of 5 drugs (streptomycin-S, isoniazid-H, rifampicin-R, pyrazinamide-Z, and etambutol-E/2 SHRZE), and one-month administration of 4 drugs (isoniazid-H, rifampicin-R, pyrazinamide-Z, and etambutol-E/1 HRZE). Then, there is the extension treatment phase and another five-month administration of 3 drugs (rifampicin-R, pyrazinamide-Z, and etambutol-E/5 RZE). The common international abbreviation for this regime is 2SHRZE/1HRZE/5RZE. If the patient takes the drugs appropriately, i.e. under the direct surveillance, any bacilli present in the sputum after 5-month chemotherapy usually become resistant to at least one or two basic bactericidal drugs (isoniazid and/or rifampicin).

Chronic tuberculosis cases belong to the category IV of tuberculosis patients. They are defined as a failure of repeated therapy according to the DOTS strategy, only when it was administered under the direct control of a medical worker. Most frequently, chronic tuberculosis patients undergo two series of first line anti-tuberculosis chemotherapy, and sometimes even more than two complete or incomplete cycles. In these patients, the percent of acquired resistance is very high and it is usually MDR.

Regardless of the extent to which the implementation of tuberculosis control national program has come, the development of bacterial resistance in newly diseased patients who have never before been treated, i.e. the development of primary resistance, is always the consequence of the level of acquired resistance in the community. The greater the number of patients

who throw out the resistant bacilli during or after the treatment the higher is the risk of transmitting those bacilli to healthy individuals and of appearing of new cases of primary resistance. Primary and acquired resistance differ in terms of prevalence and severity [8,9].

During the initial phase of tuberculosis control national program implementation, the old cases (previously inadequately treated or treated by non-standardized chemotherapy regimes) can represent up to a half of the recorded cases. Thus, acquired resistance emerges as the priority problem, and its degree is 50% to 80% in previously treated patients [2,4,7,10,12,15].

The priority task is the application of standardized therapeutic regimes according to the DOTS strategy, with clearly defined patient categories, and with the aim to prevent the development of new resistance cases. Even when the number of patients with MDR tuberculosis is high, the main priority of the tuberculosis control national program is not the treatment of MDR tuberculosis but its prevention [8,9,13,17].

How does MDR tuberculosis originate

The phenomenon of MDR tuberculosis is conditioned solely by the human factor, and so is resistance to any antibiotic. Therefore, according to the WHO recommendations, a doctor who is treating tuberculosis, besides being systematic, should follow the DOTS program and assess the treatment results in a clinically and microbiologically adequate way, s/he should be authoritative and reliable both for the patient and their family, especially in the prolonged treatment phase. It is understood that behind each of the above items stands medical knowledge of the doctor in charge.

It should be known that *Mycobacterium tuberculosis* has that special genetic tendency towards not only creating resistance, but also surviving with both high metabolic activity and significantly decreased, even up to the so-called "bacilli hibernation" stage. *M. tuberculosis* survives in both acidic and alkaline environments, both inside and outside the cells [17]. Therefore, the successful therapy always means the administration of several drugs, mono-therapy is never used, the drugs are always used in full therapeutic dose and long enough in order to affect all the metabolically more or less active bacilli, inside or outside the cells. Administration of one drug or of inadequate drug combination results in the development of resistance in two or three weeks [2,8-10,14,17].

Possible role of doctors in development of MDR tuberculosis

Tuberculosis develops resistance to drugs usually as a consequence of a human mistake in the following: prescribing chemotherapy, provision of drugs, surveillance of the patients and making important decisions about further treatment and drug administration.

In order not to make a mistake in prescribing therapy, a doctor should carefully assess the localization and severity of tuberculosis, paying attention to the extensi-

ty of pulmonary changes. It is especially important that the patient category is properly determined by collecting data about possible previous tuberculosis treatments.

The most frequent mistakes happen when a category II patient is treated as a category I patient, when inappropriate chemotherapy is prescribed in cases of multi-resistant pulmonary tuberculosis (administration of only two or three drugs in the initial treatment phase in newly found, directly positive patients whose bacilli are initially resistant to isoniazid) [8-10]. Another frequent mistake is including only one additional drug if the previous therapy has failed, or repeatedly including one more drug in recurrent TB.

Mistakes in provision of drugs arise in poor patients who cannot afford drugs in the prolonged phase due to the lack of financial means or health insurance. A possible reason may be a short-term or long-term shortage of anti-tubercular drugs, which is frequently conditioned by poor organization and/or financial restrictions in health service. Some cases of administration of a drug or a combination of drugs with the unknown expiration date and bioavailability leading to MDR TB have been reported.

The possibility of making a mistake in surveillance of the patient and opting for further treatment is a special clinical challenge for all doctors working on tuberculosis treatment. The moment of particular significance in tuberculosis treatment is when the doctor should become suspicious that a patient suffering from MDR tuberculosis is in front of him. The suspicion can be based on two reasons:

- when the laboratory gives a report that strains resistant to rifampicin and isoniazid have been isolated,
- when a direct microscopy M+ positive patient fails to respond to the standard repeated DOTS strategy regime as for the category II.

Under the circumstances described in the latter situation, the doctor should find out the cause of failing to achieve the improvement. The practice has shown that the doctor is more likely dealing with a patient who has not been on medication than with one suffering from MDR tuberculosis. Then, the doctor should explain the significance of the previous treatment to the patient, and find out how long the patient has actually been using drugs. If the patient gives vague answers, the doctor should find a way to check the circumstances with the patient's family. The doctor should always be aware of the simple fact that the official launching of tuberculosis control national program does not mean that this particular patient has been on the adequate anti-tuberculosis therapy.

While waiting for the laboratory to verify the resistance, the doctor should find out the answers to the following questions:

- has the patient been resistant from the beginning of the treatment?
- in case of not taking drugs, has the patient failed to respond to the therapy even in the absence of acquired resistance?

- by not taking drugs, has the patient developed resistance and to which drugs?

Even when the laboratory finding is positive regarding drug resistance, the doctor should be doubtful about the laboratory reliability and possibility of making a human mistake in marking the sputum sample, so he should critically assess the patient's clinical condition and his radiological finding. Every clinical and radiological finding which is not in accordance with the laboratory resistance test should be checked in the national laboratory, and the decision about further treatment should not be made before this report arrives.

Criteria for assessing the repeated treatment failure should be thoroughly considered. The main criterion for assessing the treatment failure is mostly when the finding obtained by direct sputum microscopy is positive, but even in case of the positive finding after 2-3 months, it still does not mean that the treatment has failed. Then, it should be checked whether and how the patient has been taking the drugs. Sometimes, in spite of the adequate treatment, in cases of extensive changes with many excavations full of bacilli, it takes much longer to make the sputum negative [10].

The signs indicating the absence of favourable therapeutic response and/or aggravation can be assessed by x-rays, so it is recommended to exclude pneumonia, pulmonary thromboembolism and especially bronchial carcinoma by performing additional examinations. The least reliable sign of the treatment failure is the clinical assessment of the patient. In cases when the patient's condition seems deteriorated, but there are no laboratory or radiological findings to corroborate the suspected aggravation of tuberculosis, it is most probable that this condition is not associated with tuberculosis.

When a tuberculosis patient is still persistently positive after 5-6 months, the treatment has probably failed; and the most frequent reason for the failure in such circumstances is not taking drugs. However, if the patient does take drugs regularly, the most likely reason of so long bacillary positivism is MDR tuberculosis. We should have in mind that the presence of big caverns is associated with occasional M⁺, and that those samples give negative cultures, since the patient coughs out dead bacilli.

In case when the culture is positive, and direct microscopy shows negative findings, it is grounded to expect good treatment outcome, and it is likely to happen soon.

However, if the findings are still positive in the 5th or 6th month of the treatment, the patient must undergo anti-tuberculosis sensitivity test in order to choose further treatment as fast as possible.

The well-known "rising and falling" phenomenon causes a situation in which a patient becomes M⁻, and later he becomes and stays M⁺. That is the certain sign of treatment failure, caused by not taking drugs or by acquiring drug resistance in most of the cases.

There are several important pieces of advice for the doctors treating tuberculosis: the reports on resistance should not be taken for granted, because mistakes are

always possible; positive findings should always be well-analyzed and if the results do not match, they should be discussed with a microbiologist; the sensitivity tests should be repeated in other reference laboratories as well as in the national laboratory, and the change of therapy should not be rushed.

Mistakes in drug administration arise from not implementing direct medical surveillance of drug intake during the initial phase or from the patient's ignorance about the importance of treatment resulting from insufficient information or inadequate explanation given by the doctor before the treatment [14,15].

Global XDR tuberculosis problem

In 2006, the WHO informed the public about the global existence of extremely drug-resistant tuberculosis, they defined its meaning, and recommended the ways of its prevention and control [11,12,16,17]. XDR TB is practically incurable tuberculosis with currently available first and second line anti-tuberculosis drugs, with mortality rate higher than in MDR TB [7,15]. As it has been mentioned earlier, it is defined as a case of the patient with tuberculosis resistant to at least two first line drugs – isoniazid H and rifampicin R, resistant to chinolones and at least one injection of second line anti-tuberculosis drug (kanamycin, capreomycin or amikacin). Epidemiological data about genetic research of XDR strains *M. Tuberculosis* show that it is not only one strain of *Mycobacterium tuberculosis* [7,16–21], that it appears world wide, in South Africa as well as in the developed West Europe and the USA [20–23]. In East Europe, West Asia and South Korea 2%, in the USA 4%, in Latvia 19% of the isolated MDR *M. Tuberculosis* are, according to the definition, actually XDR. In developed western countries, XDR TB can be found in the previously treated tuberculosis patients, while in South Africa those are mostly never before treated HIV positive patients. In that "hot region", 41% of the diseased are with MDR TB, out of who 24% have XDR TB. Genetic researches in Norway, Italy and Germany have not proved that the XDR TB diagnosed in these countries was transmitted by immigrants [7,16,19,20,22, 23]. These data are alarming, and they appeal for correct treatment with the surveillance of all new tuberculosis patients. That is the only and most certain way to fight against escalation of multi drug-resistant and extremely drug-resistant tuberculosis, which represents a big global health problem of the 21st century.

Conclusion

The basic postulate of tuberculosis control in the world, including our country, is the treatment of new category I patients, because by their proper treatment and surveillance we will prevent the development of resistance to first line anti-tuberculosis drug, in the form of multi drug-resistant tuberculosis as well as extensively drug-resistant tuberculosis, which is practically an incurable illness in 21st century.

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Sažetak

Veličina problema tuberkuloze ogleda se u činjenici da je jedna trećina svetske populacije inficirana tuberkulozom. I u XXI veku M. tuberculosis ubija više ljudi nego bilo koji drugi infektivni agens. Definisane slučajeve rezistencije – Slučajevi rezistentne tuberkuloze precizno su definisani po preporukama Svetske zdravstvene organizacije na primarnu, inicijalnu i stečenu multirezistenciju i ekstremno izraženu rezistenciju. Nastanak rezistencije objašnjava se primenom jednog leka ili neadekvatne kombinacije lekova kod obolelog od tuberkuloze. Moguća uloga lekara u nastanku multirezistentne tuberkuloze je velika i rezistencija zapravo najčešće i nastaje zbog grešaka u

propisivanju hemoterapije, nabavci lekova, praćenju obolelog i donošenju važnih odluka o daljem tretmanu, kao i zbog grešaka u načinu davanja lekova obolelom. Problem ekstremno rezistentne tuberkuloze u svetu postaje alarmantan. U Južnoj Africi sreće se čak 24% novoobolelih sa ovom formom tuberkuloze. Samo adekvantim lečenjem po strategiji direktno nadziranog kratkotrajnog režima za pravilno kategorisane slučajeve tuberkuloze može se sprečiti eskalacija ekstremno rezistentne tuberkuloze, koja je praktično neizlečiva bolest u XXI veku.

Glavne reči: Tuberkuloza; Multi rezistentna tuberkuloza; Ekstrameno rezistentna tuberkuloza; Antituberkulotici

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