CURRENT ISSUES OF RESISTANT TUBERCULOSIS AND SMOKING (review)

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Abstract

Tuberculosis and smoking are among the most pressing issues in the modern health care system in the world. Tuberculosis patients who smoke are confirmed to demonstrate reduced effectiveness of anti-tuberculosis therapy, unsatisfactory prognosis of a specific disease, higher risk of treatment failure and mortality from this disease. Diseases such as HIV and alcoholism increase ineffective treatment in tobacco smokers. In addition, smoking leads to increased virulence of the causative agent of tuberculosis – Mycobacterium tuberculosis.

Key words: *tuberculosis, smoking, Mycobacterium tuberculosis, multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis.*

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. Until the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS. TB is caused by the bacillus *Mycobacterium tuberculosis* (MTB), which is spread when people who are sick with TB expel bacteria into the air (e.g. by coughing). The disease typically affects the lungs (pulmonary TB) but can affect other sites. Most people (about 90%) who develop the disease are adults, with more cases among men than women. About a quarter of the world's population is infected with MTB [1].

Since 1995, the WHO has recorded a TB epidemic in Ukraine and today this problem is relevant in our country [2].

The resistance of MTB to anti-tuberculosis drugs is one of the most serious problems of modern tuberculosis. The structure of resistance of MTB to drugs is of great importance for making specific decisions about the treatment of patients with tuberculosis. According to international standards, the following categories of resistance of MTB to anti-tuberculosis drugs are distinguished:

- Mono-resistance: resistance to one first-line anti-TB drug only [3].
- Poly-resistance: resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin [3].
- Multidrug-resistant TB (MDR-TB) is: resistance of MTB strains to at least isoniazid and rifampicin, the cornerstone medicines for the treatment of TB [4].
- Rifampicin-resistant TB (RR-TB) disease on its own requires similar clinical management as MDR-TB [5].
- Pre-extensively drug-resistant tuberculosis (XDR-TB) is: TB caused by MTB strains that fulfill the definition of multidrug resistant and rifampicin-resistant TB (MDR/RR-TB) and which are also resistant to any fluoroquinolone [5].

XDR-TB is TB caused by MTB strains that fulfill the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug (Group A drugs are the most potent group of drugs in the ranking of second-line medicines for the treatment of drug-resistant forms of TB using longer treatment regimens and comprise levofloxacin, moxifloxacin, bedaquiline and linezolid) [5].

Ukraine is among the top 10 countries with the highest burden of TB and M/XDR-TB in the world. In addition, Ukraine belongs to the group of 18 high-priority countries in the European region [6]. Every year, the rates of resistant TB in Ukraine are growing steadily.

The emergence of drug-resistant strains of MTB, the isolation of which is a characteristic feature of resistant tuberculosis, has become an obstacle to the elimination of the disease. M/XDR-TB

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is an extremely important part of the current TB epidemic. The spread of M/XDR-TB is facilitated by the high reproductive capacity of resistant strains of MTB [2].

Today, the problem of tuberculosis has gone beyond the purely medical field and has acquired the status of a nationwide problem, given that TB is a socially dangerous infectious disease, and the consequences pose a threat to the economy and national security of our country [6].

Today in Ukraine, as well as around the world, there is a tendency to the increase in the number of patients with M/XDR-TB, which is one of the most unfavorable forms of the disease due to epidemiological danger [7]. Of particular concern is the increase in the number of patients with new cases of M/XDR-TB against a background of a decrease in the number of patients with preserved susceptibility to MTB in general. In 2014, Ukraine was among the top five countries in the world with the highest number of M\XDR-TB cases. According to the WHO estimates, in 2016 the incidence of TB in Ukraine is at the level of 87 per 100 thousand population, with Ukraine ranked 4th in the world in the number of cases of M/XDR-TB and last in terms of effectiveness of treatment of this category of patients in world [6]. According to the national and international experts, the main causes of the epidemic situation in Ukraine, as well as in Europe are low detection and inadequate treatment of TB and M/XDR-TB [6]. This problem causes global economic losses for Ukraine. Thus, over the past few years, the losses from TB in Ukraine amount to about UAH 3.5 billion. per year [2].

Treatment of patients with M/XDR-TB is characterized by low efficiency (below 50%), long duration and requires long-term use of toxic drugs. The results of treatment of patients depend on a number of social and economic and medical factors, the severity of the tuberculosis process, the variant of resistance of MTB, concomitant pathology, antimycobacterial therapy and tolerability, the patient's commitment to treatment, and the presence of bad habits such as smoking [8, 9].

Thus, M/XDR-TB remains an extremely important issue of tuberculosis, timely diagnosis and effective treatment of which by reducing the overall duration of treatment of patients and improving the regime require further research and implementation of their results in practice.

Another problem in the world is smoking. Smoking is an acquired habit of inhaling the smoke of smoldering dried tobacco leaves. Tobacco use in any form kills and sickens millions of people every year [10]. Over 8 million people died from a tobacco-related disease in 2019 [11]. The number of annual deaths can be expected to keep growing even once rates of tobacco use are in decline, because tobacco kills its users and people exposed to its emissions slowly [12]. There is a lot of convincing scientific evidence in recent years about the harmful effects of smoking on human health. In this regard, the constant increase in the number of proponents of smoking in many countries, and especially in Ukraine, cannot be ignored [13].

According to the WHO, in 2020, about a third of the adult population of the Earth smoked, which is the numerical equivalent of 1.37 billion people aged 15 and older. In 2019, 8 million people died as a result of smoking, which is about 22 thousand deaths daily [14].

Smoking is the most common bad habit in the world. Tobacco addiction is included in the International Classification of Diseases [14].

According to statistics, 40.4% of adult men and 9% of adult women smoke daily in Ukraine; among young people – 45% of boys and 35% of girls. In total, there are about 9 million active smokers in the country, which is a third of the total working population. At least 100,000 Ukrainians join the ranks of smokers every year. Ukraine's economic losses from tobacco are about $ 2 billion annually. According to official statistics, 120,000 people die each year from smoking-related diseases in Ukraine [14–16].

There is also a direct link between smoking and an increased risk of developing tuberculosis in people who smoke [17].

Tobacco smoke plays a special role in the pathogenesis of tuberculosis. For example, there were significantly more alveolar macrophages from smokers compared with nonsmokers or ex-smokers. Alveolar macrophages from smokers could not control intracellular MTB growth. Nonsmokers' alveolar macrophages generated significantly more tumor necrosis factor (TNF)-α, IFN-γ, and IL-1β after MTB infection compared with uninfected alveolar macrophages. However, MTB-infected alveolar macrophages from smokers did not secrete significantly more TNF-α, IFN-γ, and IL-1β compared with uninfected smokers' alveolar macrophages. Alveolar macrophages taken from ex-smokers also failed to secrete significantly increased TNF-α, IFN-γ, and IL-1β after MTB infection. Both smokers' and nonsmokers' alveolar macrophages induced T-regulatory cell phenotype responses in allogeneic admixed

T-cells. Even after MTB infection, alveolar macrophages continued to drive this regulatory phenotype [18].

Thereby, in smokers, the pulmonary compartment has a number of macrophage-specific immune impairments that provide some mechanistic explanations whereby cigarette smoking renders a patient susceptible to TB infection and disease [18].

The role that cigarette smoke plays in the pathogenesis of TB is related to ciliary dysfunction, to a reduced immune response, and to defects in the immune response of macrophages, with or without a decrease in the CD4 count, increasing susceptibility to infection with MTB [19]. The alveolar macrophage binds to the bacillus through complement receptors 1, 3 and 4. Activated lymphocytes release cytokines while recruiting macrophages, fibroblasts, and other lymphocytes. The major cytokine involved in granuloma formation is TNF-α, which is released by macrophages immediately after exposure to M. tuberculosis antigens. The TNF-α activates macrophages and dendritic cells. In smokers, nicotine, acting through the α7 nicotinic receptor, reduces the production of TNF-α by macrophages, thereby preventing its protective action and favoring the development of tuberculosis [20,21]. In addition, the secretion of interleukin-12 (IL-12) by macrophages induces the production of gamma-interferon (IFN-γ) in natural killer cells. This aspect of the immune response aims to destroy MTB by forming a fibrous granuloma. Cigarette smoke selectively promotes low production of IL-12 and TNF-α, preventing the formation of granulomas, which would contain infection at this stage in immunocompetent individuals, creating conditions for the development of active tuberculosis [22].

Several epidemiological studies have identified the cigarette smoke as a risk factor for the infection and development of tuberculosis. Nicotine is considered the main immunomodulatory molecule of the cigarette. A study from Mexico found that nicotine decreases the production of HBD-2, HBD-3, and LL-37 in T2P during the infection with MTB promoting its intracellular growth [23].

Some studies have shown that men with a history of TB are four times more likely to develop airway obstruction than men without it [24].

Passive and active exposure to cigarette smoke is associated with an increased risk of TB. This is shown by some previous studies, which show a strong correlation between smoking and TB. In addition, secondhand smoke is moderately correlated with TB and the need for re-treatment [25]. At the same time, the risk of MTB is higher in children living in a region with a high incidence of TB, parents who smoke [26]. A study of children who have had family contacts with TB patients has shown that secondhand smoke, as evidenced by the measurement of nicotine levels in the urine, is a major risk factor for active tuberculosis [27].

Clinical studies have shown that smoking in TB patients has a significant effect on one of the main indicators of recovery in a specific process, namely the conversion of MTB. Thus, TB patients who smoke tobacco are at high risk for late conversion of MTB culture [28, 29]. In addition, some studies have shown that smoking is a risk factor for drug-resistant forms of TB [30].

Failure to treat is an important element in the treatment process for TB patients. Some studies have found that smoking, HIV-positive status, and positive sputum smear microscopy were important factors in TB treatment failure [31, 32]. In addition, according to some authors, the increased risk of treatment failure in TB and smoking is alcohol abuse [33]. Some studies have also shown an association between smoking and tuberculosis recurrence [34, 35].

Another crucial point in the control of tuberculosis is the abandonment of treatment. Smoking has been associated with the abandonment of tuberculosis treatment, and that association has been found to be independent of alcohol or illicit drug use. Therefore, abandonment of tuberculosis treatment might be related to the psychosocial aspects of smoking, the predominance of males, and the lower socioeconomic status of the affected populations, all of which are factors associated with lower rates of adherence to treatment [36].

A prospective study conducted in China shows that smoking is an independent risk factor for TB infection, especially in the elderly, and has shown a direct correlation between smoking history (pack-years) and the risk of latent TB infection [37]. Some studies have shown that when latent TB is diagnosed with IFN-γ in blood, the proportion of false-negative results is higher among smokers than among non-smokers [38]. In addition, this study shows that smoking has a negative effect on the results of tuberculosis treatment [38, 39].

Another study not only shows that smoking reduces the chances of recovery from tuberculosis, but increases the chances of quitting smoking than inactive smokers [40]. Another study found that patients with TB who stop smoking may have better outcomes than those who do not. Health

professionals should support patients in stopping smoking [41].

Some studies note that the direct effects of cigarette smoke on infected cell culture treated with anti-TB drugs interfere with TB treatment and weaken the host's immunity [42]. This can be very important for patients who smoke and do not smoke, but are in the same ward where second-hand smoke can contribute to slower recovery or even failure of TB treatment.

According to the WHO, the mortality rate associated with tuberculosis is significantly higher in smokers than in those who do not have this bad habit. Among people with tuberculosis, smokers are nine times more likely to die from tuberculosis than non-smokers [43–45]. When smokers quit smoking, the risk of death due to tuberculosis drops significantly (by 65% compared with that observed for those who continue smoking), which indicates that smoking cessation is an important factor in reducing TB-related mortality [46].

TB, COVID-19 and smoking are high-prevalence entities with public health consequences. All of these diseases have a great impact on the immune system. There is also upcoming evidence which suggests that smoking and TB increase the risk of severe COVID-19 symptoms [47].

Smoking is considered to be one of the main causes of COPD. At the same time, TB-pulmonary makes a significant contribution to the causal relationship of COPD. However, the underlying pathogenesis of TB-associated COPD is unclear. The study authors showed that patients with TB-related COPD have enhanced inflammatory responses that may be linked to fatty acid pathways and tryptophan catabolism [48].

Some authors have analyzed the impact of cigarette smoke components on MTB, the causative agent of TB. The authors report the impact of cigarette smoke condensate (CSC) on survival, mutation frequency, and gene expression of MTB in vitro. Authors show that exposure of virulent MTB to cigarette smoke increases the mutation frequency of the pathogen and strongly induces the expression of the regulon controlled by SigH – a global transcriptional regulator of oxidative stress [49]. Also, these authors have previously shown that SigH to be required for to respond to oxidative stress, survival, and granuloma formation in vivo [50]. A high-SigH expression phenotype is known to be associated with greater virulence of MTB. In patients with pulmonary TB who smoke, these changes may therefore play an important, yet unexplored, role in the treatment efficacy by potentially enhancing the virulence of tubercle bacilli [49]. Some studies have shown that CSC does not affect the growth of colonies of the standard MTB H37Rv strains in vitro [51]. But at the same time, some studies show that CSC increases the multiplication of MTB in epithelial cells [52].

Thus, reducing the number of people who smoke tobacco can increase the effectiveness of treatment, better prognosis and reduce mortality from TB. In addition, prevention of smoking will not increase the virulence of MTB.

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The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

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