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REVIEW

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What factors may influence epidemiological situation of tuberculosis in Poland and in the world?

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Abstract

The authors present the review of factors influencing epidemiological situation of tuberculosis in Poland and in the world. The groups of increased risk of tuberculosis, and clinical conditions predisposing to activation of latent tuberculosis infection (LTBI) such as HIV, uremia, diabetes mellitus, transplantation of organs, treatment with glucocorticosteroids and with antibodies to TNF and to its receptors, were presented. The higher prevalence and worse prognosis of tuberculosis in elderly people was emphasised. The methods of LTBI recognition, according to recent recommendations, with special consideration to patients in immunosupression, were shown. Methods of treatment to prevent LTBI activation, according to WHO experts, were also presented. All data were discussed in relation to the actual epidemiological situation of tuberculosis in Poland.

Key words: tuberculosis, immunology, epidemiology, risk groups, latent tuberculosis infection, diagnosis, treatment

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Introduction

Tuberculosis (TB) is still one of the most common infectious diseases worldwide. One third of the world population is infected with tubercle bacilli. According to epidemiological estimations, in 2014, 9.6 million of people were diagnosed with TB worldwide and 1.5 milion of patients died of this disease [1].

The epidemiological situation of TB is different in various parts of the world. In 2014, the highest estimated tuberculosis incidence rates were noted in South-East Asia (211/100 000) and in Africa (281/100 000) — in Lesotho, South Africa and Swaziland, an estimated incidence reached 1000/100 000. The lowest incidence rates were noted in North America (3.1/100 000 — in the US and 5.2/100 000 in Canada) [1]. The countries with TB incidence rate below 10/100 000 are approaching the elimination phase of the disease. In 2013, there were 18 such countries in the European Union and European Economic Area [2].

In Poland - a great improvement of epidemiological situation of TB has been achieved over the past 60 years, illustrated by the decrease in notification rate from 290.4/100 000 in 1957 to 17.4/100 000 in 2014 [3]. According to the ECDC criteria, Poland is already the low-incidence country. However, the incidence of TB in Poland is still higher than the average for the European Union (12.7/100 000 in 2013) [2].

In the countries with a low incidence of TB, a higher prevalence of disease in certain risk groups is observed. Groups at increased risk of

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TB include imigrants from the countries with high prevalence of tuberculosis, poor people, prisoners, homeless persons, alcohol abusers, drug addicts and individuals infected with human immunodeficiency virus (HIV). These vulnerable and hard-to-reach groups require the special care [4]. Epidemiological phenomena observed in the low-incidence countries are also found in Poland. The Polish group of patients with TB includes a larger proportion of unemployed and homeless people, compared to the entire population [5, 6].

Despite lowering of incidence rate of TB in Poland, mortality rate (calculated on the basis of death certificates), was 1.4/100 000 in 2013, therefore it was nearly twice as high as the average in the European Union [2, 3]. One of the reasons of such finding, may be the delay in the recognition of the disease. In one of the greatest centers for tuberculosis treatment in Poland, Otwock, sputum positive patients had been symptomatic for 3–6 months, before tuberculosis was recognised. In addition, in 80% of newly admitted patients, the advanced disease was recognised, with chest X-ray lesions exceeding three lung fields [7, 8]. Nevertheless, the same situation was described in other countries. In the US, a great decline of registered TB cases occured in the years 1993–2006. At the same time, the proportion of patients with advanced pulmonary tuberculosis increased from 18.5% to 26.1% [9]. The increased prevalence of advanced TB was even more pronounced in populations not regarded as being at risk of this disease, in white people, and in those born in the US [9].

The other reason for relatively high TB-related mortality in Poland may be attributed to the low proportion of patients with positive treatment results. In 2013, the success of treatment has been achieved only in 58.2% of patients with culture confirmed pulmonary tuberculosis. 2.6% of culture positive patients died of TB and 7.1% defaulted their treatment. In addition, no information concerning the fate of 20% of sputum positive patients was obtained [3].

This poor adherance to treatment in some populations of Polish patients was probably caused by poor social conditions, unemployment, alcoholism, low education, and not rarely — homelessness [5, 6, 10, 11]. The same causes for inadequate treatment results were also observed in other countries [4, 12].

Nevertheless, this situation indicates that the problem of tuberculosis in Poland is not solved, and that it may be useful to remind various medical conditions increasing the risk of tuberculosis. According to international standards, knowledge about TB risk factors is essential for proper and immediate diagnosis of tuberculosis [13].

Factors influencing susceptibility to TB infection

It is known that infection with tubercle bacilli most often spreads by inhalation of little air droplets containing the microbes. Their source is usually a person with cavitary tuberculosis of the lung. TB bacilli very often penetrate the respiratory system without causing any infection. The susceptibility to infection and to development of active disease may depend, among others, on the age of the exposed person, the genetic backgrounds, social status, eventual addictions, coexisiting diseases, and their treatment [14–19].

There are several very rare genetic abnormalities called „Mendelian susceptibility to mycobacterial diseases" combined mainly with mutations of receptors to interferon gamma (IFN gamma) and interleukin 12 (IL 12). Such patients are very prone to develop disseminated disease, not only after the contact with tubercle bacilli but also with nontuberculous mycobacteria and sometimes even after BCG vaccination. They are also very sensitive to the infection with *Salmonella sp*. and with other intracellular bacteria and fungi [14].

More often however, the diversity of host genetic factors is caused by different ethnicity of the population, and this phenomenon is responsible for different rates of infection and disease in different ethnic groups [15–17].

Other factors influencing the infection rate after exposition are as follows: the density of infected air droplets in the atmosphere, the duration of exposition and the degree of virulence of the particular species of tubercle bacilli [15]. One of them, identified by van Soolingen in China, was called Beijing [20]. The Beijing strain is more virulent *in vitro* and in experimental animals comparing to other TB genotypes [21]. It has also the increased ability to become drug resistant [21]. In addition, it can modulate immune response of the host [22]. Beijing strains constitute 13% of phenotypes identified worldwide. They were most prevalent in Asia, but have been also found in many other parts of the world, and were responsible for local epidemics [23]. In Poland, Beijing strains were identified by spoligotyping in 6.5% of isolates obtained between 2007 and 2011 [24]. The percentage of drug resistant strains was higher among Beijing comparing to non-Beijing strains (MDR 38% vs 5.8%, and XDR — 4% vs 1.4%, respectively) [24].

Latent tuberculosis infection

In about 95% of infected persons, tubercle bacilli persist in the organism, but do not proliferate (or proliferate only occasionally), and do not cause the development of disease. Such a clinical situation was called latent tuberculosis infection (LTBI). LTBI protects to some extent against TB reinfection, which is especially important in the countries with high TB prevalence.

However, the equilibrium of LTBI can be disturbed by advanced age, poor conditions of life (malnutrition), addictions (alcohol, narcotics, cigarettes), silicosis, other diseases (HIV, diabetes, renal insufficiency, neoplasms of hematopoietic system) or their treatment (anti-TNF, immunosuppresive treatment, glucocorticoisteroids or others).

LTBI can be recognised by tests based on the ability of the sensitized memory lymphocytes and other cells to recognise the antigens of *M. tuberculosis*. Tuberculin skin test (TST) is based on measuring of induration caused by subcutaneous reaction of immunocompetent cells with the antigens included in tuberculin. Tuberculin used in TST include antigens of *M. tuberculosis* but also antigens of BCG and non-tuberculous mycobacteria. Thus the reaction may be falsely positive in the patients who received BCG vacination or in those infected with non-tuberculous mycobacteria. More specific tests (IGRAs) are based on measuring the amount of IFN gamma released after exposition of mononuclear cells to *M. tuberculosis* antigens (Quantiferon-Tb Gold) or by counting cells which produce IFN gamma after such exposition (T.SPOT.Tb). IGRAs are more specific than TST because they are based on recognition of antigens specific for *M. tuberculosis*. In addition, IGRAs are more sensitive than TST in the state of immunosupression. Nevertheless, in profound immunosupression both tests can be negative. On the other hand, the positive test result, does not differentiate between the infection and active disease [25].

Diseases responsible for activation of LTBI

HIV

One of the most important risk factors for activation of LTBI and the development of active disease is HIV infection. Tubercle bacilli and HIV are reciprocally synergistic. HIV drives susceptibility to infection with tubercle bacilli and progression to active tuberculosis but also tubercle bacilli promote HIV replication [26].

Most cases of HIV infection are noted in south Africa, Asia, Latin America and Eastern Europe, but infection is diagnosed worldwide [26]. Globally, the estimated number of tuberculosis combined with HIV infection was 1.2 mln in 2014 [1]. In Poland in 2013, only 1097 cases of HIV and 151 of AIDS were diagnosed, and 123 deaths in the course od AIDS were identified [27]. Tuberculosis was AIDS indicator disease in 35 of the registered cases [28].

The risk of developing active tuberculosis is about 20 times greater in the HIV infected person than in others [26]. The susceptibility depends on the degree of immunosuppresion, measured by number of CD4 T lymphocytes in the peripheral blood. If it is lower than 200 cells/ml, tuberculosis presents with disseminated lesions and extrapulmonary localisations, but less cavities. TST is usually negative [26].

The situation has changed after the introduction of highly active antiretoviral treatment (HAART). The frequency of tuberculosis decreased, nevertheless, it still occures about five times more frequently than in patients not coinfected with HIV [29]. Treatment with HAART creates however another problems. There is some interaction between those drugs and rifampicin, and in addition, there is a risk of development of immune reconstitution inflammatory syndrome (IRIS) [30, 31].

IRIS manifests itself by the sudden progression of already treated tuberculosis (paradoxical tuberculosis-associated IRIS) or by the appearance of tuberculosis not diagnosed before (unmasking tuberculosis-associated IRIS). The development and course of tuberculosis in such a case is usually very abrupt, and may be the cause of death of the patient [26, 30, 31].

It is presumed that this syndrome is dependent on too great, too quick and unbalanced regeneration of the immunologic system after reduction of the virus load in the course of HAART and excessive response to *M. tuberculosis* antigens. This may be confirmed by the presence of various cytokines in patients' blood and usually a good effect of treatment with glucocorticosteroids [32].

There were many debates concerning the time of HAART introduction in persons already treated for tuberculosis. IRIS develops more frequently and has more severe consequences if HAART is introduced early. On the other hand, patients in whom introduction of HAART is detained, more often die from tuberculosis. Therefore, current standards of TB care propose to introduce HAART early, after 2, but not later than after 8 weeks of antituberculous treatment [13, 33].

TB remains a great health care problem when combined with HIV infection. The difficulties concerning treatment of these conditions have been illustrated by the paper published by Marcy *et al.* [34]. The authors describe the group of 661 patients in the state of deep immunosupression (CD4 T count was lower than 200/ml), treated with HAART and antituberculous drugs. 149 patients died in the course of treatment and in 28.2% — the cause of death was tuberculosis [34].

The number of deaths from tuberculosis in HIV infected persons depends on local epidemiology. Podlekareva *et al.* had proved that as many as 48.5% of HIV positive patients from Eastern Europe died from tuberculosis [35]. In Western Europe the number of deaths from tuberculosis at the same time was only 18.5% [35]. In the report of Lucejko *et al.*, during the prolonged observation of 389 patients with HIV infection in Poland, tuberculosis was diagnosed in 41 (10%). 15% of them died of tuberculosis [36].

Globally in 2014, 390,000 deaths from TB in HIV infected patients occurred [1]. The increased death rate from tuberculosis in HIV depends to some extent on its delayed recognition. Diagnosing tuberculosis in immunosupression is difficult, thus it is important to take into acount the spectrum of symptoms. In the case of cough, elevated temperature and sweating, it is reasonable to perform sputum, and eventually BAL culture for tuberculous bacilli, even if chest x-ray is inconclusive [37]. Because persons with HIV infection and pulmonary tuberculosis frequently have negative sputum smears, rapid molecular tests directed at the recognition of TB such as Xpert MTB/RIF, should be performed in such patients as the initial diagnostic test. Xpert MTB/RIF increases the chance of recognising TB in this group of patients. The overall sensitivity of this method in HIV infected population with TB was 79% (61% — for persons with smear-negative, culture positive TB and 97% — for smear-positive specimens) and the specificity was 98% [13].

End stage renal disease with uremia

There are profound alterations in immune responses associated with uremia and exacerbated by dialysis [38]. Those changes were associated with impaired activation of T lymphocytes [39] and macrophages [40]. Incidence of active tuberculosis in the patients treated with long-term dialysis is 6.9–52.5 higher than in the general population of the same region. The additional risk factors in this group of patients are the following: advanced age, diabetes mellitus, the presence of fibrotic lesions on chest X-ray and the period of dialysis exceeding 12 months [38]. In addition, the effect of antituberculous therapy is worse in this group than in controls without uremia. They significantly more often develop drug induced hepatitis and die during treatment [41].

Diabetes mellitus (DM)

The link between DM and tuberculosis has been recognised for centuries. It is known that TB occurs 3 times more often in patients with DM than in others [42, 43]. The risk is greater if DM is not well controlled. Hyperglycemia and the deficit of insulin production have harmful effects on lymphocytes and macrophages. Thus some immunosuppression linked with DM is observed [44] and the delay in diagnosis is noted [45]. This is probably the cause of more advanced pulmonary disease presenting with cavities in newly recognised patients with tuberculosis and DM, comparing to those without DM [42, 46]. DM is not only an important risk factor for tuberculosis but may also affect the disease course and treatment response.

Increasing problem of tuberculosis recognised in DM patients is due to the fact of global increase of DM incidence, in correlation with the growing prevalence of obesity. There were 171 million cases of diabetes diagnosed in 2000, and it is calculated that the number will increase to 366 — 440 million in 2030 [47].

Tuberculosis in transplant recipients

Development of tuberculosis after transplantation may concern 0.4−15.2% of all transplant recipients, i.e. 20 to 74 times more frequently than in non-immunocompromised persons from the same region [48, 49]. Tuberculosis after transplantation usually develops due to activation of LTBI but it can also be caused by the transplantation of the organ infected with *M. tuberculosis* [49]. Therefore, every living donor must be precisely examined to exclude the presence of the disease. In case of any doubt about the quality of organ from the dead donor, transplantation should be renounced, and if it is not possible, biopsies and cultures of the organ should be performed [49].

Every patient on a waiting list to transplantation should be checked for LTBI and especially for active tuberculosis [50]. It is much better to introduce antituberculous treatment or LTBI therapy before transplantation. Antituberculous therapy in the transplant recipient may be more difficult, because of the interaction between rifampicin and calcineurin inhibitors (cyclosporine

and tacrolimus), and between rapamycin and glucocorticosteroids [49].

The prognosis of patient with active TB, which develops after transplantation, is poor. Clinical presentation is often atypical, more than half of the patients present extrapulmonary or disseminated disease [51].

Drugs that influence immunity to tuberculosis

Oral glucocorticosteroids

It was proved that patients treated with glucocorticosteroids have the increased risk of developing TB, independent of other factors. The risk, according to analysis made in the United Kingdom, was 2.8-fold greater for patients taking less than 15 mg of prednisone daily and 7.7-fold greater for those who were treated with a higher dose [52]. It depends, however, on the local epidemiology of tuberculosis, since it was 1.35% in Spain and 13.8% in Philipines [53]. In addition, it was showed that patients receiving glucocorticosteroids had the diameter TST infiltration smaller than 5 mm [54].

Immunosuppressive drugs

Profound immunosuppression was caused by calcineurin inhibitors, cyclosporine and tacrolimus, and it was dose dependent [55]. This is the reason for the greater risk of activation of tuberculosis after transplantation of the lung than after kidney transplantation [49, 50].

TNF antagonists

TNF plays a great role in pathogenesis of acute and chronic inflammation such as rheumatic arthritis, ankylosis, spondylitis and inflammatory bowel disease [56]. Treatment of those sicknesses with TNF antagonists is one of the greatest progress in medicine.

On the other hand, TNF together with IFN gamma plays a great role in the immunology of tuberculosis [15, 19, 57]. It increases the phagocytic activity of macrophages and enhances the killing of intracellular bacteria [15, 19, 56, 57]. Thus treating with anti-TNF monoclonal antibodies (infliximab, adalimumamb, certolizumab) or antibodies for its receptors (etanercept) can provoke activation of LTBI. The reported frequency of this complication differs and depends on the prevalence of tuberculosis in the local population. Reactivation of LTBI occurs more frequently in the patients using anti-TNF antibodies than in those who use the antagonists to its receptors [56]. The disease usually progresses rapidly and is frequently disseminated.

As nearly as all cases of tuberculosis in the course of anti-TNF therapy were caused by the activation of LTBI, there are many national guidelines, including Polish, concerning the algorithm of LTBI diagnosing and the use of chemoprophylaxis in those infected, before the beginning of anti-TNF therapy [58]. This prevents, to a large extent, the development of active TB in patients treated with anti-TNF drugs, although TB may occur in some cases, mostly in the first year of anti -TNF treatment [59]. Biologic drugs with another mechanism of action, used to treat inflammatory autoimmune diseases, also increase the risk of tuberculosis and require screening towards tuberculosis and LTBI prior to the administration [58].

The role of age

The most vulnerable to development of disease after infection with tubercle bacilli are young children and old people [60]. In young children, the immunologic system is not mature and in old persons it is less efficient.

In Poland, BCG vaccination after birth and relatively good epidemiological situation, diminished the problem of active tuberculosis in children. In 2014, there were only 1.2/100 000 cases of tuberculosis in children from 0 to 14 years of age, as opposed to 30.4/100 000 cases of tuberculosis diagnosed in the group of persons above 65 years of age. Due to some immunosuppression, older persons have more disseminated disease and less cavities than the younger ones. In addition, due to atypical symptoms of tuberculosis and due to coexisting diseases, the recognition of active tuberculosis in the elderly is more difficult. In 2013, the death rate from tuberculosis among persons above 65 years old was 3.7/100000 in contrast to all the remaining groups of age, in whom it was 1.4/100 000. 50% of the Polish patients who died from tuberculosis in 2013 were over 65 years of age [2].

The same trend was observed in other countries with relatively good epidemiological situation. In the report from Israel, 75% of persons who died from tuberculosis were above 65 years of age [61].

The role of cigarettes smoking

It was documented that persons smoking cigarettes were more often infected with tubercle bacilli [62] and were more often diagnosed with active disease [1]. They usually present with more advanced lesions [63] and more often suffer from

the disease recurrence [64]. Cigarette smokers are also a at greater risk of death from tuberculosis [65].

In the experimental work, it was demonstrated that macrophages obtained from healthy nonsmoking adults had the diminished possibility to stop reproduction of bacilli BCG after exposure to smoke of cigarettes [66].

Diagnosis of LBTI in immunosuppression

There are many publications that refer to the value of various tests to diagnose LTBI in the state of immunosuppression, among others, the analysis published by TBNET in 2014 [67].

It included 1537 patients with HIV, chronic renal failure, rheumatic arthritis, with solid organ or stem transplantation and 211 immunocompetent control subjects from 17 centres in 11 European countries. All subjects were tested with TST, and both IGRAs. According to the study results, IGRAs were less influenced by imunosupression than TST. However, the indeterminate IGRAs' results were combined with higher immunosuppresion.

TB developed in 11 of all immunosupressed patients in the course of later observation (in 10 HIV patients and 1 organ transplant recipient). In half of them LTBI was not detected by any of the three tests. On the contrary, all three tests were positive only in 3 of those 11 patients.

Although every test was helpful to predict tuberculosis, the authors suggested that TST may be superior to IGRAs for the assessment of risk of active tuberculosis during the prolonged observation of HIV infected patients. Nevertheless, they suggested using both IGRA and TST in diagnosing LTBI in immunosuppression [67]. Similar conclusions were presented by Munoz *et al.* [58] who observed 726 patients treated with anti-TNF for 10 years. The suggestion that TST should be added to IGRA in diagnosis LTBI in immunosuppression was also made by some other authors [68, 69].

Before the introduction of IGRA, some experts used to diagnose LTBI in immunosupression with two step TST [40]. When the first TST was negative, second application of tuberculin after one week, could give positive result (booster effect). Nowadays two step TST is not recommended because the result of the second test is regarded as less specific [59].

It should be noted that in the countries, where entire population was BCG vaccinated (e.g. in Poland), it is recommended using solely IGRA in screening for LTBI before biologic treatment. To exclude LTBI in the immunocompromised patients, it is not enough to perform the TST or IGRA tests, but it is also important to collect the detailed past medical history, especially concerning any tests done before and their results, any contact with tuberculosis, and tuberculosis diagnosed in the past. It is also important to perform X-ray of the chest. The presence of fibrosis in the apex of lungs is considered to be indicative of previous tuberculosis infection. According to the recommendations, those patients should receive chemotherapy without any further TST or IGRA testing. Nevertheless, culture of sputum, urine and occasionally of BAL, should be done in those patients, as in others in whom active tuberculosis is suspected.

According to WHO recommendations, systematic testing for LTBI is not recommended in the persons with DM, alcohol abusers and tobacco smokers [70].

Chemotherapy for LTBI

It was proved that chemotherapy of LTBI prevents to a great extent the development of active TB, both in HIV infected persons and those treated with anti-TNF drugs [71].

According to WHO, there are actually four regimens recommended for LTBI treatment [25, 70]:

Isoniazid alone for 6 or 9 months daily (5mg/kg daily adults, 10 mg/kg children but not more than 300 mg/day)

Rifampin alone for 3 to 4 months (adults and children 10 mg/kg — maximum 450 mg for those < 45 kg and maximum 600 mg for those > 45 kg)

Isoniazyd plus rifampin for 3–4 months (doses like in scheme with rifampin alone)

Weekly rifapentine plus isoniazid for 3 months (rifapentine adults and children 15–30 mg/kg -900 mg maximum), isoniazid 15 mg/kg (900 mg maximum).

Summary

Epidemiological situation of TB worldwide is influenced by different factors, among others: TB strains virulence and drug resistance, the amount of population belonging to the risk groups, and the organisation of health care. Despite the fact that TB incidence rate in many counries has been lowered, the achievement of elimination phase of disease is difficult due to economic factors, immigration and increasing number of patients belonging to the risk groups of LTBI reactivation.

Conflict of interest

The authors declare no conflict of interest.

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