

REVIEWS

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Tuberculin Skin Test in Diagnosis of Latent Tuberculosis Infection

Próba tuberkulinowa w diagnostyce zakażenia gruźlicą

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Abstract

Identification and treatment of latent tuberculous infection is one of the important measures to control the incidence of active tuberculosis. The tuberculin skin test is a useful tool in diagnosing latent tuberculous infection in selected high-risk populations. It should be placed only in cases where treatment of latent tuberculosis is considered if the test turns positive. It should not be used as a screening tool in general population, nor should it be employed to detect cases of active tuberculosis. Newer techniques of detection of delayed hypersensitivity to *Mycobacteria* antigens show promising results. Their current high costs limit their widespread use. The effects of BCG vaccination wane with time, and prior BCG vaccination should not be used as an argument against treatment in high-risk patients (Adv Clin Exp Med 2005, 14, 4, 799–806).

Key words: tuberculosis, latent infection, tuberculin skin test.

Streszczenie

Wykrywanie utajonego zakażenia gruźlicą jest jedną z podstawowych metod zmniejszenia zapadalności na gruźlicę. Śródskórna próba tuberkulinowa jest powszechnie stosowanym testem wykrywającym zakażenie gruźlicze w środowiskach o wysokim ryzyku. Badanie to powinno się wykonywać jedynie u chorych, których zamierza się leczyć, jeśli próba okaże się dodatnia. Próba tuberkulinowa nie służy do wykrywania przypadków aktywnej gruźlicy. Badania przeprowadzone z użyciem nowych testów laboratoryjnych wskazują na ich większą czułość i swoistość w porównaniu z próbą tuberkulinową. Wysokie koszty tych testów nie pozwalają jednak jak dotąd na ich bardziej rozpowszechnione użycie. Wpływ szczepienia BCG na wyniki śródskórnej próby tuberkulinowej zanika z czasem, a przebieg szczepienia BCG nie powinno stanowić argumentu przeciwko leczeniu osób o wysokim ryzyku zakażenia utajonego (Adv Clin Exp Med 2005, 14, 4, 799–806).

Słowa kluczowe: gruźlica, zakażenie utajone, próba tuberkulinowa.

Tuberculosis as an Epidemiologic Problem

Tuberculosis has affected humanity for centuries. Despite advances in diagnosis and therapy, tuberculosis remains the most common infectious cause of death worldwide. It is estimated that one third of the world's population is infected with *Mycobacterium tuberculosis*. From this pool, according to the World Health Organization's estimate, 8.8 million of people per year develop active

tuberculosis and 1.8 million die from it [1]. Poor, underdeveloped countries carry the highest burden of tuberculosis – the average incidence of tuberculosis in Africa is 350 cases per 100.000 people per year [1]. On the other hand, public health efforts in the developed countries have resulted in a greatly decreased incidence of the disease. For example, the incidence of tuberculosis in the United States has fallen to 5.1 cases per 100.000 people [2]. Poland is considered a medium incidence country, with 39.9 cases per 100.000 people in 2000 [3].

Pathophysiology
of Tuberculosis Infection
and Tuberculosis Disease

Tuberculosis (TB) is defined as the disease caused by one of the members of *Mycobacterium tuberculosis* (MTB) complex, which includes *Mycobacterium tuberculosis*, *M. bovis*, *M. africanum*, and *M. microti*. Humans are the only natural hosts of MTB bacteria. Inhalation of these bacilli results in either clearance of the bacteria without apparent infection or disease, latent tuberculous infection, or progressive primary disease. Five to ten per cent of patients with latent TB infection will develop the most common form of tuberculosis, secondary (reactivation) TB disease later in life [4, 5]. This risk of progression is substantially higher in patients with acquired immunodeficiency syndrome (AIDS); in this group, it is estimated to be 7–10% per year [6]. It is essential to distinguish between the infection of the host by *Mycobacterium tuberculosis* bacilli, TB infection, and the active disease caused by this pathogen, TB disease. While one third of the world’s people have been infected with *Mycobacterium tuberculosis* (that is, have TB infection), only a minority of these have developed or will in the future develop TB disease.

The pathophysiology of tuberculosis depends on the interaction between the bacteria and the immune system of the infected host. *Mycobacterium tuberculosis* bacilli, aerosolized in moisture droplets coughed up by an infected individual, are inhaled by an exposed individual and deposited in the distal airspace of the lung. If the bacilli are not removed by mucociliary clearance, they are phagocytosed by macrophages. This initiates a T-cell-mediated immune response that results in recruitment of monocytes, lymphocytes, and neutrophils, leading to formation of granulomata. If mycobacterial replication is not controlled by the immune response, the bacilli spread in regional, most commonly hilar, lymph nodes. The primary tubercle, consisting of a coalescence of granulomata, with regional lymph node involvement, is called the Ghon complex.

The immune response to infection develops over 2–6 weeks concurrently with the initial proliferation of mycobacteria. An effective cell-mediated immune response results in limitation of the disease, with isolation of *Mycobacterium tuberculosis* bacilli in a dormant state within granulomata. An ineffective cell-mediated response fails to limit proliferation of the organisms, allowing bacilli to spread further, and resulting in primary tuberculosis. Primary tuberculosis usually

takes the form of pulmonary parenchymal inflammation, most commonly involving the lower or middle lobes, or extrapulmonary disease such as lymphadenitis or pleural disease. Primary TB disease may also be associated with hematogenous spread of bacilli, leading to disseminated or miliary tuberculosis.

Reactivation, or secondary tuberculosis occurs after an initial effective immune response limits the infection, and then later, dormant *Mycobacterium tuberculosis* bacilli escape immune system control and begin to proliferate within the lung or other tissues. It is the most common form of TB disease, most frequently localized in the parenchyma of the lung apices. Many factors have been associated with reactivation of tuberculosis; it occurs most commonly in states associated with decreased immunity due to HIV infection, steroids and other immunosuppressive drugs, malignancy, malnutrition, or end-stage renal disease, or conditions associated with lung parenchyma damage, such as silicosis (Table 1) [7]. Recent tuberculosis infection, as evidenced by a new tuberculin skin

Table 1. Conditions associated with progression of latent tuberculosis to active disease [7]

Tabela 1. Uwarunkowania związane z rozwojem utajonej postaci gruźlicy w aktywną [7]

Condition (Uwarunkowanie)	Incidence of active tuberculosis per 1000 patient- years (Zapadalność na aktywną gruźlicę na 1000 pacjentolat)
Recent tuberculosis infection – less than 1 year (Zakażenie gruźlicą w ciągu ostatniego roku)	12.9
Non-recent TB infection 1–7 years (Odległe zakażenie gruźlicą – 1–7 lat temu)	1.6
HIV infection (Zakażenie HIV)	35–162
Injection drug use, HIV positive (Używanie dożylnych narkotyków przez osobę zakażoną HIV)	76
Injection drug use, HIV negative or unknown (Używanie dożylnych narkotyków przez osobę o ujemnym lub nieznanym statusie HIV)	10
Silicosis (Krzemica)	68
Underweight by > 15% (Niedowaga > 15%)	2.6

test conversion, is also associated with an increased risk of progression of the disease. On the other hand, treatment of latent infection with effective antimycobacterial drugs results in killing of the bacilli and lowers the risk of progression to active TB disease by up to 90% in compliant patients (reviewed in [7]). Identifying and treating patients with the latent infection and a high risk of progression of tuberculosis is therefore an effective method of preventing the development of active TB disease.

Tuberculin Skin Test

The cell-mediated immune response belonging to type IV immune reaction of the host to *Mycobacteria* antigens can be assessed by the tuberculin skin test (TST). Tuberculin was initially prepared by Koch as a sterilized filtrate of the broth culture of *Mycobacteria*. The intradermal route of tuberculin administration was first introduced by Mantoux in the early twentieth century [8]. The original tuberculin formulation was subsequently modified; currently-used purified protein derivative (PPD) is a precipitate of the mycobacterial culture, and consists of a mixture of small (< 10-kDa) antigens. As different PPD preparations vary in their ability to induce a hypersensitivity reaction, they are standardized against a standard batch prepared in 1935. A delayed hypersensitivity reaction to the PPD antigens takes 48–72 hours to fully develop. In a positive reaction, the inflammatory infiltrate consists mainly of lymphocytes and macrophages.

In the usual method, tuberculin is administered by intradermal injection on the extensor surface of the forearm, away from the veins, using a 27-gauge needle. The needle should then be advanced within the skin, and the injection performed with the tip of the needle a short distance beyond the site of skin puncture, which prevents leakage of the tuberculin after the needle is withdrawn. Proper placement of a tuberculin skin test should result in a clearly visible elevation of the skin (Fig. 1).

The tuberculin skin test should be read 48–72 hours after placement. The greatest diameter of skin induration, but not the surrounding erythema, is measured. The “roller-pen” technique is the most commonly used to measure the diameter of the skin reaction. A ball-point pen is rolled on the skin surface at some angle to it, until it is “stopped” by the indurated skin, thereby indicating the margin of induration. The measurement is taken after the contralateral edge of the induration is marked in the same way (Fig. 2). There is con-



Fig. 1. Tuberculin skin test – a wheal, which is elevated about 1 mm above the surrounding skin, is formed with an orange-peel-like surface. (Source: *STD Slide Gallery*, <http://www.hc-sc.gc.ca/pphb-dgspssp/slm-maa/slides/tbtest/index.html>, Health Canada, 1998. Reproduced with the permission of the Minister of Public Works and Government Services Canada, 2004)

Ryc. 1. Śródkórna próba tuberkuliniowa – owalne wzniesienie o powierzchni skóry pomarańczowej wysokości około 1 mm nad otaczającą skórę. (Źródło: *STD Slide Gallery*, <http://www.hc-sc.gc.ca/pphb-dgspssp/slm-maa/slides/tbtest/index.html>, Health Canada, 1998. Reprodukacja za zgodą Ministra Robót Publicznych i Usług Rządowych Kanady, 2004)



Fig. 2. Reading the tuberculin skin test – roller ball technique. Using a ballpoint pen, start from the periphery of the test site and move toward the centre. The pen will usually stop at the edge of the reaction site, making measurement easier. (Source: *STD Slide Gallery*, <http://www.hc-sc.gc.ca/pphb-dgspssp/slm-maa/slides/tbtest/index.html>, Health Canada, (1998). Reproduced with the permission of the Minister of Public Works and Government Services Canada, 2004)

Ryc. 2. Odczytywanie wyniku śródkórnej próby tuberkulinowej za pomocą długopisu. Przesuwając długopis od zewnętrznych części próby, należy kierować się ku środkowi. Długopis zatrzyma się w miejscu, gdzie doszło do reakcji na próbę, co ułatwia pomiar. (Źródło: *STD Slide Gallery*, <http://www.hc-sc.gc.ca/pphb-dgspssp/slm-maa/slides/tbtest/index.html>, Health Canada, 1998. Reprodukacja za zgodą Ministra Robót Publicznych i Usług Rządowych Kanady, 2004)

siderable interobserver variability in readings of the tuberculin skin test, so both the placement and the reading of TST should be performed by experienced personnel [9].

Interpretation of a TST

There are a number of factors that may be responsible for a false-negative or false-positive tuberculin skin reaction (Table 2). Specificity and sensitivity of the TST are affected by the relative prevalence of factors causing false-positive and false-negative results, respectively. Given the high prevalence of tuberculosis in Poland, the tuber-

Table 2. Factors causing false-negative and false-positive tuberculin skin tests

Tabela 2. Czynniki powodujące fałszywie negatywny i fałszywie pozytywny wynik śródskórnej próby tuberkulinowej

Factors that may cause a false-negative tuberculin skin test (Czynniki, które mogą powodować fałszywie negatywny wynik śródskórnej próby tuberkulinowej)	Factors that may cause a false-positive tuberculin skin test (Czynniki, które mogą powodować fałszywie pozytywny wynik śródskórnej próby tuberkulinowej)
Acute infections (Ostre zakażenie) Recent live virus vaccinations (Niedawno przebyte szczepienia żywymi wirusami) Immunosuppression, including HIV infection (Immunosupresja, w tym zakażenie HIV) Chronic renal failure (Przewlekła niewydolność nerek) Low protein states (Hipoproteinemia) Disorders of the lymphoid organs (Choroby układu chłonnego) Age (Wiek) Drugs (Leki) Stress (Stres) Improper storage, adsorption of the tuberculin (Nieprawidłowe przechowywanie szczepionki) Administration-related factors (Czynniki związane z podaniem szczepionki) Reading-related factors (Czynniki związane z odczytem próby)	Inappropriately high dose of tuberculin (Nieprawidłowo duża dawka tuberkuliny) Infection with nontuberculous <i>Mycobacteria</i> (Zakażenie prątkami atypowymi) Prior BCG immunization (Przebyte szczepienie BCG)

culin skin test has relatively high positive predictive value and low negative predictive value.

Despite the extensive and long-standing experience with tuberculin skin testing, it is still unclear what a “positive tuberculin skin test” is. Poland adopted the WHO guidelines on diagnosis and treatment of tuberculosis; according to these guidelines, a TST reaction of 10 mm or more is considered positive [10]. This relatively low cut-off assures higher sensitivity of the TST, but at the cost of its specificity, especially in Poland, where BCG (see below) is used. Other countries have adopted a more diversified approach, with lower cut-off sizes for high-risk patients and higher cut-off sizes for general population. In the United States, a 5-mm reaction is considered positive in high-risk groups (HIV-infected individuals, other immunosuppressed patients, including those on immunosuppressive drugs, or status post organ transplantation, recent contacts of an active TB case, or patients with radiographic evidence of prior active tuberculosis). A 10-mm reaction is considered positive in groups with intermediate risk for tuberculosis (recent immigrants from high-prevalence countries, residents and employees of high-risk congregate facilities like jails, shelters or hospitals, mycobacteriology laboratory personnel, persons with high-risk conditions: silicosis, diabetes, end-stage renal disease, hematologic malignancies, and children less than 4 years old). Finally a 15-mm reaction is considered positive in other low-risk persons [7]. These variable cut-offs attempt to compensate for the main drawback of the TST: that reactivity to tuberculin tends to be the lowest in individuals who have elevated expected prevalence of TB infection (e.g. health-care workers), and those with the highest risk of progression to active disease, should the infection occur (e.g. HIV-infected individuals).

An interesting approach to defining of a positive tuberculin test is the so-called “grey zone” approach. In addition to regular biological characteristics of the TST itself, this approach takes into consideration the physician’s wishes regarding performance of the test, i.e. the desired certainty of ruling in or ruling out the diagnosis of tuberculous infection [11]. Using this approach, it was possible to define lower and higher cut-offs of 7.8 and 16.6 mm for ruling out and confirming the diagnosis of TB infection with 95% certainty, respectively. With these cut-offs, the authors were able to classify 61–66% of HIV-infected patients with a suspicion of tuberculosis. The TST result for the remaining 34–39% of patients was within the “grey zone”. That is, to achieve the same 95% certainty of diagnosis, these patients would require other tests to confirm or rule out TB infection.

Bacillus Calmette-Guérin (BCG) Vaccination

Bacillus Calmette-Guérin (BCG) vaccination was developed in the early twentieth century. BCG vaccine contains an attenuated strain of *Mycobacterium bovis*. By provision of antigens that are shared with *M. tuberculosis*, it leads to the development of immune response against *M. tuberculosis*. Although the effectiveness of BCG in preventing tuberculosis is still debated, there is general agreement that it has a protective effect against miliary tuberculosis and TB meningitis in children [12]. BCG vaccination is mandatory in many countries in the world, including Poland. It is estimated that over 85% of children in the world receive BCG by 12 months of age [13]. The Polish vaccination calendar includes BCG vaccination in the first day of life, at 11–13 months if the scar from the previous vaccination is less than 3 mm, at 7 years of age, and then at 12 and 18 years of age, if the TST is negative [14].

The effects of BCG vaccination on the tuberculin skin test have been examined in a recent meta-analysis [15]. As expected, persons vaccinated with BCG were more likely to have a positive tuberculin skin test, but this reaction almost never exceeded 15 mm. The authors confirmed that the effect of BCG on TST reactivity waned with time and was significantly diminished 15 years after the last dose. The immune response, as evidenced by a positive skin test, is more likely to wane in persons immunized in the neonatal period than in those who received BCG later in life [16]. The skin reaction to tuberculin can be increased in BCG-treated persons by the application of the second dose of tuberculin 48 hours to 6 weeks after the first dose (“booster phenomenon”) [17]. This led to a common practice of application of two consecutive doses of tuberculin (“two-step test”), 1–3 weeks apart; the result of the second test was felt to represent the “true” reactivity. Unfortunately, the same booster effect is seen in patients with healed tuberculosis, and in patients infected with nontuberculous *Mycobacteria*. Also, repeated tuberculin testing may lead to the development of immunity to it, similar to the immunity observed in BCG-treated individuals [18].

Other Tests

Two *in vitro* tests have recently been extensively studied and showed promising results in diagnosing latent TB infection. The first, QUANTIFERON®-TB, relies on the *in vitro* release

of interferon- γ (IFN- γ) by whole blood lymphocytes incubated overnight with purified protein derivative, and a similar antigen extract from *Mycobacterium avium complex* bacteria. It had 83% agreement with a concurrently placed TST, and was able to detect patients with positive TST due to nontuberculous *Mycobacteria* exposure [19]. QUANTIFERON®-TB has been recently approved for use in the United States.

Modified versions of the interferon-release test have recently been evaluated in clinical studies, as well. Instead of PPD, Brock et al. used two antigens, ESAT-6 and CFP-10, to stimulate lymphocytes *in vitro*. ESAT-6 and CFP-10 are secreted by *Mycobacterium tuberculosis*, are absent from *Mycobacterium bovis* and a vast majority of nontuberculous *Mycobacteria* [20]. Used in this setting, ESAT-6 and CFP-10-based IFN- γ release test showed high concordance of results with simultaneously performed TST. Results of this IFN- γ release test were not affected by prior BCG vaccination [20]. Similarly, another ESAT-6-based interferon release test, enzyme-linked immunospot (ELISPOT®), was shown to have 89% agreement with TST in a study of an outbreak of tuberculosis related to single index case. ELISPOT was better associated with proximity to the case and the duration of exposure [21]. This test seems to retain its high sensitivity even in immunosuppressed, TST-negative populations [22]. The sensitivity of the ESAT-6 test in a group of 39 HIV-positive Zambian patients with tuberculosis was reported to be as high as 90% [23].

Recommendations on use of IFN- γ -based tests do not differ from the ones for the tuberculin skin test. These tests should be performed primarily in high- and moderate-risk individuals, for whom treatment is contemplated, if they test positive. Tuberculin skin test can be performed as a confirmatory test in low-risk individuals that tested positive with an IFN- γ -based test [24].

High cost is a limiting factor in more widespread use of the newly-developed *in vitro* tests. The IFN- γ release test (QUANTIFERON®-TB) costs about \$30 per study. An advantage of both *in vitro* tests is that they require only one contact of the tested individual with healthcare personnel, as opposed to the two contacts required to place and read the TST. Failure to follow-up for reading a TST is common, and results in lost opportunities to treat infected individuals.

Uses of the Tuberculin Skin Test

In clinical practice, the tuberculin skin test is used primarily to detect persons with latent tuberculosis infection. Before a TST is placed, a careful

analysis of pre-test probability of TB infection should be performed. Ideally, testing should be limited to those with elevated risk of infection and those with higher risk of progression to active disease. Also, testing should be limited to those individuals in whom treatment of TB infection would be contemplated, if they test positive. Children, especially infants, are frequently tested even at lower levels of pre-test probability of TB infection. This practice is based on the tendency of children to develop severe, extrapulmonary tuberculosis, and their generally excellent tolerance of medications used for treatment of TB infection. If a BCG-naïve individual had a positive skin test in the past, there is no value in ever repeating the test.

Criteria for application and interpretation of tuberculin skin tests in BCG-treated individuals are far less clear. As delayed cellular immunity wanes with time, the tuberculin skin test can, in the authors' opinion, be applied and interpreted in the same way as in BCG-naïve individuals if more than 15 years have elapsed since the last time BCG was administered. The American Thoracic Society recommends approaching BCG-treated patients who move to the United States the same way as the non-BCG-treated majority of the U.S. population, with the same interpretation criteria [7]. The goal of this recommendation is to maintain high sensitivity at the cost of lower specificity. The authors of this approach accept higher false-positive rates, leading to unnecessary treatment of TB infection in some patients in the predominantly BCG-naïve American population. Given the high (> 90%) use of BCG in Poland, the direct application of these recommendations would likely lead to high proportion of false-positive tests, especially among the adolescents and young adults, whose last BCG vaccination was within a few years. On the other hand, the British Thoracic Society recommends against use of the TST in individuals with recent contact with tuberculosis, if they were BCG-treated [25].

Another common use of a tuberculin skin test in Poland is to verify the development of immunity in children receiving BCG. According to published recommendations [14], the tuberculin skin test is administered to all adolescents aged 12 and 18; only if it is negative, they are subsequently re-immunized with BCG. There are little scientific data to support this practice [26], and it is not recommended by the World Health Organization [13]. BCG vaccination is as reliable as the TST in detecting TB infection; in individuals infected with *Mycobacteria tuberculosis* the usual sequence of lesions following BCG vaccination (induration – papule – ulcer – scar) has an accelerated course, with the papule appearing as early as 48 hours following the injection (Koch's phenom-

enon). Complications of BCG administration develop with similar frequency in children with tuberculosis and in healthy children [27, 28]. Contrary to popular belief, neither the presence nor the size of a reaction to tuberculin predicts the development of protective immunity against tuberculosis after BCG vaccination [29].

The tuberculin skin test is commonly used as an adjunct to support the diagnosis of active tuberculosis. It should be stressed that TST positivity alone does not confirm the diagnosis of active tuberculosis. Similarly, absence of reactivity does not rule out active TB. The presence or absence of active tuberculosis must be determined by careful history, physical examination, and radiographic examination of the chest, and supported by microbiologic analysis (smear and culture) of sputum or other diagnostic specimens.

As mentioned before, evidence of latent *Mycobacterium tuberculosis* infection, indicated by a positive tuberculin skin test, should lead to consideration of therapy for latent TB infection. Discussion of specific regimens used in this therapy is beyond the scope of this article, but is described in detail in recent ATS and WHO guidelines [7, 10].

Conclusions

Detection of active tuberculosis through sputum examination of suspected cases is clearly a primary method to battle tuberculosis worldwide, especially in the high-incidence countries. As the incidence of tuberculosis in Poland continues to fall, these efforts should be supplemented with identification of persons with latent tuberculosis who are at high risk of progression to active disease. These groups include HIV-infected patients, intravenous drug users, persons with structural lung disease, and those recently infected with tuberculosis. The incidence of active tuberculosis in Poland's immediate neighbors, Belarus, Lithuania and Ukraine is substantially higher than in Poland, reaching 50–75 cases per 100,000 [3]. Some areas of the former Soviet Union are projected to have an incidence close to 500 cases per 100,000 by year 2010 [30]. Migrants from these and other high-incidence countries should therefore be considered high-risk and screened for latent tuberculosis. Eradication of this pool of dormant tuberculosis will be crucial in controlling the global epidemic of tuberculosis [31].

The best way to successfully diagnose latent tuberculosis is not clear. The ease and relative low cost of the tuberculin skin test makes it an attractive tool in the detection of latent tuberculosis in

developing countries. On the other hand, the performance of this almost one hundred-year-old test is clearly suboptimal. The most undesirable feature of this test is poor sensitivity in patients with high risk of TB infection (especially in patients with HIV infection) and high risk of progression to active tuberculosis. Another major drawback of the TST is its poor specificity in BCG-treated patients at risk of latent tuberculosis. New tech-

niques of detecting delayed hypersensitivity to *Mycobacterium tuberculosis* show promising results. Among these techniques, those relying on antigens that are unrelated to tuberculin (and thus can separate the immune response due to BCG vaccination and the one related to true latent TB infection) will likely become tests of choice in the near future. Unfortunately, their high cost currently limits their more widespread use.

References

- [1] WHO: Tuberculosis fact sheet, <http://www.who.int/mediacentre/factsheets/fs104/en/>, 2004.
- [2] CDC: Tuberculosis cases and case rates per 100,000 population, United States, 1953–2003, <http://www.cdc.gov/nchstp/tb/surv/surv2003/PDF/T1.pdf>, 2004.
- [3] Antoine D, Schwoebel V, Veen J, Raviglione MC, Rieder HL: Surveillance of tuberculosis in the WHO European Region, 1995–1996. *Eurosurveillance* 1998, 3, 103–114.
- [4] Marks GB, Bai J, Simpson SE, Sullivan EA, Stewart GJ: Incidence of tuberculosis among a cohort of tuberculin-positive refugees in Australia: reappraising the estimates of risk. *Am J Respir Crit Care Med* 2000, 162, 1851–1854.
- [5] Comstock GW: Epidemiology of tuberculosis. *Am Rev Respir Dis* 1982, 125, 8–15.
- [6] Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, Walker AT, Friedland GH: A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med* 1989, 320, 545–550.
- [7] American Thoracic Society: Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR Recomm Rep* 2000, 49, 1–51.
- [8] Mantoux C: L'intradermo-reaction a la tuberculin et son interpretation clinique. *Presse Med* 1910, 18, 10–13.
- [9] Ozuah PO, Burton W, Lerro KA, Rosenstock J, Mulvihill M: Assessing the validity of tuberculin skin test readings by trained professionals and patients. *Chest* 1999, 116, 104–106.
- [10] Podręcznik gruźlicy – zalecenia NPZG (Handbook of tuberculosis – guidelines of the National Program for the Treatment of Tuberculosis). Instytut Gruźlicy i Chorób Płuc (Institute of Tuberculosis and Lung Diseases), Warsaw, 2001, 1–97.
- [11] Coste J, Pouchot J: A grey zone for quantitative diagnostic and screening tests. *Int J Epidemiol* 2003, 32, 304–313.
- [12] Rodrigues LC, Diwan VK, Wheeler JG: Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *Int J Epidemiol* 1993, 22, 1154–1158.
- [13] Fine PE, Carneiro IAM, Milstien JB, Clements CJ: Issues relating to the use of BCG in immunization programmes. Geneva, 1999, 1–45.
- [14] Kalendarz szczepień dzieci i młodzieży. Załącznik nr 1 do Rozporządzenia Ministra Zdrowia z dnia 21 czerwca 2000 r. (Dz. U. Nr 55, poz. 664), 2000.
- [15] Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM: A meta-analysis of the effect of Bacille Calmette Guerin vaccination on tuberculin skin test measurements. *Thorax* 2002, 57, 804–809.
- [16] Menzies D: What does tuberculin reactivity after bacille Calmette-Guerin vaccination tell us? *Clin Infect Dis* 2000, 31 Suppl 3, S71–74.
- [17] Horowitz HW, Luciano BB, Kadel JR, Wormser GP: Tuberculin skin test conversion in hospital employees vaccinated with bacille Calmette-Guerin: recent *Mycobacterium tuberculosis* infection or booster effect? *Am J Infect Control* 1995, 23, 181–187.
- [18] Sepulveda RL, Ferrer X, Latrach C, Sorensen RU: The influence of Calmette-Guerin bacillus immunization on the booster effect of tuberculin testing in healthy young adults. *Am Rev Respir Dis* 1990, 142, 24–28.
- [19] Mazurek GH, LoBue PA, Daley CL, Bernardo J, Lardizabal AA, Bishai WR, Iademarco MF, Rothel JS: Comparison of a whole-blood interferon gamma assay with tuberculin skin testing for detecting latent *Mycobacterium tuberculosis* infection. *JAMA* 2001, 286, 1740–1747.
- [20] Brock I, Weldingh K, Lillebaek T, Follmann F, Andersen P: Comparison of a New Specific Blood Test and the Skin Test in Tuberculosis Contacts. *Am J Respir Crit Care Med* 2004, 170, 65–69.
- [21] Ewer K, Deeks J, Alvarez L, Bryant G, Waller S, Andersen P, Monk P, Lalvani A: Comparison of T-cell-based assay with tuberculin skin test for diagnosis of *Mycobacterium tuberculosis* infection in a school tuberculosis outbreak. *Lancet* 2003, 361, 1168–1173.
- [22] Richeldi L, Ewer K, Losi M, Hansell DM, Roversi P, Fabbri LM, Lalvani A: Early diagnosis of subclinical multidrug-resistant tuberculosis. *Ann Intern Med* 2004, 140, 709–713.
- [23] Chapman AL, Munkanta M, Wilkinson KA, Pathan AA, Ewer K, Ayles H, Reece WH, Mwinga A, Godfrey-Faussett P, Lalvani A: Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of *Mycobacterium tuberculosis*-specific T cells. *AIDS* 2002, 16, 2285–2293.
- [24] Mazurek GH, Villarino ME: Guidelines for using the QuantiFERON-TB test for diagnosing latent

- Mycobacterium tuberculosis infection. Centers for Disease Control and Prevention. MMWR Recomm Rep 2003, 52, 15–18.
- [25] Joint Tuberculosis Committee of the British Thoracic Society: Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Thorax 2000, 55, 877–901.
- [26] **Bothamley GH, Cooper E, Shingadia D, Mellanby A:** Tuberculin testing before BCG vaccination. BMJ 2003, 327, 243–244.
- [27] **Kapoor RK, Wakhlu I, Gupta PK, Saksena PN:** Diagnostic utility of BCG test in children. J Indian Med Assoc 1982, 78, 176–180.
- [28] **Bhandari NR, Bhambal SS, Beohar V:** Diagnostic value of BCG test in childhood tuberculosis. Indian Pediatr 1984, 21, 555–559.
- [29] **al-Kassimi FA, al-Hajjaj MS, al-Orainey IO, Bamgboye EA:** Does the protective effect of neonatal BCG correlate with vaccine-induced tuberculin reaction? Am J Respir Crit Care Med 1995, 152, 1575–1578.
- [30] **Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C:** Tuberculosis. Lancet 2003, 362, 887–899.
- [31] **Dye C, Garnett GP, Sleeman K, Williams BG:** Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. Lancet 1998, 352, 1886–1891.

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