INVITED ARTICLE

Problems in diagnosis and treatment of tuberculosis infection

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Abstract

Tuberculosis is still a major health problem in industrialized countries due to specific socioeconomic factors and there is the growing need of new rapid and accurate diagnostic methods, in order to achieve higher sensitivity and specificity compared to traditional methods of microscopic sputum examination and culture. Such methods, recently introduced, are nucleic acid amplification (NAA) tests, used directly on clinical specimens and blood tests (QuantiFERON-TB, T-SPOT.TB test), measuring the IFN-γ released by stimulated T cells. Furthermore, new drugs for the disease need to be developed, aiming to better treatment results and to prevention of Multiple Drug Resistance (MDR) cases. Critical aspects in the management of drug resistance cases should be the careful choices of drugs combination, the close follow up of the patients alongside with the patient's adherence to therapy. The role of national and international tuberculosis programs is invaluable in TB control and therapy, as well as the collaboration of all the health system departments. However, most of the clinical problems that may arise are addressed by the International Standards for Tuberculosis Care- ISTC and these guidelines should be taken into consideration, at least until future research provides more promising diagnostic and therapeutic modalities for control of the disease. Hippokratia 2009; 13 (1): 20-22

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Key words: tuberculosis, diagnosis, therapy

The global tuberculosis (TB) epidemic results in about 9 million new cases and in 2 million deaths annually. Although the disease seems to be limited in the developed countries, it still remains a major problem in industrialized countries. In these countries, socioeconomic factors such as immigration, rapid increase in poverty, malnutrition, war, and limited medication access are recognized as the most important reasons of the resurgence of TB. The determinants of high risk under these conditions are mostly host related factors, such as comorbidities, chronic use of corticosteroids, immunosuppression, drug resistance and HIV infection[1]. Yet, the National Tuberculosis Programms that should address and resolve the problem of TB prevention and treatment are usually weakening and underfunding.

The early diagnosis and adequate treatment of infectious patients with pulmonary TB are considered necessary to reduce transmission of Mycobacterium Tuberculosis (MT) and to achieve the disease elimination. Furthermore, the early identification and treatment of individuals with Latent TB Infection (LTBI), who are at high risk to develop active infection, is crucial for disease control.

Thereafter, the need of new rapid and accurate diagnostic methods has emerged, in order to achieve higher sensitivity and specificity compared to traditional methods of microscopic sputum examination and culture. On the other hand, there is the need of new drug development, aiming to better treatment results and to prevention of Multiple Drug Resistance (MDR) cases.

The Tuberculosis Skin Test (TST) has been in use for the diagnosis of tuberculosis infection since 1910. TST or intradermal Mantoux is the oldest diagnostic test and despite the diagnostic limitations it is included in the WHO latest recommendations for TB control[2]. TST is based on a protein–purified derivate (PPD), resulting from a culture filtrate of tubercle bacilli containing over 200 antigens common both in bacilli Chalmette-Guerin vaccine (BCG) and in most non tuberculosis bacteria. Consequently, the TST specificity is low and also the ability to distinguish LTBI is limited[2,3].

TST reading needs 48-72 hours after the initial administration. Errors in performing and reading can produce incorrect results that can be avoided with well training personnel. Subsequent TST can produce false positive results because of booster phenomenon (anamnestic immune reaction). False negative TST test may occur in severe illness, including active TB or immunosuppressed patients.

Taking into consideration TST limitations, extensive research has resulted in the development of new diagnostic procedures, such as the nucleic acid amplification (NAA) tests that can be used directly on clinical specimens (sputum)[2,3]. These tests amplify target nucleic acid regions in viable or nonviable bacilli, which uniquely identify MT complex. There are in-house assays and commercial kits. The in-house tests are based on PCR assays developed by each laboratory and are dependent on

laboratory methods. Two of the commercially available tests, the Amplicor MTB test (Roche diagnostics System) and the Amplifier Mycobacterial Tuberculosis Direct test (Gen Probe, Inc San Diego) have been recently approved by FDA.

The NAA tests have high specificity to confirm that positive sputum smear is due to Mycobacterium Tuberculosis, but low sensitivity in patients with negative sputum smear. The time needed for NAA tests is less than sputum culture for MT, so they can be promptly used to rule in patients with pulmonary TB infection. In patients with clinical suspicion of LTBI it has been shown that NAA tests are more accurate than TST.

The NAA test results must always be confirmed by sputum culture for pulmonary TB infection and it is worth to mention that NAA tests have low specificity and sensitivity for extra-pulmonary TB. Because of these limitations, current bibliographic evidence suggest that NAA cannot replace sputum microscopy and culture in TB diagnosis and that NAA tests cannot be used in the evaluation of treatment effectiveness in patients receiving therapy.

Several immune based tests have also been developed aiming to improve diagnostic procedures of TB infection. Serologic tests are commercially available and they are based on the detection of the antibody immune response to MT. The antibody detection kits differ in their features, depending on the kind and the site of the target antigen and also on the incubation techniques. Systematic reviews, regarding antibody detection tests, have showed that they vary widely in performance and sensitivity. Current available data suggest that these tests alone are insufficient for the accurate diagnosis of TB infection and in the present time they cannot replace sputum culture[4].

Recent research in the field of mycobacterium genomics has resulted in the identification of a specific MT genomic segment named region of difference-1 (RD-1). Two proteins in RD-1, the ESAT-6 and the CFP-10 are targets for T-cell in TB infected patients. Based in this antigen-specific T-cell reaction, two new diagnostic methods have been developed for MT infection. These blood tests measure the IFN-γ released by T cells after stimulation by MT antigens, which are more specific because they are not shared with BCG and nontuberculosis mycobacteria species of clinical relevance[2,3,5,6].

There are two types of commercially available blood tests: the QuantiFERON-TB which is based in whole blood ELISA, developed in Australia in 1980 and the T-SPOT.TB test developed in UK in 1990. The QuantiFERON-TB has the FDA approve and it is recommended to replace TST. According to US guidelines, all persons with TB suspicion should have their blood tested and in case the test becomes positive they should be considered as TB infected. The T-SPOT.TB test has been approved in some European countries under certain circumstances. The UK guidelines recommend the use of blood test in positive TST and in every person with suspected false negative TST. The major advantages of these blood tests are their speed and simplicity compared with microscopy, their high sensitivity in the detection of false negative TST in LTBI and also the ability to discern false positive TST in BCG vaccinated individuals.

Despite these strengths, there are some limitations in these new diagnostic tools. It is most important that there is not a gold standard method for comparison and validation and the available data do not include all the cases of LTBI or active TB cases, especially in regards with high risk immunosuppressed patients. Also, there are remarkable differences between the two tests in terms with sensitivity and more studies are required to define their positive predictive value[7].

A fundamental key point for the successful control of TB is the early diagnosis and immediate initiation of treatment. This critical interval is influenced by several factors depending on the individual's socio-economic condition, the severity of symptoms, the coexistence of other pulmonary disease with chronic cough, low access in health services, old age, female sex and low awareness of the disease.

Previous studies from countries with high incidence of TB have highlighted socio-demographic characteristics, financial status and stigma fear as determinants for important delay in patients seeking care from a specialist. For these reason the private sector is the first choice for more than 2/3 of the patients. In these countries, it might take too long to reach health care facilities and usually care is provided from non-specialized individuals. Consequently, in most cases the profound delay in diagnosis and treatment seems to be the vicious cycle of repeated visits at the same health care levels resulting in nonspecific antibiotics treatment and failure to access specialized TB services[8].

It is worth noting that despite the high incidence and the severity of TB infection, no new drugs have been introduced and the combination of 3 or 4 first-line drugs remains necessary for a long time. In general, successful treatment outcomes depend on the susceptibility of the bacterial strain to anti TB drugs, the duration of therapy and the adherence of patient to the recommended care. The current standard chemotherapeutic regiment for active TB requires the administration of a multidrug combination for 6 months.

A major problem in the management of TB infection is the development of MDR-TB in the two most commonly used drugs: isoniazide and rifambicine. MDR-TB is characterized as a significant problem by WHO as 300.000 new MDR cases are recognized every year. Drug resistance occurs due to inadequate treatment or infection by a high resistance strain. Treatment of MDR-TB is more intensive and requires the use of second line drugs, which are more toxic and less effective. The prognostic value of drug resistance tests depends on the previously administered drugs and their action on the MB[9,10].

The careful choices of drugs combination, the close follow up of the patients alongside with patient adherence to therapy are critical aspects in the management of drug resistance cases. It is obvious that the role of national and international tuberculosis programs is invaluable in TB control and therapy.

The WHO has recommended Direct Observed Therapy (DOT) to improve TB care requirements and has planned the eradication of TB until 2015. The introduced programme includes:

1. The improvement of DOT delivering
2. The control of special TB cases as in HIV infected people and the problem of MDR-TB
3. The support and activation of National TB control programs
4. The collaboration of all involved health system departments and the promotion of research.

The International Standards for Tuberculosis Care-ISTC[11] are considered to be the current guide for all who are involved in TB patient care and addressed the most common clinical problems in the disease management. Since the new diagnostic blood tests are not available in every country, the ISTC recommendations for Tb diagnosis are based on chest X-ray findings and sputum culture results. The chest X-ray can and should be used for TB diagnosis in case of negative sputum. The evaluation of the response to the initial antibiotic therapy is very important in case of negative sputum smear. In suspicion of TB infection, careful antibiotic administration is mandatory especially for flourocinolones, because they are active for MT and may cover the TB infection and cause delay in appropriate therapy.

In conclusion, the collaboration of all the health system departments in the management of TB is significant, since the patient may seek health care either from private medical practice or national care and the main goals are the early diagnosis and start of treatment. Furthermore, most of the clinical problems that may arise are addressed by ISTC and these guidelines should always be taken into consideration, at least until future research provides more promising diagnostic and therapeutic modalities for the disease control.

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