Editorial

Latent Tuberculosis in the light of the New International Guidelines

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The management of latent tuberculosis infection is a frequently raised issue in everyday clinical practice· however differences of opinion are not uncommon. Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active tuberculosis[1]. In LTBI a dynamic balance is observed between bacilli and immune system resulting in their control along with persistent bacterial viability. The exact immunologic background of this balance remains under investigation. The classic view of LTBI and active tuberculosis as separate entities has been recently challenged. Instead, a spectrum of interactions between *M. tuberculosis* and the immune system has been proposed[2,3].

The rate of progression of LTBI to active disease has been estimated to 5-10% and is higher the first 2 years after infection[1]. LTBI reactivation accounts for the majority of new tuberculosis cases and that is especially true for low-incidence countries[4]. In the setting of an anti-tuberculosis program the significance of LTBI detection and treatment strongly depends on the tuberculosis incidence in the community. In high-incidence countries, where the disease burden is high but the resources limited, the main aim of the anti-tuberculosis program is reduction of tuberculosis-related morbidity and mortality by limiting transmission. LTBI detection and treatment are performed only in vulnerable groups such as contacts under 5 years of age and HIV positive individuals. On the other hand, in countries with low incidence of tuberculosis, where the disease burden is limited and the resources adequate, the program's main goal, apart from reduction of morbidity, is the elimination of *M. tuberculosis* in the community. In this case detection and treatment of LTBI become utterly significant since LTBI is the reservoir of *M. tuberculosis* in the community. Therefore LTBI management is expanded further from the previously mentioned groups[5].

The significance of LTBI management is highlighted by the recent guidelines by the World Health Organization (WHO), which clarify the indications of LTBI detection and treatment[1]. **The first principle in LTBI management is that testing is reserved only for high-risk individuals aiming in treatment initiation.** On the contrary testing of low-risk individuals is not recommended[6-8]. According to WHO guidelines in high-income and upper-middle income countries with estimated tuberculosis incidence less than 100 per 100.000 population, such as Greece[1]:

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Systematic testing and treatment of LTBI **should be performed** in HIV positive persons, adults and children who are contacts of pulmonary tuberculosis cases, patients initiating anti-TNF-α treatment, patients receiving dialysis, patients preparing for organ or haematologic transplantation and patients with silicosis.

Systematic testing and treatment of LTBI **should be considered** in prisoners, health-care workers, immigrants from high tuberculosis burden countries, homeless persons and illicit drug users.

Systematic testing and treatment of LTBI **is not recommended** in people with diabetes, people with harmful alcohol use, smokers and underweight people[1].

The detection of LTBI in school workers performed in Greece is not internationally recommended. This type of testing would only make sense if treatment for LTBI was systematically administered in positive individuals and if mantoux was performed every two years in order to detect recent conversion.

The second principle in LTBI management is the detection of possible active tuberculosis before initiation of LTBI treatment[1]. Initiating treatment for LTBI in a patient with active disease would obviously pose significant dangers for development of resistance. The first step is screening for symptoms indicative for active disease such as cough, haemoptysis, fever, night sweats, weight loss, fatigue. If these symptoms are absent, the second step is testing by mantoux or interferon gamma release assays (IGRA). If these tests are positive a chest x-ray is performed. Chest x-ray is also indicated in contacts if they are immunocompromised, under 5 years of age, or symptomatic even with negative mantoux or IGRA[9].

LTBI diagnosis is based on the detection of the immune response to the *in vivo* (by mantoux) or *ex vivo* (by IGRAs) stimulation by *M. tuberculosis* antigens, since direct detection of *M. tuberculosis* is not possible in LTBI. The IGRAs' major advantage is higher specificity. In contrast to mantoux, IGRAs are not affected by previous vaccination or infection with the majority of non tuberculous mycobacteria. However significant drawbacks are also associated with IGRAs, such as their frequent conversions (from a negative to a positive result) and reversions (from a positive to a positive result) when serially performed per example in health care workers[2], cost, which is not covered by insurance and need for trained personnel.

LTBI diagnosis is compromised in Greece since the vaccination of the whole population at school age significantly limits mantoux credibility. According to the international guidelines[6,7,9] **IGRAs are the method of choice for LTBI detection in vaccinated individuals. Alternatively every positive mantoux test in a vaccinated person should be followed by IGRA. A negative IGRA generally overrules a positive mantoux test in adults.**

According to the European guidelines for contact investigation in persons vaccinated at school age, when IGRAs are not available[9]:

A mantoux test should be optimally performed only at 8 weeks after the last contact with the source. In this case a second mantoux is not needed and the possibility of false interpretation of booster phenomenon as a mantoux conversion is avoided.

In immunocompetent persons with high risk of infection (close contacts of smear positive patients) a mantoux test of 15mm or above is considered positive[9].

There is some skepticism regarding the above mentioned 15mm limit since on a previously published survey on the anti-tuberculosis programs in several European countries different approaches were observed. Specifically, out of 22 countries 10mm is considered as the limit of a positive mantoux test for vaccinated contacts in 14 countries, while 15mm is considered to be the limit in the remaining 8[10]. The effect of BCG vaccination on mantoux clearly wanes over time. However a specific borderline cannot be determined. In an interesting study 20-25% of vaccinated contacts with a mantoux test >15mmm had negative IGRAs[11]. Moreover difficult to interpret differences between mantoux test and IGRAs are sometimes observed. Hence decision to treat should be individualized. **The third principle in LTBI management is that mantoux/IGRA interpretation and decision to treat should be individualized with consideration of the details of every case. Treatment should be initiated only after risks and benefits are discussed.**

Isoniazid for 6-12 months has been considered the cornerstone for LTBI treatment, with an efficacy of 60-90%[2]. Analysis of previously published data has led to the conclusion that the benefit of isoniazid increases progressively when it is administered for up to 9-10 months and stabilizes thereafter. As a consequence the 9-month isoniazid regimen has been recommended as adequate treatment[12]. It should be noted however that in high-incidence areas the protective effect of isoniazid in HIV positive individuals wanes overtime and continuous protection is maintained through a lifetime duration of treatment or alternatively for 36 months[2].

Two recent data have raised questions on the superiority of the 9-month isoniazid regimen. Firstly a meta-analysis of 11 studies including 73.375 patients has shown

the 6-month regimen to be as effective as the 12-month regimen[13]. Secondly a recent meta-analysis has concluded that rifamycin-containing regimens show at least if not more efficacy in the reduction of disease development risk with the same if not less hepatotoxicity[14]. In that setting, according to the recent WHO guidelines the following treatment options for LTBI are recommended[1]: 6-month isoniazid, or 9-month isoniazid, or 3-month weekly rifapentine plus isoniazid, or 3-4 months isoniazid plus rifampicin, or 3-4 months rifampicin alone. There was a consensus on the equivalence of the first three regimens. However, the panel could not reach a consensus on the equivalence of the remaining regimens and the majority of the panel voted for 3-4 months isoniazid plus rifampicin and 4 months rifampicin alone. The previously proposed regimen of pyrazinamide and rifampicin has been abandoned due to severe hepatotoxicity[1,7,15].

The selection of the treatment regimen should be based on the resistance profile of the transmitting source if known, the estimated compliance to treatment since shorter regimens are usually associated with better compliance, previous history of allergy to anti-tuberculosis drugs and possibility of interaction with other medications with anti-tuberculosis drugs and especially rifampicin.

The possibility of creation of drug resistance due to LTBI treatment is a frequently asked question. This question has been clearly answered for isoniazid since several studies have shown that isoniazid administration is not associated with increased rates of disease due to isoniazid resistant strains[15]. Because of the very few numbers of *M. tuberculosis* in a latently infected individual, the possibility of resistant bacilli being present and surviving under the pressure of an one-drug regimen is negligible and should not determine the choice of the treatment regimen.

Management of contacts of multi-drug resistant cases is more complicated and several views have been published[15]. However, according to the recent WHO guidelines[1], strict clinical observation and close monitoring for the development of disease for two years is preferred over the provision of preventive treatment. Nevertheless in situations when the benefits of treatment outweigh the risks, for instance in contacts < 5 years of age, an individually tailored treatment regimen can be considered, based on the resistance profile of the source and in collaboration with an expert on multi-drug resistant tuberculosis[1].

LTBI is an intriguing scientific field with significant recent trials and remarkable developments. The complexity of management of every-day issues, which are certainly not limited to the ones mentioned here, renders necessary the continuous update of chest physicians and the implementation of international guidelines. However, since Greece indisputably presents several special features and the management of LTBI is primarily a matter of public health, the need for adoption and implementation of national guidelines is urgent.

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