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Current strategies for infectious diseases management

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Latent tuberculosis infection: approach and therapeutic schemes

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ABSTRACT

Tuberculosis continues to be a major public health problem. A priority objective is the implementation of early diagnosis, contact investigation and latent tuberculosis infection (LTBI) testing. World Health Organization (WHO) concludes that there is no gold standard for the diagnosis of LTBI; both the tuberculin test and IGRA (interferon gamma release assays) indirectly identify tuberculosis infection; both tests are considered acceptable but imperfect. WHO recommends that regimens that include rifamycins are equally effective but less toxic and more adherent than long regimens with isoniazid.

Keywords: latent tuberculosis, IGRA, Tuberculin test, Isoniazid

INTRODUCTION

Tuberculosis is a global public health problem. According to data from the World Health Organization (WHO), there are approximately 10 million new cases and 1.3 million deaths per year. The global incidence is 142 cases per 100,000 people per year, although 8 countries report >400 cases per 100,000 patients per year [1]. Data in Spain show an incidence of 9.4 cases per 100,000 patients per year, a ratio between children and adults of 0.3%, with HIV-infected patients accounting for 4.8% of all tuberculosis cases [2]. The objectives of the Spanish Plan for tuberculosis include: a) improving information, b) improving the therapeutic success rate and c) maintaining an annual incidence below 4%, through the implementation of early diagnosis, the study of contacts and the analysis of latent tuberculosis infection in certain groups [2].

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LATENT TUBERCULOSIS INFECTION (LTBI)

We define LTBI as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinical manifestations of active tuberculosis disease. Approximately 5-10% of LTBI will develop TB disease (50% in the first 5 years) and the highest risk of progression occurs in the presence of immunosuppression or in children <5 years. Following the WHO recommendation "decision to test is a decision to treat" [1], the Plan for the Prevention and Control of Tuberculosis of the Spanish Ministry of Health recommends ruling out LTBI in contacts of a patient with TB disease, people with HIV infection and patients in the following circumstances [2]: initiation of treatment with biological or immunosuppressive therapies, dialysis, candidates for solid organ or hematopoietic progenitor transplantation, silicosis or in the presence of fibrotic changes in chest X-rays. And it should be evaluated in the following groups: a) health centers, b) microbiology laboratories, c) penitentiary institutions, d) homes for the elderly, e) shelters or refuges for the homeless, f) care centers for immigrants on their arrival in Spain, g) aid workers or military personnel in countries with a high incidence and who have traveled temporarily to countries with a high incidence.

DIAGNOSIS OF LTBI

It is performed by the tuberculin skin test (TST), or Mantoux test, or by interferon gamma release assays (IGRA). A positive TST is considered positive if there is a skin induration greater than 5 mm. It indicates the presence of immune reaction to: a) *M. tuberculosis* complex, including *M. tuberculosis, M. bovis, M. africanum, M. microtii, M. tuberculosis* sups *caprae*, b) non-tuberculous mycobacterial infection, c) previous BCG vaccination (from week +4) [3]. Reactions >15 mm are unlikely to be related to BCG or atypical mycobacteria [3]. IGRA tests include: Elispot or Quantiferon

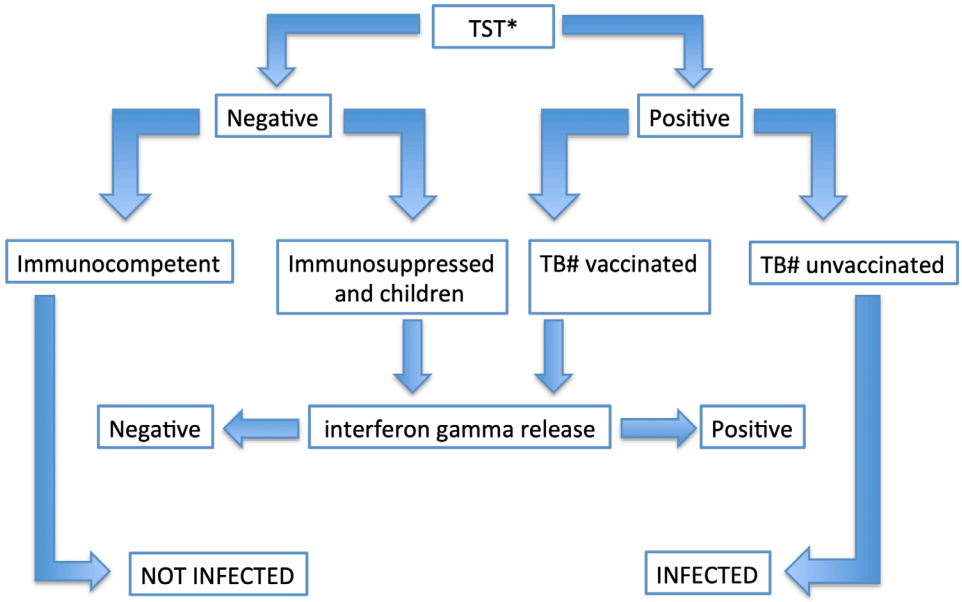

Figure 1 | **Algorithm for prophylaxis in latent tuberculosis infection [9]**

ELISA. The antigens encoded by RD1: ESAT-6 and CPF-10 are highly specific for *M. tuberculosis, M. africanum* and *M. bovis* and are not present in any of the species included in BCG or non-tuberculous mycobacteria, except *M. kansasi, M. marinum* and *M. szulgai* [4,5]. This confers high specificity and negative predictive value to IGRA [6]. Abubakar I et al. in a prospective study conducted with 10,000 patients, contacts of active tuberculosis or migrants from endemic area, confirmed a very high negative predictive value for tuberculin and IGRA testing (<1.9x1000 pac-years with negative tests) and a better positive predictive value with IGRA Elispot (13.2 x 1000 pac-years) or Quantiferon (10. 1 x 1000 pac-years) with respect to TST > 5 mm (6.8 x 1000 pac-years) [7]. WHO concludes that there is no gold standard for the diagnosis of LTBI. Both, TST and IGRA, indirectly identify tuberculous infection; both tests are considered acceptable but imperfect [1]. WHO recommends TST in countries with a high incidence of tuberculosis based on a review of comparative studies between the two tests that show similar prediction, being less costly and technically complex than IGRA. In countries with resources and incidence <100/100,000h, TST or IGRA can be used interchangeably. For the screening strategy, the concentric circles model is applied: high transmission risk (exposure >6h per day with the source) ⇒ intermediate transmission risk (exposure <6h per day with the source) ⇒ low or sporadic transmission risk (non-daily contact). Contact investigation will be expanded until the rate of positive results was indistinguishable from the community. Qantiferon TB-Gold-Plus, which incorporates a fourth tube that collects interferon production by CD4 and CD8 lymphocytes, unlike Quantiferon TB-Gold which only collects CD4, has recently entered the market [8]. Given an earlier CD8 response than CD4, the difference between the two tubes could suggest a recent contact and a greater indication for prophylaxis; however, this advantage has not been confirmed in some studies [8]. In Spain, recently the consensus between the societies of Infectious Diseases (SEIMC) and Pneumology (SEPAR) has reviewed the recommendations for the application of both tests (TST or IGRA) [9]. Given the greater sensitivity of IGRA in children and immunocompromised patients and its greater specificity in BCG vaccinated patients, an algorithm for the application and sequence of both techniques in clinical practice has been proposed (Figure 1).

NEW RISK GROUPS

Biological therapies, in addition to the previously mentioned groups, constitute a new target population for the diagnosis of LTBI and the indication of chemoprophylaxis. In recent years the irruption of biological therapies in the treatment of inflammatory and oncologic pathologies with the consequent risk of tuberculosis has broadened these indications [10]. There are numerous biological therapies and therapeutic targets. The European Society of Infectious Diseases (ESCMID) in a recent consensus document has highlighted the use of the following therapies as a population at higher risk of tuberculosis: anti-TNFs, anti-interleukin 6, anti-interleukin 12-23, anti-interleukin 17, anti-CD52, anti JAK-STAT [11].

GUIDELINES FOR ANTITUBERCULOSIS PROPHYLAXIS

One of the most significant changes in this field in recent years is the recommendation of short regimens with the incorporation of rifamycins. World Health Organization, in 2020 recommendations, using 9- or 6-months isoniazid regimens as a comparator, has analyzed the efficacy and adherence of short regimens of isoniazid + rifamycins (rifampicin or rifapentine) or rifampicin in monotherapy [12]. These recommendations conclude that regimens that include rifamycins are equally effective but less toxic and more adherent than long regimens with isoniazid, and establish the following range of priority in their indications: a) preferred: 3 months of daily isonazid + weekly rifapentine (strong recommendation, moderate evidence), b) preferred: 4 months of daily rifampicin (strong recommendation, moderate evidence, especially obtained in patients without HIV infection), c) preferred: 3 months of daily isoniazid + daily rifampicin (conditional recommendation, very low evidence in patients without HIV infection or low in HIV infection), d) alternative: 6 months of daily isoniazid (strong recommendation, moderate evidence in patients without HIV infection), e) alternative: 9 months of daily isoniazid (conditional recommendation, moderate evidence) [12].

CONFLICT OF INTEREST

Authors declare no conflict of interest

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