Artículo de revisión

Early diagnosis and treatment of latent tuberculosis infection

Diagnóstico y tratamiento temprano de la infección de tuberculosis latente

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Abstract

Latent tuberculosis infection is a major health problem worldwide. People with latent tuberculosis infection have a lifetime risk of developing active tuberculosis approximately 5 % to 10%. Patients with latent tuberculosis infection were infected with *Mycobacterium tuberculosis*. Therefore, early diagnosis and treatment of a latent tuberculosis infection are very important. Patients with latent tuberculosis infection do not have the symptoms, signs, radiographic, and bacteriological evidence of active tuberculosis. Consequently, these patients are not contagious to others. Patients with latent tuberculosis infection usually have a positive tuberculin skin test or interferon-gamma release assays test. Systematic testing is recommended for all patients that are at risk for latent tuberculosis infection. The treatment of latent tuberculosis is recommended for patients that are at increased risk for developing active tuberculosis. The medications recommended to treat latent tuberculosis infection are isoniazid, rifampin, and a combination of isoniazid and rifapentine, and isoniazid and rifampin combination regimens. The most common side effect of these medications is hepatotoxicity. Therefore, patient monitoring during treatment should occur every month to evaluate medications side effects and adherence to medications.

Post-treatment patient follow-up is very important, but serial or repeats chest radiography is not recommended.

Keywords: Latent tuberculosis, infection, diagnosis, treatment, medications.

Resumen

La infección de tuberculosis latente es un gran problema de salud a nivel mundial. Las personas con infección de tuberculosis latente tienen un riesgo de desarrollar tuberculosis activa en aproximadamente 5 % a 10 % en toda su vida. Pacientes con infección de tuberculosis latente fueron infectados con *Mycobacterium tuberculosis*, por lo tanto, diagnóstico y tratamiento temprano de la infección de tuberculosis latente es muy importante. Pacientes con infección de tuberculosis latente son asintomáticos, no tienen signos físicos o radiográficos anormales, y no tienen evidencia bacteriológica de tuberculosis activa. Consecuentemente, estos pacientes no son contagiosos a otras personas. Pacientes con infección de tuberculosis latente usualmente son positivos para las pruebas de la tuberculina o Interferon-Gamma Release Assays. Pruebas sistemáticas son recomendadas para todos los pacientes que están en riesgo de presentar infección de tuberculosis latente. El tratamiento de tuberculosis latente es recomendado para los pacientes que tienen un elevado riesgo de desarrollar tuberculosis activa. Los medicamentos recomendados para el tratamiento de la infección de tuberculosis latente son isoniacida, rifampicina, y una combinación de isoniacida y rifapentin, y la combinación de isoniacida y rifampicina. El efecto secundario más común de estos medicamentos es hepatotoxicidad. Por lo tanto, la monitorización de estos pacientes durante el tratamiento debería ser cada mes, para evaluar efectos secundarios de los medicamentos y la adherencia al tratamiento.

Es muy importante dar seguimiento después del tratamiento, pero hacer radiografías repetidas de pulmones no es recomendado.

Palabras clave: Tuberculosis latente, infección, diagnóstico, tratamiento, medicamentos.

Introduction

The global prevalence of LTBI is difficult to measure, but previous studies estimated more than two billion people have LTBI worldwide [1]. LTBI could cause reactivation and development of active TB within a large number of people [2].

The lifetime risk of developing active TB for a person with LTBI is approximately 5% to 10% [3]. Some people may develop the TB disease within the first 5 years of the initial infection. The patient's risk of developing the active TB disease depends on the host's immunological status [3].

Ecuador reported to the WHO a total of 5,157 cases of tuberculosis in 2014; therefore, the incidence rate estimated in Ecuador was 32 per 100,000 population (4). The Ecuadorian population was approximately 16 million in 2014 (4). Ecuador was considered an upper-middle income country. Consequently, LTBI early diagnosis and treatment should be recommended in Ecuador (3).

The most important goals of prevention and control of TB are testing patients who are at a high risk for LTBI or at a high risk of developing active TB once infected with the *Mycobacterium tuberculosis*. Therefore, diagnosing patients with LTBI is important in order to control and eliminate the TB disease (5). Treating patients with LTBI can prevent infected persons from developing active TB and can also stop the spread of the disease (5).

Diagnosis and treatment of LTBI can reduce the risk of developing the active TB disease, but there is not a gold standard diagnostic test for LTBI. However, there are two tests available for the diagnosis of LTBI: the tuberculin skin test (TST) and the gamma interferon (IFN-γ) release assay (6).

The decision to treat LTBI should be considered based on patient risks of reactivation to the active TB disease. Also, the preventive treatment of LTBI should be based on the potential risk of antituberculosis medication (2).

Methods

The following databases were used to search for the initial sources for this clinical review article. The databases were Trip Database, PubMed, Medline, Cochrane Database of Systematic Review, and Global Health. Several search terms were used to identify sources for this clinical review article. The search terms included latent tuberculosis infection, diagnosis, and treatment. Boolean strings were considered for the literature search. Two Boolean strings were used: diagnosis AND treatment and latent tuberculosis AND infection. Sources from the last 5 years have been considered for inclusion in the review of the literature.

The inclusion criteria for this clinical review article were literature published since 2010, English-language text, peer-reviewed articles, and Web sites relating to the early diagnosis and treatment of latent tuberculosis infection. The exclusion criteria were literature published before 2010, text not published in English, articles not peer-reviewed, and Web sites not relating to the early diagnosis and treatment of latent tuberculosis infection.

Discussion

Definition of latent tuberculosis infection

LTBI is the *Mycobacterium tuberculosis* infection of the person's body (5). The patient does not have signs, symptoms, radiographic, and bacteriologic evidence of the active TB disease (5).

Clinical Evaluation

Patients with LTBI are asymptomatic (5). During a physical examination, there is no evidence of active TB [4]. TST or interferon-gamma release assays (IGRAs) tests are usually positive. Chest radiography is normal. Sputum smear and culture are negative(5). Patients with LTBI are non-contagious to others. However, patients should still be considered for treatment of LTBI to

prevent the active TB disease (5). It is very important to identify all patients that are at risk for LTBI Table 1.

Table 1. Identification of patients at risk for latent tuberculosis infection (5)

Patients at risk for LTBI	Patients at increased risk of progression from LTBI to active TB disease
• Persons in close contact with a patient with active TB • Immigrants from a TB-endemic region • Persons that work or reside in facilities or institutions with people that are at risk for TB: ▪ Hospitals that take patients with TB ▪ Homeless shelters ▪ Correctional facilities ▪ Nursing homes ▪ Facilities for patients with HIV infections/AIDS	• HIV infection • Injection drug users • Radiography evidence of previous healed TB • Underweight (10% below ideal) • Medical conditions: silicosis, diabetes mellitus, chronic renal failure, gastrectomy, jejunoileal bypass, solid organ transplant, head and neck cancer, prolonged use of corticosteroids, treatment with immunosuppressive agents • persons with previous TST negative, but within a 2 years period that person became TST positive • Infants and children under 5 years old who had a positive TST are also persons at risk for developing the TB disease

For developed and middle-income countries with an estimated TB incidence of less than 100 per 100,000 population, the WHO recommended the following. Systematic testing and treatment of LTBI should be done for patients living with HIV, adults and children who are in contact with patients who had pulmonary TB, patients initiating anti-tumor necrosis factor (TNF) treatment, patients on dialysis, patients preparing for organ or hematologic transplantation, and patients with silicosis (3). Conditional recommendations for systematic testing and treatment of LTBI should be considered for people in jail, health care workers, immigrants from high TB incidence countries, homeless people, and illicit drug users. Systematic testing and treatment for LTBI were not recommended for people with diabetes, harmful alcohol users, tobacco smokers, and people with low body weight (3).

For developing and middle-income countries, the WHO also recommended the systematic testing and treatment of LTBI (3). Patients living with HIV and children younger than 5 years old who are living in a household with patients with active TB or are in close contact with patients with active TB should have the systematic testing and treatment for LTBI (3).

Diagnosis of latent tuberculosis infection

The diagnosis of LTBI should be based on evidence from medical history, TST or IGRAs test results, chest radiography, physical examination, and in some cases, sputum examination (5). TB testing should be targeted only to high-risk groups with the intention to give treatment if the LTBI is detected. Unfocused population-based testing was not recommended and might lead to unnecessary treatment (5).

Tuberculin skin test. The TST will become positive if a person was infected with *Mycobacterium tuberculosis* and a delayed-type hypersensitivity reaction may be detected 2 to 8 weeks after TB infection (5). The TST is performed using the Mantoux technique. The intradermal injection used is five tuberculin units of purified protein derivative (PPD) or two tuberculin units of PPD RT23. If the person has cell-mediated immunity to these tuberculin antigens, a delayed-type hypersensitivity reaction will occur in 48 to 72 hours; therefore, the reaction will produce a localized induration of the skin at the injection site (6).

The TST might produce false positive and false negative results. The most important causes of false-positive results are nontuberculosis mycobacterium infection and previous bacillus-Calmette-Guerin (BCG) vaccination (6), but according to CDC, the interpretation of the TST results are the same for people who had the BCG vaccination because of most BCG cross-reactions lesson with time (5). The TST false negative responses can occur in

immunocompromised patients, such as HIV patients, patients on immunosuppressive medications, and people with active TB disease (2). The interpretation of TST is described in **Table 2.**

Table 2. Interpretation of tuberculin skin test (5)

Reaction measured in millimeters	Patient risk of developing TB infection
5 mm or more of induration	**Positive in high-risk patients:** • HIV patients • Person with a recent contact with a person with an active TB disease • Persons with abnormal chest radiography consistent with previously having TB • Organ transplanted patients • Immunosuppressed patients
10 mm or more of induration	**Positive in the following persons:** • Recent immigrants from high prevalent areas • Intravenous drug users • Residents of correctional facilities, homeless shelters, and hospital workers • People working in a mycobacteriology laboratory • People with medical conditions that increase the risk of developing active TB • Infants, children less than 5 years old, and children and adolescents exposed to adults with active TB disease
15 mm or more of induration	**Positive in persons who are not at risk of developing active TB diseases:** • Persons that require TST for employment or school attendance

Interferon-gamma release assays. The IGRAs tests are blood tests of cell-mediated immune responses to the *Mycobacterium tuberculosis* antigens and proteins (6). The IGRAs tests are more specific than TST for *Mycobacterium tuberculosis* because IGRAs are not encoded to any BCG vaccines genomes or most nontuberculosis mycobacterium species (6).

There are two U.S. Food and Drug Administration (FDA) approved IGRAs tests available in the United States and in many other countries. QuantiFERON-TB Gold-in-Tube test (QFT-GIT) and the T-SPOT.TB test (5, 6). The QFT-GIT assay was an enzyme-linked immunosorbent assay (ELISA) based test and the results were reported as quantification of IFN-γ in

international units (IU) per milliliter (6). A patient was considered positive for *Mycobacterium tuberculosis* infection if the IFN-γ response to TB antigens was more than the test cutoff references (6).

The T-SPOT.TB test is an enzyme-linked immunosorbent spot (ELISPOT) assay. It was performed using a peripheral blood mononuclear cells. The results were reported as the number of INF-γ producing T cells (6). Patients were considered positive for *Mycobacterium tuberculosis* infection if the spot counts in the TB antigen wells was above a specific threshold relative to the negative control wells (6).

The IGRAs had more than 95% specificity to diagnose LTBI in low incidence places and the specificity was not affected by the BCG vaccination (6). The TST specificity was 97% in places not vaccinated with the BCG, but the TST specificity was approximately 60% in populations vaccinated with BCG; however, the TST specificity depends on when and how often the BCG was given in the particular place or population (6). The sensitivity was approximately 90% for T-SPOT. TB assay, QFT 80%, and TST 80% respectively. IGRAs sensitivity was also lower in HIV-positive patients and in children (6).

IGRAs methods of testing were preferred for people that had poor rates of returning for TST reading, such as homeless people and persons who had BCG vaccinations (5). The TST was also the preferred test for children less than 5 years old (5). The TST and IGRAs tests were not recommended for routine use. However, these tests were used in certain situations, such as for HIV-infected patients and for children younger than 5 years who were exposed to a person with active TB. In these particular patients, both tests could be useful to diagnose LTBI (5).

Algorithm for the diagnosis of latent tuberculosis infection

Table 3. Algorithm for the diagnosis of LTBI (3)

- A patient at risk of LTBI or TB should be asked if he/she has the following symptoms:
  - Cough
  - Hemoptysis
  - Fever
  - Night sweats
  - Weight loss
  - Chest pain
  - Shortness of breath
  - Fatigue

• If the patient is asymptomatic, a TST or IGRA test should be performed
  • If TST or IGRA test is positive, patient should have a chest radiography
  • If the chest radiography is normal, patient should be treated for LTBI
  • If the chest radiography was abnormal, patient should be investigated for active TB
	• If the patient is symptomatic or positive for any of these symptoms
	  • Patient should be investigated for active TB

Treatment of latent tuberculosis infection

The treatment of LTBI prevents the progression to the active TB disease (1). The medications recommended by CDC, WHO, American Thoracic Society (ATS), and the Infectious Disease Society of America (IDSA) were isoniazid and rifampin, as well as a combination of isoniazid and rifapentine. However, the rifampin and isoniazid combination was only recommended by the WHO (2). The isoniazid and rifapentine combination regimen was not recommended for children less than two years old, patients with HIV receiving antiretroviral treatment, pregnant women or women planning to become pregnant during the treatment, and patients with LTBI with possible isoniazid or rifapentine resistance (7).

Table 4. Treatment of LTBI		
Medications	**Regimen recommended**	**Most common side effects**
Isoniazid	**Six months duration** Daily dose: 5 mg/kg for adults Maximum dose 300 mg Twice a week dose: 15 mg/kg for adults Maximum dose 900 mg The six months duration was not recommended for children [4] **Nine months duration** Daily dose: 5 mg/kg for adults and 10-20 mg/kg for children Maximum dose 300 mg Twice a week dose: 15 mg/kg for adults and 20-40 mg/kg for children Maximum dose 900 mg (5)	• Hepatotoxicity • Nausea • Vomiting • Abdominal pain • Rash • Peripheral neuropathy • Dizziness • Drowsiness • Seizures (1, 2)
Rifampin	**Four months duration** Daily dose: 10 mg/kg Maximum dose 600 mg/day (5)	• Hepatotoxicity • Flu-like symptoms • Rash • Anorexia, nausea, and abdominal pain • Neutropenia • Thrombocytopenia • Peripheral neuropathy • Nephrotoxicity (1, 2)
Isoniazid and Rifapentine	**Three months duration for adults and children more than 12 years old** Once a week: Isoniazid 15 mg/kg Maximum dose 900 mg Rifapentine dose by body weight Maximum dose 900 mg(3, 5)	• Hepatotoxicity • Hypersensitivity reaction • Petechia rash • Anorexia and nausea • Abdominal pain • Hypotension • Peripheral neuropathy (1, 2) • Body fluids can become orange in color (5)
Isoniazid and Rifampin	**Three to four months duration** Daily dose: Isoniazid 5 mg/kg for adults and 10 mg/kg for children Maximum dose 300 mg Rifampin 10 mg/kg for adult and children Maximum dose 600 mg (3)	• Hepatotoxicity • Flu-like symptoms • Anorexia, nausea, abdominal pain • Neutropenia, Thrombocytopenia • Peripheral neuropathy (1, 2)

Patient monitoring during treatment

The health care provider who treated patients with LTBI should have evaluated the patient every month for signs of hepatotoxicity, adherence to medications regimen, and symptoms of medications side effects (5). Patients should have been educated regarding medication side effects (5).

Baseline laboratory testing was recommended for patients with the following risk factors: (a) liver disorder or history of liver diseases, such as hepatitis, alcoholic hepatitis or cirrhosis; (b) alcoholics and risk for chronic liver disease; (c) HIV infection; (d) pregnancy or within three months postpartum; (e) patients taking medications for chronic medical conditions; (f) patients who had an abnormal initial test and patients at risk for hepatic disease should have routine periodic blood tests after the baseline testing; and (g) patients should have had laboratory testing if they showed symptoms of hepatoxicity (5).

If the patient was symptomatic and the transaminases levels exceeded three times the upper limit, the treatment should have been discontinued (5). If the transaminases levels exceeded five times the upper limit of normal, the treatment should have been stopped; even though, the patient did not have symptoms (5).

Post-treatment patient follow-up

The LTBI post-treatment follow-up was very important. Serial or repeat chest radiography was not recommended unless patients developed TB disease symptoms (5).

Conclusion

The lifetime risk of developing active TB is approximately 5% to 10% (3). Therefore, early diagnosis and treatment of patients with LTBI are important to prevent TB disease (5).

A person with LTBI was infected with *Mycobacterium tuberculosis*, but the patient does not have signs, symptoms, radiographic, and bacteriological evidence of the active TB disease (5).

The diagnosis of LTBI should be based on patient medical history, physical examination, TST, QuantiFERON-TB Gold-in-Tube test or T-SPOT.TB test results, chest radiography, and in some cases, sputum examination (5,6). Patients with LTBI usually have a positive TST or IGRAs test, but they are non-contagious to others (5).

Systematic testing and treatment of LTBI are recommended for patients at increased risk of progression from LTBI to active TB (3). Therefore, testing should be targeted only to high-risk groups with the intention to give treatment if the LTBI is detected. Unfocused population-based testing was not recommended and might lead to unnecessary treatment (5).

Medications recommended to treat LTBI are isoniazid, rifampin, and a combination of isoniazid and rifapentine, as well as isoniazid and rifampin combinations regimens(2). The healthcare provider should evaluate the patient every month for signs of hepatotoxicity, adherence to medications regimen, and symptoms of medication side effects (5). Patients should be educated regarding medication side effects (5). Post-treatment follow-up is very important, but repeat chest radiography is not recommended unless patients developed TB disease symptoms (5).

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