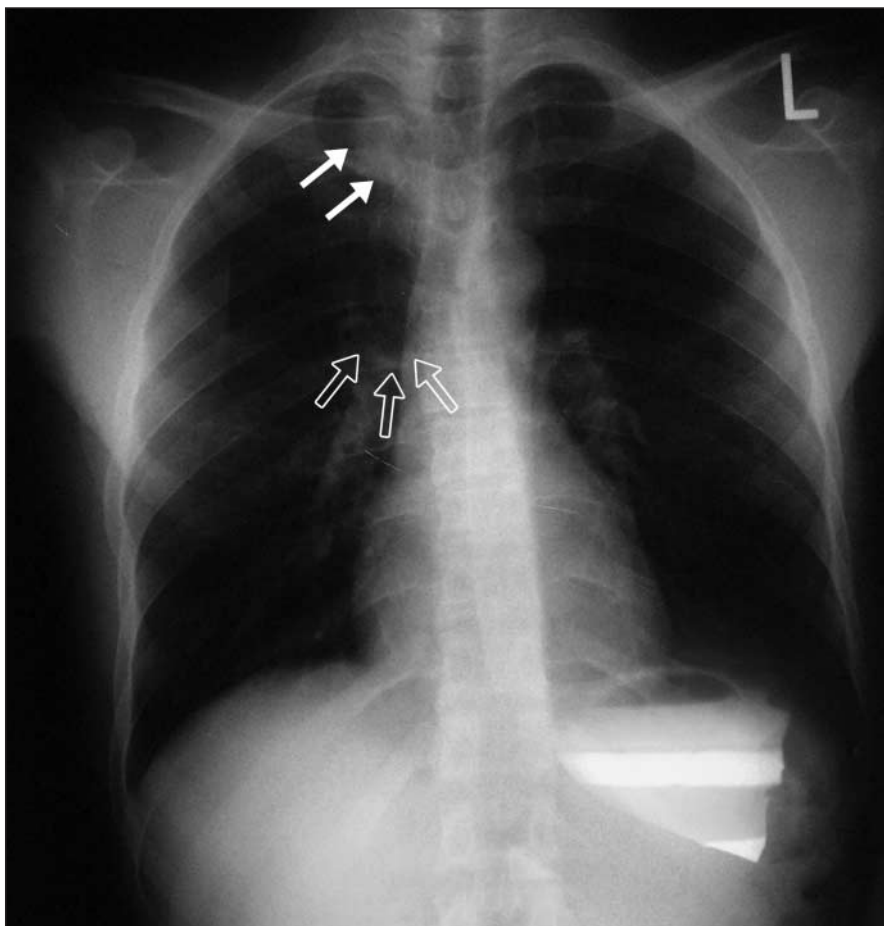


Latent tuberculosis: revised treatment guidelines

Background and epidemiology: According to 1999 estimates, 1.86 billion people — one third of the world's population — are infected with tuberculosis.¹ Most people with primary tuberculosis (TB) do not have signs or symptoms and may not know that they are infected. Their immune systems contain the tubercle bacilli in oxygen-deprived small granulomas, where the bacilli lie dormant for years. Following primary infection, the lifetime cumulative risk for active TB is estimated to be 10%.² Certain factors increase the risk of reactivation because of diminished local or systemic immunity; these include HIV infection, transplantation, silicosis, chronic renal failure, cancer, recent TB infection (within 2 years), diabetes mellitus, malnutrition and low age (less than 5 years) when first infected.²

Identifying and treating latent TB is a key component of global efforts to eliminate TB. A number of therapeutic regimens using courses and combinations of isoniazid (INH), rifampin or pyrazinamide have been presented in the literature. Recently, the American Thoracic Society and the US Centers for Disease Control and Prevention issued revised treatment recommendations for latent TB and indicated that the 2-month regimen of rifampin plus pyrazinamide *should generally not be offered* because of high rates of severe liver injury.³ The preferred regimen is INH for 9 months; alternatives are INH for 6 months or rifampin for 4 months.²

These revised treatment guidelines³ are based on data collected from cohorts of patients with latent TB in the United States who received pyrazinamide during January 2000–June 2002. The rates of severe liver injury and death were significantly higher among patients given pyrazinamide than among those given INH.³ These findings echo the results from an earlier randomized controlled trial, in which the incidence of liver injury was higher among people receiving short-course rifampin and pyrazinamide therapy for latent TB than among those receiving



A 33-year-old man immigrated to Canada from a sub-Saharan African country. A screening chest radiograph obtained during the immigration process was read as abnormal, and the man was subsequently referred to a regional tuberculosis clinic for post-immigration assessment and medical surveillance. A repeat chest radiograph revealed right apical scarring (solid arrows) with volume loss and resultant retraction of the right main-stem bronchus (hollow arrows). The man had no known history of tuberculosis exposure and was otherwise healthy. The result of an unboosted tuberculin skin test was positive (induration of 10 mm); HIV-1 and HIV-2 antibody test results were negative. An induced sputum sample did not contain visible acid-fast bacilli. A 9-month regimen of isoniazid, 300 mg/d, was completed without difficulty.

INH of standard duration (odds ratio 8.5, 95% confidence interval 1.9–76.5).⁴ The recommendation against the use of pyrazinamide for the treatment of latent TB does not apply to the appropriate use of rifampin and pyrazinamide in multidrug regimens for the treatment of active TB.⁵

The loss of the 2-month regimen of combined rifampin plus pyrazinamide leaves us with longer-duration treatment regimens for latent TB, which are

associated with high rates of noncompliance^{6,7} and may be ineffective in the face of increasing resistance to INH worldwide.⁸

Clinical management: The main tool for the diagnosis of latent TB is the Mantoux tuberculin skin test, which involves intradermal injection in the forearm of 0.1 mL of liquid containing 5 tuberculin units of PPD. Interpretation is based on measurement of the in-

duration (not erythema) 48 to 72 hours after administration.

Unfortunately, the Mantoux test is imperfect in terms of both its sensitivity and specificity. False-negative results occur, particularly in immunocompromised and elderly people. A negative result can sometimes be followed by a positive result when the test is repeated 3 weeks later. This “booster” phenomenon most often occurs in elderly people many years after infection.² The subject’s immune system initially fails to recall the prior infection; the memory is boosted with the second test. For this reason, people who must undergo serial skin testing (e.g., health care workers) should initially undergo a 2-step Mantoux test (a repeat test 3–4 weeks after the first) to avoid having a result that is positive because of boosting be incorrectly attributed to a new exposure and infection.

Immunocompromised people are at highest risk of activation of latent TB. The use of anergy testing (e.g., testing immune reactivity to *Candida* antigens concurrently with tuberculin testing) appears to be unhelpful in distinguishing true- and false-negative tuberculin test results in this population.⁹ Newer assays for latent TB, which focus on host lymphocyte responses to *Mycobacterium tuberculosis*, are not yet available in clinical practice.¹⁰

In determining whether a given skin test result indicates the need for treatment of latent TB, consideration should be given to the prior likelihood of latent TB in the tested individual, his or her immune status and the likelihood of exposure to or development of active disease (see Table 6 [page 98]

of the Canadian TB standards, available at www.hc-sc.gc.ca/pphb-dgspsp/publicat/cts-ncla00).² The provision of treatment to HIV-positive people who have a negative skin test result is a matter of some debate.¹¹ In deciding whether to treat latent TB, host factors that may predispose to reactivation of TB (underlying disease, recent skin test conversion, presence of fibronodular disease on chest radiographs) must be weighed against the risk of liver injury from therapy, which increases with age greater than 35 years.

Directly observed therapy (DOT) has become common practice in the management of people with active TB.¹² Although not currently advocated for the treatment of latent TB, the use of DOT may increase the likelihood of completion of therapy.¹³

Prevention: Identifying and treating latent TB can prevent future disease and drastically reduce public health costs by avoiding expensive outbreak investigations and management of TB. Although the bacille Calmette–Guérin vaccine reduces the risk of TB by about 50%,¹⁴ associated adverse effects and the subsequent distortion of tuberculin skin test results favour its use in only the highest risk populations, such as First Nations infants living on reserves.² A more effective vaccine is needed; such a vaccine would be a major step forward for global health efforts.¹⁵

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