Latent tuberculosis infection: old problem, new priorities

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Tuberculosis (TB) continues to take a devastating toll worldwide. This fact, coupled with a dramatic resurgence of TB in the United States and other developed countries in the early 1990s, has renewed interest in TB control in North America.

A cornerstone of any TB control program remains the prompt diagnosis and successful treatment of people with active disease. Well-documented epidemics in US inner cities a decade ago reflected a deteriorating public health infrastructure. Subsequent reinvestment interrupted TB transmission and reduced overall incidence.[1,2] In North America, active TB now results primarily from reactivated latent infection. In San Francisco, one of the cities that experienced epidemic spread in the early 1990s, the proportion of all incident cases attributed to recent community transmission fell from 22% in 1992 to 13% in 1997.[2] The remainder resulted from reactivation and involved a small group within the much larger pool of asymptomatic infected people.[2]

Among people with latent TB but no other risks, the estimated annual probability of reactivation is only 0.1%; by extrapolation, it has been estimated that only 10% of those with latent infection will *ever* develop active disease.[3] However, in individuals with latent TB who have additional clinical, epidemiologic or radiographic features, the risk is considerably higher.

In 2000, both Canadian[4] and US[5] authorities published revised recommendations for the identification and management of people with latent TB infection. Common to these guidelines was an increased emphasis on the treatment of latent TB — an important strategy for controlling the spread of the disease in low-incidence countries. In both sets of recommendations, this change in emphasis was exemplified by 2 specific measures directed at physicians: tuberculin testing to identify infected individuals at highest risk for reactivation, known as targeted tuberculin testing, and changes to the previously recommended treatment regimens.

Tuberculin skin testing with purified protein derivative remains the primary diagnostic method for detecting latent TB. Targeted tuberculin testing is a strategy designed to achieve maximum benefit and incur minimal harm. It entails offering such testing only to those at high risk of having the infection, since positive results among low-risk individuals have very low predictive power. In terms of defining those at highest risk, the single most powerful risk factor for reactivation of latent TB is HIV coinfection, associated in some studies with a more than 100-fold increase in risk.[6,7] Other major predisposing situations in which systemic or local immunity is compromised include transplantation, cancer chemotherapy, hematologic malignancies, head and neck carcinomas, long-term use of systemic corticosteroids, end-stage renal disease, and silicosis. More modest elevations in risk are associated with diabetes mellitus (types 1 and 2) and low body weight (less than 90% of ideal weight).[5]

Other risks for active TB include newly acquired infection (assumed among newly tuberculin-positive contacts of active pulmonary cases and documented by conversion from a negative skin test result to a positive one on serial testing) and radiographic abnormalities (specifically fibronodular disease, associated with a 6-fold or greater increase in risk, and granulomas, associated with a 2-fold increase), which suggest a higher burden of dormant bacilli.[8,9] Refugees and immigrants from regions where TB is endemic are also at risk, particularly within the first 5 years after their arrival in North America.[10]

It is therefore considered standard public health practice to provide tuberculin testing to anyone with newly diagnosed HIV infection, to all close contacts of patients with infectious forms of active TB, to anyone with known or suspected previous active TB who has not been adequately treated and to all foreign-born persons referred by immigration authorities for surveillance of suspected inactive TB.[5]

Other high-risk clinical situations are much less frequent, so testing usually takes place at the discretion of the care provider, often in specialized settings. For example, clinicians caring for potential transplant recipients should routinely include tuberculin skin testing in the pretransplant evaluation. Providers should also strongly consider tuberculin skin testing for patients in the other high-risk categories, including other situations where long-term immunosuppression is anticipated, such as end-stage renal disease, hematologic malignancy, diabetes and long-term systemic corticosteroid use (equivalent to at least 15 mg prednisone daily). A recent report also suggested a substantially increased risk of TB reactivation associated with the use of the anti-tumour necrosis factor alpha antibody infliximab (Remicade) in patients with Crohn's disease or rheumatoid arthritis; the authors recommended tuberculin testing prior to administration of this agent.[11]

Tuberculin testing in these specialized settings is particularly relevant when the probability of latent infection is increased, as is the case for people born in areas where TB is

endemic, those born in Canada before World War II, Aboriginal Canadians, homeless people and injection drug users. Conversely, testing is less of a priority when the expected period of immunosuppression is brief (e.g., adjuvant chemotherapy for breast cancer). Situations of uncertainty can be discussed with TB control specialists. Decisions about group screening should account for both local population characteristics and the resources needed to ensure successful treatment of latent infection, should it be diagnosed.

The yield of mass tuberculin testing programs for individuals at moderate risk (e.g., recent immigrants) is controversial.[12,13] However, attempts to screen, test and treat people who do not have clinical, occupational, radiographic or epidemiologic risks (so-called low-risk reactors) are clearly inappropriate. In this context, the prevalence of false-positive results can be high; moreover, the impact of therapy is limited, given that the baseline reactivation risk is only 0.1% per year.[3]

Limiting testing and treatment of latent infection to those most likely to experience reactivation means that the benefits generally outweigh the risks of drug toxicity, regardless of age. Previous recommendations included an age cutoff, whereby treatment was withheld from low-risk reactors who were over 35 years of age and did not have additional risk factors for reactivation. However, even before the 2000 updates, age was not a consideration when persons with additional risks (HIV-infection, close contact with active cases and so on) were considered for testing and treatment. In these contexts, the risks of reactivation — in the absence of treatment — greatly exceed those of isoniazid-related hepatotoxicity, regardless of age. The current recommendations emphasize this point and reduce confusion, by explicitly discouraging the identification of low-risk reactors. There do remain some specific situations in which age may be a concern. These are described below and in Box 1.

Detailed discussion of the tuberculin skin test and its interpretation can be found elsewhere.[14] Thresholds for treatment vary, according to the consequences of missed latent infection; these criteria are summarized in Box 1. Treatment of latent infection should begin only after active TB has been excluded, by clinical and radiologic evaluation and by microbiologic testing where warranted.

In terms of changes to treatment recommendations for latent tuberculosis, the focus is on duration of therapy, use of combination regimens and appropriate monitoring for side effects.

Isoniazid remains the drug of choice for latent TB infection. In the only randomized controlled trial to investigate treatment duration, which dates back almost 2 decades, 6 months of daily isoniazid treatment was associated with a 65% overall reduction in reactivation risk among Eastern European patients with fibrotic lesions on chest radiography.[15] A reduction of 75% was seen with 12 months of treatment. Among subjects who took at least 80% of the prescribed doses, the reported efficacy of the 6-month regimen was 69%, whereas for the 12-month course it was 93%. On the basis of those results, previous recommendations emphasized the 6-month regimen. Any gains in efficacy with 12 months of isoniazid were thought to be offset by more extensive toxic effects, greater expense and lower adherence.[16]

No randomized trial has compared 9 months of isoniazid therapy with other treatment durations. However, a 1999 reanalysis of isoniazid treatment studies conducted in Alaska during the 1950s suggested that a plateau in efficacy was reached at 9 or 10 months, with essentially no additional benefit beyond that point.[17] Hence, for all patients, 9 months of daily isoniazid therapy (10 mg/kg for children and 5 mg/kg for adults, up to a maximum of 300 mg/day for children and adults) is now the regimen of choice for

Box 1: Criteria for Treatment of Latent Tuberculosis Infection Adapted from Canadian Tuberculosis Standards[4]

HIV-infected people of any age with no tuberculin reaction (0 mm induration) or small tuberculin reactions (1–4 mm induration) require treatment for tuberculous infection if any of the following conditions apply:

- they are close contacts of infectious cases
- they are immigrants from countries where TB is endemic
- they have radiographic abnormalities compatible with inactive TB
- Anergy testing is not recommended in this context.

Induration of 5 mm or more, regardless of age, is an indication for treatment among the following groups:

- HIV-infected persons who do not belong to the risk categories just listed
- HIV-seronegative close contacts of people with active pulmonary TB
- HIV-seronegative people with fibronodular scarring visible on chest radiographs

Induration of 10 mm or more is an indication for treatment among people of any age with any of the following:

- skin test conversion from negative to positive (within a 2- year period)
- other forms of immunosuppression (e.g., transplantation)
- silicosis
- diabetes mellitus (type 1 or 2)
- low body weight (less than 90% of ideal body weight)

Treatment of latent TB infection may be *considered* in others with induration of 10 mm or more, particularly if less than or equal to 35 years of age, if they are:

- Aboriginal
- health care workers
- residents of long-term care facilities
- born in TB-endemic countries

treatment of latent TB; 6 months of daily isoniazid remains an acceptable second choice.[4,5] Twice weekly dosing may also be substituted for daily dosing, provided that a nurse or other health care professional administers and observes ingestion of all doses (so-called directly observed therapy).

Daily rifampin therapy (10 mg/kg to a maximum of 600 mg in both children and adults) for 4 months is another alternative. Although initial studies are promising,[18] there is much less published experience with this regimen. Rifampin is the first choice for contacts of persons with isoniazid-resistant active TB.[19]

The 2000 US recommendations[5] proposed an alternative 2-month regimen of daily rifampin and pyrazinamide, based on the effective (and safe) use of this combination in 791 HIV-infected patients in a multicentre randomized trial.[20] However, between February and August 2001, use of this regimen for latent TB was linked to 21 admissions to hospital for liver injury in the United States; 5 of the patients died.[21] None of these patients was known to be HIV-positive. It is noteworthy that no such outbreaks of severe hepatotoxicity have been reported with standard therapy for active TB, which includes both of these drugs.

The American Thoracic Society and the US Centers for Disease Control and Prevention now recommend that "the 2-month rifampin-pyrazinamide treatment regimen for [latent TB infection] should be used with caution."[21] This regimen is clearly contraindicated for anyone with underlying liver disease or with isoniazid-related hepatotoxicity.

Any treatment for latent TB should be prescribed and supervised by experienced clinicians, who can effectively manage adherence and side effects. Repeated liver enzyme determinations are not usually warranted; however, a baseline questionnaire for liver disease is essential, with serologic testing as indicated. Close monitoring of liver enzymes is necessary with the rifampin-pyrazinamide regimen and for all patients at risk of hepatotoxicity because of age or coexisting disease. However, Nolan and associates[22] identified only 11 cases of hepatotoxicity (none fatal) among over 11 000 patients of all ages monitored during isoniazid therapy for latent TB infection, which suggests that the risk of hepatotoxic effects related to isoniazid is extremely low, patients are appropriately selected and monitored.

In conclusion, North American TB control guidelines now place more emphasis on targeted testing and on treatment for latent infection. Targeted testing should greatly reduce the number of false-positive results and thus increase confidence in the resulting treatment decisions. Selection of high-risk patients for testing — and for longer, more effective therapy when indicated — will permit continued reductions in TB incidence, within the framework of a comprehensive TB control program.

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