Appendix 1: Clinician Summary Table: Tuberculosis

Recommendations for preventing tuberculosis from the Canadian Collaboration for Immigrant and Refugee Health

Children

Screen children and adolescents ≤ 20 years from countries with high incidence of tuberculosis (smear-positive pulmonary tuberculosis ≥ 15/100 000 population) as soon as possible after their arrival in Canada with a tuberculin skin test and recommend treatment for latent tuberculosis infection if results are positive, after ruling out active tuberculosis.

Adults

Screen all refugees, between the ages of 21 and 50 years, from countries with high incidence of tuberculosis as soon as possible after their arrival in Canada with a tuberculin skin test. Screen all other adult immigrants if they have risk factors that increase the risk of active tuberculosis with a tuberculin skin test and recommend treatment for latent tuberculosis infection if results are positive, after ruling out active tuberculosis.

Basis of recommendations

Balance of benefits and harms

The decision about whom to screen and offer treatment for latent tuberculosis is based on the balance between the potential benefit of treatment (decreasing the lifetime risk of active tuberculosis, which is influenced by age, the presence of underlying medical conditions and immigration category), versus the potential harm of hepatotoxicity (that increases with age) and the poor effectiveness of isoniazid in many settings because of suboptimal uptake of screening and treatment. For several groups, screening for latent tuberculosis should be routinely performed, and those with positive results should be offered treatment. These groups are children from countries with a high incidence of tuberculosis (number needed to treat [NNT]* 20–26; number needed to harm [NNH]* 134–268), adults with risk factors for active tuberculosis (NNT 3–20; NNH variable) and refugees < 50 years of age (NNT 15–26; NNH 49). Screening for latent tuberculosis and offering treatment could also be considered for adult refugees 50–65 years of age (NNT 20–51; NNH 9–18) and other adults without underlying medical conditions < 65 years of age if adherence to treatment could be ensured and hepatotoxicity carefully monitored to minimize harm. A decision to screen is a decision to offer treatment and to ensure adherence to treatment with appropriate counselling and monitoring.

Quality of evidence

High

Values and preferences

The guideline committee attributed more value to screening and treating latent tuberculosis infection to prevent active disease in patients and to prevent transmission of active disease and less value to the practitioner burden of screening and counselling.

*Estimated NNT and NNH are based on the following assumptions: Seven years after survival, the annual risk of active tuberculosis is 0.1%, the relative risk of active tuberculosis is highest upon arrival and decreases with time (relative risk 5.1, compared with 1.4 seven years after arrival); the patient will live to age 80 years; the efficacy of isoniazid is 90%; and adherence is 70%.

Table 3: Summary of findings table on isoniazid to prevent active tuberculosis

Patient or population: Varied: Smieja et al[24] = populations at risk for developing active tuberculosis, with HIV-positive patients excluded; Bucher et al[87] = HIV-positive patients
Setting: Varied: Smieja et al[24] = US psychiatric institutions, veterans' hospitals in US, Eastern Europe, Alaska, Hong Kong, India, etc.; Bucher et al[87] = Mexico, Haiti, US, Zambia, Uganda and Kenya
Intervention: Isoniazid treatment to prevent active tuberculosis
Comparison: No treatment
Source: Smieja MJ, Marchetti CA, Cook DJ, et al. Isoniazid for preventing tuberculosis in non-HIV infected persons [review]. *Cochrane Database Syst Rev* 1999(1):CD001363.[24]
Bucher HC, Griffith LE, Guyatt GH, et al. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized

controlled trials. *AIDS* 1999;13(4):501–7.[87]

Outcomes, risk category	Absolute effect: Risk for control group	Absolute effect: Difference with isoniazid (95% CI)	Relative effect (95% CI)	No. of participants (studies)	GRADE quality of evidence	Comments (95% CI)
Active tuberculosis*†						
Intermediate risk*	17/1000	10 fewer per 1000 (12 fewer to 8 fewer per 1000)	RR 0.40 (0.31–0.52)	73 375 (11)	Moderate‡§	NNT 99 (86–123)
Highly compliant (take > 80% of doses)*	10/10 000	7 fewer per 10 000 (8 fewer to 5 fewer per 10 000)	RR 0.20 (0.13–0.31)	15 696 (1)	High	NNT 85 (78–98)
High risk†	53/1000	32 fewer per 1000 (40 fewer to 19 fewer per 1000)	RR 0.40 (0.24–0.65)	1 875 (5)	Moderate¶	NNT 32 (25–54)
Hepatitis (follow-up: 5 yr)††	1/1000	5 more per 1000 (2 more to 11 more per 1000)	RR 5.54 (2.56–12)	20 874 (1)	Moderate	NNH 220 (91–642)

Note: CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation, NNT = number needed to harm, NNT = number needed to treat, RR = risk ratio.
*Numbers taken from Smieja et al.[24]
†In 1999 systematic review of isoniazid for tuberculosis in HIV-positive patients, this is the risk in HIV-positive, tuberculin skin test–positive patients.[87]
‡Test for heterogeneity $p = 0.02$.
§Only one study examined 6 months of isoniazid v. 12 months; risk of hepatitis and active tuberculosis not significantly different between groups.
¶Downgraded for directness, as data from developing countries.
**Thompson[88] as reported in Smieja et al.[24]

Prevalence: Tuberculosis is an important global health burden with 9.2 million new active cases and 1.5 million deaths per year (>95% occur in underdeveloped countries). Canada is a low tuberculosis incidence country with an overall rate of active tuberculosis of 5 cases/100 000 population (1621 cases reported in 2006).

Burden of illness: The foreign born account for 65% of all cases of active TB in Canada. They have a 20-fold greater incidence of tuberculosis as compared to that in the non-Aboriginal Canadian-born population (16 v. 0.8 cases/100 000 population), but with rates as high as 500 times greater for certain sub-groups. This is because in the past 40 years, the majority of new immigrants have originated from high tuberculosis incidence countries (i.e., >15 cases of smear positive pulmonary tuberculosis/100 000 population), 30–50% of whom are latently infected with tuberculosis resulting in a reservoir of approximately 1.5 million individuals in Canada with latent tuberculosis at risk for developing active tuberculosis.

Access to care: Patient barriers to include the stigma of tuberculosis and its association with HIV, linguistic barriers, and difficulties coming to appointments due to either inconvenient clinic locations or limited clinic hours. Provider barriers to offering screening to migrants are related to inadequate knowledge of which migrants should be screened or how they should be followed. Increased adherence to tuberculin skin test screening has been seen with patients reminders (letters, phone calls) and educating patients and physicians.

Key risk factors for tuberculosis: The strongest predictors for developing active tuberculosis in the foreign-born are global region of origin (highest in the foreign-born that originate from world regions with the highest global rates of tuberculosis such as Sub-Saharan Africa and Asia)., immigration category (refugees have about a two-fold increased risk for developing active tuberculosis compared to immigrants), the presence of underlying medical co-

morbidities (highest in those with deficiency in cell mediated immunity especially HIV) and the time since arrival (highest in the first year but remain elevated lifelong).

Screening Test: The tuberculin skin test and the interferon gamma release assays are the tests available for the diagnosis of latent tuberculosis infection. The sensitivity of these tests is estimated to be 70–90%, and the specificity for all tests is > 95% except for the tuberculin skin test in BCG-vaccinated individuals (60%) due to cross-reactivity.

Treatment: The efficacy of isoniazid is well established with an overall efficacy is 62% after 12 months of treatment, but increases to 93% in those who are compliant with treatment (i.e., take > 80% of doses). INH hepatotoxicity is an important side-effect that increases with age and requires close monitoring in those > 50 years of age.

Special considerations:

- Countries with a high incidence of TB include countries of Sub Sahara Africa, Asia, Central and South America and some countries in Eastern Europe.
- All individuals with a positive tuberculin skin test should have a CXR to rule out active tuberculosis. Symptoms (fever, weight loss, fatigue and night sweats) and signs (fever, wasting, lymphadenopathy, abnormal chest sounds) of active tuberculosis should be sought and appropriate investigations should be performed.
- Priority should be given to screening infants and young children (< 5 years of age) for latent tuberculosis because, if infected they are at high risk of developing active tuberculosis and active tuberculosis is more difficult to diagnose in this population.
- Medical conditions that increase risk for developing tuberculosis, include: HIV, organ transplantation, recent contact with an active case of tuberculosis, hematologic malignancy, fibronodular scarring on chest radiograph, chronic glucocorticoid treatment, diabetes, and chronic renal failure.
- To promote patients' safety and adherence, patients must be informed of the risks and benefits of treatment in a culturally and linguistically appropriate manner.

Appendix to: Greenaway C, Sandoe A, Vissandjee B, et al; for the Canadian Collaboration for Immigrant and Refugee Health.
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