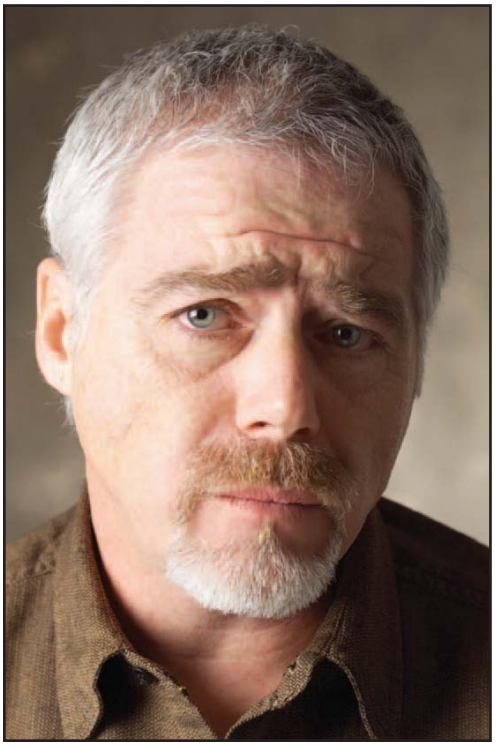

Coughing up the facts on Tuberculosis

Approximately two billion people worldwide—or roughly one-third of the world's population—are infected with mycobacterium tuberculosis.

By Andrew M. Morris, MD, MSc, FRCPC

In this article:

1. When does exposure, infection, and disease occur?
2. How do I diagnose active TB?
3. What is the initial management for a patient with suspected pulmonary TB?

With eight million new cases annually, tuberculosis (TB) causes almost two million deaths worldwide each year.[1] In Canada there are approximately 1,500 cases of TB per year, resulting in 100 deaths. From the '60s to the mid '80s, there was a steep decline in new cases and deaths. There has been a relative plateau over the past decade. Most TB cases in Canada are diagnosed in Ontario, Quebec, and British Columbia (contributing 40%, 19% and 17% respectively, of all cases). Approximately two-thirds of Canadian cases occur in foreign-born persons—predominantly from Asia and eastern Africa (*i.e.,* Somalia and Ethiopia). Most of these cases occur in the first few years of arrival in Canada. Accordingly, a disproportionate number of active TB in Canada (approximately 40%) occurs in people under 35.[2]

When does exposure, infection, and disease occur?

Mycobacterium tuberculosis is a bacterium of worldwide distribution that does not usually retain colour with Gram stain technique.

TB is an easily disseminated infection, with transmission almost always occurring by inhalation of aerosolized droplets. A person with active pulmonary TB usually creates droplet nuclei by forcefully expiring (*e.g.,* coughing, sneezing, singing). Because very small TB droplet nuclei can remain airborne for a long time, TB is easily spread. Many people, therefore, are potentially exposed to *M. tuberculosis*. The ability for a person with active pulmonary TB to effectively spread droplet nuclei and infect people is believed to be due to:

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Richard's situation

Richard, 58, presents to the emergency department (ED) with fever, cough, and sputum production. He has a history of: smoking (complicated by chronic obstructive pulmonary disease), alcoholism, and severe peripheral arterial disease requiring revascularization a few years earlier.

Medical history

This is his fifth visit to the ED, over the past six months, for community-acquired pneumonia. At least two of his prior visits necessitated hospital admission. All previous episodes were treated with levofloxacin, with good (albeit incomplete) response. All prior sputum and blood cultures have been negative. One set of sputum cultures from his first admission, collected three days after initiation of antimicrobial therapy, was negative for acid-fast bacilli and mycobacterial culture. He has no obvious risk factors for TB apart from his alcoholism, although he notes that he lives in close proximity to many homeless people and recent immigrants. He has never travelled outside of southern Ontario.

He has been in a monogamous relationship with the same woman for over 25 years. He has no pets, nor exposure to dusts or other potential allergens. He states that he has been feeling generally unwell over the past six to eight months, with weight loss, anorexia, fatigue, and drenching night sweats. He has a chronic cough, but recently there has been more shortness of breath and sputum production, accompanied by minute amounts of hemoptysis.

Examination

Physical examination reveals very little apart from a febrile (38.4C) cachectic man, with pallor.

Moderate investigations reveal:

- WBCs 15.8 x 109/L, Hb 101 g/L, Plt 514 x 109/L.
- Routine chemistry, cardiac and liver enzymes, and renal function are normal.
- Negative blood and urine cultures. Gram stains of his sputum reveal many pus cells, but commensal flora.
- Negative tuberculin skin test (image at 48h shown in Figure 1)
- A chest X-ray that shows bilateral upper lobe airspace disease (Figure 2), respiratory distress.

- the concentration of viable organisms in the host's sputum;
- the quality of air circulation and ventilation;
- physical proximity between host and susceptible recipient and;
- duration of exposure; the role of "immunity" resulting from prior infection/immunization has been recently challenged.[3]

When small (*i.e.*, less than 5 micron) droplet nuclei are inhaled or, on rare occasions, ingested, the recipient is infected. Inhalational infection usually distributes to the lower lung zone, reflecting normal ventilatory patterns. Usually, the recipient's cell-mediated immune response (CMI)—using macrophages and CD4-positive lymphocytes—is sufficient to destroy the initial tubercle bacilli, although early dissemination occurs. Dissemination of *M. tuberculosis* usually involves the lymphatics and regions of high blood flow and oxygen tension (such as the lung apices). Most dissemination is subclinical.

In about 5% of infected recipients, early destruction of the organism is inadequate and symptomatic primary disease ensues, usually in the form of primary pulmonary TB. In the remaining 95%, infection remains latent. Such patients, who usually have an active cell-mediated immune response to *M. tuber-*

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culosis, can be recognized by a positive tuberculin skin test. Should the host's CMI wane, such as with malignancy, advanced human immunodefficiency virus (HIV) infection, dialysis-dependent renal failure, or exogenous corticosteroid use, latent infection may reactivate and result in post-primary disease. Both primary and post-primary disease forms are considered "active" TB infection.

How do I diagnose active TB?

Because nearly two-thirds of active TB infection (either primary or post-primary disease) affects the lungs, the usual presentation of active TB involves a pneumonic process. Diagnosis relies on a high index of suspicion (based on epidemiology) coupled with features suggestive of TB rather than a community-acquired pneumonia: (an indolent process, usually occurring over several weeks or months, rather than days). Fever, chills, drenching night sweats, anorexia, weight loss, and other constitutional symptoms are common but non-specific. Although cough is often present, characteristically with sputum and/or hemoptysis, these features may be absent. Similarly, cachexia, fever, clubbing, and focal pulmonary findings may be present on physical examination, but most commonly are not.

Because such patients either fail to mount appropriate CMI after initial infection or have waning CMI allowing reactivation, tuberculin skin testing (which tests for TB-specific CMI) is of little value in the setting of active infection.[4] Indeed, both negative and positive skin tests may prove misleading—erroneously indicating TB in a patient with epidemiologic risk factors but a clinically-incompatible illness—or erroneously ruling out TB in an anergic patient. Instead, chest radiography and microbiologic testing are necessary adjuncts to the history and physical examination for diagnosing pulmonary TB.

Should chest radiography be performed?

Two views of the chest should be performed, recognizing that chest X-rays pick up only about 80% of cases of active TB and are non-specific. The usual radiographic abnormalities are apical in location, reflecting the pathogenesis of reactivation TB. Although airspace disease is usual, fibrosis, cicatrization (scarring with volume loss), and cavitation may also be observed. Despite these characteristic features, pulmonary TB may present with chest X-ray abnormalities or, alternatively, with a normal chest X-ray. It is felt that normal chest X-rays are more common in patients with reduced CMI, such as advanced HIV infection, endobronchial TB, and early disease.

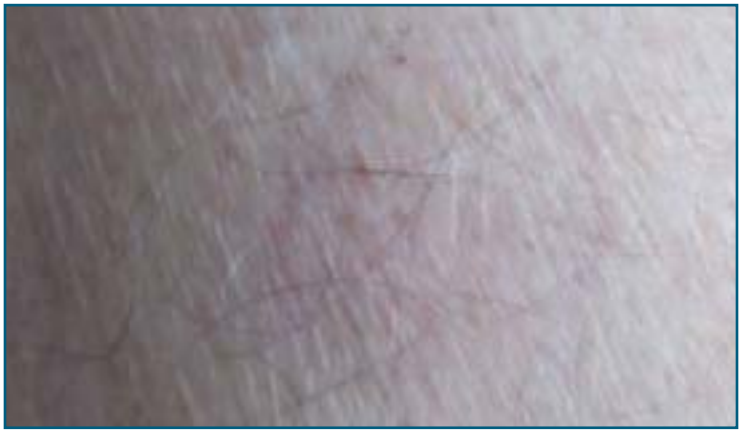

Figure 1. Negative tuberculin skin test read at 48 hours.

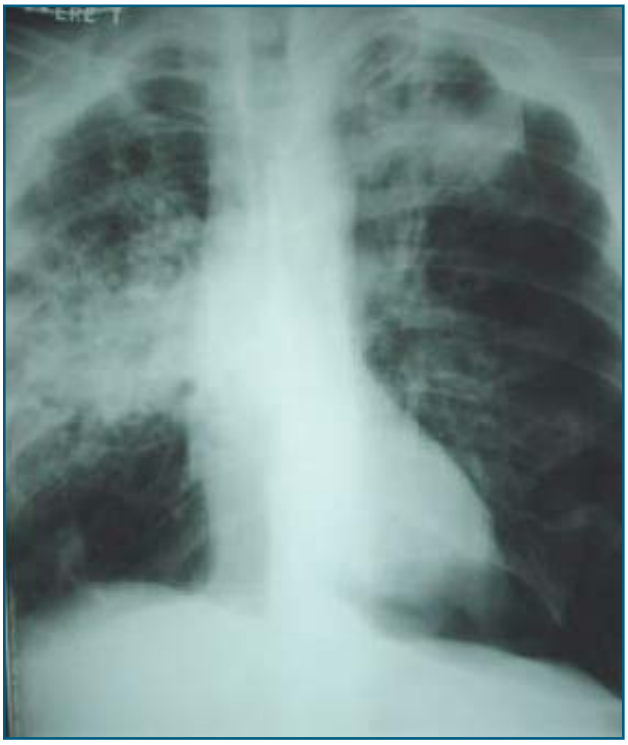

Figure 2. Chest X-ray showing bilateral upper lobe airspace disease.

How important is microbiologic testing?

Although microbiologic testing may be de-emphasized in countries where TB is endemic and health care delivery problematic, it remains an essential factor in our ability to diagnose and treat TB, while monitoring its epidemiology.[5] The most sensitive method (approximately 90%) for definitively isolating pulmonary TB is induced sputum using hypertonic saline. Serial early morning sputum samples, however, is easier and more convenient, and associated with a comparable yield (90% if three samples are sent). Although widely believed to be more sensitive for the diagnosis of pulmonary TB, bronchoscopy with broncho-alveolar lavage is less sensitive (approximately 75%, presumably because of sample dilution), expensive, and exposes risk to the patient and bronchoscopist; it should only be used in cases where other isolation methods are unsuccessful. Gastric aspiration, with a sensitivity approaching that of bronchoscopy, is often used in children or the frail elderly, who are often unable to provide sputum samples.

Samples should be sent for acid-fast bacilli staining (AFB) and mycobacterial culture. The sensitivity of the acid-fast stain for detecting *M. tuberculosis* is not only dependent on the method of collection, but is also highly dependent on staining technique and technologist expertise. Up to 80% of pulmonary TB is diagnosed by acid-fast staining (with subsequent confirmatory testing). Acid-fast testing will also result in a significant number of false-positives, usually from non-tuberculous mycobacteria, such as *M. avium-intracellulare*. Recently, many laboratories have adopted molecular amplification tests to confirm the presence of *M. tuberculosis* in smear-positive cases, with a specificity approaching 100%. The gold standard method of isolation remains (at present) mycobacterial culture, followed by DNA probing or, other confirmatory tests, such as high-performance liquid chromatography.

What is the initial management?

As mentioned earlier, identifying the patient with epidemiologic risk factors for TB with a subacute or chronic respiratory disease process compatible with pulmonary TB is of paramount importance. Such patients initially should be placed in respiratory isolation in a room with negative-pressure ventilation, with the appropriate investigations arranged (*i.e.,* chest X-ray and three sputum samples for AFB, in addition to other routine tests). Often, patients are medically stable and anti-tuberculous therapy can be deferred pending diagnostic confirmation. If there is a suspicion of community-acquired pneumonia, then effective antimicrobial therapy should be initiated. Fluoroquinolones, including ciprofloxacin and the newer respiratory quinolones, have activity against *M. tuberculosis*. Use of such agents to empirically treat pneumonia, especially before a diagnostic workup has been completed, may result in temporary improvement in the patient's symptoms accompanied by falsely negative test results for TB, and should therefore be discouraged. In fact, recent evidence suggests that empiric use of fluoroquinolones to treat community-acquired pneumonia results in a delay in the diagnosis of pulmonary TB.[6] However, if patients are medically unstable and are suspicious of the presence of TB, empiric therapy with anti-TB medications is recommended. The initial regimen for TB usually includes four agents, prior to sensitivity results (Table 1):

- isoniazid;
- a rifamycin, such as rifampin;
- pyrazinamide; and
- ethambutol.

Culture-and-sensitivity-directed therapy usually includes three active agents for two months, followed by two active agents (usually rifampin and isoniazid) for an additional four months (although other regimens have been proven successful).

Cases of confirmed TB are reportable, and require notification of public health authorities for further contact tracing. Such patients should be referred to an infectious disease specialist or respirologist for further management. In many jurisdictions in Canada, directly-observed therapy (DOT) is available. DOT has been shown to improve adherence to therapy (which is the single most important predictor of cure), while reducing secondary transmission.[7]

Table 1

Doses and common side effects of drugs used in the initial empiric management of pulmonary TB

Isoniazed (INH)	
Adult dose	5 mg/kg/day (usually 300 mg daily)
Child dose	10-20 mg/kg/day
Side-effects	hepatitis, paraesthesias
Rifampin (RIF)	
Adult dose	10 mg/kg/day (usually 600 mg daily to a maximum of 600 mg daily
Child dose	10-20 mg/kg/day
Side-effects	hepatitis, flu-like illness, drug interactions
Pyrazinamide (PZA)	
Adult and child dose	15-30 mg/kg/day (usually 1,500-2,000 mg daily)
Side-effects	hepatitis, hyperuricaemia, arthralgia
Ethambutol (EMB)	
Adult and child dose daily)	15-25 mg/kg/day (usually 800-1200mg
Side-effects	retrobulbar neuritis

How are non-respiratory forms of TB diagnosed?

M. tuberculosis can latently infect almost any body part, although cervical lymph nodes, pleura, the meninges, and the spine would be the most common non-respiratory site of TB. Once again, tuberculin skin testing for diagnosis and empirical use of fluoroquinolones should be avoided. Although radiography may be helpful, sterile site cultures are necessary to confirm the diagnosis and to identify drug-sensitivity of the organism. Although fine-needle aspiration of an affected site may yield the diagnosis, many of the extrapulmonary forms of TB are associated with very few acid-fast bacilli (so called paucibacillary TB), necessitating open biopsy.

When should I isolate a patient ?

All patients suspected of having pulmonary TB should be placed initially in respiratory isolation. Such patients can be removed if an alternate diagnosis is identified, and TB is ruled out. When to take a patient, on therapy for TB, out of isolation is more complicated. Recent molecular epidemiology suggests one-sixth of all pulmonary TB is transmitted from smear-negative patients.[8] As such, patients who are initially smear-negative can be taken out of isolation if there is clinical improvement after 14 days of effective antituberculous therapy. Patients who are smear-positive not only require evidence of sputa repeatedly free of AFB, but should also have demonstrated clinical improvement on adhered-to therapy after a minimum of two weeks of therapy.

Who should get a tuberculin skin test?

Tuberculin skin testing assumes that people with a positive skin test would get treatment of latent

tuberculous infection (LTI). Such patients can be broadly categorized into three groups:

- people at increased risk of recent exposure to active cases of TB;
- people at increased risk of latent TB infection; and
- persons at increased risk of active TB once infection has occurred.

Health-care workers fit into the first category and persons with poor CMI (including diabetes mellitus, chronic steroid use, and chronic renal failure) fit into the latter category.

What is the effect of BCG vaccination on tuberculin skin test results?

There is a relatively new wealth of information regarding BCG (bacllus Calmette-Guérin) vaccination and tuberculin skin test results. The data suggest that most newly positive skin test reactions corroborate best with recent infection with *M. tuberculosis* or possibly other mycobacteria, rather than remote BCG infection.

What is the risk of liver toxicity in patients receiving treatment of LTI?

Most patients receiving isoniazid will have a rise in liver transaminases. A U.S. Public Health Service study published in 1978 suggested the risk of isoniazid-induced hepatic failure in patients receiving treatment of LTI was age dependent, modified by alcohol use, and was 2.3% in people older than 35. A recent report suggests the overall incidence is less than 1 in 1,000.[9] Other regimens for treatment of LTI have been used, such as a two-month regimen of pyrazinamide and rifampin, but the safety of this regimen (owing to several deaths from liver toxicity) has come into question recently.[10] CME

Net Readings

1. http://www.lung.ca/tb/main.html
2. http://www.hc-sc.gc.ca/pphb-dgspsp/tbpc-latb/pubs_e.html
3. http://www.who.int/gtb/index.htm

Tuberculosis

Take-home message

- People at high risk for TB infection in Canada include (but are not limited to) recent immigrants from Asia/Africa and aboriginals.
- Exposure does not equal infection or disease.
- TB skin testing is not a useful clinical tool for active tuberculosis.
- Don't use a respiratory quinolone to treat pneumonia if you are wondering about TB.
- When in doubt, isolate.

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Suggested Readings

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