TUBERCULOSIS

Information for Health Care Providers

Third Edition 2003

THE LUNG ASSOCIATION™

When you can't breathe, nothing else matters.

TUBERCULOSIS

Information for Health Care Providers

This booklet was originally developed by the Ontario TB Control Nurses Sub-Committee in collaboration with The Lung Association. This revised edition (2003) has been prepared by members of The Lung Association Tuberculosis Committee and is published by The Lung Association.

The Lung Association is a registered charity that provides information and lung health services across Ontario. One of Canada's most respected voluntary, not-for-profit health promotion organizations, it began more than a century ago as an organization formed to prevent and stop the spread of tuberculosis. Today, it focuses primarily on the prevention and control of asthma, chronic lung disease, tobacco cessation and prevention, and the effects of air quality on lung health. Tuberculosis continues to be addressed provincially through the work of The Lung Association Tuberculosis Committee and The Lung Association's medical societies (the Ontario Respiratory Care Society and the Ontario Thoracic Society) and nationally through the Canadian Lung Association TB Working Group and involvement in international projects and organizations such as StopTB and the International Union Against Tuberculosis and Lung Disease (IUATLD).

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1. Preface

Tuberculosis (TB) is still a problem. At the present time there are approximately 1700 new cases of TB in Canada each year with about 650 of these cases occurring in Ontario. Over the past two decades, the clinical presentation of TB cases has changed, drug resistance has become an increasing problem, new methods of diagnosis have been introduced, and approaches to case management and public health practice have been revised.

Many Canadian physicians and other health care providers have little or no experience with TB. This has occurred because the incidence of TB has declined since the 1950s due to the availability of effective antibiotics and improved disease management. However, TB has not gone away. Although Canada is a low incidence country for TB the disease continues to be a significant global problem.

The aim of this booklet is to increase health care provider awareness of TB as a possible diagnosis, to provide guidelines for case management, and to increase knowledge of the appropriate use and choice of preventative therapy for latent TB infection.

This booklet contains basic information about TB and is intended for use as a reference for health care providers. It is not meant to provide detailed answers to all public health or clinical questions about TB. Further consultation with a TB specialist is recommended if an active case of TB is suspected or confirmed.

2. Epidemiology of Tuberculosis

2.1 INCIDENCE

It has been estimated that one-third of the people in the world are infected with latent tuberculosis. World-wide there are about eight million new cases of tuberculosis a year with two million deaths attributed to this disease annually, making it the leading cause of death from an infectious disease.

Rates of tuberculosis are highest in countries where poverty, crowding and lack of health care programs are characteristic. In 1999, the World Health Organization identified twenty-three high-burden countries, five of which had a rate of tuberculosis exceeding 400 cases per 100,000 population.

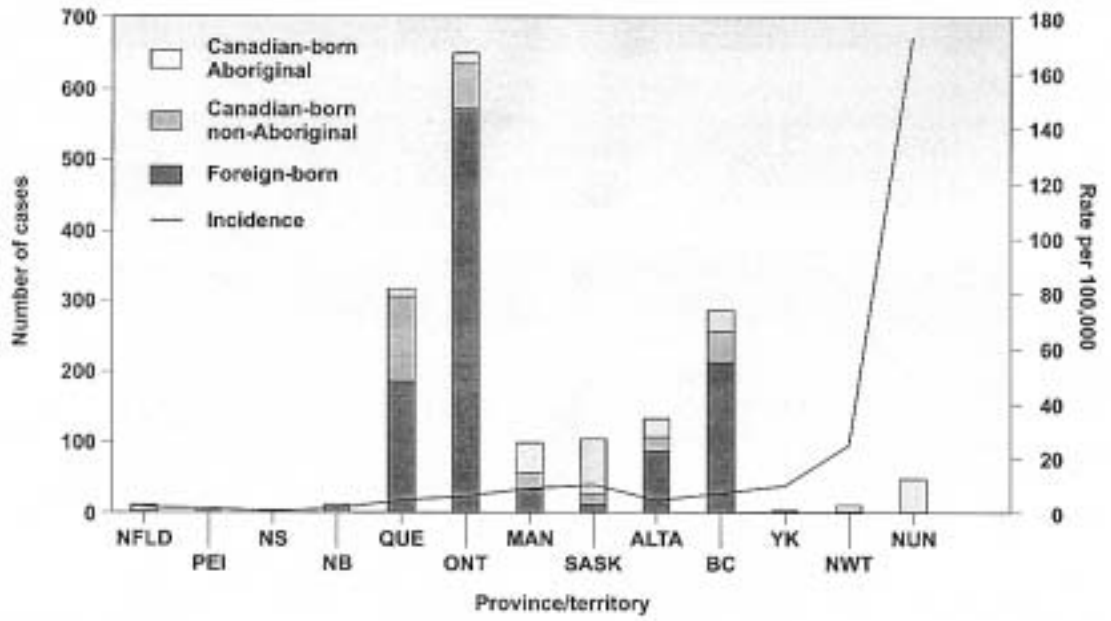
Canada's tuberculosis rate in 2000 was 5.5 per 100,000. Approximately 65% of these cases occurred in persons who were foreign-born. Canadian-born aboriginal people accounted for 18% of cases while Canadian-born non-aboriginal cases comprised 15% of the total. (Tuberculosis in Canada 2000, p. 18).

FIGURE 1 ESTIMATED INCIDENCE OF TB, 23 HIGH-BURDEN COUNTRIES: 1999

RANK # OF ESTIMATED CASES	COUNTRY	RATE PER 100,00
1	India	185.1
2	China	102.6
3	Indonesia	282.0
4	Nigeria	300.2
5	Bangladesh	241.0
6	Pakistan	176.6
7	Philippines	314.3
8	Ethiopia	373.2
9	South Africa	493.7
10	Russian Federation	123.0
11	Congo - DR	300.0
12	Vietnam	189.3
13	Kenya	416.3
14	Brazil	70.2
15	Tanzania, U. Rep.	341.5
16	Thailand	141.3
17	Mozambique	409.6
18	Myanmar	168.7
19	Uganda	340.5
20	Afghanistan	323.9
21	Zimbabwe	563.8
22	Cambodia	557.3
23	Peru	229.9
Total high-burden countries		178.2
Global total		140.9

Source: Adapted from Tuberculosis in Canada – 2000 Appendix III Health Canada 2003
From WHO Report 2001 – Global Tuberculosis Control (WHO/CDS/2001.287)

FIGURE 2 DISTRIBUTION OF TUBERCULOSIS CASES BY ORIGIN AND INCIDENCE – PROVINCES/TERRITORIES: 2000



Source: Tuberculosis in Canada-2000 Figure 16

2.2 DRUG RESISTANCE

Tuberculosis is an infectious disease that is preventable, treatable and curable. However, the emergence of drug resistance has become a formidable challenge.

There are two types of resistance: primary and secondary. Primary resistance occurs in individuals who are infected with a strain of resistant tuberculosis. Secondary resistance occurs during treatment, either because the drug regimen is not adequate or because the individual fails to take the drugs correctly.

The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) have jointly sponsored a global surveillance project which monitors drug resistance. Results from the 62 geographical settings that provided data (1996-1999) demonstrated tuberculosis resistance among participating countries was 11.1% to any drug and 2.0% to Isoniazid and Rifampin. Isolates resistant to both Isoniazid and Rifampin are classified as multi-drug resistant (MDR).

There are regions of the world that are considered to be "hot spots" for MDR-TB. These include: Estonia, Henan Province (China), Latvia, Ivanova Oblast and Tomsk Oblast in the Russian Federation, the Islamic Republic of Iran and Latvia.

The prevalence in Canada of any drug resistance was 10.1% and MDR-TB was 1.0% in 2001. However, in Ontario and in particular the Greater Toronto Area (GTA), the rate of drug resistance tends to be much higher (14% in Ontario in 2000). (PHERO 2000)

2.3 HIGH RISK GROUPS

Tuberculosis should be considered in the differential diagnosis of individuals from the following high risk groups:

- Close contacts of individuals with known or suspected active TB;
- Foreign-born individuals from endemic areas who have arrived in Canada within the past five years;
- Persons who are homeless or underhoused;
- Persons with HIV infection and AIDS;
- Persons with high risk medical conditions such as transplantation, silicosis, chronic renal failure, carcinoma of the head and neck and diabetes;
- Aboriginal people;
- Persons at risk due to occupational exposure (e.g., hospital and shelter staff/volunteers);
- Alcoholics and IV drug users;
- Staff and residents of long-term care institutions (e.g., nursing homes and correctional facilities);
- Individuals with a history of past TB disease;
- Elderly people who lived through an era when TB was common or who have come from an endemic country.

3. Pathophysiology

Moist droplets containing the tubercle bacillus are transmitted from one person to another during coughing or sneezing. Larger particles fall to the ground, while the smaller ones rapidly evaporate, leaving droplet nuclei small enough to be inhaled. These nuclei are carried by air currents and are breathed into the lungs where they constitute an infection hazard. Viable bacilli must reach the lung tissue for infection to be established. This primary infection grows and spreads through the blood and regional lymphatic system. It settles in secondary sites including:

- apices of the lungs
- larynx
- long bones
- genitourinary tract
- adrenals
- eye
- pleura
- lymph nodes (cervical chain)
- central nervous system
- pericardium
- skin
- ear

Cellular immunity against the tubercle bacillus develops within twelve weeks post-exposure. The outcome of the disease depends on the body's immunity: the bacilli may be killed, may be sealed off (encapsulated), remaining dormant for years or may progress to active disease. The development of the positive tuberculin reaction indicates the development of cell-mediated immunity to the tubercle bacillus and establishes the diagnosis of TB infection. A weakened cellular immune system may allow multiplication of previously dormant bacilli and activation of the disease. Infection with HIV or any other significant impairment to the cellular immune system (e.g., prolonged corticosteroid therapy, cyclosporine, etc.) increases the risk of rapid progression from infection to the development of active tuberculosis.

Approximately 5% of persons who have been infected with tuberculosis will progress to active disease within two years of exposure to the disease. Another 5% will go on to develop active disease sometime later in their lifetime. Persons with HIV infection or other immunocompromising conditions will be much more likely to progress to active disease after being infected with tuberculosis.

The risk of developing active tuberculosis may be 100 times greater in people infected with HIV than in the general population

Tubercle bacilli can survive in the dormant stage for years. This is known as latent tuberculosis infection (LTBI). The risk of progression to active disease can be reduced if prophylactic treatment is received (see LTBI Section).

4. Transmission

Tuberculosis is not a highly infectious disease. Transmission usually requires close, frequent and prolonged exposure to a source case. Infection is normally transmitted from an individual with tuberculosis of the respiratory tract. However, transmission may also occur from extra-pulmonary tuberculosis when infected fluid (e.g., fluid from a draining abscess) becomes aerosolized such as during dressing changes.

A person with active pulmonary tuberculosis can infect a large number of individuals, particularly if he or she has advanced, symptomatic disease. On average an **untreated** person with pulmonary tuberculosis infects 10 – 15 others per year. The following factors must be present for the transmission of the disease to occur:

- Viable bacilli in the source fluid (typically sputum);
- Fluid aerosolization caused by coughing, speaking, sneezing, singing or certain medical procedures (e.g., bronchoscopy);
- Adequate concentration of bacilli in the air;
- A susceptible host;
- A sufficient length of time during which the host is breathing bacillary-ladened air.

FIGURE 3 INFECTIOUSNESS

MORE INFECTIOUS:	Pulmonary	Smear POSITIVE	Culture Positive
LESS INFECTIOUS:	Pulmonary	Smear NEGATIVE	Culture Positive
RARELY INFECTIOUS:	Extrapulmonary (no evidence of pulmonary disease)		

The urgency of contact follow-up depends upon the infectiousness of the source case.

5. Diagnosis

5.1 SYMPTOMS

The presentation of TB can be quite diverse depending on the duration and site of disease activation. Classic symptoms for pulmonary tuberculosis include cough (productive or non-productive) for three or more weeks, hemoptysis in advanced disease, and non specific systemic symptoms such as fatigue, anorexia, weight loss and low grade fever. It is important to note that pulmonary tuberculosis can occur without a cough and in some cases may present as completely asymptomatic.

Tuberculosis can also be extrapulmonary and the presenting symptoms are often site specific such as lymph node swelling in lymphatic disease, headaches/neck stiffness/neurologic changes in meningeal disease, bone pain/joint swelling in osteomyelitis, lower back pain in Potts (spinal abscess) disease, recurrent sterile pyurea (urinary tract infections) in renal disease and abdominal pain/infertility in genitourinary disease.

HIV/AIDS

The presentation of tuberculosis in the HIV/AIDS patient can often be atypical and systemic symptoms can be very similar to symptoms associated with HIV and other co-infections. These patients also tend to have more extrapulmonary presentations.

Pediatrics

Most children who have TB disease in North America are asymptomatic and are discovered as part of the contact investigation of adult cases. Typically these children have x-ray abnormalities but appear entirely well, without clinical signs.

In contrast, children in resource poor, high incidence countries, where screening is not widely available, are identified because of significant involvement of almost any organ system. This pattern is also seen in Canada, chiefly in immigrant children.

Older children and adolescents are more likely to experience reactivation disease, and often have the classic triad of symptoms of fever, weight loss and night sweats. Signs are still unusual and may be quite subtle.

Miliary disease is much more common in young infants and in the immunocompromised. Miliary refers to diffuse tiny nodules, similar in size to millet seeds, which are seen on x-ray. Hepatosplenomegaly and weight loss are frequent as is hemophagocytosis. The skin test is often negative.

Children co-infected with HIV and TB have an accelerated progression from infection to TB disease. Although co-infected adults often have atypical presentations with extrapulmonary disease, children with HIV infection usually present with typical childhood disease. The skin test is often negative: a search for an infectious adult or adolescent is an important clue to the diagnosis.

5.2 DIAGNOSTIC STUDIES

Diagnostic studies might include chest x-ray, serial sputum examination, bronchoscopy with bronchoalveolar lavage, exploratory laparotomy or tissue biopsy. The following reviews some of the most common diagnostic techniques.

CHEST X-RAY

Chest x-ray is an excellent test for determining active pulmonary tuberculosis. The classic presentation is infiltrates, nodules and/or cavities in the apices of the lungs. Tuberculosis can occasionally present as infiltrate in the lower lobes especially during primary infection and in individuals who are immunocompromised. If any abnormality including granuloma or fibrosis/scarring is seen, it is recommended that further investigation be considered.

HIV/AIDS

Chest x-rays may have a typical or atypical presentation in patients with HIV/AIDS. Patients may tend to have hilar lymphademopathy or may have a completely normal chest x-ray in advanced HIV disease.

Pediatrics

Chest x-rays are important but may be difficult to interpret in a young child. A lateral view is important to evaluate for hilar lymphadenopathy, a hallmark of primary tuberculosis. Parenchymal lesions may be anywhere in primary disease, and are typically, but certainly not always, apical in reactivation disease.

SMEARS

Mycobacterium is a rod-shaped organism that has a high lipid containing cell wall. This cell wall does not stain easily; therefore during the staining process it requires specialized heat and increased concentration of stain in order to achieve any stain uptake. Once staining occurs, it is quite difficult to remove with the usual acid and alcohol solutions. This is defined as acid-fast bacilli (AFB). (CTS p.19) The specificity of acid-fast stain is quite high. Both *M. tuberculosis* and other *Atypical Mycobacteria* will test positive for AFB. However, in patients with a result of “acid-fast bacilli seen”, *M. tuberculosis* must always be assumed until it has been ruled out by AMTD and/or culture (see below).

Smear results can be a crude indication of the infectiousness of the active TB case. The results are reported by the number of bacilli seen in microscopic fields and may be “scarce”, “moderate” or “numerous”. This is highly dependent on the amount of disease, the number of samples obtained as well as the patient’s ability to provide an adequate sample. In order to achieve a “scarce” result with the auramine staining process, the sputum sample must contain at least 1,000-10,000 bacilli/ml (100,000 bacilli/ml with Ziehl-Neelsen stain).

A negative smear result does not rule out the diagnosis of tuberculosis and as few as 10 to 100 viable organisms can grow on culture. Patients with negative AFB smears but positive cultures can still transmit tuberculosis. (Behr MA et al. 1999)

A negative AFB result should be carefully considered in conjunction with the clinical and radiological presentation.

AMPLIFIED MYCOBACTERIUM TUBERCULOSIS DIRECT TEST (AMTD GEN-PROBE)

The AMTD is currently being used in the Public Health Laboratory to detect *Mycobacterium Tuberculosis* Complex directly from clinical specimens. This test detects the presence of MTB ribosomal RNA (rRNA) in the specimen and has a sensitivity and specificity greater than 97% in smear-positive respiratory specimens. Studies of smear-negative specimens and non-respiratory specimens have shown that sensitivity in these instances is somewhat decreased. The following are the Public Health Laboratory criteria for AMTD testing:

1. New patient smear-positive respiratory specimens;
2. Smear-positive respiratory specimens from patients previously identified as having ATYPICAL mycobacterium infection (the AMTD is only done once – subsequent specimens will not have AMTD done);
3. Smear-positive respiratory specimens from patients 12 months after the initial laboratory isolation of MTB Complex.

CULTURE AND SENSITIVITY

Culture and sensitivity are essential to determine if the treatment regimen is appropriate for the patient's specific tuberculosis organism. *Mycobacterium tuberculosis* complex is grown on an egg-based medium. Tuberculosis is a slow-growing mycobacterium that may take 2 to 8 weeks to obtain final culture results. MTB Complex includes *M. tuberculosis, M. bovis*, excluding the BCG strain, and *M. africanum.* The most clinically significant mycobacterium pathogen in humans is *M. tuberculosis*.

Sensitivity testing is initially performed for the first-line anti-tuberculosis medications. The result can usually be expected approximately 1 to 2 weeks after the culture has grown. Second-line drug sensitivities are only carried out if resistance is found to first-line antibiotics.

PATHOLOGY

Pathology examination is often helpful in tissue biopsy to determine a tuberculosis diagnosis. Acid-fast bacilli and/or caseating granuloma may be seen on microscopic examination. While this is highly suspicious for the diagnosis of tuberculosis, the tissue should be sent for further testing such as culture and sensitivity and polymer chain reaction (PCR testing).

It is important that tissue for culture is placed in saline solution and not in formalin which will destroy the TB organism.

5.3 SPECIMEN COLLECTION

Specimens obtained by health care providers are typically sent to private or hospital laboratories and from there are sent to the *PUBLIC HEALTH LABORATORY* (PHL) for processing. Proper labeling with the patient's name, type of specimen and specified lab tests required is essential.

SPUTUM

A series of three sputum specimens is recommended. If the patient denies a cough, sputum samples should still be attempted. Collection should occur in the early morning after awakening. The specimens should be obtained from a deep productive cough on 3 consecutive days. Sputum samples should be refrigerated to prevent any overgrowth by other contaminating bacteria. If the initial series of sputum smears are all negative and the clinical/radiological suspicion of tuberculosis remains high, then a further series of three specimens is recommended. Sputum may be expectorated or induced. Bronchoscopy may also need to be considered at this point.

GASTRIC ASPIRATE

Gastric aspirate is often used in children with suspected pulmonary tuberculosis as it is usually impossible to obtain a sputum sample. During sleep the mucociliary mechanism in their respiratory tract sweeps mucus, which may contain TB bacilli, into the mouth. The material is swallowed and the gastric aspirate may be a source to obtain organisms especially if the stomach has not emptied.

Tips for Obtaining Gastric Aspirates

Aspirates are obtained after a long sleep, at least 6 hours, and before the stomach has emptied. Patients should not drink or eat anything overnight to prevent the stomach emptying; avoid exposure to the smell or sight of food, which may encourage gastric emptying. The ideal time is just at the time of waking. Aspirate the stomach contents first. Then instill no more than 50ml of sterile distilled water - the sort used for infant feeding is suitable - aspirate back and add the aspirate to the first specimen. As soon as possible, place specimens in a gastric lavage kit for *Mycobacterium tuberculosis.* There is a special buffer, usually sodium carbonate, in the tube that is essential to prevent rapid death of the organisms.

FIGURE 4 OTHER SPECIMENS

SPECIMEN TYPE	SPECIMEN REQUIREMENTS	SPECIAL INSTRUCTIONS	UNACCEPTABLE SPECIMENS
Abscess contents, aspirated fluid	As much as possible in sterile plastic container	Cleanse skin with alcohol before aspirating sample. Collect specimen on swab, and place in aerobic transport medium only if volume is insufficient for aspiration by needle and syringe.	Dry swab
Blood	10-mL SPS (yellow top) or 10 mL heparin (green top) blood collection tube	Disinfect site as for routine blood culture. Mix tube contents immediately after collection	Blood collected in EDTA, which greatly inhibits mycobacterial growth even in trace amounts(3). Coagulated blood. Serum. Plasma. Blood in bacterial blood culture medium.
Body fluids (pleural, pericardial, peritoneal, etc.)	As much as possible (10-15mL minimum) in sterile container.	Disinfect site with alcohol if collecting by needle and syringe. Volume of 10ml may be directly inoculated into BACTEC 13 A vial	
Bone	Bone in sterile container without fixative or preservative.		Specimen submitted in formalin
Bone marrow	As much as possible in sterile collection tube or SPS or heparin tube	Collect aseptically. Mix anti-coagulant tube contents immediately following collection	
Bronchoalveolar lavage or bronchial washing	>5mL in sterile container	Avoid contaminating bronchoscope with tap water. Saprophytic mycobacteria may produce false positive culture or smear results	
Bronchial brushing	Sterile container. Add sterile saline if small amount		
CSF	>2mL in sterile container	Send maximum volume attainable	
Gastric lavage fluid (for children less than 5 years of age)	>5-10mL in sterile gastric container supplied from the Provincial health lab. Collect in the morning, before the patient gets out of bed in order to obtain sputum swallowed during sleep	Collect fasting early-morning specimen on 3 consecutive days. Laboratory provides gastric collection jars containing sodium carbonate. If gastric container not available- Adjust specimen to neutral pH with 100 mg of sodium carbonate immediately following collection.	Specimen that has not been neutralized.
Lymph node	Node or portion in sterile container without fixative or preservative. A small amount of sterile saline may be added.	Collect aseptically and avoid indigenous microbiota. Select caseous portion if available. Do not wrap in gauze. Freezing decreases the yield.	Specimen submitted in formalin
Skin lesion material	Submit biopsy specimens in sterile containers without fixative or preservative. Submit aspirate in syringe with Luer lock cap, needle removed.	Swabs in transport medium (Amies or Stuarts) are acceptable only if biopsy sample or aspirate is not obtainable. For cutaneous ulcer, collect biopsy sample from periphery of lesion or aspirate material from under margin of lesion. If infection was acquired in Africa, Australia, Mexico, South America, Indonesia, New Guinea, or Malaysia note this on the request because *M ulcerans* may require prolonged incubation for primary isolation	Dry swab
Stool	>1g in sterile, wax-free, disposable container	Collect specimen directly into container or transfer from bedpan or plastic wrap stretched over toilet bowl.	Frozen specimen. Specimen that has been in contact with water in the toilet
Tissue biopsy sample	1 g of tissue, if possible, in sterile container without fixative or preservative	Collect aseptically and avoid indigenous microbiota. Select caseous portion if available. Do not wrap in gauze. Freezing decreases the yield.	Specimen submitted in formalin
Transtracheal aspirate	As much as possible in syringe with Luer lock cap, needle removed, or other sterile container		Do not submit specimens in endotracheal tubes
Urine	As much as possible (minimum 40mL) of first morning specimen obtained by catherization or midstream clean catch in sterile container. For suprapubic tap, as much as possible in syringe with Luer cap or other sterile container.	Collect first morning specimen on 3 consecutive days. Accept only one specimen/day. Organisms accumulate in bladder overnight so first morning void provides best yield. Specimens collected at other times are dilute and are not optimal	24-h pooled specimens; urine from catheter bag, specimens of 40 mL unless larger volume is not obtainable. Urine specimens should only be tested if renal TB is suspected, not as routine screening

Source: Adapted from Ministry of Health and Long-term Care Publication. Reprinted with permission.

6. Reporting Requirements

TUBERCULOSIS IS A REPORTABLE COMMUNICABLE DISEASE.

Under the Health Protection and Promotion Act of Ontario, physicians and other health care professionals, including laboratory technicians and infection control practitioners, must report cases of **active** tuberculosis disease and **latent** tuberculosis infection to the local Medical Officer of Health in the jurisdiction in which they practise.

It is important to report active cases of tuberculosis in a timely manner to ensure that the follow-up of contacts can begin without delay.

Physicians and other health care professionals who undertake the clinical management of cases of active tuberculosis must report any non-adherence to treatment and missed appointments. Under the Health Protection and Promotion Act, the Medical Officer of Health can order an individual with active infectious tuberculosis disease to comply with treatment.

Physicians must provide information requested by the Medical Officer of Health, including interim and final reports on all cases of active tuberculosis, x-ray findings, smear and culture results.

7. Treatment and Management of Active Tuberculosis Disease

7.1 GENERAL INFORMATION

Referral to a TB specialist is recommended for all cases of active tuberculosis.

The initial treatment of TB should *ALWAYS* include four anti-tuberculosis medications until sensitivity results are obtained (see specific treatment regimens below). The drug sensitivity reports will follow the culture results within one to two weeks.

The possibility of drug resistance should *ALWAYS* be considered, especially in patients with a previous history of tuberculosis or in patients who are from a country with a high prevalence of drug-resistant strains such as India, Korea, Philippines, Southeast Asia, the former Soviet Union and Africa. If patients have been previously treated for TB, they are at high risk for drug resistance to one or more anti-tuberculosis medications. In these situations, it is highly recommended that patients be referred to a specialized centre prior to initiating treatment.

Drugs for the treatment of both active tuberculosis disease and latent tuberculosis infection are publicly funded in Ontario. This includes first-line and second-line drugs and pyridoxine (Vitamin B6). Contact your local health unit to order TB medications.

To prevent drug resistance, health care providers must emphasize the need for patient adherence to drug treatments. Patient education about TB disease, how resistance occurs and strategies to take medication should be reviewed with the patient **at every visit.** Every patient should have a prompt referral to the local public health unit requesting Directly Observed Therapy (DOT) when available to assist with TB education, and monitoring and to facilitate compliance.

7.2 FULLY SENSITIVE PULMONARY TUBERCULOSIS

FIGURE 5 RECOMMENDED TREATMENT REGIMENS

Consultation with a specialist is advised.

Preferred Rx: 6 Month Regimen

INH + RMP + PZA for 2 months
followed by
INH + RMP for 4 months

EMB is added to the initial phase
until drug resistance is ruled out

THE EFFECTIVENESS OF TREATMENT
DEPENDS ON ADHERENCE TO THERAPY

INH=Isoniazid, RIF=Rifampin, PZA=Pyrazinamide, EMB=Ethambutol

When PZA is contraindicated, INH and RMP
is given for 9 months; EMB is added initially until
drug sensitivities are available.

- intermittent treatment regimes should only be initiated with the support of the Directly Observed Therapy Program (DOT) at the local public health unit.

FIGURE 6 DOSAGE RECOMMENDATION FOR THE INITIAL TREATMENT OF TUBERCULOSIS IN CHILDREN* AND ADULTS

DOSAGE						
	DAILY DOSE		TWICE-WEEKLY DOSE		THRICE-WEEKLY DOSE	
DRUGS	CHILDREN	ADULTS	CHILDREN	ADULTS	CHILDREN	ADULTS
Isoniazid, mg/kg	10-20 Max 300 mg	5 Max 300 mg	20-40 Max 900 mg	15 max Max 900 mg	20-40 Max 900 mg	15 max Max 900 mg
Rifampin, mg/kg	10-20 Max 600 mg	10 Max 600 mg	10-20 Max 600 mg	10 Max 600 mg	10-20 Max 600 mg	10 Max 600 mg
Pyrazinamide, mg/kg	15-30 Max 2 g	15-30 Max 2 g	50-70 Max 4 g	50-70 Max 4 g	50-70 Max 3 g	50-70 Max 3 g
Ethambutol, mg/kg**	15-25	15-25	50	50	25-30	25-30

* Children 12 years of age or less.

** Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (less than 8 years of age). However, ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or susceptibility is likely.

Source: American Journal of Respiratory & Critical Care Medicine, Vol. 149, 1994.

Warning: Every effort has been made to ensure the accuracy of the dosages of drugs and the prescribing information included in this book. Nevertheless, those prescribing these drugs are urged to follow carefully the manufacturers' printed instructions.

FIGURE 7 ANTI-TUBERCULOSIS DRUG INFORMATION

DRUG	MAJOR ADVERSE REACTIONS	MONITORING	REMARKS
Isoniazid (INH)	Hepatitis Hypersensitivity Peripheral neuritis	Symptoms SGOT*	■ Phenytoin (Dilantin) toxicity (if taken together, increases the serum concentration of both drugs). ■ Pyridoxine (25-50mg) may be given to prevent peripheral neuritis. ■ With disulfiram (Antabuse), may lead to behaviour and coordination disturbances. ■ Aluminum Hydroxide Gel decreases gastro-intestinal absorption of INH. INH should be administered at least one hour before the antacid.
Rifampin (RMP)	Liver toxicity Hypersensitivity Gastroenteritis	SGOT/SGPT* Platelets count Bilirubin	■ Decreases effectiveness of the contraceptive pill. ■ Increases anti-coagulant drug requirement. ■ May accelerate metabolism of drugs by the liver, e.g., anticoagulants, oral hypoglycemics, corticosteroids, digitalis compounds, oral contraceptives, EMB, methadone, estrogen, digoxin, sulfonylureas, antiarrythmic agents. ■ An orange-red discoloration of sweat, tears, urine, saliva and feces is harmless. ■ May also precipitate Addisonian crisis among those with marginal adrenal function.
Pyrazinamide (PZA)	Hyperuricemia Arthralgia Gastric irritation Hepatotoxicity	SGOT/SGPT*	■ Benemid or allopurinol may be given to reduce serum uric acid.
Ethambutol (EMB)	Retrobulbar neuritis (rare at 15mg/kg) Hypersensitivity	Visual acuity and colour perception at baseline and monthly on therapy	■ Patient should report any visual changes to physician immediately.

*Baseline and PRN. The purpose of LFTs is to detect problems before side effects occur (CTS p. 90-1)

Monitoring and Follow-up

It is recommended that patients with active tuberculosis be seen by the treating physician/clinic on a monthly basis.

- **HIV serology:** HIV test all persons with TB disease;
- **Liver function testing** is recommended to establish a baseline and at follow-up visits, as necessary, to ensure hepatic stability on medications;
- **X-ray** follow-up is recommended on a monthly basis especially for the first few months that the patient is on treatment to ensure radiographic improvement. Once the patient is showing improvement and sputum conversion, the frequency can be cut back;
- **Sputum** monitoring is recommended on a monthly basis until the **CULTURE is converted to NO GROWTH.** Additional sputum should be obtained at the end of therapy or more frequently if clinical or radiological improvement is slow; (CTS p. 95) Although it is recognized the patient's symptoms such as cough may subside within the first two months of treatment, sputum samples should still be obtained to document culture conversion. Patients who do not convert their sputum should be considered **TREATMENT FAILURES.**

"TREATMENT FAILURE is defined as two or more positive cultures over an interval of 1 month, after 5 or 6 months of treatment or two positive cultures in different months during the last 3 months of treatment" (CTS p. 95). This may be due to:

- inadequate treatment regimen;
- non-adherence to treatment regimen;
- malabsorption issues;
- development of drug resistance.

The public health lab will repeat the sensitivities on cases of treatment failure to ensure there is no drug resistance. Treatment failure requires more complex and longer treatment regimens.

NEVER add a single drug to a failing regimen. Referral to a TB specialist is recommended with patients that experience treatment failure.

7.3 FULLY SENSITIVE EXTRA-PULMONARY TUBERCULOSIS

Extrapulmonary tuberculosis uses the same treatment regimen as pulmonary tuberculosis. The duration should be lengthened in cases such as CNS, renal, lymph node and bone tuberculosis.

Monitoring and Follow-up

It is recommended that patients with active tuberculosis be seen by the treating physician/clinic on at least a monthly basis.

- **HIV serology:** HIV test all persons with TB disease;
- **Liver function testing** is recommended to establish a baseline and at follow-up visits, as necessary, to ensure hepatic stability on medications;
- **Other Monitoring:** radiological and/or microbiologic culture conversion monitoring is recommended and is dependent on the extrapulmonary site.

7.4 RESISTANT TUBERCULOSIS (PULMONARY AND EXTRA-PULMONARY)

The prevalence of resistance to one or more anti-tuberculosis drugs in Ontario is approximately 14% (PHERO 2000). Isoniazid is the most common drug to which resistance is found. Multi-drug resistant TB (MDR-TB) is defined as resistance to INH and RIF with or without other drug resistance. The rate of MDR-TB in Ontario is approximately 1% but in urban areas such as Toronto it is as high as 3%. The possibility of drug resistance should ALWAYS be considered, especially in patients with a previous history of tuberculosis or in patients who are from areas with a high prevalence of drug-resistant tuberculosis such as India, Korea, Philippines, Southeast Asia, the former Soviet Union and Africa.

If the patient has been previously treated for TB, he/she is at high risk for drug resistance. In these situations, it is highly recommended that the patient be referred to a specialized centre prior to initiating treatment since the management is complex and lengthy. The patient will be started on appropriate treatment regimens to cover the possible resistance pattern until the culture and sensitivity can be obtained. (CTS p. 86) Second-line anti-tuberculosis medications are obtained free-of-charge through the local public health unit.

PREVENTING DRUG RESISTANCE

- start treatment with 4 anti-tuberculosis drugs;
- never add a single drug to a failing regimen;
- ensure that patients take their medication correctly (use DOT if available).

7.5 PREGNANCY

Tuberculosis disease should be treated without delay when discovered during pregnancy. Isoniazid, rifampin and ethambutol are not known to have teratogenic effects on the human fetus and the risk of allowing the disease to continue unchecked far outweighs the theoretical risk of therapy. Studies on PZA in pregnancy have not been undertaken. When PZA is not used, the duration of treatment should be at least 9 months. Breastfeeding is not contraindicated. (CTS p. 94) Although congenital tuberculosis is extremely rare, it should be in the differential diagnosis when doing fetal/infant assessment when the mother has been diagnosed with active tuberculosis disease.

7.6 PEDIATRICS

Tuberculosis disease in children is treated in the same manner as disease in adults. Gastric aspirates (see Diagnosis section) are obtained when sputum is not available. This is true in children less than 5 years of age. Routine monitoring of liver function is not recommended, however advise parents that the medicine should be held and medical attention sought if anorexia, nausea, vomiting or jaundice occurs. In addition, the patient should be seen by a physician monthly to evaluate for toxicity. Pyridoxine supplementation is given to selected children receiving INH.

7.7 HIV/AIDS

Persons with TB and HIV co-infection respond well to standard TB drugs. However, certain anti-tuberculosis medications such as rifampin (RIF) maybe contraindicated with HIV anti-retroviral therapy and alternatives such as rifabutin need to be substituted. The duration of treatment is 6-9 months assuming adherence and satisfactory clinical and microbiological response has been obtained. (see Monitoring above)

7.8 ADMITTING TO HOSPITAL CASES OF ACTIVE TUBERCULOSIS

Hospitalization is not generally required for active tuberculosis patients unless:

- the patient is very ill and requires further investigation and/or treatment to ensure he/she is clinically stable;
- the patient has immunocompromised persons living in their home, e.g., young children/infants, persons infected with HIV, etc.;
- the patient is homeless or lives in a shelter;
- the patient lives in a residential home;
- drug resistance is suspected;
- an acceptable therapeutic regime needs to be established and monitored closely in patients with potential intolerance issues (CTS p. 93).

If the patient is being treated as an outpatient only, referral and partnership with the local public health unit (DOT program if available) is essential. Referral should occur as soon as a diagnosis is made.

8. In-Hospital Management of Tuberculosis

8.1 TRIAGE

PURPOSE

Tuberculosis (TB) is an infectious airborne disease. People with undiagnosed TB disease often seek care in Emergency Departments. **Early identification** of patients with suspected TB and implementation of appropriate **Airborne Precautions** are important. This will reduce the risk of transmission of TB to health care workers, patients, visitors, volunteers and other people in the health care facility. (See Figure 8).

8.2 AIRBORNE PRECAUTIONS

All health care facilities must assess for the TB risk classification of the facility (low or moderate to high), classification of TB exposure of the health care workers' activities (low, intermediate or high) and protocols in place to either admit TB patients or transfer out to an appropriate facility.

Infection is transmitted almost exclusively through the airborne route. Droplet nuclei are created by forceful expiration such as coughing, sneezing or singing and also by certain procedures such as bronchoscope or irrigation. The droplet nuclei contain tubercle bacilli which can be inhaled by others.

It is recommended that all patients with suspected or confirmed active pulmonary tuberculosis who are admitted to the hospital have the following:

1 Airborne precautions, e.g., a newly constructed room for airborne precautions has a minimum of 9 air changes per hour and existing facilities have at least 6 air changes per hour. The direction of airflow is from the hall into the room ("negative pressure"). Air from the room may be exhausted to the outdoors or if re-circulated back into the building, it should be passed through a HEPA (High Efficiency Particulate Air) filter. Air changes and direction of airflow should be verified at least every 6 months. Direction of airflow should be tested with smoke tubes at all four corners of the door;

2 Windows and doors to the patient's room are closed and the patient has dedicated toileting facilities;
3 Appropriate particulate respirator masks are available outside the patient's room entrance and are worn by everyone that enters the patient's room;
4 Appropriate airborne precaution signage is posted in a visible location;
5 Patients are masked when they leave the room;
6 Instructions are given to patients to cover their mouth and nose with tissues when coughing or sneezing;
7 Limitation of the number of health care providers/visitors/family that enter and leave the room;
8 Education of the patient/patient's family on the importance of the requirements for airborne precautions;
9 Elective procedures are postponed until the patient is non-infectious;
10 Notification of the appropriate medical personnel for clinical assessment/follow-up;
11 Notification of the Infection Control Practitioner.

8.3 CRITERIA FOR DISCONTINUING AIRBORNE PRECAUTIONS IN CONFIRMED TB CASES

The degree and duration of contagiousness of patients after initiation of effective therapy can vary. Therefore, airborne precautions should be continued until patients are assessed as non-infectious. Discontinuing airborne precautions should **NOT** be based on a fixed interval of treatment (e.g., 2 weeks) but rather on evidence of clinical and if possible, bacteriological improvement. Consultation to discontinue airborne precautions should include nursing staff, the infectious disease physician and other physicians, infection control practitioners and the local public health unit.

A case-by-case assessment MUST be done, which includes:

- Documented microbiologic improvement (e.g., sputum smear "scarce/negative" on 3 separate days) AND
- Radiological improvement AND
- Clinical improvement AND
- Drug regimen is adequate and the patient's tuberculosis culture is known to be fully sensitive to first-line drugs. A minimum of 2 weeks of treatment may be adequate to render the patient with minimal disease non-infectious. However, 2 weeks may not be adequate for patients who have advanced disease such as sputum smear "moderate/numerous" and have large amounts of disease on radiological reports, especially cavities.
- A patient with MDR-TB should remain on airborne precautions for the duration of hospitalization or until 3 consecutive sputum cultures are negative for mycobacterium.

Suspect/known cases of non-respiratory (extrapulmonary) tuberculosis should always be assessed for the presence of respiratory TB disease.

8.4 DISCHARGE PLANNING

All discharge planning for active tuberculosis patients should begin as soon as the diagnosis is made and must be done in partnership with the local public health unit. The following patients with active pulmonary tuberculosis should not be discharged into the community until they are deemed non-infectious:

- Patients who have multi-drug resistant tuberculosis (MDR-TB);
- Patients who reside with immunocompromised individuals (e.g., HIV);
- Patients who have young children/infants in the household that have not started treatment for LTBI;
- Patients who reside in homeless shelters or group home settings.

Due to the length and complexity of tuberculosis treatment, many patients may find their therapy difficult to adhere to or may experience side effects to the medications. At the time of discharge planning, consideration should be given to having the patient take their medications through Directly Observed Therapy (DOT – see section 9.4) if it is available at the local public health unit. The DOT program will provide education and support to the patient and their family. The World Health Organization recommends that all active tuberculosis patients have DOT whenever possible.

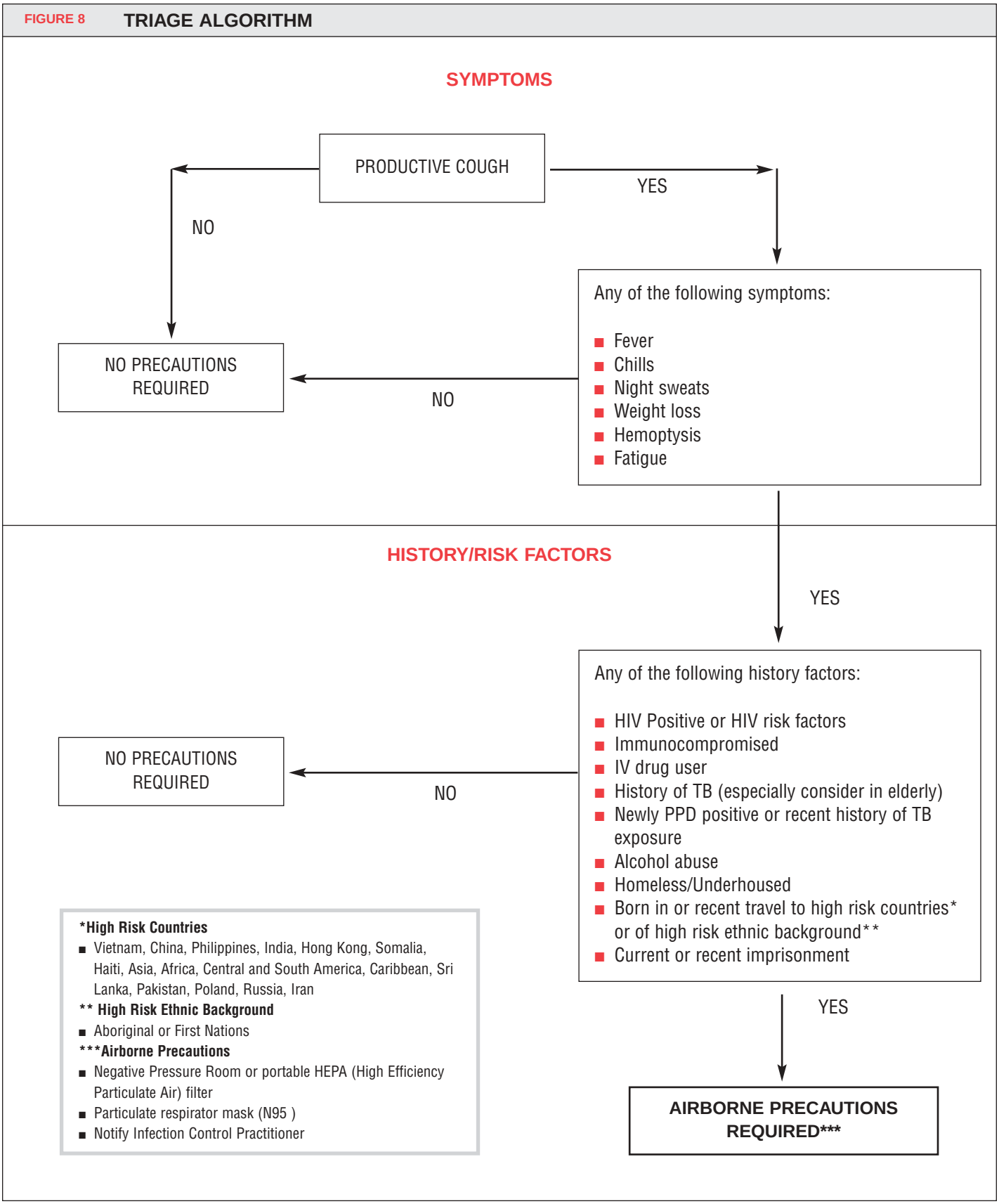
8.5 HEALTH CARE WORKERS' (HCW) BASELINE TUBERCULIN SKIN TEST (TST)

At the time of hiring, all health care workers (HCW) should have a two-step TST unless they have a documented prior positive tuberculin test. If prior results are used, these should be transcribed into the employee's health record. Annual TST is recommended for staff involved in moderate risk activities in moderate to high-risk hospitals (6 or more TB admissions per year or a ratio of less than 100 potentially exposed health care workers per TB admission per year). Consideration should be given to more frequent tuberculin skin testing for HCW involved in high-risk activities in all hospitals, e.g., staff from bronchoscopy, sputum induction and pentamidine aerosol, autopsy and TB and pathology laboratories. (CTS p. 210)

8.6 TST FOLLOWING UNPROTECTED EXPOSURE

The hospital must have a process to contact and assess all HCW including volunteers, contractors, or agency personnel at the facility who had unprotected exposure to an infectious case of tuberculosis. Usually the Occupational Health and Safety Department will co-ordinate the initial (within 8 weeks) TST for exposed personnel unless there is a history of prior treatment for TB or a documented prior positive TST, followed by a 3 month (8 to 12 weeks after contact) repeat TST. All positive TST and TST conversions are reportable to Public Health. Health care workers with a positive TST should have a medical referral. (CTS p. 218)

FIGURE 8 **TRIAGE ALGORITHM**



9. Community Management Issues

9.1 CONTACT FOLLOW-UP

Persons who have been in contact with an individual who has active, untreated, pulmonary tuberculosis (the index case) are at risk of contracting the infection. The more infectious the individual and the longer and closer the contact, the more likely they are to become infected. Contacts who have lower immunity, such as children under six years of age and persons who are HIV positive, are at higher risk of contracting tuberculosis infection/disease and should be given priority during contact investigations.

Contact follow-up is the responsibility of Public Health. Under the Health Protection and Promotion Act of Ontario, all health units must have a program in place to trace and investigate contacts of tuberculosis cases according to a set protocol. The protocol calls for the screening of contacts in order to find a source case, and the treatment of infected contacts, if indicated, to prevent progression from latent TB infection to active disease.

Most often contacts deemed to be at risk are referred for follow-up to their own physicians. However, in group settings such as schools, shelters for the homeless and workplaces, public health staff may hold screening clinics to facilitate the follow-up of large numbers of people. Individuals who test positive during these screening clinics are referred to a physician for further assessment and management.

When the index case has drug-resistant tuberculosis, contacts should be referred to a physician who has experience in dealing with resistant TB.

9.2 PATIENT AND FAMILY EDUCATION

Myths, misinformation and stigma about tuberculosis continue to be problems. It is therefore very important for the individual with a newly diagnosed case of tuberculosis to receive accurate and timely information about the disease. Education should begin at the time of diagnosis and continue until all of the patient's questions have been answered and he/she is knowledgeable about:

- the cause of tuberculosis;
- how to prevent transmission to others;
- side effects to watch for with anti-tuberculosis medication;
- why prolonged treatment is required and why it is important to take anti-tuberculosis medication as prescribed (adherence to therapy).

9.3 RETURN TO WORK AND SCHOOL

The decision regarding when a person with active pulmonary tuberculosis can return to work or school must be based upon:

1 Characteristics of the individual:

- determination that the person has been adhering to the treatment as prescribed for at least two weeks;
- resolution of symptoms (e.g., person is no longer coughing).

2 Characteristics of the disease:

- if the disease is extensive (e.g., cavitary) then three negative AFB smears, taken on different days, should be present before the person can return to work or school;
- if drug resistance is suspected then the person must not be allowed to return to school or work until the sensitivity is determined and it is certain that the treatment regimen is adequate;
- if the person has multi-drug resistant tuberculosis, they should not return to work or school until they have 3 negative cultures taken on different days.

3 Characteristics of the work/school environment:

- persons who work in or attend a high risk setting (e.g., those who work with: HIV infected people, children 5 years of age or under, the elderly, hospitalized patients, homeless or incarcerated individuals) should not be allowed to return to work/school until the sensitivity is known and it can be determined that the treatment is adequate; and
- three negative AFB smears have been obtained from specimens collected on different days; and
- treatment has been in progress for at least two weeks.

9.4 DIRECTLY OBSERVED THERAPY (DOT)

Adherence to an effective treatment regimen is essential to cure tuberculosis, reduce the risk of transmission and prevent the development of drug-resistant strains. The best way to ensure adherence to treatment is for a health care provider to watch a person with tuberculosis take all of their prescribed medication. In Ontario, DOT is usually available through health units.

All persons with tuberculosis should be assessed for the need for DOT and persons on intermittent regimens must receive DOT. When resources are limited, individuals with pulmonary tuberculosis who have the following risk factors should receive priority:

- those with suspected or known drug resistance;
- those with relapsed/re-activated disease;
- those with substance use problems (e.g., alcohol or drugs);
- homeless or underhoused individuals;
- those with co-morbid conditions (e.g., HIV/AIDS, diabetes, end-stage renal disease);
- persons who fail to keep follow-up appointments or have a history of non-adherence;
- children and adolescents;
- those with mental health concerns/cognitive impairments.

The DOT worker not only observes the person taking their medication but can also monitor for side effects of the drugs, watch for signs indicating relapse, ensure the person attends follow-up appointments, educate about tuberculosis and provide ongoing support, assistance and referral for other issues (e.g., housing, welfare). In some jurisdictions, incentives and enablers (e.g., bus tickets, food supplements, clothing) may be available for persons on DOT.

9.5 MANAGEMENT OF NON-ADHERENCE TO THERAPY

Persons with active tuberculosis must take their medication as prescribed. When they fail to do this, they are at risk of infecting others, relapsing and/or developing drug-resistant tuberculosis.

Adequate treatment for tuberculosis involves taking several drugs every day for 6 months or more. As an individual's symptoms resolve, there may be less motivation to remember to take all of these drugs all of the time. The person may not realize the danger in not taking their drugs as prescribed or they may feel that these risks were exaggerated by the health provider as nothing may happen for some time.

DOT eliminates the risk of non-adherence. However, if the person is self-medicating, then it is important to maintain regular contact in order to ask key questions about adherence. These questions should include:

- Are you taking your medication every day? If not, what days have you missed?
- Are you having any side effects from the drugs?
- When was your last medical appointment? When is your next appointment?
- Do you have any symptoms of illness?

Other methods of monitoring adherence include:

- Contact the treating physician/clinic to ensure that the person has kept their follow-up appointments and that they are making appropriate clinical improvement (e.g., sputum has converted, x-ray has improved);
- Make a home visit, carry out a physical assessment and conduct a pill count.

When serious non-adherence is determined (e.g., less than 80% of the anti-tuberculosis medication has been taken), the individual should be placed on DOT and the treating physician/clinic should be notified. If the person refuses DOT, an "Order" under the Health Protection and Promotion Act should be considered. In Ontario, tuberculosis is considered a virulent communicable disease and as such, persons with tuberculosis can be ordered to comply with treatment and/or isolation and may even be detained against their will to protect the public.

Health units will collaborate with treating physicians and clinics to draft Orders under the Health Protection and Promotion Act when it is determined that the community is at risk and all other methods to encourage adherence have failed.

10. TUBERCULOSIS SCREENING

TUBERCULOSIS IS PREVENTABLE

A significant number of new active tuberculosis cases come from the pool of people who have been infected with tubercle bacilli in the past. This is referred to as Latent Tuberculosis Infection (LTBI). The World Health Organization estimates that one-third of the world's population has LTBI. Treatment for LTBI is an important component in preventing future tuberculosis disease and transmission. The following sections discuss TB skin testing, screening issues (contacts/high risk targeted) and preventive treatment for LTBI.

10.1 TB SKIN TESTING

GENERAL INFORMATION

TB skin testing is a useful tool for diagnosing tuberculosis infection. This test is NOT as helpful in the diagnosis of active tuberculosis and can have a "false negative" result in advanced active disease and/or immunocompromised patients. It is recommended that all individuals with suspected active tuberculosis and/or a positive skin test undergo further investigation (chest x-ray and 3 sputum specimens for AFB, C&S). (See Diagnosis section)

FIGURE 9 MANTOUX TEST METHOD (CTS p. 46-48)

1 0.1ml of tuberculin using 5TU (PPD) is injected intradermally on the volar aspect of the arm.

2 A wheal 6 - 10mm in diameter should appear at the needle point. If no wheal appears or if the fluid substantially leaks out, inject again at another site.

3 Read the test at 48 - 72 hours and document the size of **induration** in mm. The reaction of those who are elderly or being tested for the first time may develop more slowly and may not peak until after 72 hours. Patients should always have their tests interpreted by a health care practitioner. They never read their own skin tests. (see Figure 11 for skin test readings)

Only the INDURATED area should be measured, not erythema (redness).

4 A punctured vial of 5TU PPD should be discarded after *one month* due to possible contamination and loss of potency. (Date vial when opened). Failure to store and handle the tuberculin preparation as recommended will result in a loss of potency and inaccurate test results or false negative results.

5 All *POSITIVE* skin tests should be reported to your local public health unit.

Under the Health Protection and Promotion Act, "private physicians will report to the local Medical Officer of Health in his/her area of practice all persons with latent tuberculosis infection as soon as possible after forming the opinion that the person is or may be infected with an agent of a communicable disease" (S26).

CONTRAINDICATIONS TO TUBERCULIN SKIN TESTING

When to Avoid Skin Testing

Do not conduct skin testing in:

1 anyone with a previous severe reaction (e.g., blistering, necrosis or ulceration) to a TB skin test;
2 anyone with known active TB or known treatment in the past (the Mantoux test does not distinguish between prior and recent infection, and will not yield any useful information in this case.);
3 anyone with extensive burns or eczema;
4 anyone with a documented previous positive reaction read by a knowledgeable healthcare worker.

When to Defer Skin Testing

Defer tuberculin skin testing for:

1 anyone with viral infections (e.g., rubeola, mumps, influenza), which may temporarily depress the reactivity to the Mantoux test. **Defer** skin testing for 4 to 6 weeks after the infection;
2 anyone immunized with a **live** viral vaccine (e.g., MMR - measles/mumps/rubella, varicella vaccines), which may temporarily depress the reactivity to the Mantoux test.

Options: either administer the Mantoux test **before** or **simultaneously** with the live, viral vaccine (e.g., MMR) or defer skin testing for 4 to 6 weeks after immunization with a live, viral vaccine.

When Not to Defer Skin Testing

Do not defer skin testing for:

1 people who have been immunized with a non-live-virus vaccine (e.g., diphtheria, tetanus, polio, pertussis), which do not suppress the reaction;
2 pregnant women. Pregnancy is NOT a contraindication for tuberculosis skin testing;
3 anyone who had a previous BCG vaccination;
4 anyone who has a history of significant test reaction in the past (without a severe reaction/blistering/ulceration/necrosis at the site) but the reaction was not documented in millimetres. (CTS, Tubersol product monograph)

A POSITIVE SKIN TEST REACTOR must have a physical examination, chest x-ray and sputum samples to rule out active disease. If there is no evidence of active disease, treatment for LTBI should be considered. *Initiating treatment such as INH, prior to thoroughly ruling out active disease, puts the patient at risk for creating INH-resistant TB.*

If treatment for LTBI is REFUSED OR CONTRAINDICATED, the patient should be informed about the symptoms of active tuberculosis disease and advised to seek medical attention if these develop. The risk of active tuberculosis disease developing in someone who is infected with LTBI is approximately 10% over a lifetime and is greatest in the first two years after infection. This risk increases significantly with immunocompromising diseases such as HIV (10% chance per year of life), diabetes, cancer, chronic renal failure and immunosuppressive drug therapy.

TB SKIN TESTING AND BCG VACCINE

Field studies indicate that BCG vaccine does not prevent tuberculosis infection. Once an individual has been infected, this vaccine has been shown to reduce disseminated tuberculosis, primarily in young children. (CTS ch. 111-E)

The interpretation of the tuberculin skin test result should ignore the history of BCG vaccination (as a cause of a positive tuberculin reaction) if:

- BCG was given in infancy (in all population groups);
- BCG was given (at any age) in a person who comes from a country with a high rate of tuberculosis **or** who is an Aboriginal Canadian;
- BCG was given (at any age) in a person who is at high risk for tuberculosis (i.e., contact of an active case of tuberculosis; person with abnormal chest x-ray; someone with HIV infection).

TWO-STEP TUBERCULIN SKIN TEST

The two-step tuberculin skin test is used to rule out the booster phenomenon

A positive tuberculin skin test may gradually wane over the years. The first skin test in persons whose exposure history is unknown or potentially may have been at risk for exposure to *M. tuberculosis* several years earlier, may have a negative test result. However, this initial test may stimulate the individual's immune response and a positive reaction may occur when the person is retested one or more weeks later. This delayed response is termed the "booster" phenomenon. The two-step skin test provides an accurate "baseline" for individuals who will have future or serial testing. If a true baseline is not obtained with a two-step test and the individual is tested again at a future date, a positive result may be misinterpreted as a new infection or "conversion" when it may represent a "booster" phenomenon.

The two-step skin test requires the administration of two tuberculin (5TU PPD) skin tests. If the reaction to the first test is negative, a second test is given 1-3 weeks later. Repeated tuberculin testing does not sensitize uninfected persons.

Indications for the Two-Step Skin Test (CTS p. 51-52)

1 Perform two-step tuberculin skin testing if subsequent testing will be conducted at regular intervals, for instance, among health care workers;
2 Use the two-step test with residents of long-term care facilities who may be tested subsequently, if there is a suspected exposure, to ensure an accurate baseline result to guide post-exposure management;
3 Consider a two-step baseline test in other appropriate situations (e.g., staff in correctional facilities).

The two-step skin test should not be used as the baseline test for people who are recent contacts of an infectious active tuberculosis case. In contacts, any change from negative to positive must be considered a conversion and further investigation and treatment is required.

10.2 SCREENING ISSUES

1 CONTACTS OF PULMONARY TUBERCULOSIS

The primary purpose of contact investigations is to:

- Identify and treat secondary active tuberculosis cases;
- Identify individuals who have been infected with tuberculosis (LTBI) and offer treatment;
- Identify the source case if the active tuberculosis case is a child, or in a case of primary tuberculosis.

Conversion of the skin test from negative to positive after exposure to tuberculosis may take 8 to 12 weeks. Therefore if skin testing is performed before 8 weeks of the last exposure and the result is negative, a second skin test must be repeated (8 to 12 weeks after the contact's last possible exposure to the active case).

Previous Negative or Unknown Reactors

A positive skin test reaction includes indurations:

- > 5mm - regardless of BCG history;
- previously 5-9mm; now increased by 6mm or more (converter).

Previous Positive Reactors or Previous History of Treatment for Tuberculosis or LTBI

Once a person has a documented positive skin test or has been previously treated for active tuberculosis, there is no need to repeat the skin test even in exposure situations. These contacts should be evaluated for signs and symptoms of tuberculosis and if necessary further investigation to rule out active disease should be carried out. (See Diagnosis section)

HIV or Other Immunocompromised Conditions

HIV positive individuals or severely immunocompromised individuals, REGARDLESS OF TST STATUS, should be offered preventive treatment for LTBI.

Pediatric

Children (especially those less than 6 years of age) whose skin test is negative on the first test should still undergo symptom review, chest x-ray and, if necessary, sputum cultures or gastric aspirates to rule out active tuberculosis. Treatment for LTBI should be initiated immediately once active disease has been ruled out. Treatment for LTBI may be stopped if the second skin test, 8 to 12 weeks after last exposure, is also negative.

2 TARGETED SCREENING

Certain groups should be considered for tuberculosis skin test screening (usually delivered at the level of the primary care provider). The Canadian Tuberculosis Standards recommends the following:

- individuals with high risk medical conditions (e.g., chronic renal failure, diabetes mellitus);
- individuals that have recently arrived in Canada who were born in a TB endemic country;
- individuals at risk of active tuberculosis who are employed in settings where they may infect infants or persons who are immunosuppressed (e.g., day nursery, HIV shelters);
- alcoholics and injection drug users;
- homeless and underhoused;
- Aboriginal populations with a high incidence of active tuberculosis;
- residents and workers in environments such as long-term care institutions, corrections facilities, and psychiatric facilities;
- individuals with risk of occupational exposure such as health care workers;
- travelers who are going to areas with a high prevalence of tuberculosis and have high risk medical conditions, plan to stay for a prolonged period (>1 year) or will be participating in high risk activities (e.g., health care work, refugee care). (CTS p.189-190)

11. Treatment & Management of Latent Tuberculosis Infection

11.1 GENERAL INFORMATION

Treatment for latent tuberculosis infection is undertaken to prevent active disease in infected persons thereby preventing transmission to others. Health care providers should consider treatment for persons with positive TB skin tests (see below). The decision to offer treatment for LTBI should be made after weighing risk factors and the benefits of treatment against the potential risks of drug toxicity.

11.2 SKIN TEST REACTIONS

Negative Skin Test Reactions

- People who are immunosuppressed may have a false negative skin test associated with *anergy* and individuals who have advanced active tuberculosis disease may also have false negative skin test results.

> Anergy: The failure of a subject to respond to skin test antigens of infectious agents to which they have had prior exposure (may be due to severe immunodeficiency, such as occurs with HIV infection). (CTS p. 237)

- Close household contacts who are under the age of six years or are severely immunosuppressed (even if the initial tuberculin skin test is negative) should be investigated for active disease. Treatment for LTBI should then be initiated until the second tuberculin skin test result is known. If the repeat skin test (3 months after last contact) is negative, treatment for LTBI can be discontinued. If the repeat skin test is positive, complete the course of treatment for LTBI. (CTS, Red Book)

Investigation for active disease must be completed prior to initiating treatment for LTBI.

FIGURE 10 POSITIVE SKIN TEST POSTER

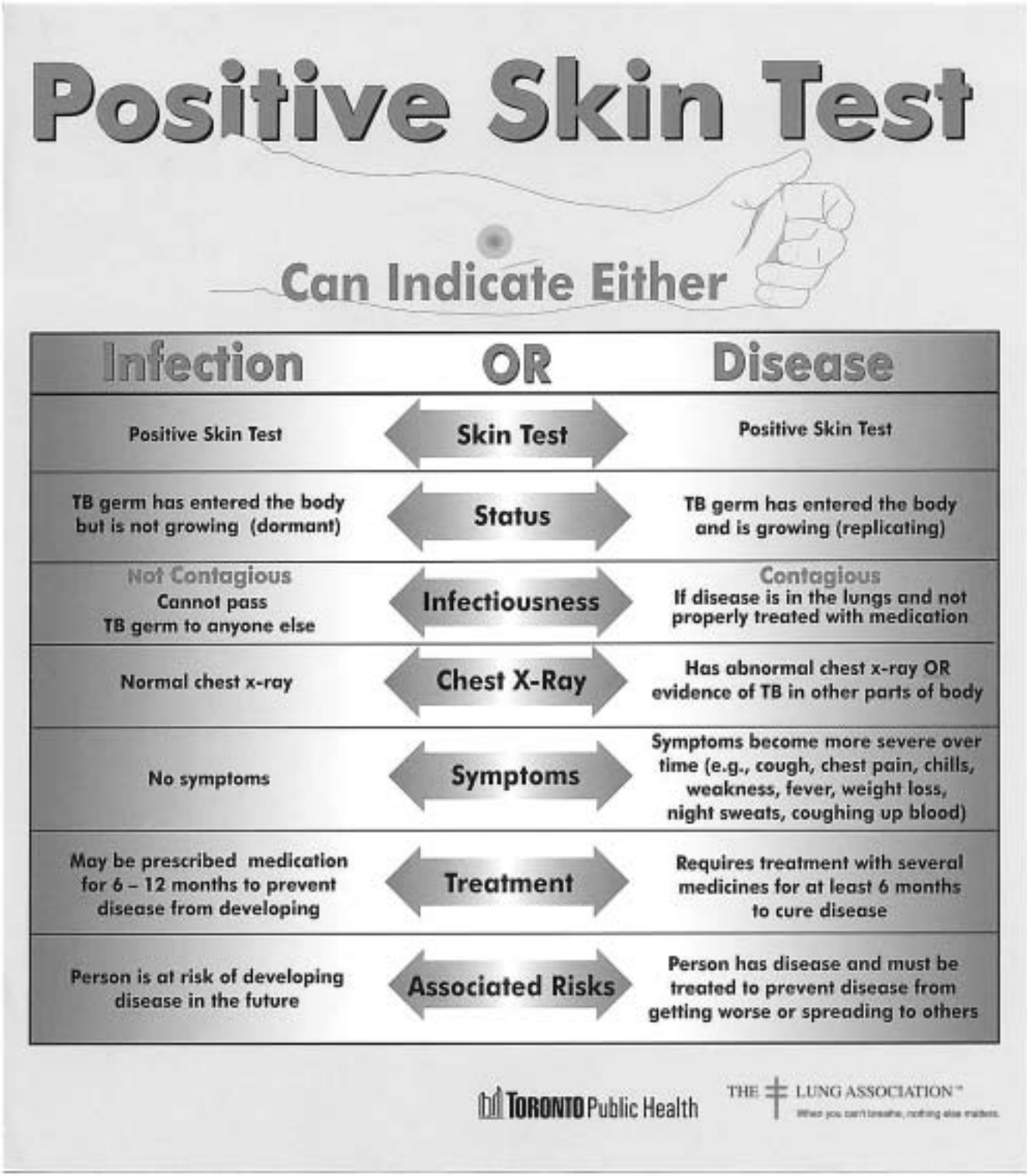


FIGURE 11 POSITIVE SKIN TEST REACTIONS		
TUBERCULIN REACTION SIZE	INDICATION	DURATION OF THERAPY
> 5mm+	– *Household contact* – *Presence of lung scar* (compatible with TB but never previously treated, such as fibro-nodular disease) – *HIV infection and immunosuppressive conditions* (prolonged corticosteriod or immunosuppressive drug therapy)	9 months 9-12 months
> 10mm*	– *Converter (within 2 years)* *High risk groups:* a) Foreign-born from TB endemic regions b) Aboriginal c) Health care workers d) Resident in communal care – *Medical condition that suppresses immune competence:*** a) > 10% below ideal body weight b) chronic renal failure c) diabetes mellitus d) some haematologic malignancies e) silicosis f) organ transplantation g) prolonged immunosuppressive drug therapy h) *People with immunosuppression, who have previously received treatment for LTBI and who have been recently re-exposed to an active case of TB should be considered for repeat treatment of LTBI.*	9 months

+ Tuberculin reaction size <5mm is not normally considered significant but in the presence of immunosuppression may be important (i.e., HIV infection and high risk of tuberculosis infection).

* Recent studies suggest that the risk of hepatotoxicity associated with INH treatment for LTBI, among individuals >35 years of age, may have been previously overestimated. An individual who fits one or more of the above criteria should be considered for treatment regardless of age.

**Some references (Red Book) recommend that all immunocompromised persons receive treatment for LTBI.

11.3 RECOMMENDED TREATMENT REGIMEN FOR LTBI

FIGURE 12 DOSAGE OF ISONIAZID (CTS p. 97)	
Adults:	300 mg daily
Children:	10 – 15 mg/kg/day (max 300 mg/day)

** *Vitamin B6 (pyridoxine 25 mg daily) should be given with INH to children and anyone with a condition that predisposes him/her to peripheral neuropathy (e.g., malnutrition, alcoholism, diabetes mellitus, uraemia and pregnancy).*

Isoniazid and pyridoxine (Vit B6 prophylaxis for peripheral neuritis) can be ordered at no charge through your local health unit. Consider providing intermittent Directly Observed Prophylactic Therapy (DOPT) in situations where the patient may have potential problems with compliance, staff resources permitting. (Tuberculosis, Red Book) The intermittent twice weekly supervised treatment dose is: INH 900 mg/dose in adults [20 – 40 mg/kg to a maximum of 900 mg dose in children]. (CTS p. 97)

Proven Effectiveness

INH is the only drug that has been field tested and proven effective as a treatment for LTBI. Given daily for at least six months and optimally for 12 months, isoniazid reduces the risk of an infected person developing active TB. (CTS, Red Book) A 1982 large, controlled trial indicated that those who complied with the therapy and took 80% or more of the assigned medication, achieved protection of 31%, 69% and 93% with the 3-6-12 month regimens respectively. (Tuberculosis p. 242) The beneficial effects of INH in persons with a positive skin test persist for up to 20 years and presumably for life. (Red Book, Tuberculosis)

Contraindications:

1 INH should not be used alone in the presence of known or suspected active TB disease because monotherapy may lead to the development of drug resistance;
2 There is a high likelihood that the patient has been exposed to an organism that is resistant to INH;
3 The patient has a history of INH-associated hepatic injury;
4 The patient has a history of severe adverse reaction to INH, such as drug fever, rash or arthritis;
5 The patient has acute or active liver disease of any etiology; preventive therapy may be prescribed once the liver disease has been resolved (HbsAg positivity is *not* a contraindication unless it is associated with chronic hepatitis). (CTS p. 90, Red Book)

Alternatives

When INH is contraindicated – either because of past history of side effects or exposure to an isoniazid resistant organism, rifampin (RIF) for four months may be used. As the effectiveness of this alternative regimen has not been proven the patient should be monitored closely and referral to a TB specialist is recommended.

11.4 SIDE EFFECTS OF MEDICATIONS

Patients should be advised to notify their health care provider immediately if they experience any side effects from INH therapy, such as:

1 unexplained anorexia, nausea, vomiting, fatigue, or weakness of more than 3 days duration;
2 persistent paraesthesia of hands and/or feet;
3 dark urine;
4 jaundice;
5 rash;
6 fever of more than 3 days duration;
7 abdominal tenderness, especially right upper quadrant discomfort;
8 arthralgia.

The risk of INH-induced hepatitis increases with age as follows: (CTS p. 101)

0-19yrs	–	rare (0.001%)
20-34	–	0.2%
35-49	–	1.5%
>49	–	2.4%

Death due to INH toxicity is rare. To prevent severe complications from INH toxicity, monitor patients closely.

Monitoring During INH Therapy

Monitor closely anyone with any of the following characteristics or conditions for drug side effects and complications; i.e., individuals who:

1 are age 35 and over;
2 have chronic liver disease of any etiology;
3 may be pregnant;
4 consume alcohol daily, especially if there is evidence of hepatic dysfunction at baseline testing;
5 have peripheral neuropathy of any etiology, or a condition that might predispose him or her to peripheral neuropathy, such as diabetes;
6 are using another medication that may cause drug interactions.

Clinical Monitoring

1 Take a baseline medical history and conduct physical examination for all patients before starting therapy;
2 Order a baseline liver function test (AST, ALT, Bili) for adult patients before starting INH prophylaxis. Some centres recommend testing monthly for the first three months and then testing only if symptoms of hepatotoxicity develop. About 10% to 20% of patients will experience a transient, mild, symptomless elevation of transaminase, usually within the first six months. These levels usually return to normal while the patients are still taking INH. If any of the measurements exceeds three to five times the upper limit of normal or if the patient reports symptoms of adverse reactions, treatment should be discontinued. (CPS, CTS, Core Curriculum)

11.5 HIV

HIV positive persons should be prescribed the same dose and duration of INH as the HIV negative population.

11.6 PREGNANCY

Although INH anti-tuberculosis medication has not been shown to be teratogenic, it is not recommended during pregnancy except in recently infected women or women who have high risk medical conditions, such as HIV infection. Consider deferring treatment for LTBI at least until the second trimester in these high risk women and until the postpartum period for all others. The possibility of active disease must be ruled out. When treatment for LTBI is deferred, both the patient and physician should watch for any symptoms of active TB disease. (CTS, Core Curriculum)

11.7 PEDIATRICS

Children (especially those less than 6 years of age) whose skin test is negative on the first test should still undergo symptom review, chest x-ray and, if necessary, sputum cultures or gastric aspirates to rule out active tuberculosis. Treatment for LTBI should be initiated immediately once active disease has been ruled out. Treatment for LTBI may be stopped if the second skin test, 8 to 12 weeks after last exposure, is also negative.

Children do not need baseline laboratory tests unless they have a known or suspected underlying abnormality. (Red Book, Core Curriculum) When children begin drug therapy, inform parents or guardians about symptoms associated with the most common adverse reactions.

11.8 MANAGING CLOSE CONTACTS EXPOSED TO DRUG-RESISTANT ACTIVE CASES

When a source patient has a resistant tuberculosis organism, infected contacts should be managed with drugs to which the source case is sensitive and in consultation with an expert in TB.

12. Atypical Mycobacteria

Species of atypical mycobacteria include *M. avium complex, M. fortuitum, M. gordonae, M. kansasii* and *M. xenopi.* These organisms may present with symptoms suggestive of pulmonary TB. They are non-contagious and are frequently found as environmental contaminants.

Atypical mycobacteria presents as an "opportunistic" infection in the immunocompromised individual. Be aware of possible co-infections with *M. tuberculosis complex.* The disease process may be self-limiting, chronic or life-threatening.

Decisions to treat should be based on clinical presentation and demonstrating 3 consecutive sputum specimens that grow the organism. The length of treatment is at the discretion of the physician.

Drugs for the treatment of atypical mycobacteria are not supplied through the Public Health TB Control Program and are not provided free-of-charge.

13. Summary

The control of TB depends on the achievement of the following three goals:

1 Persons with TB must be adequately treated;
2 Persons, who are infected, but not ill, must be prevented from becoming infectious;
3 Persons not yet infected must be prevented from acquiring infection.

Neither Health Care Providers nor Public Health Officials can achieve the control of tuberculosis without each other.

Let's work together.

14. Basic Classification Terms

EXTENT OF DISEASE

Pulmonary

Primary tuberculosis: The clinical or pathologic picture of first infection (primary) in children or adults is the same. In children, there is a greater frequency of bronchial compression and consequent collapse of bronchial segments due to lymph node enlargement, as well as greater frequency of complications due to dissemination, such as meningitis.

Minimal: Disease is of slight to moderate density, without demonstrable cavitation. It may be unilateral or bilateral, but the total extent, regardless of distribution, should not exceed the volume of lung on one side, which is present above the second costochondral junction and the spine of the fourth or the body of the fifth thoracic vertebra. The category includes disease not visible radiologically but confirmed bacteriologically.

Moderately Advanced: Disease may be present in one or both lungs, but the total extent, if disease is of slight to moderate density, should not exceed the total volume of one lung or the equivalent in both lungs. If the disease is dense and confluent, the extent should be limited to one-third of the volume of one lung. Total diameter of cavitation, if present, must be less than 4cm.

Far Advanced: This category includes all disease more extensive than moderately advanced.

CLINICAL ACTIVITY

New Active Case: No documented evidence of history of previously active tuberculosis.

Reactivated Case: Documented evidence of history of previous active disease which becomes inactive. The period of time during which there was inactivity should be specified.

Converter: Person with a documented change from a negative to a positive skin test. If the former skin test result is known, conversion is defined as: an increase in size of the TB skin test of 6mm or more **and** a change from negative to positive within the past 2 years (using the 5mm or 10mm cut point as appropriate.).

For recent converters, risk of disease is highest in the first two years following infection.

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16. Other Resources

The Lung Association (Order by calling 1-800-972-2636):
- Facts about Your Lungs: Tuberculosis (pamphlet)
- Positive Skin Test Poster (see p. 20)
- Tuberculosis: Key Issues for Health Care Providers -19 minute videotape

Canadian Lung Association website (includes pamphlet in languages other than English): www.lung.ca

StopTB Canada website: www.stoptb.ca

Contact your local health unit for additional TB resources.

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