BC Centre for Disease Control

Clinical Prevention Services

TB Treatment: To Cure and Protect

Session Three of a Four-Part Webinar Series
Presented in Partnership with the
BC Lung Association

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Overview

- Principles of TB treatment
- Medications and regimens commonly used for TB treatment
- Potential adverse effects related to TB treatment
- Monitoring during TB treatment
- TB drug resistance
- DOT
- TB treatment and smoking – Veda Peters, BCLA
- Q&A

Learning Objectives

At the end of this webinar, participants will be able to:

- Explain the basic principles of TB treatment
- Identify the drugs most commonly used in the treatment of TB disease and LTBI
- Describe the regimens most commonly used for TB disease and LTBI
- Identify the most common adverse reactions associated with treatment of TB disease and LTBI
- Describe the recommended monitoring for clients on treatment for TB disease or LTBI
- Explain the impact of TB drug resistance on treatment of TB disease and LTBI
- Define directly observed treatment (DOT) and describe how DOT contributes to comprehensive, patient-centred treatment programs

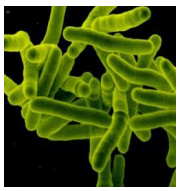
Abbreviations and Key Terms

- **TB bacteria:** bacteria that can cause TB disease
- **LTBI:** latent TB infection
- **DR-TB:** Drug-resistant TB disease
- **Cavity/Cavitation:** a chest X-ray finding in some cases of pulmonary TB disease

Tuberculosis - Etiology

***Mycobacterium tuberculosis* complex**: several closely related mycobacteria that cause TB disease

- *M. tuberculosis* including MTB subspecies, *canetti*
- *M. bovis*
- *M. africanum*
- *M. caprae*
- *M. microti*
- *M. pinnipedii*



What is Tuberculosis (TB)?

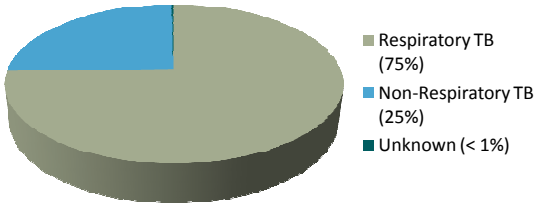
- An infectious disease
- Often (but not always) attacks the lungs
- Usually (but not always) curable with appropriate treatment
- Untreated, can be fatal
- Typically, only cases with respiratory disease transmit

Types of TB Disease

TB disease

Non-respiratory TB	Respiratory TB
droplet nuclei can be released under some circumstances	typically infectious prior to treatment

Types of TB Disease by Main Diagnostic Site (Canada, 2011)

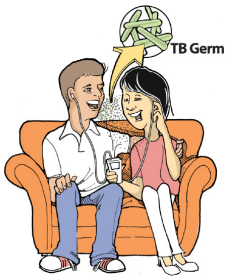


Note: 2011 data provisional until release of Tuberculosis in Canada, 2011
Source: Public Health Agency of Canada. Tuberculosis in Canada 2011 – Pre-Release. Ottawa (Canada): Minister of Public Works and Government Services Canada; 2012

How is TB Transmitted?

How is TB Transmitted?

When a person with infectious **TB disease** coughs, sneezes, sings or shouts, TB germs are passed into the air in "**droplet nuclei**".



People become infected with TB germs by inhaling droplet nuclei.

How Common is TB? TB in Canada: 2011

Origin	Cases	Rate / 100 000
Foreign-born	1081 (67%)	13.5
North American Indian (Status)*	176	20.4
North American Indian (Non-status)*	2	--
Inuit*	106	177.6
Metis*	21	6.0
Canadian-born non-Aboriginal	186 (12%)	0.7
Birthplace unknown	8	--

**19% of cases were of Aboriginal origin*

Note: 2011 data provisional until release of Tuberculosis in Canada, 2011
Source: Public Health Agency of Canada. Tuberculosis in Canada 2011 – Pre-Release. Ottawa (Canada): Minister of Public Works and Government Services Canada; 2012

How Common is TB? TB in British Columbia (2011)

Origin	Cases
Foreign-born	194
Aboriginal*	26
Canadian-born non-Aboriginal	34
Other and Unknown	15
BC Total	269

* includes Registered and Non-registered aboriginal, both on- and off-reserve

Source: BCCDC, F. Hutton, April 4, 2013

TB Pathogenesis: Initial Infection

Infection with TB bacteria

~ 5% → "primary" TB disease

~ 95% → latent TB infection (LTBI)

What is "Primary TB Disease"?

- ~5% of newly infected are unable to limit bacterial replication
- TB disease will develop within 18 to 24 months or sooner (e.g., if immune suppressed)
- Pleural TB, TB meningitis, and miliary TB are often presentations of primary TB disease
- Children under 5 years of age and persons with HIV/AIDS are at greatest risk

Latent TB Infection (LTBI)

The term 'LTBI' is used to describe the situation when a person is infected with TB bacteria but has not developed TB disease.

TB Pathogenesis: Reactivation

LTBI

~ 95% → continued LTBI

~ 5%* (over lifetime) → eventually develop "reactivation" or "post-primary" TB disease

Latent TB Infection vs. TB Disease

LATENT TB INFECTION

- TB bacteria in the body; bacteria are inactive (latent)
- Does not feel sick; no symptoms
- **NOT contagious**
- Could develop TB disease if TB bacteria become active and begin to multiply
- Treatment can **PREVENT** development of TB disease in future

TB DISEASE

- TB bacteria in the body; bacteria are active and multiplying
- Feels sick; symptoms such as fever, weight loss, fatigue
- **Could spread TB bacteria if contagious** form of disease
- Almost always curable if diagnosed in time and treated appropriately

Who is at "High Risk" for TB Disease?

Positive TST/IGRA or recent exposure **AND** :

- **HIV/AIDS**
- Chronic renal failure - hemodialysis
- Cancer of head, neck (or lung)
- Transplant
- Silicosis
- Chest X-ray findings = fibronodular disease
- Under 5 years of age

Who is at "Increased Risk" for TB Disease?

Positive TST/IGRA less than 2 years ago **AND**:

- Underweight
- Chest x-ray findings = granuloma
- Diabetes
- Immune suppressing treatment (e.g., prednisone, Embryl, Remicade, chemotherapy - can cause false negative TST)
- Smoker

Preventing TB: Treatment of LTBI

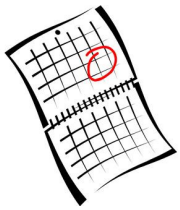
Important individual and public health benefits if given to people at increased risk for developing TB disease, for example, those with:

- Recent infection (e.g., contacts)
- HIV and other immune suppressing conditions, immune suppressing treatments/medications
- Chronic renal failure / hemodialysis
- Diabetes

LTBI Treatment Regimens

- Current standard for treatment of LTBI in BC is isoniazid (INH) and Vit B6 taken for 9 months
- Treatment can be daily or intermittent (e.g., twice weekly); intermittent therapy must be directly observed
- Alternative regimens are used for those who cannot tolerate INH or who are presumed to be infected with an INH-resistant organism (e.g., contacts to DR-TB)

What is "Window Period Prophylaxis"?



LTBI treatment given to contacts under 5 years of age.

WPP is given for the time between the first (negative) post-exposure TST and when a follow-up TST is done **at least** 8 weeks after the child's last exposure to the contagious case.

If TST #2 is negative, WPP is usually stopped.

What is "Presumptive LTBI Treatment"?

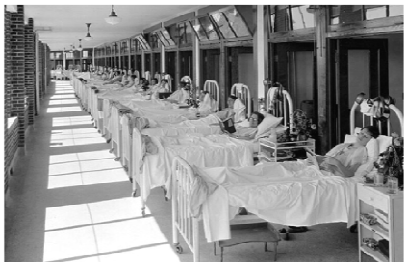
Treatment given to contacts at high risk for developing TB disease, and in whom testing for TB infection might not be reliable (e.g., contacts advanced immune suppression)

Unlike WPP, presumptive LTBI treatment does **NOT** stop if the repeat post-exposure TST is negative.

Monitoring during LTBI Treatment: Potential Adverse Effects of INH

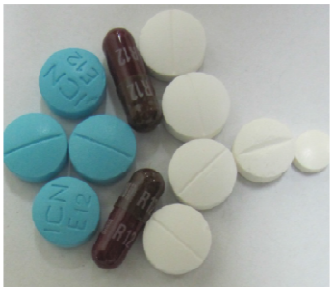
- **Hepatotoxic:** risk increases with older age, daily alcohol consumption, pre-existing liver disease (particularly hepatitis C)
- **Peripheral neuropathy:** Vitamin B6 given to prevent
- **Rash, nausea, vomiting:** more likely with intermittent regimens – could indicate liver toxicity
- **Other:** anemia, fatigue, drowsiness, headaches, mild hair loss, acne

Treatment and Cure of TB Disease (then)



Waverly Hills Tuberculosis Sanatorium, 1926.

Treatment and Cure of TB Disease (now)



Objectives of TB Treatment

1. Rapid killing of TB bacteria to improve clinical condition of the patient and prevent:
   - Complications
   - Death
   - Transmission
2. Prevent development or worsening of drug resistance
3. Prevent relapse (life-long cure)

Principles of TB Treatment

1. Always treat with a multiple drug regimen; in Canada treatment regimens typically include isoniazid (INH), rifampin (RMP), pyrazinamide (PZA), and ethambutol (EMB)
2. Never add a single drug to a failing regimen
3. Determine duration of therapy based on drugs used, clinical response, and extent of disease
4. Consider directly observed therapy

TB Treatment – An Overview

Treatment for TB disease is given in two phases:

1. **Initial (intensive) Phase**: Multiple drugs (INH, RMP, PZA, EMB) used in combination for at least 2 months, preferably given as daily doses.
2. **Continuation Phase**: Minimum of two drugs (INH, RMP) given in combination. Dosing can be daily or intermittent. Duration of continuation phase is variable, 4 months minimum. Often it can take a number of months to determine appropriate length of treatment.

Drugs Used in Treatment of TB Disease

In Canada, anti-TB drugs are divided into two broad categories:

1. **First-line Drugs:** effective, can be taken orally, and are generally well-tolerated
2. **Second-line Drugs:** fluoroquinolones, injectables and many "older" anti-TB drugs used in the 1950s and 1960s

First-line Anti-TB Drugs in Canada: Isoniazid (INH)

- Highly effective, bactericidal, prevents development of drug resistance
- Bactericidal
- Prevents development of drug resistance
- If not given for the full duration of treatment, treatment must be prolonged
- As when used for LTBI, generally given with Vitamin B6 to prevent peripheral neuropathy

First-line Anti-TB Drugs in Canada: Rifampin (RMP)

- Most potent anti-TB drug
- Bactericidal
- Prevents development of drug resistance
- Prevents relapse
- If not given for the full duration of treatment, treatment must be prolonged
- Rifabutin (RBT) is similar; used when drug interactions are of concern

First-line Anti-TB Drugs in Canada: Pyrazinamide (PZA)

- Bactericidal during first 2 months of treatment only
- Does not protect against drug resistance
- Does not appear to reduce relapse rates
- If not given for the entire first 2 months, total duration of therapy should be at least 9 months

First-line Anti-TB Drugs in Canada: Ethambutol (EMB)

- Least effective of the first-line drugs for bactericidal activity or prevention of relapse
- Included in the initial phase while results of drug susceptibility testing are pending; typically discontinued once isolate is confirmed to be fully susceptible (fully sensitive) and patient is tolerating treatment

Second-line Anti-TB Drugs in Canada

- **Fluoroquinolones (FQN):** highly efficacious for TB, taken orally, well tolerated. Used with drug resistance and/or intolerance to first-line anti-TB drugs.
- **Injectables:** e.g., streptomycin, amikacin, kanamycin, capreomycin

Potential Adverse Reactions to INH

- **Hepatotoxic:** risk increases with older age, daily alcohol consumption, pre-existing liver disease (particularly hepatitis C)
- **Peripheral neuropathy:** Vitamin B6 given to prevent
- **Rash, nausea, vomiting:** more likely with intermittent regimens and when RMP also used
- **Other:** Anemia, fatigue, drowsiness, headaches, mild hair loss, acne

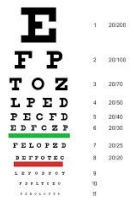
Potential Adverse Reactions to RMP

- **Hypersensitivity reactions:** rash, fever, abdominal pain, thrombocytopenia, hypotensive reaction
- **Drug interactions:** accelerates clearance of many drugs metabolized by the liver including estrogens (e.g., birth control), coumadin, anticonvulsants, methadone, digoxin
- **Hepatotoxic** when combined with other drugs – rarely hepatotoxic on its own

Potential Adverse Reactions to PZA

- **Hepatotoxic:** most common cause of drug-induced hepatotoxicity in patients on standard TB treatment
- **Arthralgias:** can be very painful but well-managed with non-steriodal anti-inflammatory drugs
- **Elevated serum uric acid levels:** gout is rare
- **Other:** GI upset

Potential Adverse Reactions to EMB



- **Visual impairment:** decreased visual acuity, visual fields or colour vision. Risk factors include: higher doses (e.g., 25 mg/kg) for extended periods, older age, renal impairment. **Monthly nursing assessment of visual acuity and red-green colour discrimination is recommended.**
- **Other:** rash

Summary of Most Common Adverse Reactions to Anti-TB Drugs

- Rash (any drug)
- GI intolerance (any drug)
- Hepatotoxicity (PZA, INH, RMP)
- Peripheral neuropathy (INH)
- Optic neuritis (EMB)
- Gout (PZA)

Monitoring During TB Treatment – 1. Adverse Events

- Recognition of adverse drug reactions is an essential part of the treatment program for providers **AND** patients
- Follow recommendations for baseline and routine monitoring of liver enzymes and other values (e.g., CBC, platelets)
- Reinforce signs/symptoms of adverse drug reactions with patients frequently; ensure they know what to do if any develop

Anti-TB Drugs and Rash

- Can be caused by any anti-TB drug
- Mild itch or slight rash can usually be treated symptomatically without changing TB regimen
- Generalized rash might require intervention and possibly, changes to TB regimen
- Petechial rash suggests thrombocytopenia

Anti-TB Drugs and GI Intolerance

- Can be caused by many anti-TB drugs, particularly during first few weeks of treatment
- Symptoms can include nausea, vomiting, poor appetite, abdominal pain
- Can be symptoms of drug-related hepatitis; rule out (e.g., ALT/AST)
- If no hepatitis, consider changing dosing time, taking dose with food, taking dose at bedtime (if not on DOT) *Note: antacids can interfere with TB drug absorption!*

Anti-TB Drugs and Hepatotoxicity

- Elevations in AST/ALT are expected and common; the role of nurse is to identify and bring forward to physician for management
- Drug-induced hepatotoxicity can be caused by PZA, INH or RMP (in that order)
- Symptoms can be non-specific; feeling "unwell" could be the first indication. Others:
  - GI intolerance (nausea, vomiting, poor appetite, abdominal pain)
  - Jaundice

Management of Potential Adverse Events

Adverse events can be complicated to confirm and to manage; assessment by a physician at an outpatient TB clinic or by the patient's private physician should be sought when signs or symptoms suggestive of an adverse event are identified.

Monitoring During TB Treatment – 2. Response to Treatment

- Response to treatment should be monitored clinically (e.g., reduced signs/symptoms), radiographically, and microbiologically
- To assess response to therapy and contagiousness, AFB smear positive cases should submit sputum specimens regularly until smear converts to negative

Monitoring During TB Treatment – 2. Response to Treatment

- Sputum should be cultured at end of second month of treatment (to assess risk of relapse) and at completion of therapy (proof of cure)
- Chest radiography (X-ray) should be done after 2 months and 6 months of treatment to assess response, potential complications and risk of relapse
- Additional and/or more frequent monitoring might be recommended for some cases

What is Drug Resistant TB Disease?

TB disease caused by an organism that is resistant to one or more of the first-line anti-TB drugs: isoniazid, rifampin, pyrazinamide, and ethambutol.

What is the Impact of Drug Resistance on Treatment of LTBI or TB Disease?

- Impact varies according to which drug or drugs the organism is resistant to and what role(s) the drugs play in the treatment regimen
- LTBI is generally treated with INH, therefore if the organism is INH-resistant, treatment might not prevent development of TB disease
- Treatment of DR-TB can be complex, lengthy, poorly tolerated, and very expensive

What Can be Done to Prevent Drug Resistant TB Disease?

- Prompt detection, isolation and treatment of all contagious cases (reduces transmission)
- Drug susceptibility testing of all laboratory-confirmed cases, leads to…
- Appropriate treatment regimens (appropriate drugs, dosing, duration)
- Directly observed treatment programs support adherence to anti-TB medications

What is Directly Observed Treatment?

In its simplest form, directly observed treatment (DOT) involves watching the patient swallow **each dose** of medication.

How Does DOT Contribute to TB Care?

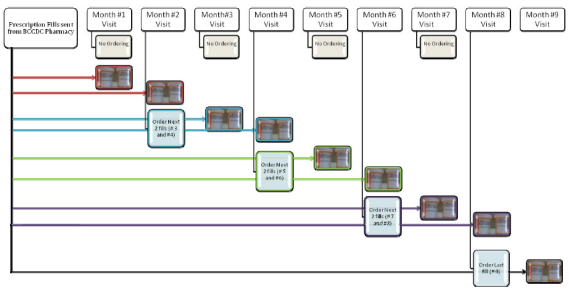
In addition to supporting adherence to TB treatment, comprehensive DOT programs can also provide opportunities for:

- More frequent monitoring for adverse events
- Educating clients about TB and their treatment
- Improving contact investigations, e.g., by identifying individuals and transmission locations that might have been missed

When Should DOT be Considered?

- Clients with drug-resistant TB disease
- Clients with treatment failure or documented relapsed disease
- Populations with previously documented high rates of non-completion
- Children and adolescents

Ordering Anti-TB Medications – LTBI Example



Note: Although 2 months of medications are supplied with each pharmacy refill, clients should be monitored for adverse events and adherence each month.