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|  <p>Winnipeg Regional Health Authority Office régional de la santé de Winnipeg Caring for Health À l'écoute de notre santé</p> <p>PRIMARY CARE PRACTICE GUIDELINES</p> | <p>Practice Guideline: Process for monitoring INH administration in adults being treated for LTBI (ADULT)</p> | <p>Guideline Number: <i>PCPG # 15</i></p> |
| | <p>Approved By: Primary Care Management Team</p> | <p>Pages: <i>1 of 6</i></p> |
| | <p>Approval Date: March 17, 2015</p> | <p>Supersedes: <i>New</i></p> |

INTENT

- To provide clinical practice and operational guidance to Primary Care clinical teams to ensure consistency in the monitoring of INH administration for the treatment of latent tuberculosis infection (LTBI) in adults.
- To provide the minimum recommended clinical and laboratory monitoring (including in rural and/or remote communities) needed to treat INH for LTBI, as well as recommended actions when INH liver toxicity is suspected or confirmed.

DEFINITIONS

Active TB disease: active clinical disease due to *Mycobacterium tuberculosis* (MTb) that is usually symptomatic and for which microbiologic tests are usually positive and radiologic tests usually abnormal.

Latent tuberculosis infection (LTBI): the presence of latent or dormant infection with MTb. Persons with LTBI have no evidence of clinically active TB disease, i.e. they have no symptoms, no evidence of radiologic changes that suggest active TB disease and negative microbiologic tests; they are not infectious.

INH: isoniazid (INH) is an anti-tuberculosis antibiotic that is used in combination with other anti-TB medications to treat active TB disease; but can also be used alone to treat latent tuberculosis infection (LTBI). A course of INH taken once daily (or 2 to 3 times weekly) for 6 to 9 months is used to treat LTBI.


Nursing Station: a field unit/facility staffed (primarily with nurses but may also include visiting physicians, dentist, mental health counsellor, physiotherapist, pediatrician and other specialties) in order to carry out community and primary health care programs including: out-patient treatment and short-term in-patient care, public health services, chronic disease management, acute and emergency care.

Primary Care Provider: a provider who is specialized in latent Tuberculosis and legally authorized to order and receive results of tests, and are able to prescribe medication, in this instance Physicians and Nurse Practitioners. They must also receive Latent Tuberculosis education and training through WRHA Integrated Tuberculosis Services. The Primary Care Provider is ultimately responsible to initiate baseline and follow up testing, monitoring and adjusting INH labs and medication doses.

Primary Care Nurses: role may include follow up with tracking of lab results, review them, and alert the prescriber to abnormal results.

Clinical Support Staff: unregulated health care workers, e.g., Primary Care Assistants, Unit Assistants, Nursing Assistants or Medical Office Assistants, or equivalent role.

Individual: refers to Patient and / or Client

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BACKGROUND


- The Canadian TB Standards (7th edition) provide recommendations for the monitoring of liver enzymes during administration of 9-month INH treatment courses for the management of LTBI (Chapter 6 – page 49A-50A). These recommendations are admittedly based on “very weak evidence” as there is little to no published data to guide the monitoring of liver enzyme tests during the administration of INH.
- The Canadian TB Standards recommendations are based on the ready availability of monthly medical evaluations and do not take into account INH monitoring challenges in remote communities.
- The LTBI Committee of WRHA Integrated TB Services have made slightly modified recommendations (informed by the CTS 7th ed) for the baseline and follow up monitoring of liver enzymes during the administration of INH to treat LTBI.
- Baseline ALT testing is recommended for everyone (regardless of age) being started on INH. During the 9-month course of INH therapy, monthly testing of ALT is recommended for all persons over the age of 35 years and/or with other risk factors regardless of age (including pregnancy or first 3 months postpartum, daily alcohol consumption, or concomitant treatment with other hepatotoxic drugs, chronic liver disease, or baseline elevation of ALT to >2X upper limit of normal [ULN]).

GUIDELINE

1.0 PROCEDURE (Monitoring Liver Enzymes)


1.1 Baseline testing:

- 1.1.1 Baseline alanine aminotransferase (ALT) testing is recommended for everyone being started on INH for LTBI treatment. Nursing Station staff or Primary Care Providers should ensure that this baseline testing has been performed.
- 1.1.2 Bilirubin testing is optional and may be considered based on clinical suspicion of underlying liver disease and/or age >50 years. Some Nursing Station staff or Primary Care Providers may also order baseline bilirubin testing based on the remoteness of the community and desire for additional baseline results.

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1.2 Follow up testing:

- 1.2.1 During the course of INH therapy for LTBI, monthly testing of liver enzymes (minimally an ALT; bilirubin is optional) is recommended for all persons over the age of 35 years.
- 1.2.2 Monthly ALT (bilirubin optional) testing is also recommended for persons with other “liver” risk factors regardless of age, including pregnancy or first 3 months postpartum, daily alcohol consumption, or concomitant treatment with other hepatotoxic drugs, chronic liver disease, or baseline elevation of ALT to >2X ULN.
- 1.2.3 Some Primary Care Providers may choose to order monthly ALT (and possibly bilirubin) based on the remoteness of the community and desire for additional monitoring.
- 1.2.4 Nursing Station staff and Primary Care clinic teams have a shared responsibility and should ensure that all follow up monthly ALT (and bilirubin if ordered) testing is performed, in addition to a monthly clinical assessment of each person taking INH for LTBI.
- 1.2.5 Clinic team communication is expected between the LTBI prescribing Physician/Nurse Practitioner, Nursing Station Nurses / Primary Care Nurses and Clinic Support Staff to ensure role clarity for each aspect of Latent Tuberculosis follow- up and monitoring. Ensuring tests are done and consultations have occurred is a shared responsibility among: Primary Care Providers, other members of the clinical team such as Nurses, Clinical Support Staff and certain learners (Health Care Students, Residents); Laboratories, Diagnostic Imaging and Specialty Service Providers; and individuals. Efforts to follow-up on outstanding orders should be guided by clinical urgency and the principles of patient self-management and choice as per PCOG #30 Results Management: Outstanding Orders <http://home.wrha.mb.ca/prog/primarycare/files/PCOG30-ResultsMgt-OO.pdf>.
- 1.2.6 Clinical Support Staff are responsible for: manual tracking of letters, daily monitoring and management of the status of tracked orders, documenting relevant information in the report, and bringing items of concern to the attention of the Primary Care Provider. Additionally, Clinical Support Staff could be requested to ensure a monthly clinic appointment for assessment of each individual taking INH for LTBI. If the Primary Care Provider provides direction to Clinical Support Staff they will follow up with the individual (appointment reminders, following up to reschedule a missed appointment).
- 1.2.7 Monthly clinical assessment by Nursing Station Nurses or Primary Care Nurses consists of symptom review, with particular attention to symptoms associated with liver toxicity (fatigue, weakness, vague abdominal pain, right upper quadrant pain,

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anorexia, itching, easy bruising, yellow skin). Nursing Station or Primary Care Nurses are to notify the Primary Care Provider of any symptoms.

- 1.2.8 Any symptoms listed in 1.2.7 should lead to prompt review by the Primary Care Provider of laboratory results to ensure that symptoms are not due to liver enzyme elevations.


2.0 PROCEDURE (Responding to suspected INH liver toxicity)

2.1 ALT slightly elevated but less than 3 times upper limit of normal (ULN):

- 2.1.1 Continue INH.
- 2.1.2 Nursing Station staff or Primary Care Nurse could communicate results to the individual and Primary Care Provider to review whether the individual is at increased risk for INH liver injury (such as underlying chronic liver disease, other medications including acetaminophen or anti-epileptic medications, or heavy alcohol use).
- 2.1.3 Nursing Station staff or the Primary Care Provider is responsible to advise the Primary Care Nurse to encourage the individual to avoid or minimize use of acetaminophen or alcohol (as appropriate).
- 2.1.4 Nursing Station staff or Primary Care Provider is responsible for ordering the test to repeat liver enzymes in one week.

2.2 ALT elevated >3 times (but less than 5 times) ULN with no symptoms of liver toxicity:

- 2.2.1 Continue INH.
- 2.2.2 Nursing Station staff or Primary Care Nurse to communicate the results to the individual and monitors closely for symptoms of INH liver toxicity (see 1.2.7) and reports any symptoms to Primary Care Provider.
- 2.2.3 Nursing Station staff or Primary Care Provider is responsible to review whether the individual is at increased risk for INH liver injury (such as underlying chronic liver disease, other medications including acetaminophen or anti-epileptic medications, or heavy alcohol use).
- 2.2.4 Nursing Station staff or Primary Care Provider and Primary Care Nurse encourages the individual to avoid or minimize use of acetaminophen or alcohol (as appropriate).

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2.2.5 Nursing Station staff or Primary Care Provider is responsible to repeat liver enzymes in one week.

2.2.6 If becomes symptomatic, go to 2.3.

2.3 ALT elevated >3 times (but less than 5 times) ULN with symptoms of liver toxicity:

2.3.1 The Nursing Station staff or Primary Care Provider would give direction to stop the INH and complete the following:

2.3.1.1 Repeat ALT and obtain AST, total and direct bilirubin, INR, and albumin as soon as possible.

2.3.1.2 Follow liver enzymes every 5 to 7 days. If they elevate further to >5 times ULN or if direct bilirubin elevated, go to 2.4.

2.3.1.3 Continue to check liver enzymes weekly until back to normal. Nursing Station staff or Primary Care Provider would give direction to arrange appointment to review adverse reaction.

2.4 ALT elevated >5 times ULN (or doubling of ALT if INH started with baseline elevation of ALT, or elevation in direct bilirubin):

2.4.1 Nursing Station staff or Primary Care Provider would give direction to stop the INH and complete the following:

2.4.1.1 If has symptoms of liver toxicity, an urgent clinical evaluation is warranted. If clinically unwell with multiple symptoms or if jaundiced, notify Primary Care Provider immediately and consider hospitalization to expedite further evaluation.


2.4.1.2 If no symptoms, repeat ALT and obtain AST, alkaline phosphatase, GGT, total and direct bilirubin, INR, and albumin as soon as possible.

2.4.1.3 If no symptoms, but direct bilirubin or INR are elevated, notify Primary Care Provider and consider hospitalization to expedite further evaluation including hepatic ultrasound (to exclude other causes of liver toxicity – see 2.4.1.4).

2.4.1.4 Consider other causes of liver toxicity including acute viral hepatitis (HAV, HBV, HCV), other medications (acetaminophen), and obstructive jaundice (galls stones).

2.4.1.5 If no symptoms and direct bilirubin and INR are normal, follow liver enzymes every 5 to 7 days until results return to normal (which may take a few weeks).

2.4.2 When ALT <2 times ULN, Primary Care Provider may restart INH and repeat ALT on day 3 and day 7 of re-challenge to make sure that ALT is not rising again. If ALT rises again, and more than 4 months of INH is needed to complete LTBI therapy, then it would be faster (and safer if no other drug interactions) to give rifampin 600 mg daily x4 months.

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- 2.4.3 If liver enzymes elevate further or fail to normalize, Primary Care Provider should consider consultation with hepatologist.

SCOPE: Applicable exclusively to WRHA Primary Care Direct Operations Clinics (Access Downtown) and can be adopted by the Community Health Agencies (Klinik), who provide Adult treatment for Latent TB Infection (either twice weekly Directly Observed Therapy or daily self-administered therapy), by Latent TB clinicians who work in collaboration with the WRHA Population and Public Health Program TB team and First Nations and Inuit Health Branch.

Consultation Process: Integrated Tuberculosis Services: TB Identification Committee, LTBI Committee, ITBS Management Committee & ITBS Oversight Committee

SOURCE/REFERENCES

1. Public Health Agency of Canada (2014) *Canadian Tuberculosis Standards 7th ed.*

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