

Treatment with Isoniazid or Rifampin for Latent Tuberculosis Infection: Population-Based Study
of Hepatotoxicity, Completion, and Costs

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Appendix Table S1: ICD9/10 Diagnostic Codes and American Hospital Formulary Code used for identifying baseline TB-related risk factors, psychiatric diagnosis, and severe hepatic adverse events in RAMQ

| ICD9 /ICD10/AHFS/DIN/CCI/CCP codes * | Description |
|--|---|
| 140-172, 174-195.8, 200-208, 238.6, C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97 | Cancer (malignant neoplasms)† |
| 250, E10-E14 | Diabetes† |
| 042-044, V08, B20-B22, B24, Z21, AHF=81808 | HIV/AIDS† |
| 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583, 585-586, 588, V42.0, V45.1, V56.1, I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18, N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2 | Renal Disease† |
| V42.0,V 42.1, V42.6, V42.7, V42.81,V42.83, V42.84, Z94.0-Z94.4, Z94.6, Z94.8 | Solid organ (liver, kidney, heart, lung, pancreas, intestine) or bone marrow transplant |
| 502, J62 | Silicosis |
| DIN= 2242903,2274728,2258595,2244016 | Treatment with TNF-alpha inhibitors |
| 290-319, F10-F19 | Psychiatric diagnosis |
| 456.0-456.21, 572.2-572.8, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K71.9, K76.5, K76.6, K76.7 | Liver disease† |
| Hepatic necrosis (570, <i>K71.1</i>), toxic hepatitis (573.3, <i>K71.2</i> , <i>K71.6</i> , <i>K71.9</i>), hepatic encephalopathy (572.2, <i>K72.0</i> , <i>K72.9</i>), liver transplant (CCP=6249; CCI=1OA85) | Hepatotoxicity† |
| Leprosy (030, A30); osteomyelitis (730, M86); brucellosis (023, A23); multidrug resistant <i>Staphylococcus aureus</i> -MRSA (041.11, 014.12, 038.12, 482.42, A49.0, B95.6, A41.0, G00.3, P36.2, Z22.3, J15.2, L00, P23.2) | Other longer-term RIF indications |

*AHFS=American Hospital Formulary Service; DIN=Health Canada Drug Identification Number; CCI=Canadian Classification of Health Interventions; CCP=Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures

†derived from Quan adaptation of the Charlson-Deyo score ²²

‡ derived from Myers (2007)¹⁶

Appendix Table S2: Summary of direct cost data sources and inputs*

| Health service use type | Unit costs | Data source |
|-------------------------|--------------|---|
| Hospitalization | \$1390 | Per diem inpatient room rate (regular ward) at MUHC hospitals for Quebec resident patients ¹⁷ |
| ED visit | \$183.08 | Hospital billing rate for Quebec resident patients, ambulatory urgent care ¹⁸ |
| Day procedure | \$183.08 | Hospital billing rate for Quebec resident patients, minor day surgery in operating room ¹⁸ |
| Physician visit | Exact values | Actual billed costs paid by RAMQ |
| Drugs dispensed | Exact values | Actual billed costs paid by RAMQ, including drug cost and pharmacist dispensing fee, minus deductible and co-pay paid by patients |

* Costs reported in 2011 Canadian dollars (rounded to the nearest dollar). Actual billed costs used for physician billing and drugs dispensed, adjusted to 2011 dollars using the Consumer Price Index (<https://www.bankofcanada.ca/rates/related/inflation-calculator/>). MUHC=McGill University Health Centre

Appendix Table S3: Charlson-Deyo Comorbidity Index, Quan Adaptation (ICD9 and ICD10)

| ICD-9/ ICD-10 Codes | Description | Weight |
|---|---|---------------|
| 410.x, 412.x, I21.x, I22.x, I25.2 | Myocardial Infarction | 1 |
| 428.x, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0 | Congestive heart failure | 1 |
| 443.9, 441.x, 785.4, V43.4, I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9 | Peripheral vascular disease | 1 |
| 430.x-438.x, G45.x, G46.x, H34.0, 160.x-169.x | Cerebrovascular disease | 1 |
| 290.x, F00.x-F03.x, F05.1, G30.x, G31.1 | Dementia | 1 |
| 490.x-505.x, 506.x, 127.8, 127.9, J04.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3 | Chronic pulmonary disease | 1 |
| 710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725.x, M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0 | Rheumatic disease | 1 |
| 531.x-534.x | Peptic ulcer disease | 1 |
| 571.2, 571.4-571.6, B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.2-K76.4, K76.8, K76.9, Z94.4 | Mild liver disease | 1 |
| 250.0-250.3, 250.7, E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 | Diabetes without chronic complication | 1 |
| 250.4-250.6, E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7 | Diabetes with chronic complication | 2 |
| 344.1, 342.x, G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9 | Hemiplegia or paraplegia | 2 |
| 582.x, 583.x-583.7, 585.x, 586.x, 588.x, I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N26.0, Z49.0-Z49.2, Z94.0, Z99.2 | Renal disease | 2 |
| 140.x-172.x, 174.x-195.8, 200.x-208.x, C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x | Any malignancy, including leukemia and lymphoma | 2 |
| 456.0-456.21, 572.2-572.8, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K71.9, K76.5, K76.6, K76.7 | Moderate or severe liver disease | 2 |
| 196.x-199.1, C77.x-C80.x | Metastatic solid tumor | 3 |
| 042.x-044.x, B20.x, B22.x, B24.x | HIV/AIDS | 6 |

Source: Quan et al ²²

Appendix Table S4: Summary of Severe Hepatic Adverse Events, Quebec, 2003-2007

| | Relevant hospital diagnosis or intervention | Diag type* | Hospital dates (in, out) | Primary diagnosis; interventions | Drug | Last drug day | Switch day | Death day | SAE | SAE+ transplant† | SAE+ death† |
|----|---|------------|--------------------------|---|------|---------------|----------------|-----------|---------|------------------|-------------|
| 1 | Toxic hepatitis | P | 202, 216 | Toxic hepatitis | H | 204 | - | - | Hepatic | - | - |
| 2 | Toxic hepatitis | P | 22, 34 | Toxic hepatitis | H | 30 | - | - | Hepatic | - | - |
| 3 | Toxic hepatitis | P | 33, 36 | Toxic hepatitis | H | 30 | 30 | - | Hepatic | - | - |
| 4 | Toxic hepatitis | P | 59, 63 | Toxic hepatitis | H | 58 | - | - | Hepatic | - | - |
| 5 | Toxic hepatitis | P | 106, 145 | Toxic hepatitis, Liver transplant | H | 61 | - | - | Hepatic | Yes | - |
| 6 | Toxic hepatitis | P | 124, 130 | Toxic hepatitis | H | 127 | - | - | Hepatic | - | - |
| 7 | Toxic hepatitis | P | 266, 298 | Acute hepatic failure (S); Sepsis (death) | H | 247 | | 298 | Hepatic | - | Yes |
| 8 | Toxic hepatitis | P | 134, 147 | Toxic hepatitis | H | 135 | - | - | Hepatic | - | - |
| 9 | Toxic hepatitis | S | 108, 112 | Pulmonary eosinophilia (P) | H | 90 | | | Hepatic | - | - |
| 10 | Toxic hepatitis | S | 226, 253 | Epilepsy NOS | H | 236 | - | - | Hepatic | - | - |
| 11 | Toxic hepatitis | P | 24, 28 & 117, 186 | Poisoning by anti-mycobacterials (S) | H | 30 | - | - | Hepatic | - | - |
| 12 | Toxic hepatitis | S | 63, 85 | Poisoning by anti-mycobacterials (P) | H | 90 | - | - | Hepatic | - | - |
| 13 | Toxic hepatitis | S | 31, 39 | Poisoning by anti-mycobacterials (S) | R | 56 | - | - | Hepatic | - | - |
| 14 | Toxic hepatitis | P | 91, 205 | Liver transplant | H | 30 | Start R at 202 | - | Hepatic | Yes | - |
| 15 | Toxic hepatitis | P | 169, 173 | Poisoning by anti-mycobacterials (S) | H | 180 | - | - | Hepatic | - | - |
| 16 | Toxic hepatitis | S | 313, 320 | Poisoning by anti-mycobacterials (P) | H | 330 | - | - | Hepatic | | |

*P=primary; A=acute; S=secondary; H=Isoniazid; R=Rifampin

†The five-year age ranges of the two patients who underwent transplants were 20-24 years and 50-54 years, and the patient who died had an age range of 45-49 years

Appendix Table S5: Sensitivity analyses of relative risk estimates of LTBI treatment completion (INH vs RMP), Quebec, 2003-2007 (n=10,559)

| Measures of LTBI treatment completion | | Patients completing treatment n | % (95% CI) |
|---|------|------------------------------------|------------|
| <u>Dispensed 100% of doses, on-time (primary analysis)</u> | | | |
| 4RMP (120 doses/6 months) | 468 | 53.5 (50.2-56.8) | |
| 9INH (270 doses/12 months) | 3570 | 36.9 (35.9-37.8) | |
| 4RMP:9INH, RR (95% CI) | | 1.5 (1.3-1.7)* | |
| <u>Dispensed 100% of doses, ever (sensitivity analysis #1)</u> | | | |
| 4RMP (120 doses) | 488 | 55.7 (52.4-59.0) | |
| 9INH (270 doses) | 3796 | 39.2 (38.2-40.2) | |
| 4RMP:9INH, RR (95% CI) | | 1.5 (1.3-1.7)* | |
| <u>Dispensed 100% of doses, ever, and including hospitalizations with discharge within 15 days before index date or admission within 30 days after last drug dispensation date as LTBI treatment days (sensitivity analysis #2) †</u> | | | |
| 4RMP (120 doses) | 492 | 56.2 (52.9-59.5) | |
| 9INH (270 doses) | 3825 | 39.5 (38.5-40.5) | |
| 4RMP:9INH, RR (95% CI) | | 1.5 (1.3-1.7)* | |
| <u>Dispensed 100% of doses, on-time, excluding patients with hospitalizations with discharge within 15 days before index date, or admission within 30 days after last drug dispensation date (sensitivity analysis #3)</u> | | | |
| 4RMP (120 doses/6 months) | 446 | 61.6 (58.1-65.2) | |
| 9INH (270 doses/12 months) | 3359 | 37.1 (36.1-38.1) | |
| 4RMP:9INH, RR (95% CI) | | 1.7 (1.5-1.9)* | |
| <u>Dispensed 100% of doses, on-time, excluding patients with switches between LTBI regimens (sensitivity analysis #4)</u> | | | |
| 4RMP (120 doses/6 months) | 471 | 54.6 (51.3-58.0) | |
| 9INH (270 doses/12 months) | 3576 | 38.5 (37.5-39.5) | |
| 4RMP:9INH, RR (95% CI) | | 1.5 (1.3-1.8)* | |

Abbreviations: RR= risk ratio, CI=confidence interval; RMP=rifampin, INH=isoniazid

* RR's and 95% CIs estimated using log-binomial regression with GEE methods to account for clustering of patients within physicians, adjusted for sex, age group, any Charlson co-morbidities, HIV, physician licensing, and hospitalization in the past year