

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Therapeutic Substitution of Drugs for the Treatment of Tuberculosis: Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to requests@cadth.ca

Research Questions

1. What are the evidence-based guidelines regarding the therapeutic substitution of different drugs for the treatment of tuberculosis when there is a shortage of, or limited access to, the first line treatment?
2. What are the evidence-based guidelines regarding the therapeutic substitution of different drugs for the treatment of tuberculosis when there is an intolerance of the first line treatment?
3. What are the evidence-based guidelines regarding the therapeutic substitution of different drugs for the treatment of tuberculosis when there is resistance to one of the drugs in the first line treatment?

Key Findings

Three evidence-based guidelines were identified regarding the therapeutic substitution of different drugs for the treatment of tuberculosis when there is resistance to one of the drugs in the first line treatment. No relevant evidence-based guidelines were identified regarding the therapeutic substitution of different drugs for the treatment of tuberculosis when there is a shortage or intolerance of the first line treatment

Methods

A limited literature search was conducted by an information specialist on key resources including Medline via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were tuberculosis and second-line therapy. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and guidelines. The search was also limited to English language documents published between Jan 1, 2010 and Jun 10, 2020. Internet links were provided, where available.

This report is a component of a larger CADTH Condition Level Review on tuberculosis. A condition level review is an assessment that incorporates all aspects of a condition, from prevention, detection, treatment, and management. For more information on CADTH’s Condition Level Review of tuberculosis, please visit the project page (<https://www.cadth.ca/tuberculosis>).

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	People receiving drug treatment for active or latent tuberculosis
Interventions	First-line drug treatments for tuberculosis
Comparators	Second-line or substituted drug treatment for tuberculosis

Outcomes	Recommendations (e.g., which drug(s) can be substituted for each other in tuberculosis treatment regimens in the case of shortage, intolerance, or single drug resistance)
Study Designs	Health technology assessments, systematic reviews, evidence-based guidelines

Results

Three evidence-based guidelines¹⁻³ were identified regarding the therapeutic substitution of different drugs for the treatment of tuberculosis (TB) when there is resistance to one of the drugs in the first line treatment. No relevant evidence-based guidelines were identified regarding the therapeutic substitution of different drugs for the treatment of TB when there is a shortage or intolerance of the first line treatment. No relevant health technology assessments or systematic reviews of guidelines were identified.

References of potential interest that did not meet the inclusion criteria are provided in the appendix.

Overall Summary of Findings

Three evidence-based guidelines¹⁻³ were identified regarding the therapeutic substitution of different drugs for the treatment of TB when there is resistance to one of the drugs in the first line treatment. All three guidelines recommended drug substitutions in the case of single drug resistance to isoniazid.¹⁻³ A summary of relevant recommendations is provided in Table 2.

No relevant guidelines were found regarding the therapeutic substitution of different drugs for the treatment of TB when there is a shortage or intolerance of the first line treatment; therefore, no summary can be provided.

Table 2: Summary of Relevant Recommendations

Summary of Recommendations	
American Thoracic Society, 2019 ¹	
<ul style="list-style-type: none"> Pyrazinamide should be included in the treatment regimen of patients with isoniazid-resistant TB (page e96). (conditional recommendation, very low certainty in the evidence) 	
World Health Organization, 2019 ²	
<ul style="list-style-type: none"> Patients with isoniazid-resistant TB should be treated with rifampicin, ethambutol, pyrazinamide, and levofloxacin for six months (page 9). (conditional recommendation, very low certainty in the estimates of effect) Patients with isoniazid-resistant TB should not be treated with streptomycin or other injectable agents (page 9). (conditional recommendation, very low certainty in the estimates of effect) 	
Public Health Agency of Canada, 2014 ³	
<ul style="list-style-type: none"> Isoniazid can be substituted with moxifloxacin or levofloxacin in the treatment regimen of patients with isoniazid-resistant TB (page 14). (strong recommendation, moderate evidence) 	

TB = tuberculosis

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Guidelines and Recommendations

1. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis: an official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Care Med*. 2019;200(1):e93-e142. <https://www.atsjournals.org/doi/pdf/10.1164/rccm.201909-1874ST>. Accessed 2020 Jun 24.
See: Summary of recommendations, Recommendation #11, page e96
2. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva (CH): World Health Organization; 2019:
<https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1>. Accessed 2020 Jun 24.
See: Current policy recommendations on treatment and care for DR-TB, Regimens for isoniazid-resistant tuberculosis (Hr-TB), page 9
3. Canadian Tuberculosis standards, Chapter 8: drug-resistant Tuberculosis. Ottawa (ON): Public Health Agency of Canada; 2014:
<https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/tbpc-latb/pubs/tb-canada-7/assets/pdf/tb-standards-tb-normes-ch8-eng.pdf>. Accessed 2020 Jun 24.
See: Management of Drug-Resistant TB, Resistance to INH With Or Without Resistance To SM, page 14

Appendix — Further Information

Previous CADTH Reports

4. Treatment of Tuberculosis: a review of guidelines (*CADTH Rapid response report: summary with critical appraisal*). Ottawa (ON): CADTH; 2020:
<https://www.cadth.ca/treatment-tuberculosis-review-guidelines>. Accessed 2020 Jun 24.

Clinical Practice Guidelines – Unclear Methodology

5. Caminero JA, Garcia-Garcia JM, Cayla JA, Garcia-Perez FJ, Palacios JJ, Ruiz-Manzano J. Update of SEPAR guideline <<diagnosis and treatment of drug-resistant Tuberculosis>>. *Arch Bronconeumol*. 2020;S0300-2896(20)30101-0.
[PubMed: PM32446667](#)
6. Clinical guidelines & standard operating procedure for the implementation of the short & long DR-TB regimens for adults, adolescents and children. Cape Town (ZA): Western Cape Government; 2018:
https://www.westerncape.gov.za/assets/departments/health/tuberculosis_-_dr_tb_clinical_guidelines_2018.pdf. Accessed 2020 Jun 24.

Review Articles

7. Pranger AD, van der Werf TS, Kosterink JGW, Alffenaar JWC. The role of fluoroquinolones in the treatment of Tuberculosis in 2019. *Drugs*. 2019;79(2):161–171.
[PubMed: PM30617959](#)
8. Chang KC, Yew WW, Sotgiu G. Clinical research in the treatment of tuberculosis: current status and future prospects. *Int J Tuberc Lung Dis*. 2015;19(12):1417-1427.
[PubMed: PM26614181](#)
9. Conde MB, Lapa ESJR. New regimens for reducing the duration of the treatment of drug-susceptible pulmonary tuberculosis. *Drug Dev*. 2011;72(6):501-508.
[PubMed: PM22267888](#)

Additional References

10. Halton Region. Tuberculosis drug shortage. 2020:
<https://www.halton.ca/getmedia/bb38db57-de3c-459e-84df-26c89b6ff689/HE-efax-20-04-09-tuberculosis-drug-shortage.aspx>. Accessed 2020 Jun 24.
11. National shortage of rifampin. Mississauga (ON): Region of Peel; 2019:
<https://www.peelregion.ca/health/professionals/tools/updates2019/2019-07-16-hpu-vol-12-no-22.pdf>. Accessed 2020 Jun 24.
See: Alternatives to Rifampin for LTBI treatment
12. York Region. Ontario rifampin shortage ends: alternative treatment resources available, update to York Region health care providers as of August 30, 2019;
https://www.york.ca/wps/wcm/connect/yorkpublic/e64e8352-b2d5-4441-ad50-2b035a473072/Rifampin_shortage_endsAug_2019.pdf?MOD=AJPERES&CVID=mPzVw7D. Accessed 2020 Jun 24.
See: Latent TB Infection Treatment Regimens, page 2

13. Chapter 6: treatment of Tuberculosis disease. In: *Core curriculum on Tuberculosis: what the clinician should know*. Atlanta (GA): Centers for Disease Control and Prevention; 2013: <https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf>. Accessed 2020 Jun 24.
See: Current Anti-TB Drugs, page 151