SYNOPSIS

Review of Update on the management of chronic hepatitis C: 2018 consensus guidelines from the Canadian Association for the Study of the Liver

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Key Messages of Synopsis

- Hepatitis C virus (HCV) has a high prevalence with national estimates of approximately 1% of the overall Canadian population being anti-HCV-positive, between 0.64% to 0.71% living with chronic HCV infection, and approximately 44% of those living with chronic HCV infection remaining undiagnosed.¹
- Risk-factor based screening is universally recommended to identify undiagnosed infection in those at elevated risk of HCV. Recent Canadian guidelines have disagreed in terms of whether birth cohort population-based screening for Baby Boomers should be added to risk-factor screening.
- The recent 2018 guideline from the Canadian Association for the Study of the Liver (CASL) by Shah et al, has recommended population-based screening for Baby-Boomers in addition to risk-factor based screening to address the burden of illness and under-diagnosis in this age cohort.²
- This synopsis is a summary and critical appraisal of the strengths and limitations of the Baby-Boomer screening recommendation by Shah et al.
Background on HCV Screening

There are approximately 3,500 newly reported cases of HCV annually in Ontario, and in a 2010 burden of illness report, it was the highest burden reportable infectious agent in Ontario based on potential years of life lost. National estimates by the Public Health Agency of Canada (PHAC), using a back-calculation methodology, estimated that 0.64% to 0.71% of the Canadian population has chronic HCV, and this was highest among those born between 1955-1959 (1.5%), followed by those born in 1950-1954 (1.25%). The same model estimated that 44% of those with chronic HCV were unaware of their infection. Early identification of HCV exposure and current infectious status through testing for HCV RNA are necessary steps to ensure timely engagement in care and treatment in order to prevent long-term complications (such as cirrhosis, liver cancer and death) and to reduce the risk of transmission to others. In recent years, treatment options, such as direct acting antivirals (DAAs), have become highly effective as well as safer and more tolerable, affordable and accessible.

In 2018, the Canadian Association for the Study of the Liver (CASL) published guidelines on the management of chronic hepatitis C which recommended population-based screening for those born between 1945-1975 in addition to risk-factor based screening. Public Health Ontario’s (PHOs) objective was to conduct a critical appraisal of the population-based screening recommendation included in the guideline, including both the published manuscript and the online Appendix. It should be noted the CASL guideline also addressed treatment recommendations which are not covered in this synopsis.

In addition to the CASL guideline, there have been a number of other recent relevant guidelines from Canadian jurisdictions regarding HCV screening, including the following:

- Nationally, the Public Health Agency of Canada recommends screening individuals for hepatitis C using a risk-based approach.
  - This recommendation is based on the 2017 Canadian Task Force on Preventive Health Care recommendation against screening for hepatitis C in asymptomatic Canadian adults unless they are at risk for hepatitis C infection (strong recommendation, very low quality evidence).
- The 2016 Canadian Liver Foundation’s Hepatitis C Screening and Testing Quick Reference Guide included a recommendation for birth cohort screening of all adults born between 1945-1975. This Guide is an infographic listed in the Clinical Practice Guidelines section of the Canadian Liver Foundation’s website. It does not describe the basis of this recommendation or have a reference to a guideline on which this recommendation is based.
- A 2017 guideline from Quebec did not find the data to be sufficiently compelling to justify a systematic screening program for those born between 1950 to 1969, but recommended considering offering one-time opportunistic screening of those born between 1950 and 1969 regardless of other risk factors.
Summary of 2018 CASL Guideline

The CASL recommendation under ‘screening and linkage to care’ was:

To increase the identification of the large proportion of persons living with undiagnosed HCV, we recommend that screening be both risk-based and target the birth cohort of individuals born from 1945 to 1975, which currently encompasses the majority of persons chronically infected with HCV in Canada. (Class 2a – weight of evidence or opinion is in favour of usefulness or efficacy, Level C – only consensus opinions of experts, case studies, or standard of care).

The online Appendix version of the recommendation is similar except that the birth cohort years included are from 1945 to 1970.

The authors listed four reasons for supporting birth cohort screening:

1. HCV prevalence is highest in the Baby Boomer birth cohort and that the burden of liver disease is expected to increase in this population. Supporting evidence for this statement included an Ontario laboratory serosurvey study and a national modeling estimate study.
   - The Ontario study was a serosurvey of laboratory samples of individuals born between 1945 and 1974 where seroprevalence rates, based on anti-HCV antibodies, were highest in those born between 1950-54 and 1960-64 (1.98% each), followed by those born in 1955-1959 (1.80%), 1965-1969 (1.38%), 1970-74 (1.14%) and 1945-1950 (1.02%).
   - The PHAC modeling study estimated chronic HCV prevalence in Canada between 1991 and 2011. Based on estimates for 2011, they found that those born between 1955 and 1959 had the highest prevalence of chronic HCV (1.5%), followed by those born in 1950-54 (1.25%), 1960-64 (1.2%), 1965-69 (1.1%) and 1970-74 (0.8%).

2. Approximately 44-70% of HCV-infected Canadians are unaware of their infection. Supporting evidence for this statement includes two studies.
   - The upper estimate (70%) is based on an analysis from the 2007-2009 and 2009-2011 Canadian Health Measures Survey comparing seroprevalence of anti-HCV antibody to participant’s (14-79 years old) awareness of their infection status, and found that 69.5% (95%CI: 49.3% to 84.3%) were unaware of their infection.
   - The lower estimate (44%) is a based on the PHAC modeling estimate described above.
   - The CASL recommendation also noted that risk-based strategies perpetuate stigma associated with HCV, whereas population-based screening normalizes the process.
3. New lowered pricing for HCV treatment makes screen-and-treat strategies even more cost-effective than previously estimated.

   - Previous cost-effectiveness estimates include a 2015 Canadian study that concluded “in Canada, a 1-time program to screen for and treat HCV infection, aimed at birth cohort populations (25-64 years or 45-64 years of age) is likely to be cost-effective.”\textsuperscript{10} The ages for one-time screening in this cost-effectiveness analysis translate into birth cohorts of 1951-1990 or 1951-1971.

4. Canada will not meet World Health Organization 2030 HCV elimination targets without birth cohort screening.

The authors also listed five rebuttals to the 2017 CTFPHC Guideline that recommended against Baby Boomer screening, indicating that in the CTFPHC Guideline document:

   I. There was an overemphasis on harms of screening
   II. Benefits of screening were under-valued
   III. Costs of therapy used were inaccurate and misleading, and included mention of outdated treatment regimens
   IV. Costs of no therapy for patients with HCV were not included
   V. Concerns about the diagnostic accuracy of HCV testing are inaccurate and outdated

Study Methodological Rigour and Transparency

Two PHO reviewers assessed the CASL population-based screening recommendation using a modified approach to the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument. The recommendation was assessed broadly within the six domains of the AGREE II instrument without assigning numeric scoring to each domain and without a numeric score to the overall assessment. The reviewers also did not provide a statement on whether they would recommend the use of this guideline. An overall assessment was determined based on the overall quality of the recommendation after consideration of the six domains; this assessment involves judgement by the reviewers and is subjective.\textsuperscript{11} The synopsis was reviewed by all contributors.

1. Scope and Purpose

   This guideline updates previous guidance from CASL published in 2015.\textsuperscript{12} The 2015 version of this guideline did not include specific screening recommendations, and the stated scope of the 2018 guideline document did not include making recommendations on screening.
The scope of the 2018 guideline was “to support clinical practice, it makes recommendations on the assessment, evaluation and management of HCV-infected persons.” The specific health question and target population of this guideline is the clinical management of HCV-infected persons. Nonetheless, the 2018 guideline documents do make screening recommendations for the Baby Boomer cohort.

2. Stakeholder Involvement

- Stakeholder input was received from nine CASL members including physicians and allied health workers.
- Persons with lived experience of HCV and persons who are born between 1945 and 1975 were not included in the guideline development or review.

3. Rigour of Development

- The primary section author reviewed the previous 2015 guideline, added the new recommendations and graded the evidence. The secondary author reviewed the recommendations and supporting evidence and disagreements were resolved by consensus.
- The entire guideline panel reviewed the recommendations with support from two-thirds of the members required for recommendation inclusion and grading. The panel used the same grading system (class of evidence levels 1-3 and grade of evidence A-C) as their 2015 recommendations.
- The literature review did not specifically include ‘screening’ as part of the search strategy. The results of the search strategy and the papers reviewed in developing the recommendation are not published in the manuscript or the Appendix.
- There is no description of critical appraisal tools used to assess the quality of studies included as supporting literature.
- The methods did not describe whether any established framework or methodology, such as procedures used by the CTFPHC, the United States Preventive Services Task Force, or Public Health England, was used in the process of developing this screening recommendation.

4. Clarity of Presentation

- There is inconsistency between the published manuscript and the online Appendix in terms of the birth cohort years included in the recommendation, and it is unclear which cohort
(1945-75 in the published manuscript vs. 1945-70 in the Appendix) is the intended/preferred option.

- There is inconsistency between the supporting literature for the HCV prevalence and cost-effectiveness and the recommendation in terms of the years chosen for inclusion as the Baby Boomer cohort.
  - In the referenced PHAC modeling study, the birth cohort between 1955 to 1979 had an increasing prevalence of chronic HCV from 1991 to 2011, whereas the birth cohort between 1945 to 1954 had a decreasing prevalence in that time frame. While the prevalence in the 1945 to 1954 cohort was still higher than the overall prevalence in the population, it is unclear how the authors of the CASL guideline assessed these declining trends in their determination of which cohorts to recommend for screening.
  - The guideline does not establish a specific chronic HCV prevalence threshold above which screening is considered cost-effective. Without a threshold to assess each five-year birth cohort within the 1945 to 1975 birth years, it is unclear why the entire 30 years range was included in the recommendation.

- The referenced 2015 Canadian cost-effectiveness study used a baseline scenario of screening in those born between 1951 and 1990 or 1951 and 1971. The guideline does not discuss the applicability of these results to their recommendation of the 1945 to 1975 birth cohort.

5. Applicability

- The two main supporting articles on population prevalence referenced by the CASL recommendation are based on national modeling estimates and Ontario seroprevalence. Because of the inclusion of Ontario data, these estimates have greater applicability to Ontario than to the rest of Canada.

- The article cited as the source for the upper end estimate of the undiagnosed fraction of HCV infected Canadians (70%) is based on a national survey from 2007 to 2011, and may not reflect more recent efforts to raise awareness and testing of HCV with the advent of new therapies.

- The cost-effectiveness study cited by the CASL recommendation likely had a higher cost per quality of life years saved than are expected to result from current cost-effectiveness analyses given recent decreases in HCV treatment pricing and improvement in outcomes associated with treatment.

- The authors of the CASL recommendation have not included feasibility considerations for the implementation of a one-time population-based birth cohort screening program, such as:
  - The clinical, social and ethical acceptability to patients and providers
6. **Editorial Independence**

- The guideline panel consisted of co-chairs appointed by the CASL Executive Committee and six selected panel members. Members of the guideline panel disclosed financial relationships with HCV treatment pharmaceutical companies and were not excluded from voting on recommendations.

- The authors declared that no funding, direct or in-kind, was provided to the guideline panel for the guideline development.

- CASL membership vetted the guideline for the presence of commercial bias. The financial relationships of the CASL members who vetted the guidelines were not included.

Overall, the main strength of the CASL recommendation for population-based screening is the authors’ identification of the high prevalence of chronic HCV in this population and the undiagnosed burden of illness. The authors also include important considerations of the new lower costs associated with treatment, new evidence on health benefits of treatment, and the potential for stigma associated with risk-based screening. The main limitation is the absence of a described methodological framework for guiding the development of this recommendation, and thereby to assess the validity of the recommendation. This also includes absence of a feasibility assessment for implementing population-based screening from which to assess applicability. There is a lack of clarity in application of findings from supporting literature and potential for bias based on stakeholder involvement and editorial independence. As such, the overall quality of this screening recommendation was assessed as relatively low.

**Ontario Applicability**

The treatment of HCV has been significantly improved with the advent of DAAs which are safe, better tolerated and highly effective treatment options. Ontario has recently updated the drug formulary such that DAA treatment is available to essentially all patients with chronic HCV infection.¹⁷

Interpretation of the recent recommendation to include population-based screening for HCV for those born between 1945 and 1975 should consider the strengths and limitations of this guideline recommendation and its applicability at the individual and population levels.
References


Synopsis: HCV screening recommendations


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