

The management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the Liver

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Chronic hepatitis C virus (HCV) is a highly burdensome public health problem in Canada, causing more years of life lost than any other infectious disease in the country.¹⁻³ A recent modelling study suggested that about 252 000 Canadians (uncertainty interval: 178 000–315 000 Canadians) were chronically infected in 2013. The birth cohort of 1945–1975 has the highest prevalence of chronic HCV infection, yet it is estimated that up to 70% of this group have not been tested for HCV.⁴

Although the overall prevalence of chronic hepatitis C is declining, complications of the disease are increasing because of aging of the infected population and progression of liver fibrosis.¹⁻³ Modelling data suggest that if nothing is done to change the current situation, cases of decompensated cirrhosis, hepatocellular carcinoma and liver-related mortality will increase by 80%, 205% and 160%, respectively, by 2035 compared with 2013 levels.²

The primary objective of anti-HCV therapy is complete eradication of the virus, termed a sustained virologic response, which is defined as absence of viremia 12 weeks after completion of therapy.⁵ Once achieved, sustained virologic response is considered a true cure of the viral infection, as late relapses are very uncommon.^{6,7} Sustained virologic response is associated with long-term health benefits that include improved quality of life^{8,9} and liver histology,^{10,11} and reduced incidence of hepatocellular carcinoma,¹² liver-related morbidity and mortality,¹³⁻¹⁵ and all-cause mortality.¹²

Since the last Canadian guideline on the management of chronic HCV infection from the Canadian Association for the Study of the Liver was published in 2015,¹⁶ there have been remarkable treatment advances. Thus, there was a need for an updated, evidence-based guideline.

Scope

This guideline was written to assist physicians and other health care professionals in the management of adult patients with chronic HCV infection. To support clinical practice, it makes rec-

KEY POINTS

- Hepatitis C is a major public health problem in Canada that is underdiagnosed and undertreated; birth cohort screening would benefit population health outcomes.
- Pretreatment evaluation of an infected patient should include clinical evaluation, viral load, genotype and a fibrosis stage assessment.
- The treatment of hepatitis C has become safer, better tolerated and more effective owing to the availability of direct-acting antivirals for nearly all patients; this guideline advocates against the use of any interferon-based treatment regimens and for the use of all-oral regimens for all infected patients.
- The treatment of infected patients should be individualized to maximize chance of success, especially for difficult-to-cure populations, including patients with renal failure, decompensated cirrhosis, and active substance use disorders.
- After treatment, the follow-up of successfully treated patients depends on whether they are cirrhotic; patients with cirrhosis require life-long surveillance for the development of hepatocellular cancer.

ommendations on the assessment, evaluation and management of HCV-infected persons. Treatment recommendations are given for specific patient populations divided by HCV genotype (and subtype), treatment history (naive or experienced) and the presence or absence of cirrhosis. Subpopulations with special considerations are discussed individually, including chronic kidney disease, decompensated cirrhosis, post-liver transplant, people who inject drugs and acute HCV infection. This guideline does not address HIV/HCV coinfection, and we refer readers to the existing Canadian guideline for this population.¹⁷

Methods

Guideline panel composition

The Executive Committee of the Canadian Association for the

Study of the Liver appointed two co-chairs of the guideline panel (H.S. and J.F.). The co-chairs selected six other members of the guideline panel based on their expertise in specific areas of HCV management, including hepatology, infectious disease, public health, clinical care, research and epidemiology.

Guideline development

Two panel members were assigned to each guideline section (epidemiology, screening, treatment indications and contraindications, pretreatment assessment, antiviral therapy [genotype 1 (G1) naive, G1 experienced, G2, G3, G4, G5/6], resistance, special populations [chronic kidney disease, decompensated cirrhosis, liver transplant, people who use drugs, acute HCV, direct-acting antiviral failures]), one to serve as the primary section author and the other as a secondary reviewer. A focused literature search for both published and unpublished literature was undertaken to update the evidence base used in the 2015 guideline. In brief, the literature search was conducted in MEDLINE (Jan. 15, 2015 to Oct. 31, 2016), using the following search terms: hepatitis C, hepatitis and treatment. English-language articles were included. There were no other exclusion criteria. The literature search was updated (Oct. 17, 2017) before publication to capture any recent studies.

Section authors screened the search results for studies relevant to their section topics. Potentially relevant citations were retrieved and reviewed in full text, as well as unpublished abstracts presented at international hepatology and infectious disease conferences. Abstract authors were contacted to provide additional details as required. After review of the relevant 2015 guideline recommendations, the primary author for each section drafted the new recommendations and graded the supporting evidence, using the rating scheme from the American College of Cardiology Foundation and the American Heart Association practice guideline,^{18,19} as used in similar practice guidelines by the Canadian Association for the Study of the Liver.²⁰ Recommendations were assigned a class (reflecting benefit versus risk) and level of evidence (assessing strength of certainty) (Box 1).

The secondary author reviewed recommendations and supporting evidence for each section, and any disagreements were resolved by consensus. In most cases, the text of the 2015 guideline was modified for this update. The entire guideline panel then reviewed all recommendations and supporting evidence through dedicated recorded teleconferences. For a recommendation to be included in the guideline, consensus on the recommendation, including grading (class of recommendation, level of evidence), was required and defined as a two-thirds majority. Voting was done electronically by email for recommendations for which there was not consensus.

Stakeholder input

Although the guideline panel did not include any patient representatives, a final draft version of the guideline was circulated by email for comment to the entire membership of the Canadian Association for the Study of the Liver and community organizations that represented patients. Substantive comments were received from nine association members, including physicians and allied health workers. The guideline panel reviewed all com-

ments received and made revisions to the guideline after discussion; a two-thirds majority agreement was required for a change to be incorporated. The executive of the Canadian Association for the Study of the Liver reviewed and approved this final version.

Management of competing interests

Members of the guideline panel have financial relationships with pharmaceutical companies related to HCV therapeutics. All members signed a commitment and competing interest statement at the outset of guideline development. Individuals with relevant disclosures were not excluded from voting on recommendations. However, in order to manage competing interests, the final guideline was vetted by the Canadian Association for the Study of the Liver membership, and specifically by the association's executive, to evaluate the presence of commercial bias. No funding, direct or in kind, was provided to the guideline panel for this work.

Recommendations

This abridged document summarizes key recommendations for practice and supporting evidence, which is expanded upon in the full guideline (available in Appendix 1, www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.170453/-/DC1).

Screening and linkage to care

To increase the identification of the large proportion of persons living with undiagnosed HCV, we recommend that screening be both

Box 1: Grading system for recommendations²⁰

Classification	Description
Class of evidence	
Class 1	Conditions for which there is evidence or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful and effective.
Class 2	Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of a diagnostic evaluation, procedure or treatment.
Class 2a	Weight of evidence or opinion is in favour of usefulness or efficacy.
Class 2b	Usefulness or efficacy is less well established by evidence or opinion.
Class 3	Conditions for which there is evidence or general agreement that a diagnostic evaluation, procedure or treatment is not useful or effective and in some cases may be harmful.
Grade of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial, or nonrandomized studies.
Level C	Only consensus opinions of experts, case studies, or standard of care.

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 of recommendation: 2a; level of evidence: C).

A high proportion of Canadians with chronic HCV infection remain undiagnosed, with credible estimates ranging from 44% to 70%.^{4,23} The asymptomatic nature and slow progression of the infection require that individuals be identified through screening. Individuals at increased risk of infection should be tested for HCV (Box 2). In addition, based on a high prevalence and low testing rate among baby boomers, a strategy of one-time screening of all individuals born between 1945 and 1975 has been shown to be cost-effective and should be implemented in Canada.²⁵

We recommend that anti-HCV antibody testing be the diagnostic test of choice for initial screening. If positive, a confirmatory HCV RNA polymerase chain reaction test is required to confirm chronic infection. In those with previous spontaneous or treatment-induced clearance and those with suspected acute infection, HCV RNA is the screening test of choice because anti-HCV antibody tests remain positive for life, even after spontaneous or treatment-induced clearance of HCV (class of recommendation: 1; level of evidence: A).

Initial screening should test for HCV antibodies (anti-HCV) with confirmation of active infection with HCV RNA in those who test antibody positive.^{26,27} Some individuals (15%–30%) may spontaneously clear infection shortly after acquisition, with no long-term consequences. Such individuals will test positive for anti-HCV antibodies but negative for HCV RNA;²⁸ notably, they are not protected from reinfection. Once chronic (beyond six months), spontaneous clearance of HCV is extremely uncommon.²⁸

We suggest that all individuals who test positive for HCV RNA be evaluated by practitioners with experience in HCV management (class of recommendation: 1; level of evidence: C).

Despite a diagnosis of chronic hepatitis C, many patients are never seen by HCV experts, leading to low rates of treatment uptake and screening for complications.²⁹ Training primary care providers, addiction specialists, nurses and nurse practitioners to provide HCV care, as well as using telemedicine approaches (e.g., Project ECHO) to co-manage patients, can lead to delivery of high-quality HCV treatment with outcomes similar to those achieved in academic centres.^{30,31} Expansion of nonspecialist HCV care will be required in Canada to ensure that all infected individuals receive appropriate care.

Treatment

All patients with chronic HCV infection should be considered candidates for antiviral therapy (class of recommendation: 1; level of evidence: A).

The landscape of antiviral treatment for hepatitis C is changing rapidly. With the markedly improved efficacy and safety of current therapy based on direct-acting antiviral agents and the well-documented benefits of achieving sustained virologic response, there is no longer any medical justification to restrict therapy, except in individuals with severe comorbidities and short life expectancy unrelated to HCV infection. As such, all indi-

viduals with chronic HCV infection should be considered candidates for antiviral therapy.³²

Prompt initiation of treatment should occur in certain patient subgroups, especially those with advanced liver fibrosis (F3 [bridging fibrosis] or F4 [cirrhosis]), according to the Meta-analysis of Histological Data in Viral Hepatitis [METAVIR] classification,³³ and those with extrahepatic manifestations of HCV infection.³⁴

Patients with mild fibrosis (F0–F2) should also be considered for treatment. Viral eradication in this group improves health-related quality of life^{8,9} and may prevent incident infections in those at risk of infecting others (e.g., people engaged in high-risk activities).³⁵

Notably, a careful review by the Canadian Agency for Drugs and Technologies in Health (CADTH) showed that treatment of HCV with interferon-free direct-acting antiviral agent-based therapy is cost-effective at all stages of fibrosis.³⁶ Recent negotiated price reductions should make treatment more cost-effective (through the pan-Canadian Pharmaceutical Alliance). Although some regions in Canada continue to limit access to treatment to those with hepatic fibrosis, there is no medical or epidemiological evidence to support restrictions based on fibrosis stage.^{32,37–40} Price reductions have led to removal of restrictions in many jurisdictions.

Pretreatment evaluation

Initial evaluation should include questions about risk factors for viral acquisition to determine risks for transmission and estimate

Box 2: Populations for whom testing for hepatitis C virus (HCV) is recommended

Risk factor–based screening²⁴

- History of current or past (even once) injection drug use*
- Received health care or personal services where there is a lack of infection prevention and control practices
- Received a blood transfusion, blood products or organ transplant before 1992 in Canada
- History of or current incarceration
- Born or resided in a region where hepatitis C prevalence is > 3%, such as:
 - Central, East and South Asia;
 - Australasia and Oceania;
 - Eastern Europe;
 - Sub-Saharan Africa;
 - North Africa or Middle East
- Born to a mother who is HCV-infected
- History of sexual contact or sharing of personal care items with someone who is HCV-infected*
- HIV infection, particularly men who have sex with men*
- Received chronic hemodialysis treatment
- Elevated alanine aminotransferase

Population-based screening²⁵

- Born between the years 1945 and 1975

*Retesting should be performed at least once per year in those individuals who are engaged in ongoing high-risk activities and must be done with HCV RNA, as anti-HCV will remain positive even after achievement of sustained virologic response.

duration of infection, signs and symptoms of advanced liver disease or extrahepatic manifestations of chronic hepatitis C (e.g., rash, renal disease) and the presence of cofactors that may accelerate disease progression (e.g., alcohol, obesity, coinfections). Necessary laboratory testing includes virologic tests to confirm and characterize the infection (HCV RNA viral load, HCV genotype), liver biochemistry and function, abdominal ultrasound, an assessment of fibrosis stage and tests to rule out coinfections, such as hepatitis B virus and HIV (see Table 1 and Supplemental Table 2b in Appendix 1 for more information).

Determination of HCV RNA, genotype and subtype (i.e., 1a v. 1b) is helpful in the management of patients with chronic HCV infection (class of recommendation: 1; level of evidence: A).

Documentation of viremia (detectable HCV RNA) is required to confirm active HCV infection. Some treatment regimens vary, depending on the level of HCV RNA; however, for most regimens, the HCV RNA level does not influence therapeutic decision-making.⁴¹ New regimens are effective against all HCV genotypes, and thus genotyping is not absolutely required before therapy if a pan-genotypic regimen is used, particularly in patients who do not have cirrhosis.^{42–46} However, many regimens are genotype- and/or subtype-specific, and even with pan-genotypic regimens, efficacy varies by genotype, which may be relevant for patients and providers to know before starting therapy.^{43,46} As such, genotyping before starting therapy is still recommended.

Liver fibrosis assessment to identify or exclude advanced fibrosis or cirrhosis is essential to the management of patients with chronic HCV infection (class of recommendation: 1; level of evidence: A).

An assessment of liver fibrosis is essential in all infected individuals. Identifying patients with cirrhosis is particularly important because of their increased risk of hepatic complications, lower treatment response and requirement for hepatocellular carcinoma surveillance, even after achievement of sustained virologic response.^{12,47,48} In those without overt evidence of cirrhosis on history or exam (e.g., ascites, encephalopathy) or routine tests (e.g., nodular shrunken liver or splenomegaly on ultrasound), an additional dedicated fibrosis assessment is required. Notably, absence of clinical signs or symptoms and even normal radiological findings do not adequately rule out cirrhosis.²¹

Numerous noninvasive alternatives to liver biopsy have been developed,⁴⁹ including serum markers (e.g., the Aspartate Amino-transferase to Platelet Ratio Index [APRI],⁵⁰ FIB-4, FibroTest⁵¹), transient elastography (FibroScan, Echosens, Paris, France^{52–55}) and other imaging-based tools. These tests are highly accurate for ruling out cirrhosis, the most important and clinically relevant issue.⁵⁶ However, practitioners should be aware of the caveats associated with noninvasive approaches to fibrosis staging to allow for correct interpretation.

Direct-acting antiviral agents

Given the efficacy and markedly improved safety and tolerability of interferon-free direct-acting antiviral agent regimens, regimens containing pegylated interferon- α are no longer recommended for

patients with HCV infection (class of recommendation 3; level of evidence: A).

Multiple steps in the HCV life cycle have proven attractive targets for novel pharmacologic therapies (Appendix 1, Supplemental Figure 1). Agents that target the nonstructural 3/4A (NS3/4A) serine protease (-previr), the NS5B RNA-dependent RNA polymerase (-buvir) and the NS5A protein (-asvir) have been developed and approved for clinical use.⁵⁷ Although initial approvals of direct-acting antiviral agents involved regimens administered in combination with pegylated interferon- α , approvals since 2014 have been exclusively for interferon-free treatment regimens. Given the markedly improved efficacy, tolerability and safety of regimens that combine various direct-acting antiviral agents compared with regimens containing interferon, all patients would benefit from interferon-free therapy.^{42,46,58,59} Therefore, interferon-free regimens are recommended as first-line therapy for all indications.

Different classes of direct-acting antiviral agents have been combined to overcome drug resistance. However, substitutions in the viral sequence that are associated with resistance to antivirals (resistance-associated substitutions), particularly to NS5A inhibitors, may be present in some patients even before they receive therapy. For patients with genotype 1a and genotype 3 infections, the presence of baseline resistance may affect treatment choices, and we suggest testing in certain circumstances (see Appendix 1 for more details). For patients with other genotypes, the importance of resistance-associated substitutions is less clear and we do not recommend baseline testing.

Before beginning any direct-acting antiviral agent, potential drug–drug interactions must be considered, including those attributable to prescription and over-the-counter and herbal preparations. We suggest referring to an online updated database of drug–drug interactions before starting therapy (e.g., www.hep-druginteractions.org).

Treatment regimens

The suggested work-up before beginning HCV therapy is outlined in Table 1, with approved direct-acting antiviral agents HCV regimens in Canada listed in Table 2. Table 3 outlines treatment recommendations for people who have never received previous HCV treatment (treatment-naive) without cirrhosis. Regimens are recommended by HCV genotype, with the duration in weeks indicated. Treatment recommendations for people who have never received HCV treatment (treatment-naive) with compensated cirrhosis are similarly outlined in Table 4. Recommendations for people who have been treated previously and for those with specific comorbidities (i.e., chronic kidney disease, decompensated cirrhosis, post-liver transplantation, hepatitis B coinfection, injection drug use and others) are available in Appendix 1.

For all recommendations, the primary criteria for selecting a recommended regimen were antiviral efficacy (rate of sustained virologic response) and safety in phase III trials. Although some regimens may require longer duration of therapy, have more drug interactions, additional adverse effects or a higher pill burden, or require the use of ribavirin, such regimens were still listed

as “recommended” if robust data demonstrated high efficacy and safety. For regimens in which resistance testing is recommended, strategies for patients with and without detectable resistance-associated substitutions are listed.

For each HCV genotype, multiple approved regimens are available. The comprehensive efficacy and safety data supporting the recommendation of each regimen for each population are provided in Appendix 1.

Table 1: Suggested work-up before beginning HCV therapy

Category	Investigation	Considerations
Routine bloodwork	<ul style="list-style-type: none"> Complete blood count Liver enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase) Liver function (bilirubin, INR, albumin) Creatinine 	<ul style="list-style-type: none"> Low platelets and elevated bilirubin or INR are suggestive of cirrhosis Renal function is important to determine safety of some regimens
Serology to exclude other infections	<ul style="list-style-type: none"> HIV Hepatitis B (HBsAg, anti-HBs, anti-HBc) 	<ul style="list-style-type: none"> If HIV-positive, treatment for HIV must take drug interactions into consideration If HBsAg-positive or anti-HBc-positive, see section on HBV coinfection (risk of HBV reactivation) (Appendix 1)
Serology to exclude other common liver diseases	<ul style="list-style-type: none"> Transferrin saturation (hemochromatosis) IgG 	<ul style="list-style-type: none"> Elevated immunoglobulin G may reflect cirrhosis or possibly autoimmune hepatitis
Staging of liver disease	<ul style="list-style-type: none"> APRI* FibroTest (serum panel)† Ultrasound* Transient elastography† 	<ul style="list-style-type: none"> All persons with HCV must have evaluation of fibrosis to exclude cirrhosis. Normal ultrasound does not exclude cirrhosis.²¹ APRI < 0.7 has a very high negative predictive value to exclude cirrhosis²²
HCV-specific	<ul style="list-style-type: none"> HCV genotype and HCV RNA Resistance testing (may be useful in select circumstances) 	<ul style="list-style-type: none"> To select appropriate regimen, and consideration for addition of ribavirin.

Note: anti-HBc = hepatitis B core antibody, anti-HBs = hepatitis B surface antibody, APRI = Aspartate Aminotransferase to Platelet Ratio Index, HBsAg = hepatitis B virus surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IgG = immunoglobulin G, INR = international normalized ratio.

*All persons with HCV should have a baseline ultrasound and evaluation of fibrosis.

†Where available, use noninvasive technologies (e.g., transient elastography [Fibroscan], shear-wave elastography, MR-Elastography, or FibroTest).

Table 2: Health Canada–approved direct-acting antiviral regimens in Canada

Regimen	Genotype	Pills per day	Duration (wk)	Comments
Genotype-specific treatment regimens				
Elbasvir/grazoprevir (Zepatier)	1a, 1b, 4	1	12–16	Resistance testing recommended before use in genotype 1a
Ledipasvir/sofosbuvir (Harvoni)	1a, 1b, 4, 5, 6	1	8–24	
Paritaprevir/ritonavir/ombitasvir + dasabuvir (Holkira Pak)	1, 1b	4	8–24	Ribavirin must be added for genotype 1a
Paritaprevir/ritonavir/ombitasvir (Technivie)	4	2	12	Ribavirin must be added
Sofosbuvir + daclatasvir (Sovaldi + Daklinza)	1a, 1b, 3	2	12–24	
Pan-genotypic regimens				
Glecaprevir/pibrentasvir (Maviret)	1–6	3	8–16	
Sofosbuvir/velpatasvir (Epclusa)	1–6	1	12	
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)	1–6	1	12	Approved only for direct-acting antiviral agent failures

Table 3: Recommended regimens and durations (weeks) for patients without cirrhosis who have never been treated, according to HCV genotype*

Regimen	HCV genotype						
	1a	1b	2	3	4	5	6
Ledipasvir/sofosbuvir (Harvoni)	8–12 wk†	8–12 wk†	NR	+ ribavirin 12 wk	12 wk	12 wk	12 wk
Elbasvir/grazoprevir (Zepatier)	12–16 wk ± ribavirin‡	8–12 wk§	NR	+ sofosbuvir x 12 wk	12 wk	NR	NR
Paritaprevir/ritonavir/ombitasvir + dasabuvir (Holkira Pak)	+ ribavirin 12 wk	12 wk	NR	NR	Paritaprevir/ ritonavir/ ombitasvir + ribavirin 12 wk	NR	NR
Sofosbuvir + daclatasvir (Sovaldi + Daklinza)	12 wk	12 wk	12 wk	12 wk	NR	NR	NR
Sofosbuvir/velpatasvir (Epclusa)	12 wk	12 wk	12 wk	12 wk	12 wk	12 wk	12 wk
Glecaprevir/pibrentasvir (Maviret)	8 wk	8 wk	8 wk	8 wk	8 wk	8 wk	8 wk
Sofosbuvir/velpatasvir/voxilarevir (Vosevi)¶	NR	NR	NR	NR	NR	NR	NR

Note: HCV = hepatitis C virus, HIV = human immunodeficiency virus, NR = not recommended.

*Where indicated, to be dosed according to weight: ≤ 75 kg: 1000 mg daily; ≥ 75 kg: 1200 mg daily. See Appendix 1 for reference supporting recommendations.

†In individuals without cirrhosis and without HIV with a viral load < 6 million IU/mL, an 8-week regimen of ledipasvir/sofosbuvir may be considered.

‡Resistance testing suggested for people with genotype 1a infection before treatment with elbasvir/grazoprevir. If resistance to nonstructural 5A (NS5A) inhibitors is present, treatment should be extended to 16 weeks with the addition of weight-based ribavirin.

§Eight weeks recommended in treatment-naïve patients with fibrosis stages F0–F2. For those with F3 or F4, 12 weeks of therapy should be given.

¶Reserved for individuals who have been treated previously with direct-acting antiviral agents.

Table 4: Recommended regimens and durations (weeks) for patients with compensated cirrhosis who have never been treated, according to HCV genotype*

Regimen	HCV genotype						
	1a	1b	2	3	4	5	6
Ledipasvir/sofosbuvir (Harvoni)	12 wk ± ribavirin†	12 wk	NR	+ ribavirin 12 wk	12 wk	12 wk	12 wk
Elbasvir/grazoprevir (Zepatier)	12–16 wk ± ribavirin†	12 wk	NR	+ sofosbuvir x 12 wk	12 wk	NR	NR
Paritaprevir/ritonavir/ombitasvir + dasabuvir (Holkira Pak)	+ RBV 12 wk	12 wk	NR	NR	Paritaprevir/ ritonavir/ ombitasvir + ribavirin 12 wk	NR	NR
Sofosbuvir + daclatasvir (Sovaldi + Daklinza)	24 wk	24 wk	24 wk	24 wk ± ribavirin	NR	NR	NR
Sofosbuvir/velpatasvir (Epclusa)	12 wk	12 wk	12 wk	12 wk ± ribavirin‡	12 wk	12 wk	12 wk
Glecaprevir/pibrentasvir (Maviret)	12 wk	12 wk	12 wk	12 wk	12 wk	12 wk	12 wk
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)	NR	NR	NR	NR	NR	NR	NR

Note: HCV = hepatitis C virus, NR = not recommended, RBV = ribavirin.

*Where indicated, to be dosed according to weight: ≤ 75 kg: 1000 mg daily; ≥ 75 kg: 1200 mg daily. See Appendix 1 for reference supporting recommendations.

†Resistance testing suggested for people with genotype 1a infection with compensated cirrhosis before treatment with ledipasvir/sofosbuvir or elbasvir/grazoprevir. If resistance to nonstructural 5A (NS5A) inhibitors is present, treatment should be extended to 16 weeks with the addition of weight-based ribavirin.

‡Resistance testing suggested for people with genotype 3 infection with compensated cirrhosis before treatment with sofosbuvir/velpatasvir. If resistance to NS5A inhibitors is present, addition of weight-based ribavirin may be considered.

Genotype 1: Genotype 1 is the most prevalent HCV genotype in Canada and most patients are infected with either genotype 1a or 1b.⁶⁰ Subtyping is important because some regimens are more effective against genotype 1b than 1a.⁶¹ Treatment recommendations for treatment-naïve patients without cirrhosis (Table 3) and with compensated cirrhosis (Table 4) are listed by genotype and subtype. Baseline resistance testing is recommended in clinical situations for which outcomes differ and alternative treatment strategies exist.

Genotype 2: Although high sustained virologic response rates were achieved with interferon-based therapy for genotype 2 infection, the improved tolerability, shorter course and improved sustained virologic response rates with interferon-free regimens justify their use.^{43,44,62} Treatment recommendations are presented for patients who are treatment-naïve without cirrhosis (Table 3) or with compensated cirrhosis (Table 4).

Genotype 3: Genotype 3 infection is associated with more aggressive natural history, faster progression to cirrhosis and higher rates of hepatocellular carcinoma than other HCV genotypes.⁶³ Patients with HCV genotype 3 and cirrhosis have lower sustained virologic response rates than other populations treated with direct-acting antiviral agents.⁴³ Treatment recommendations are presented for patients who are treatment-naïve without cirrhosis (Table 3) or with compensated cirrhosis (Table 4).

Genotypes 4, 5, 6: Genotype 4 is very diverse, with multiple subtypes; however, to date no clear difference in response has been observed by subtype. Studies of genotype 5 and genotype 6 are limited because of the low prevalence of these patients with these HCV genotypes in Europe and North America. Treatment recommendations are presented for patients who are treatment-naïve without cirrhosis (Table 3) or with compensated cirrhosis (Table 4).

Decompensated cirrhosis and post-liver transplantation: Decompensated cirrhosis refers to present or history of ascites, esophageal variceal hemorrhage, jaundice or hepatic encephalopathy. Patients with decompensated cirrhosis have a high risk of morbidity and short-term liver-related mortality and thus should be treated in centres experienced in managing end-stage liver disease. Notably, all protease inhibitors (grazoprevir, glecaprevir, paritaprevir, voxilaprevir, simeprevir) are contraindicated in patients with decompensated cirrhosis, because these drugs are hepatically metabolized and may accumulate to very high and toxic levels in patients with impaired hepatic function.⁶⁴ Although regimens that are not based on protease inhibitors appear safe, instances of hepatotoxicity or worsening decompensation during treatment have been reported.⁶⁵ The benefits of antiviral therapy must be carefully weighed against the risks of on-treatment complications and the prospect of limited improvement with sustained virologic response in patients with decompensated cirrhosis. No firm criteria have been established to identify patients who should defer treatment until after transplantation. However, we suggest that patients with Model for

End-stage Liver Disease (MELD) scores above 15 to 18 may benefit from deferral of therapy.^{66–70} Patients with decompensated cirrhosis should be evaluated in centres that have experience with end-stage liver disease because of the risk of worsening decompensation during therapy. Specific recommendations for treatment of decompensated cirrhosis are presented in Appendix 1. Results of treatment after liver transplantation are similar to those in the nontransplant setting (Appendix 1). However, drug–drug interactions must be carefully considered in all patients.

Posttreatment follow-up

Patients who achieve sustained virologic response and do not have cirrhosis require no specific liver-related follow-up. In those with ongoing risk exposures, annual HCV RNA testing to assess for reinfection is suggested (class of recommendation: 1; level of evidence: B).

For patients without cirrhosis who achieve sustained virologic response, no specific follow-up is required. Patients will remain anti-HCV antibody-positive for life, but are not protected from reinfection.⁷¹ The risk of late relapse is extremely low^{72,73} and repeat HCV RNA testing is warranted only in those with unexplained alanine aminotransferase elevation or with ongoing risk exposures (e.g., people who inject drugs), in whom annual HCV RNA testing should be considered. Individuals who are reinfected should be managed in the same way as anyone with primary HCV, with a continued strong emphasis on harm reduction practices.⁷⁴

Patients who achieve sustained virologic response and have cirrhosis require ongoing screening for hepatocellular carcinoma indefinitely (class of recommendation: 1; level of evidence: B).

For patients who have cirrhosis before the start of therapy, ongoing follow-up is required. Surveillance for hepatocellular carcinoma with biannual ultrasound should be continued indefinitely after sustained virologic response is achieved, even if non-invasive tests no longer suggest the presence of cirrhosis.^{75–79} For those with a treated hepatocellular carcinoma before sustained virologic response, close surveillance is required after HCV treatment, with some reports suggesting an increased risk of recurrence of hepatocellular carcinoma after viral clearance.^{80,81}

Patients who do not achieve sustained virologic response should be considered for retreatment with a salvage regimen (class of recommendation: 1; level of evidence: A).

For patients who do not achieve sustained virologic response, issues such as adherence and drug–drug interactions should be discussed and retreatment should be considered. Salvage regimens have recently been approved that have high efficacy and similar safety to other direct-acting antiviral agent regimens. The fixed-dose combination single-tablet regimen of sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is effective against all HCV genotypes with sustained virologic response rates above 95% in patients who did not achieve sustained virologic response after a course of first-line antiviral therapy based on direct-acting antiviral agents.⁸² Other salvage regimens, including the combination of glecaprevir/pibrentasvir, have been less well studied for retreatment.⁸³ Details about retreatment are included in Appendix 1.

Implementation

This synopsis and the full version of the guideline (Appendix 1) is posted on the Canadian Association for the Study of the Liver website (www.hepatology.ca/). In addition, a custom searchable website is being developed so practitioners can navigate directly to the patient profile of interest. This guideline will be presented to policy-makers for integration into Canadian treatment funding models.

The impact of these guidelines on resource utilization is unknown. However, there is strong evidence demonstrating the cost-effectiveness of hepatitis C treatment for all patient subgroups at all levels of fibrosis.^{25,84,85} Increased screening efforts and treatment uptake will be required to meet the World Health Organization targets for elimination of HCV as a public health problem by 2030.

This document will be updated annually and revised versions of recommendations will be placed on the Canadian Association for the Study of the Liver website immediately.

Other guidelines

The treatment recommendations in this guideline update are markedly changed from the previous Canadian Association for the Study of the Liver treatment guidelines because of multiple advances in the field since their publication, including the development of pan-genotypic regimens, retreatment options after nonresponse to direct-acting antiviral agents and treatment options for populations with substantial medical comorbidities.¹⁶ The current recommendations are very similar to those of other recent guidelines from national and international societies, including the European Association for the Study of the Liver⁸⁶ and the American Association for the Study of Liver Disease and Infectious Disease Society of America.⁸⁷

The notable differences from these other societies' recommendations are greater use of resistance testing to guide therapy in our guideline and support for a broader list of recommended therapies in our guideline for some populations. The rationale for these differences is detailed in Appendix 1.

Briefly, new data have emerged to support the use of resistance testing for certain regimens and certain populations, and testing is readily available in Canada. The guideline panel chose to recommend regimens equally where the efficacy and safety data were similar and where they were supported by high-quality evidence without strong consideration of factors that may influence the choice of therapy for an individual patient (e.g., pill burden, drug interactions), but that do not affect overall efficacy or safety of the regimen. Importantly, regimen-specific factors may have a major influence for individuals considering therapy and should be discussed thoroughly by practitioners to help choose the preferred treatment option for a given individual.

The Canadian Task Force for Preventive Health recently published recommendations against screening individuals who are not at high risk of HCV infection.⁸⁸ They did not recommend screening the Baby Boomer birth cohort (1945–1975). The guideline panel strongly disagreed with the task force recommendations and unanimously agreed that the current evidence

supports one-time screening of the baby boomer birth cohort in Canada, which is in line with recommendations from other countries for birth cohort screening, most notably the United States⁸⁹ and France.⁹⁰ The rationale for the difference in screening recommendations is explained in greater detail in Appendix 1. Briefly, the panel felt that the task force overvalued the harms of screening, particularly the costs of therapy; undervalued the benefits of curative treatment; relied on outdated data on the costs of HCV therapy and HCV prevalence in Canada; and largely disregarded modelling and cost-effectiveness data supporting screening. We have advocated for screening of the baby boomer cohort for the following reasons: recent data show that the HCV prevalence is highest among the baby boomer birth cohort (1.55%), accounting for an estimated 62.7% of all HCV infections in Canada, and the burden of liver disease is expected to increase markedly in this group;^{1,91} best estimates suggest that HCV infection remains undiagnosed in 45%–70% of Canadians infected with HCV,^{4,92} indicating that the long-standing policy of screening based on risk factors has been unsuccessful. Moreover, the pan-Canadian Pharmaceutical Alliance has recently negotiated markedly lower prices for HCV therapy, leading to broader access for those who have received a diagnosis of HCV infection, making a screen-and-treat strategy even more cost-effective than previous estimates^{25,93} and overcoming the concern of the task force that patients will be diagnosed without having access to therapy.

Gaps in knowledge

Despite substantial advances between 2010 and 2017 in efficacy, safety and tolerability of treatment, many gaps in knowledge remain. We are unable to cure every infected patient, and we currently have limited treatment options for patients with decompensated cirrhosis, particularly those who have failed an all-oral regimen. These patients represent the minority of individuals with HCV infection.

In the coming years, the major challenge of HCV management will not be treatment, but rather prevention, screening and linkage to care. Although many novel models of care have been developed, the optimal strategies, particularly to reach vulnerable populations, are not clear and must be a major research priority.

The efficacy, safety and simplicity of new HCV regimens mean that therapy no longer must be provided in specialty clinics, with recent data showing high efficacy and improved patient satisfaction when HCV is treated in primary care.³¹ To reach all infected Canadians, expansion of the pool of those providing treatment will need to be a major priority, particularly among primary care providers for populations with a high burden of HCV, such as those born in countries with high prevalence of HCV infection, Indigenous populations and those in addiction services, prisons and other high-prevalence settings.

Beyond treatment, addressing HCV in Canada will require coordination of services to address harm reduction and many of the social determinants of health that have an impact on the burden and course of HCV-related disease. The development of a

coordinated National Action Plan to address HCV, as recommended by the World Health Organization, should be a priority to ensure that Canada is on track to meet the HCV elimination targets by 2030.⁹⁴

Conclusion

The landscape for HCV treatment continues to change at a rapid pace. This guideline provides updated evidence-based recommendations for the treatment of patients with HCV infection.

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