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Guidelines & Protocols Advisory Committee

Viral Hepatitis Testing

Effective Date: May 26, 2021

Scope

This guideline outlines the use of laboratory tests to diagnose acute and chronic viral hepatitis in adults (≥ 19 years) in the primary care setting.

Testing related to children or perinatally acquired viral hepatitis infection, or treatment information is outside the scope of this guideline.

Key Recommendations

To avoid duplicate testing, consider the patient's history, age and risk factors (see Table 1). Check for prior relevant vaccinations and test results before ordering tests for viral hepatitis.

Hepatitis A (HAV)

- There are very few acute HAV infections in BC. Cases relate to travel, contaminated food products or close contact with those who are infected.
- Self-limited disease not requiring ongoing serological follow-up. Post-vaccination testing is not recommended.

Hepatitis B (HBV)

- Although there is currently no cure, treatment is available for chronic HBV infection (see the Management of hepatitis B virus infection: 2018 Guidelines from the CASL and AMMI Canada).[1] Patients with chronic HBV infection should be engaged into comprehensive specialist care. Consultation or referral is ***strongly*** recommended.
- In the absence of risk factors, routine HBV testing is not needed for those born in Canada.
- One-time HBV testing for immigrants from endemic areas is recommended (see Appendix 1).
- Vaccinate individuals susceptible to HBV infection when risk factors are present (see BCCDC Immunization Manual and Table 1).
- Individuals being treated for HCV who are getting worked-up for HIV pre-exposure prophylaxis (PrEP), are immunosuppressed, or who are about to start immunosuppressive therapy, should be evaluated for prior HBV infection to assess the potential risk for reactivation of HBV (see Table 2).

Hepatitis C (HCV)

- Curative treatments (> 95 % effective) are available for those who have HCV infection (see the Management of chronic hepatitis C: 2018 guideline update from the CASL).[2]
- Patients known to have HCV infection, but who have not been previously treated and cured, should be recalled and engaged into care for HCV treatment.
- One-time HCV testing for the birth cohort 1945-1965 can be considered (see the Contoversies in Care section).
- One-time HCV testing for immigrants from endemic areas is recommended (see Appendix 1).
- Annual HCV testing for susceptible individuals with ongoing risks for HCV infection or reinfection is indicated (see Table 1 below).

- Treatment providers must establish a respectful, trust-based relationship with all patients, and need to consider HCV treatment within a holistic wellness framework.[2]
- Where appropriate, many individuals with HCV infection could benefit from further supports and enrolment into comprehensive care (e.g., opioid agonist therapy, mental health and addiction services, alcohol reduction).
- As of 2018, an estimated 28,607 people in BC living with hepatitis C infection (diagnosed and undiagnosed) remain untreated.[3]

Etiology and Risk Factors

Table 1. Risk Factors, Transmission and Epidemiology for Viral Hepatitis Infection Listed by Etiology

Hepatitis A (HAV) *Individuals vaccinated for hepatitis A, or who have resolved a natural infection, are protected from subsequent HAV infection.*		
Risk Factors	**Transmission and Clinical**	**Epidemiology**
• Consumption of contaminated food (often raw or undercooked shellfish, raw fruits or vegetables) or water. • Travel to HAV endemic regions. • Contact (including sexual contact) with someone who has HAV infection. • People who use Illicit drugs, who experience homelessness, or who are underhoused, and have gaps in access to care services.	• Fecal-oral through person-to-person contact, or exposure to contaminated food or water. • Usually self-limited, but can lead to fulminant hepatitis. It does not lead to chronic disease. • Hepatitis A vaccine is not part of routine immunization schedules, except when at higher risk of exposure (see the BCCDC Immunization Manual).	• In 2018, there were 25 reported cases of hepatitis A in BC (0.5 per 100,000).[4] • Most cases occur in unimmunized persons who have consumed contaminated food products, or who have travelled to endemic countries. • In Canada, recent HAV outbreaks have disproportionately affected gbMSM.[5] • Low and middle income countries (e.g., areas of Africa and Asia) have higher rates due to poor sanitary conditions and hygienic practices.[6,7]
Hepatitis B (HBV) *Individuals vaccinated for HBV, or who have cleared a natural HBV infection, are protected from subsequent HBV infection.*		
Risk Factors	**Transmission and Clinical**	**Epidemiology**
• Offspring of HBsAg positive parent who is giving birth. • Family history of HBV or hepatocellular carcinoma (HCC). • Immunosuppression in people with chronic or resolved HBV infection (risk of HBV Reactivation). • Sexual contact with someone who has HBV infection. • Condomless sex with multiple partners. • Born, lived in, or received healthcare in endemic regions (see Appendix 1). • History of, or current illicit drug use (includes sharing equipment used for injection, smoking or snorting). • History of, or current incarceration. • Tattoos and body piercings where infection control practices may have been poor. • HIV infection, particularly in gay, bisexual and men who have sex with men (gbMSM). • Needle stick injury or occupational exposure from an infected person. • Chronic renal failure receiving hemodialysis. • Sharing of personal care items with someone who is infected.	• Exposure to blood and body fluids (See the BCCDC Hepatitis B Guidelines for further details). • Efficiently transmitted (except in those who are vaccinated) perinatally, through parenteral contact with blood, and sexual contact with semen or vaginal fluids. • Currently there is treatment available for those with chronic HBV, but there is no cure. • Universal hepatitis B vaccine became available in BC for grade 6 students in 1992, and the infant program was introduced province-wide in 2001. • Routine boosters in immunocompetent persons are generally not necessary. • Prior documented anti-HBs ≥ 10 IU/L after receipt of a full hepatitis B vaccine series is protective, whether or not the anti-HBs is still currently detectable because immune memory persists.[1,8] See the National Advisory Committee on Immunization (NACI) statement on hepatitis B vaccine. • With chronic HBV infection, 20-25% can progress to cirrhosis and complications related to end-stage liver disease over decades.[9–11]	• In 2018, there were 12 cases of acute HBV in BC (0.2 per 100,000).[4] • Acute HBV infection is more likely to occur in persons who inject drugs or through sexual contact. • In 2018, there were 1,035 newly reported chronic/undetermined HBV cases in BC (20.7 per 100,000).[4] • The majority of chronic HBV infections occurred in persons emigrating from a country where hepatitis B is endemic (see Appendix 1).[12]

Hepatitis C (HCV)

Individuals who have cleared a prior HCV infection (whether spontaneously or through treatment) can get reinfected.

Indigenous peoples continue to be impacted at a significantly higher rate than non-Indigenous people due to historic and present colonial policies and systems that disrupt connection to land, language, and culture, and diminish Indigenous sovereignty. Historical and present intergenerational trauma contributes to the social determinants of health in Indigenous peoples and impacts HCV acquisition risks. Treatment providers must establish respectful, trust-based relationships not only with Indigenous patients, but for all patients, and need to consider HCV treatment within a holistic wellness framework.

Risk Factors	Transmission and Clinical	Epidemiology
• Born between the years 1945 to 1965 – *see Controversies in Care section.* • Received a blood transfusion, blood products or organ transplant before 1992 in Canada. • Offspring of a parent giving birth who has HCV infection (approximately 6% risk of perinatal transmission, higher if the parent giving birth is co-infected with HIV).[13,14] • Sexual transmission is rare, unless there is blood-to-blood contact with someone who has HCV infection or when engaging in condomless sex with multiple partners. • HIV infection, particularly in gbMSM. • Born, lived in or received healthcare in endemic regions (see Appendix 1). • History of, or current illicit drug use (includes sharing equipment used for injection, smoking or snorting). • History of, or current, incarceration. • Tattoos and body piercings where infection control practices may have been poor. • Chronic renal failure receiving hemodialysis. • Sharing of personal care items with someone who is infected. • Needle stick injury or occupational exposure from an infected person.	• Blood-to-blood contact. • Percutaneous exposure (e.g., shared needles) is the most efficient means of transmission. • Sexual transmission is uncommon in heterosexual populations.[15,16] • In some populations (e.g., HIV positive gbMSM) sexual transmission has been reported, and is associated with mucosal trauma (e.g., fisting), presence of genital ulcerative disease and drug use (e.g., ChemSex).[17,18] • About 75% of HCV infections become chronic and most infected people do not demonstrate symptoms. Over decades, 15-30% can progress to cirrhosis, liver failure, hepatocellular carcinoma, or require liver transplantation.[19] • HCV antibodies are not protective and do not confirm active infection. • An HCV RNA test is required to confirm active infection. • There is no hepatitis C vaccine. • Acute HCV is typically difficult to recognize because individuals are generally asymptomatic.	• In 2018, there were 1,960 newly reported cases of hepatitis C in BC (39.3 per 100,000).[4] • Around 85% of new infections in BC occur in people who inject drugs. • Chronic infections are most common amongst the 1945-1965 birth cohort,[20] who likely acquired the HCV infection through past injection drug use, receipt of contaminated blood products, or poor infection control practices.[21] • From 1999-2004, the national HCV rate was 6.7 times higher among Indigenous (First Nations, Inuit, and Métis) peoples vs. non-Indigenous people (18.9/100,000 vs. 2.8/100,000).[22]

Hepatitis D (HDV) *Rare in BC. Hepatitis B vaccine protects against HDV.*		
Risk Factors	**Transmission and Clinical**	**Epidemiology**
• Risk factors similar to HBV and HCV.	• HDV infection can only occur in patients who have HBV infection. • Transmission routes same as HBV. • HDV testing is recommended for individuals with chronic HBV infection who have resided in endemic countries or who have a history of injection drug use, and are starting treatment for chronic HBV infection. • Follow-up care for HBV/HDV co-infection is generally limited to specialists.	• 6 cases in 2018, 0.1/100,000.[4] • Most countries do not report HDV. HDV endemic areas includes areas of Central and West Africa, Central and Northern Asia, Pacific Islands, Eastern Europe and South America.[23,24]
Hepatitis E (HEV) *Rare in BC.*		
Risk Factors	**Transmission and Clinical**	**Epidemiology**
• Consumption of contaminated food or water in HEV endemic regions. • Limited risk of acquisition in Canada.	• HEV infection is a zoonosis (can be transmitted from animals to humans). • Spread by contaminated water or food products in endemic countries. • Not typically transmitted from one human to another. • Presentation is similar to HAV, but can occasionally cause chronic infection in immunosuppressed people. • Testing and follow-up care is usually limited to specialists.	• 5 cases in 2018, 0.1/100,000,[4] most travel related. • Endemic countries includes some regions of Asia, Africa, Mexico, the Middle East and South America.[25,26]

Other

Viral hepatitis may also be caused by other viruses that are not addressed in this guideline, such as Epstein-Barr Virus (EBV, Mononucleosis), Cytomegalovirus (CMV) and Parvovirus B19 (fifth disease).

Diagnosis

- See Table 2 below for Indications for HAV, HBV and HCV Testing. For further information on the tests included in Table 2, see Appendix 2 – Hepatitis Laboratory Tests and Appendix 3 – Hepatitis B Serology Results and Interpretation.
- Appendix 4 – Hepatitis A Testing Guide, Appendix 5 – Hepatitis B Testing Guide and Appendix 6 – Hepatitis C Testing Guide provide BCCDC testing flow charts.
- See the associated document: "Hepatitis C: have you been tested?" patient handout.

Applicable to all testing scenarios

- To avoid duplicate testing, consider the patient's history, age and risk factors (see Table 1 above). Check for prior relevant vaccinations and test results before ordering tests for hepatitis.
- If HCV infection has been previously established (HCV RNA positive), the patient should be treated.
- If prior anti-HCV positive, order HCV RNA to confirm status.
- Offer hepatitis B vaccine as appropriate. If previously immunized and anti-HBs < 10 IU/L, refer to the BCCDC Hepatitis B Guidelines (Fig. 5-1; Table 4-2) for post-vaccination serology follow-up.
- HIV infection shares the same transmission pathways as HBV and HCV. Offer HIV testing as appropriate. See the HIV Testing Guidelines for BC.

Table 2. Indications for HAV, HBV and HCV Testing[19]

Indication	Initial baseline testing*	Notes
Suspect acute hepatitis (jaundice and elevated ALT)	• Anti-HAV Total and anti-HAV IgM • HBsAg, anti-HBs and anti-HBc Total • Anti-HCV Select the "Acute viral hepatitis undefined etiology" box on the Standard out-patient laboratory requisition. **Acute viral hepatitis undefined etiology** Hepatitis A (anti-HAV IgM) Hepatitis B (HBsAg ± anti-HBc) Hepatitis C (anti-HCV)	• Newly positive anti-HAV-IgM, HBsAg, anti-HBc IgM and anti-HCV results are reported to Public Health by testing laboratories. • ALT is typically elevated, no need to routinely test for AST. • Acute HBV infections in BC are rare. Most HBsAg positive results in BC reflect chronic infection. • Anti-HBc IgM testing is not included in the testing protocol because the sensitivity of current HBsAg assays is such that there usually is no window between the disappearance of HBsAg and serologic evidence of resolved infection. • Symptomatic acute HCV infection is uncommon.
Newly suspected chronic viral hepatitis (risk factors, persistently elevated ALT, cirrhosis or liver cancer)	• HBsAg, anti-HBc Total and anti-HBs • Anti-HCV Select the "Chronic viral hepatitis undefined etiology" box on the Standard out-patient laboratory requisition. **Chronic viral hepatitis undefined etiology** Hepatitis B (HBsAg; anti-HBc; anti-HBs) Hepatitis C (anti-HCV)	• Most chronic viral hepatitis infections are asymptomatic. • ALT may or may not be elevated. No need to routinely test for AST. • If HBsAg is positive for > 6 months, this confirms chronic HBV infection. • The presence of anti-HCV can indicate current or past HCV infection. An HCV RNA is needed to confirm active HCV infection. Around 75% of initial HCV infections progress to chronic infection, usually within 6 months. • If already diagnosed with viral hepatitis, see Appendix 7 – Recommended Test for Individuals Already Diagnosed with Viral Hepatitis. Consult with a specialist as needed for HCV infection. Consultation with, or referral to a specialist is ***strongly*** recommended for chronic HBV infection.

Indication	Initial baseline testing*	Notes

Illicit drug use – current or ever (includes sharing drug use equipment used for injection, smoking or snorting)
 	
Persons who are, or were incarcerated
 	
Gay, bisexual and men who have sex with men (gbMSM)
	• Anti-HCV
	• If not HBV vaccinated: HBsAg, anti-HBs and anti-HBc Total
	
	If not HBV vaccinated: select the "Chronic viral hepatitis undefined etiology" box on the Standard out-patient laboratory requisition.
	
	Chronic viral hepatitis undefined etiology
	Hepatitis B (HBsAg; anti-HBc; anti-HBs)
	Hepatitis C (anti-HCV)
	
	• If HBV vaccinated: no HBV testing (also see Immunosuppressed or undergoing immunosuppressive therapy)
	
	If HBV vaccinated: write anti-HCV in the "Diagnosis" and "OTHER TESTS" sections on the Standard out-patient laboratory requisition.
		Follow-up testing
		• Offer **annual** HCV testing for susceptible individuals with ongoing acquisition risk factors.
		
		• Offer hepatitis A vaccine where appropriate.
		• Offer hepatitis B vaccine if HBV serology negative. If previously immunized, refer to the BCCDC Hepatitis B Guidelines (Fig. 5-1) for post-vaccination serology follow-up.
		• HIV infection shares the same transmission pathways as HBV and HCV. Offer HIV testing as appropriate. See the HIV Testing Guidelines for BC.
		• Where appropriate, see the:
		  ○ BC Centre for Excellence in HIV/AIDS PrEP guidelines
		  ○ BC Guidelines Opioid Use Disorder guideline
		
		Note: Sexual transmission of HCV is uncommon in heterosexual populations.[15,16] In some populations (e.g., HIV positive gbMSM) sexual transmission of HCV has been reported, and is associated with mucosal trauma (e.g., fisting), presence of genital ulcerative disease and drug use (e.g., ChemSex).[17,18]
		
		*Unless risk factors are present, HCV testing is **not** recommended as part of routine STI screening.*

Birth Cohort (1945-1965) *See the Controversies in Care section* **Immigration from or residence in areas with high prevalence of viral hepatitis** **Indigenous peoples (First Nations, Métis and Inuit)** **Receipt of health care or tattoos, other injections where infection control practices may have been poor**	• ***One-time offer, regardless of risk assessment:*** Anti-HCV • If not HBV vaccinated: HBsAg, anti-HBs and anti-HBc Total If not HBV vaccinated: select the "Chronic viral hepatitis undefined etiology" box on the Standard out-patient laboratory requisition. **Chronic viral hepatitis undefined etiology** Hepatitis B (HBsAg; anti-HBc; anti-HBs) Hepatitis C (anti-HCV) • If HBV vaccinated: no HBV testing (also see Immunosuppressed or undergoing immunosuppressive therapy) If HBV vaccinated: write anti-HCV in the "Diagnosis" and "OTHER TESTS" sections on the Standard out-patient laboratory requisition.	• *One-time* HCV testing, no need to repeat testing unless ongoing risk factors are present. • Refer to Appendix 1. • Offer hepatitis A and/or B vaccine series as appropriate.
Pregnancy	• Universal HBsAg, syphilis and HIV screening • If HCV risk factors: Anti-HCV Select the above tests on the Standard out-patient laboratory requisition for maternity care under "0-14 WEEKS: RECOMMENDED TESTS".	• If HBsAg positive, see the SOGC of Canada Hepatitis B and Pregnancy Guideline[27], the BCCDC Hepatitis B Guidelines (Fig. 5-2) and Perinatal BC's Prenatal Care Pathway. • Offer hepatitis B vaccine where appropriate. • HCV testing as appropriate if ongoing risk factors are present. • If anti-HCV positive, refer to the SOGC of Canada Reproductive Care of Women Living With Hepatitis C Infection Guideline[28] and the BCCDC Hepatitis C Guideline (Section 6-2 and Fig. 6-2).
Immunosuppressed or undergoing immunosuppressive therapy	• HBsAg, anti-HBs and anti-HBc Total Write the above tests in the "Diagnosis" and "OTHER TESTS" sections on the Standard out-patient laboratory requisition.	• Reactivation refers to an increase in HBV DNA replication in persons who are actively infected or who have a resolved HBV infection. Can occur after initiating immunosuppressive therapy or HCV DAA treatment.[29] Reactivation can cause ALT flares, and in some cases, fulminant liver failure and death.[1] • Offer hepatitis B vaccine where appropriate. • See Appendix 8 – List of Immune Compromising Treatments.

Indication	Initial baseline testing*	Notes
Persons living with viral hepatitis, to identify coinfections and those who can benefit from vaccinations	• If HBV infection: anti-HAV Total and Anti-HCV Select the "Hepatitis A (Anti-HAV total)" box Write anti-HCV in the "Diagnosis" and "OTHER TESTS" sections on the Standard out-patient laboratory requisition. **Investigation of hepatitis immune status** Hepatitis A (anti-HAV, total) • If HCV infection: anti-HAV total, and HBsAg, anti-HBs and anti-HBc Total Select the "Hepatitis A (Anti-HAV total)" box Write the other above tests in the "Diagnosis" and "OTHER TESTS" sections on the Standard out-patient laboratory requisition. **Investigation of hepatitis immune status** Hepatitis A (anti-HAV, total)	• If hepatitis B infection, screen for hepatitis C. Screen for hepatitis A to identify those who should be vaccinated. • If anti-HCV positive, screen for hepatitis A and B to identify those who should be vaccinated. All anti-HCV positive specimens are automatically screened for hepatitis A and B immunity when testing is performed at the BCCDC Public Health Laboratory (BCCDC PHL), and results are forwarded to Public Health and the ordering provider. • See Appendix 7.
Household and sexual contacts with someone with viral hepatitis	• If the case has HAV infection, no serology is indicated for the contact. • If the case has HBV infection, order HBsAg, anti-HBs and anti-HBc Total, regardless of the contact's immunization status. • If the case has HCV infection, order anti-HCV (if previously anti-HCV positive, order HCV RNA) for the contact. Write the above tests in the "Diagnosis" and "OTHER TESTS" sections on the Standard out-patient laboratory requisition	• Connect with Public Health, and vaccinate household contacts and the index case for HAV and HBV as appropriate.
Exposed to blood or body fluids: occupational needlestick or sexual assault	• Test source and exposed persons for HBV, HCV and HIV. See the: ○ BCCDC Blood and Body Fluid Exposure Management (BBFE) Guideline, Management of Percutaneous or Permucosal Exposure to Blood and Body Fluid Laboratory Requisition and Management of Percutaneous of Permucosal Exposure to Blood and Body Fluid Letter for Follow-up Physician ○ BC Centre for Excellence in HIV/AIDS PEP guidelines	

*See Appendix 2 for further information on Hepatitis Laboratory Tests and Appendix 3 for Hepatitis B Serology Results and Interpretation.

Controversies in Care: Birth Cohort Hepatitis C Testing

Based on an increased hepatitis C prevalence in certain birth cohorts, a one-time offer of HCV testing has been recommended for those born between 1945-1965. However, there is a lack of agreement with respect to the age-range cut-offs and value of one-time age cohort testing:

- In 2020, the US Preventive Services Task Force recommended HCV screening for all individuals 18 to 79 years of age, based upon SVR rates of greater than 95% with new all-oral DAA treatments and associated improved clinical outcomes.[20]
- In 2020, the CDC recommended HCV screening for all adults ≥ 18 years of age, except where HCV prevalence < 0.1%. It was expected that there would be very few settings where HCV prevalence would drop this low in the US.
- In 2017, the Canadian Task Force on Preventive Health Care recommended against birth cohort testing.[30] However this recommendation was made prior to the wide availability of effective HCV treatments when hepatitis C was not considered routinely curable for everyone, so identification of cases was of limited value. With the dramatic improvements in curability and availability of treatment coverage regardless of fibrosis staging, birth cohort testing is now recommended.
- In 2018, the Canadian Association for the Study of the Liver (CASL) recommended birth cohort testing for those born between 1945-1975 based on the estimated prevalence of hepatitis C in Canada.[2]

Additionally, concerns had been raised by several B.C. stakeholders that systemic screening of the 1945-1965 birth cohort, which represents 1.3 million people in B.C., may not provide sufficient health care value considering the cumulative costs of testing and the lack of infrastructure to prevent unnecessary repeat testing. It is anticipated that further BC prevalence data and technologies to promote appropriate testing will be available in the future, at which point these recommendations can be re-examined.

While the BCCDC favours CASL's 1945-1975 screening recommendations, it is acknowledged that this is based on a relatively low quality of evidence. However, offering one-time HCV testing to this broader age cohort and curing HCV infection in this age group would further prevent both progressive liver disease and reduce transmission of HCV to others.

Based on BC's Lifetime Prevention Schedule assessment (2020) and local epidemiology, the best evidence supports the recommendation of the 2013 US Preventive Services Task Force.[31] The BCCDC and the GPAC hepatitis working group currently accept the recommendation for a one-time offer of HCV testing for the 1945-1965 birth cohort, regardless of risk factors.

Resources

Appendices

- Appendix 1 – Hepatitis B and Hepatitis C Endemic Countries
- Appendix 2 – Hepatitis Laboratory Tests
- Appendix 3 – Hepatitis B Serology Results and Interpretation
- Appendix 4 – Hepatitis A Testing Guide
- Appendix 5 – Hepatitis B Testing Guide
- Appendix 6 – Hepatitis C Testing Guide
- Appendix 7 – Management and Recommended Tests for Individuals Already Diagnosed with Viral Hepatitis
- Appendix 8 – List of Immune Compromising Treatments CASL (2018) – Management of HBV Infection

Associated Documents

- "Hepatitis C: have you been tested?" patient handout.

Practitioner Resources

- British Columbia Centre of Disease Control www.bccdc.ca
  - See the BCCDC Communicable Disease Control Manual for the Hepatitis A, Hepatitis B, Hepatitis C and Blood and Body Fluid Guidelines: www.bccdc.ca/health-professionals/clinical-resources/communicable-disease-control-manual/communicable-disease-control
  - Hepatitis B Testing Guide: Quick Reference for Health Care Providers
  - Isolated Hepatitis B Core Antibody - Sample letter for physicians
  - Hepatitis C Testing Guide: Quick Reference for Health Care Providers
- BC Centre for Excellence in HIV/AIDS www.cfenet.ubc.ca
- Canadian Blood Services www.blood.ca

- For current blood donor information see the ABCs of eligibility, Hepatitis section.
- HAV and HEV – Patients with a history of hepatitis A or hepatitis E infection may be eligible to donate 6 months after full recovery.
- HBV and HCV – Patients with a history of acute, resolved or chronic hepatitis B or hepatitis C are not eligible to donate. Patients who have been successfully treated for hepatitis C infection are also not eligible to donate.
- Persons who have had the following test results may be eligible to donate:
  - False-reactive HBsAg or false-reactive/indeterminate anti-HCV
  - a reactive HBsAg in association with a recent hepatitis B vaccination, with subsequent seroreversion of HBsAg to non-reactive

- Centers for Disease Control www.cdc.gov
- HealthLinkBC www.healthlinkbc.ca
- Public Health Agency of Canada www.phac-aspc.gc.ca
- Educational courses:
  - American Association for the Study of Liver Disease: https://www.aasld.org/education/learn-online/liverlearning
  - BCCDC Hepatitis C Course (for public health nurses): https://learninghub.phsa.ca/Learner/Home
  - CATIE: Hepatitis C Basics and Hepatitis C Treatment: https://www.catie.ca/en/educatie
  - CDC: Viral Hepatitis Serology Online Training Videos: Hepatitis A-E: https://www.cdc.gov/hepatitis/resources/professionals/trainingresources.htm
  - INHSU: http://www.inhsu.org/education-program/
  - University of Washington: https://www.hepatitisc.uw.edu/alternate

Patient and Caregiver Resources

- British Columbia Centre of Disease Control www.bccdc.ca
  - Hepatitis health information www.bccdc.ca/health-info/diseases-conditions/hepatitis
- GetCheckedOnline getcheckedonline.com
  - GetCheckedOnline is a free and confidential online sexually transmitted infection (STI) testing service provided by the BC Centre for Disease Control. GetCheckedOnline is available at participating LifeLabs locations in the Interior (Nelson and Kamloops), Vancouver and on Vancouver Island (Victoria and Duncan).
- HealthLinkBC www.healthlinkbc.ca
  - Hepatitis A virus tests
  - Hepatitis B virus tests
  - Hepatitis B: Post-vaccination test for immunity
  - Hepatitis C virus tests
  - Hepatitis Panel
- Hepatitis C: The Basics Online Course www.bccdc.ca/health-professionals/education-development/hepatitis-c-the-basics-online-course
  - This course is designed to help people manage their self-care, whether they are at risk for catching hepatitis C, newly infected, or have lived with hepatitis C for many years.
- Hepatitis Education Canada https://www.hepatitiseducation.ca/

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Abbreviations

- AFP Alpha-fetoprotein
- ALT Alanine transaminase
- AMMI Association of Medical Microbiology and Infectious Disease
- AST Asparate aminotransferase
- BCCDC BC Centre for Disease Control
- CASL Canadian Association for the Study of the Liver
- CMV Cytomegalovirus
- DAA Direct-acting antiviral agent
- EBV Epstein-Barr virus
- HAV Hepatitis A virus
- HBIg Hepatitis B immune globulin
- HBV Hepatitis B virus
- HCC Hepatocellular carcinoma
- HCV Hepatitis C virus
- HDV Hepatitis D virus
- HEV Hepatitis E virus
- HIV Human immunodeficiency virus
- INR International normalized ratio
- PHAC Public Health Agency of Canada
- PHL Public Health Laboratory
- SVR Sustained virologic response
- TNF Tumour Necrosis Factor

This guideline is based on scientific evidence current as of the effective date.

The guideline was developed by the Guidelines and Protocols Advisory Committee in collaboration with BC's Agency for Pathology and Laboratory Medicine and adopted by the Medical Services Commission.

For more information about how BC Guidelines are developed, refer to the GPAC Handbook available at BCGuidelines.ca: GPAC Handbook.

THE GUIDELINES AND PROTOCOLS ADVISORY COMMITTEE

The principles of the Guidelines and Protocols Advisory Committee are to:

- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

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Disclaimer

Appendix 1 – Hepatitis B and Hepatitis C Endemic Countries

Complete lists of Hepatitis B and Hepatitis C endemic countries may be found in the CDC Yellow Book 2020, Chapter 4, Hepatitis B and Hepatitis C.

Offer one-time hepatitis B screening to people originating from countries with prevalence rates ≥ 2%, and immunize as appropriate.[1] **Offer one-time hepatitis C screening to people originating from countries with prevalence rates > 3%.**[2] Follow-up testing thereafter should be based upon a risk assessment.

CASL recommends screening individuals born or living in the following areas:

- Central, East and South Asia
- Australasia and Oceania
- Eastern Europe
- Sub-Saharan Africa
- North Africa or Middle East

Hepatitis B and C in British Columbia

Consideration of local data may be more relevant and able to help further guide clinical practice. The following tables list the top countries of origin of people diagnosed with hepatitis B or C in British Columbia.[3]

Hepatitis B in British Columbia

Region	Countries *In descending order of prevalence within each region*
Central, East or South Asia	China, Hong Kong, Taiwan, Korea, Japan, Vietnam, Pakistan, India, Bangladesh
Eastern Europe	Russia, Ukraine, Romania, Cyprus
South America	Brazil
Sub-Saharan Africa	Nigeria, Ghana, Somalia
North Africa or Middle East	Iran, Turkey

Hepatitis C in British Columbia

Region	Countries *In descending order of prevalence within each region*
Central, East or South Asia	China, Hong Kong, Taiwan, Vietnam, Pakistan, India
Eastern Europe	Russia, Romania, Ukraine, Cyprus
Sub-Saharan Africa	Somalia
North Africa or Middle East	Iran, Turkey, Lebanon, Egypt

1 Greenaway C, et al. Canadian Collaboration for Immigrant and Refugee Health (CCIRH). Appendix 5: Hepatitis B: evidence review for newly arriving immigrants and refugees. 2011. Available from: http://www.cmaj.ca/content/cmaj/suppl/2010/06/07/cmaj.090313.DC1/imm-hepb-5-at.pdf

2 Shah H, Bilodeau M, Burak KW, Cooper C, Klein M, Ramji A, Smyth D, Feld JJ. The management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the Liver. CMAJ. 2018 Jun 4;190(22):E677-87. Available from: http://www.cmaj.ca/content/cmaj/190/22/E677.full.pdf

3 British Columbia Hepatitis Testers Cohort (BC-HTC). Countries of origin of persons diagnosed with Hepatitis C between 2011-2015 as identified with the validated name-recognition software Onomap. Unpublished data. Note: China, Hong Kong and Taiwan are grouped due to similarities in naming.

Appendix 2 – Hepatitis Laboratory Tests

Laboratory Tests Available for HAV, HBV and HCV

Hepatitis A	Anti-HAV Total (anti-HAV IgG + anti-HAV IgM) or Anti-HAV IgG		• Immunity from past infection or vaccination. • Pre-vaccination testing is only indicated for populations where there may be higher levels of pre-existing immunity (e.g., chronic liver disease, HBV or HCV co-infection). Refer to the BCCDC Immunization Manual. • There are no indications for post-vaccination HAV serology or boosters following a complete hepatitis A vaccine series. Almost 100% of immune competent vaccine recipients will develop immunity.
	Anti-HAV IgM		Acute HAV requires confirmation with clinical history, as a positive anti-HAV IgM can indicate: • Acute hepatitis A infection. • Recent hepatitis A vaccination. About 5% of people immunized with hepatitis A vaccine will develop a positive anti-HAV IgM. • A false-positive test result, given the low prevalence of HAV infections in BC. • A remote resolved infection with HAV (can remain detectable for years after acute infection).
Hepatitis B	HBsAg	Screening tests	• Implies acute or chronic HBV infection. • Remains positive for 3-4 weeks after receipt of hepatitis B vaccine.
	Anti-HBs	Screening tests	• Immunity due to vaccination or past infection. • Remains positive for approximately 6 months following hepatitis B immune globulin (HBIg). • Anti-HBs ≥ 10 IU/L confirms a protective antibody level and does not have to be repeated if immune competent. Even with waning antibody levels, protective immunity persists for decades. • Pre-vaccination testing is appropriate only in certain populations (see the BCCDC Hepatitis B Guidelines, Section 4.4). • Post-vaccination testing is not necessary for people who do not have a known risk, except in certain populations (see the BCCDC Hepatitis B Guidelines, Section 4.5 and Table 4-2).
	Anti-HBc Total (IgG + IgM)	Screening tests	• Identifies prior HBV infection. • Not present after immunization. • Can be false positive in areas of low HBV prevalence.
	Anti-HBc IgM		• Rarely required for clinical management. Requires clinical correlation for interpretation. • Appears early in acute infection, lasting > 6 months. • Can occur in approximately 20% of people with chronic HBV infection during flares or reactivation.
	HBeAg	*Used by specialists to monitor treatment.* ***Not*** *for routine testing in general practice.*	• Indicates viral replication and correlates with higher HBV DNA levels. • Identifies infected individuals at higher risk for transmitting HBV.
	Anti-HBe	*Used by specialists to monitor treatment.* ***Not*** *for routine testing in general practice.*	• Identifies infected individuals at lower risk for transmitting HBV.
	HBV DNA	*Used by specialists to monitor treatment.* ***Not*** *for routine testing in general practice.*	• Indicates the magnitude of HBV replication and risk of disease progression. • Useful for therapeutic monitoring of chronic HBV infection. • High viral load correlates with a higher risk of cirrhosis and HCC.

Hepatitis C	Anti-HCV	• Indicates infection with HCV at some point in time. • Does not differentiate between a resolved case and current infection (approximately 25% of people will spontaneously clear an initial HCV infection). • Detectable within 5-10 weeks after infection. If immunocompromised (e.g., HIV where CD4+ is less than 50), there may be a delay in seroconversion and this can lead to a false negative. • Usually persists for life and does not need to be repeated once positive, even if successfully treated or after an infection has spontaneously cleared on its own. • Antibodies are not protective. If someone has cleared an initial HCV infection (whether spontaneously or due to treatment), they can get reinfected.
	HCV RNA	• Confirms current infection with HCV. • HCV RNA levels do not correlate with disease progression. • Used to determine successful virological cure 12 weeks post-treatment (sustained virological response, SVR12) and to monitor for HCV re-infection.
All Hepatitis	ALT, AST (not routinely required but needed to generate the APRI score), Platelets, Albumin, INR	• Elevation reflects hepatocyte injury. • Can occur in acute or chronic hepatitis and other types of liver disease. • Patients with severe cirrhosis may have ALT levels within the normal range. • The AST to Platelet Ratio Index (APRI) is an indirect method of predicting significant and severe fibrosis or cirrhosis and is one of the acceptable methods of staging needed when applying for HCV treatment coverage (www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/special-authority). • For an online APRI calculator, see www.hepatitisc.uw.edu/page/clinical-calculators/apri. • See the associated BC Guideline: Abnormal Liver Chemistry - Evaluation and Interpretation.

Appendix 3 – Hepatitis B Serology Results and Interpretation

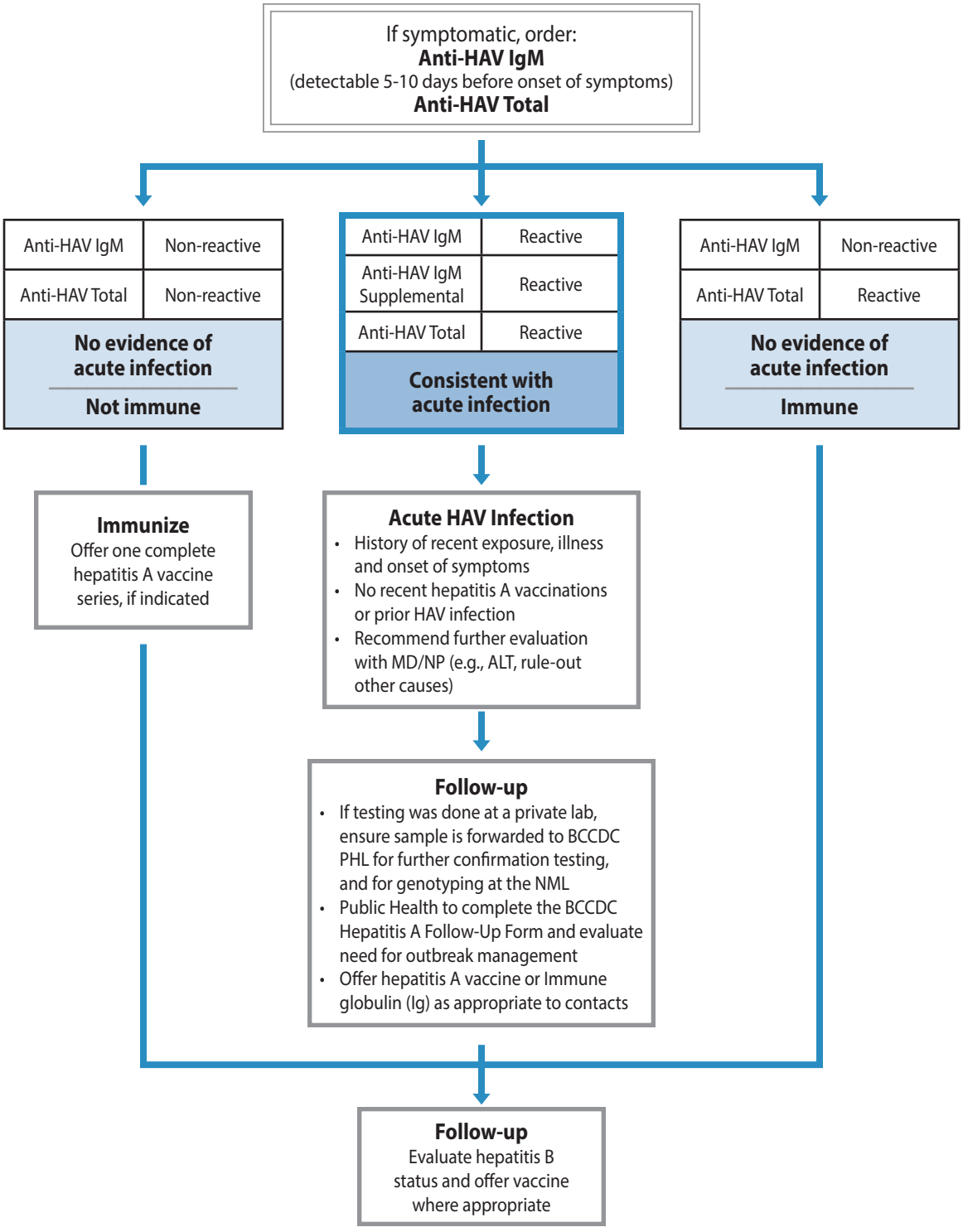
Diagnosis of HBV infection is usually through serological and virological markers. The incubation period of HBV infection ranges from 4 to 12 weeks, and has a wide spectrum of clinical manifestations. The results of hepatitis B serologic testing and their corresponding interpretation are shown in below.

HBV Serology Results and Interpretation

Serology markers						Interpretation + = reactive, - = non-reactive
HBsAg	anti-HBs	anti-HBc Total	anti-HBc IgM*	HBeAg*	anti-HBe*	
–	–	–				No evidence of HBV infection. Offer vaccine.
–	+	–				Immune due to vaccination.
–	+	+				Past HBV infection = immune; If immunosuppressed, can result in reactivation.
+	–	+	+			Acute or chronic hepatitis B infection.
+	–	+	–	+	–	Likely chronic carrier state; highly infectious.
+	–	+	–	–	+	Likely chronic carrier state; infectivity lower.
–	–	+				Four possible interpretations: 1. False positive. 2. Remote resolved infection, with persistence of anti-HBc Total and waning anti-HBs level. 3. Resolved acute infection, prior to appearance of anti-HBs. 4. Occult blood infection (chronic infection, with undetectable HBsAg level). See BCCDC Hepatitis B Guidelines (Table 5-2).
+	+	+		+/–	+/–	Very rarely patients will display HBsAg, anti-HBs and anti-HBc-Total. Such patients are typically chronically infected or may be resolving their infection. They are considered infectious.

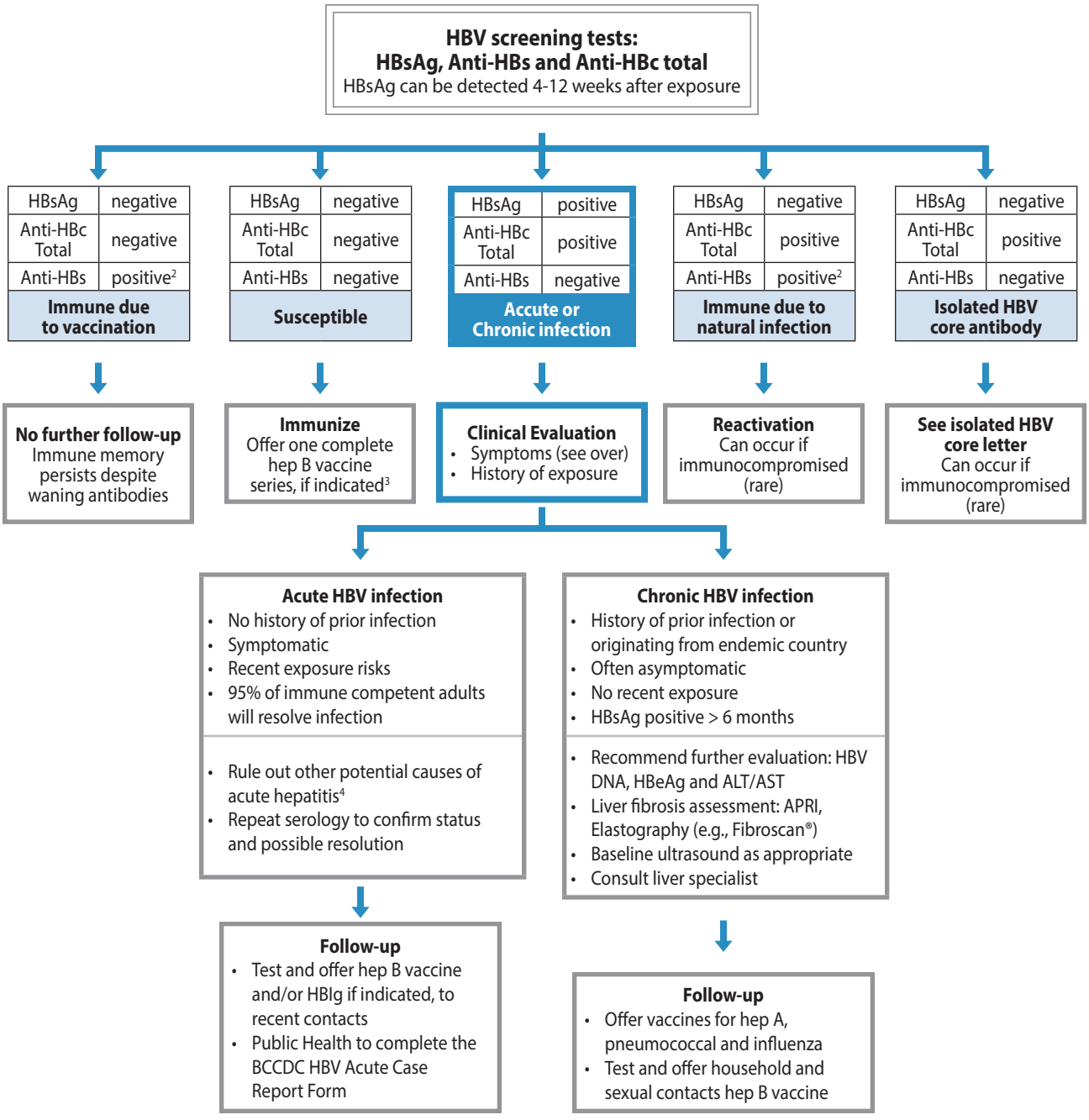
* Not needed for routine diagnosis in general practice. Should be reserved for special circumstances. Used by specialists to monitor treatment.

Appendix 4 – Hepatitis A Testing Guide[1]



[1] BCCDC Hepatitis A Guideline (2018). Available from: www.bccdc.ca/health-professionals/clinical-resources/communicable-disease-control-manual/communicable-disease-control

Appendix 5 – Hepatitis B Testing Guide[1]



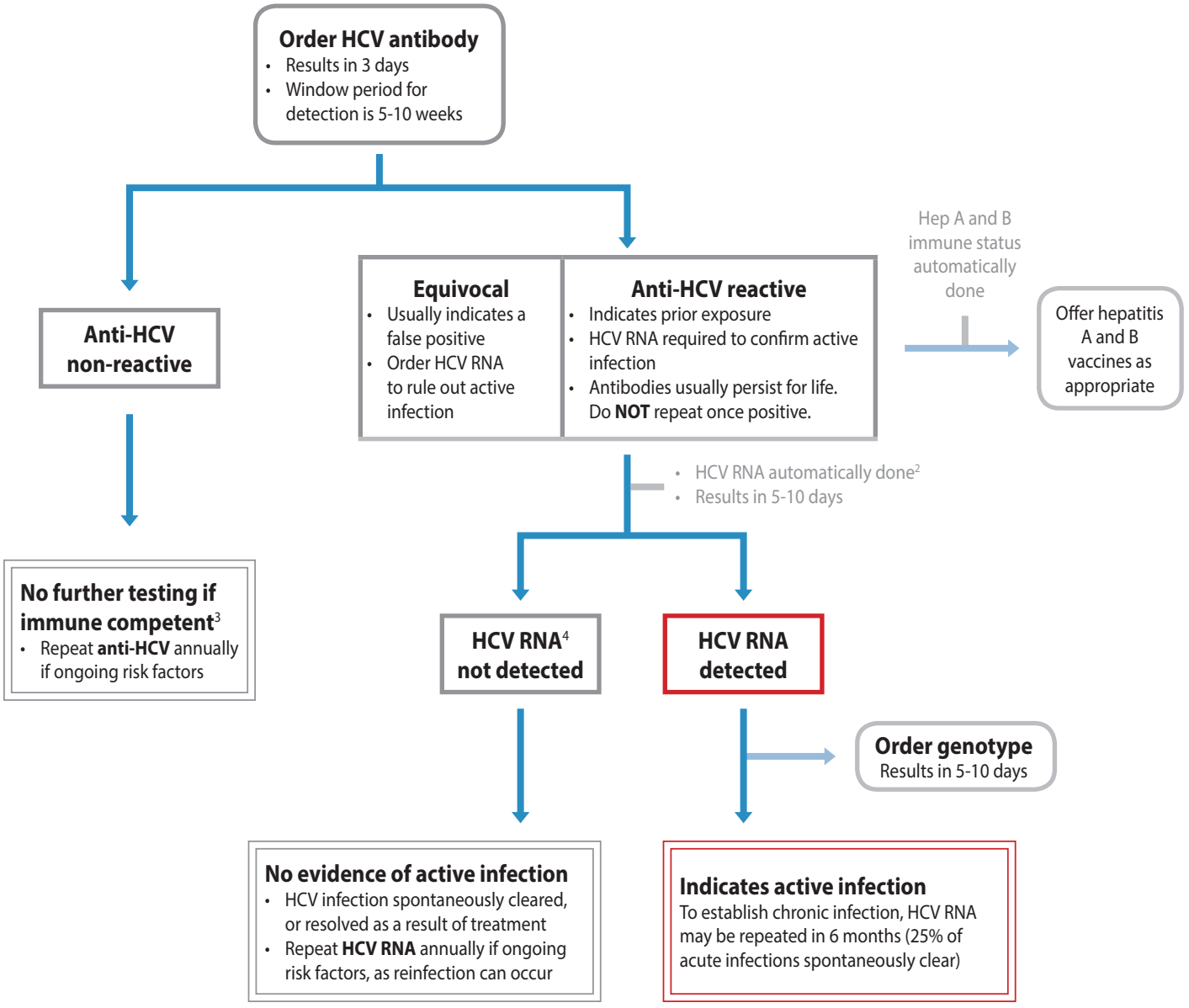
[1] BCCDC Hepatitis B Testing Guide (2018). Available from: www.bccdc.ca/health-professionals/clinical-resources/communicable-disease-control-manual/communicable-disease-control

[2] Anti-HBs ≥ 10 IU/L

[3] If prior vaccination history and/or anti-HBs is detectable but <10 IU/L, see the BCCDC Hepatitis B Guidelines and Immunization Manual For post-exposure prophylaxis, see the BCCDC Hepatitis B Guidelines Manual and Blood and Body Fluid Exposure Management Guidelines.

[4] Other infectious causes include Hepatitis A, C, D and E, Cytomegalovirus and Epstein-Barr Virus. Non-infectious causes include hepatotoxic drugs, autoimmune hepatitis, Wilson's disease, vascular causes, or other pre-existing chronic liver diseases. Screen for HIV infection.

Appendix 6 – Hepatitis C Testing Guide[1]



1 BCCDC Hepatitis B Testing Guide (2018). Available from: www.bccdc.ca/health-professionals/clinical-resources/communicable-disease-control-manual/communicable-disease-control

2 Automatic HCV RNA testing done as of January 13/20 on all ***first time*** anti-HCV reactive results, and previously anti-HCV reactive results where HCV RNA testing has ***never*** been done. Instructions will be provided on the BCCDC PHL lab result in situations where an additional EDTA tube is required for HCV RNA testing to be completed.

3 False negatives may occur in the presence of major immunosuppression (e.g., HIV infection where CD4 + < 50 cells/mm^3 and agammaglobulinemia). Order HCV RNA where appropriate.

4 Instructions will be provided on the BCCDC PHL lab result to collect an EDTA tube for HCV RNA testing to confirm an initial HCV RNA 'not detected' result.

Appendix 7 – Management and Recommended Tests for Individuals Already Diagnosed with Viral Hepatitis[1, 2, 3, 4]

Virus	Test	Frequency/Indication
Hepatitis A	Self-limited disease not requiring ongoing serological follow-up.	
Chronic hepatitis B ***Consultation with or referral to a specialist is strongly recommended.*** All patients require a thorough evaluation at baseline to determine the need for treatment.	HBV DNA	Every 6-12 months (every 3-6 months if on treatment).
	ALT	Every 6-12 months (every 3-6 months if on treatment). *AST is not required for routine diagnosis, only when the APRI score is needed to assess fibrosis for treatment.
	HBsAg	Used to assess loss of HBsAg with treatment.
	HBeAg	Could be replaced by HBV DNA. Generally limited for use by specialists to monitor patients on treatment.
	Anti-HBe	
	Non-invasive fibrosis assessment (e.g., Fibroscan®, APRI)	On treatment: consider every 2-3 years. Not on treatment: consider annually.
	Ultrasound (HCC monitoring) Note: serum alpha-fetoprotein (AFP) monitoring is not recommended if ultrasound is available	Every 6 months for the following: • All individuals of any age with cirrhosis • Asian men 40 years and older • Asian women 50 years and older • Persons of African origin aged 20 years or older (higher risk for HCC even in the absence of cirrhosis) • Family history of HCC (starting at age 40 years) • All individuals with HIV co-infection (starting at age 40 years)
	Anti-HBs	If on treatment, consider annually to check for seroconversion.
	Anti-HBc IgM, anti-HBc Total	Not indicated after initial diagnosis.
	Anti-HCV	If anti-HCV negative, annually if there are ongoing acquisition risk factors. If anti-HCV positive, annual HCV RNA if there are ongoing acquisition risk factors.
	Anti-HDV	If starting treatment and resided in an endemic country (Table 1) or prior/current IDU, screen for HDV. Consider repeating if ongoing risks of new infection.
	Note 1: Offer hepatitis A vaccine as appropriate. There are no indications for post-vaccination HAV serology (can be falsely negative) or boosters. In new hepatitis B patients testing through the BCCDC PHL, anti-HAV total is reflexively performed to identify prior hepatitis A immune status and those individuals who would benefit from hepatitis A vaccine.	
	Note 2: HBV antiviral resistance testing may be indicated for patients failing antiviral treatments. ***Requires expertise to accurately interpret. Specialist consultation is strongly recommended.***	

1 This reflects the expert opinion of the working group

2 Coffin CS, et al. (2018). Management of Hepatitis B Virus Infection: 2018 Guidelines from the Canadian Association for the Study of Liver Disease and Association of Medical Microbiology and Infectious Disease Canada. Available from: canlivj.utpjournals.press/doi/full/10.3138/canlivj.2018-0008

3 Shah H, et al (2018). The management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the liver. Available from: www.cmaj.ca/content/cmaj/190/22/E677.full.pdf

4 Shah H, et al (2018). Update on the management of chronic hepatitis C: 2018 consensus guidelines from the Canadian Association for the Study of the Liver. Available from: www.cmaj.ca/content/cmaj/suppl/2018/05/29/190.22.E677.DC1/170453-guide-1-at.pdf

Management of Chronic Hepatitis C Infection

Ongoing drug and/or alcohol use are *not* contraindications to HCV treatment. HCV treatment should be one part of a comprehensive approach to care, which should aim to address acquisition risk factors, comorbidities, and emphasize principles of harm reduction where appropriate.

The significant advances in being able to cure HCV infection, and control HBV infection, should inform who to test and engage into care. More than 95% of people with chronic HCV infection can now be cured in 8-16 weeks with newer all oral direct-acting antivirals (DAA).[5] Unlike prior interferon/ribavirin treatment, DAA's are very well-tolerated with few side effects. **Anybody known to have HCV infection, but not previously treated and cured, should be recalled and referred for treatment. *Refer to a specialist if a patient has HBV/HCV co-infection, as if*** HCV treatment is indicated, ongoing monitoring and/or treatment for HBV may be recommended to avoid reactivation of HBV infection.

Curing HCV infection reduces morbidity and mortality, and prevents forward transmission (see the Management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the Liver). Canada has signed onto the World Health Organization targets of hepatitis B and C elimination by 2030.[6] **As of 2018, an estimated 28,607 people in BC living with hepatitis C infection (diagnosed and undiagnosed) remain untreated.**[7] This highlights the importance of engaging those who have already been diagnosed into comprehensive care for hepatitis C treatment.

As of March 2018, PharmaCare registered British Columbians with chronic HCV infection are eligible for publicly-funded HCV treatment through BC's special authority program (see forms to review requirements). Coverage is subject to the rules of a patient's PharmaCare plan, including any deductibles/ ensuring patients are registered.

[5] Krajden M, Cook D, Janjua NZ. Contextualizing Canada's hepatitis C virus epidemic. Can Liver J [Internet]. 2018 Dec 1 [cited 2019 Apr 3]; Available from: https://canlivj.utpjournals.press/doi/abs/10.3138/canlivj.2018-0011

[6] WHO | Combating hepatitis B and C to reach elimination by 2030 [Internet]. WHO. [cited 2019 Apr 3]. Available from: http://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/

[7] Bartlett SR, Yu A, Chapinal N, Rossi C, Butt Z, Wong S, et al. The population level care cascade for hepatitis C in British Columbia, Canada as of 2018: Impact of Direct Acting Antivirals. Liver Int. doi: 10.1111/liv.14227.

Virus	Test	Frequency/Indication
Hepatitis C infection Consult with a specialist as needed. All individuals diagnosed with hepatitis C infection are eligible for treatment, regardless of fibrosis staging.	HCV RNA	• At baseline. • Consider at end-of-treatment (EOT). • 12 weeks after the end of treatment to assess for SVR-12 (sustained virologic response). • If SVR-12 is achieved and there is on-going risk for reinfection, annual HCV RNA testing is recommended. • As of January 13, 2020, the BCCDC PHL reflexively tests for HCV RNA on first time anti-HCV reactive results and previously reactive anti-HCV results, where HCV RNA testing has never been done.
	HCV genotype	• At baseline (this may not be required at baseline in the future with pan genotypic regimens). • If therapy fails. • If subsequent reinfection is suspected.
	CBC, liver enzymes (ALT, AST*, Alk Phos), liver function (bilirubin, INR, albumin), Creatinine, Serum transferrin saturation, IgG	At baseline. ***Consult with a specialist if eGFR < 30 mL/min or elevated IgG.*** *AST is not required for routine diagnosis, only when the APRI score is needed to assess fibrosis for treatment.
	HIV	At baseline. ***Refer to specialist if HIV/HCV co-infected.*** If HIV negative and ongoing risk factors, test every 6-12 months. Offer HIV Pre-exposure Prophylaxis (PrEP) where appropriate.
	HBV screening (HBsAg, anti-HBs, anti-HBc Total)	At baseline. Reflexively tested on all anti-HCV positive specimens performed at the BCCDC PHL. ***Refer to specialist if HBV/HCV co-infected.*** Offer hepatitis B vaccine as appropriate.
	Non-invasive fibrosis assessment (e.g., Fibroscan®, serum-based fibrosis markers such as APRI) to exclude cirrhosis. Ultrasound (a normal U/S result does not exclude cirrhosis).	At baseline. ***Refer to a specialist if showing evidence of cirrhosis (compensated or decompensated) or HCC.***
	HCV resistance testing	Not routinely recommended. Helps guide treatment in those who have previously failed treatment and those with severe liver fibrosis/decompensated liver disease. Refer to the HCV CASL Guidelines for more information. ***Requires expertise to accurately interpret. Specialist consultation is strongly recommended.***
	Note: HAV testing is reflexively done on all anti-HCV positive specimens performed at the BCCDC PHL to identify vaccination status. Offer hepatitis A vaccine as appropriate. There are no indications for HAV post-vaccination serology or boosters.	
Hepatitis D	HDV testing and follow-up care is generally limited to specialists.	
Hepatitis E	HEV testing and follow-up care is generally limited to specialists.	

Appendix 8 – List of Immune Compromising Treatments CASL (2018) – Management of HBV Infection[1]

Risk of HBV reactivation with immunosuppression and chemotherapy in HBsAg-Positive, and HBsAg-Negative, anti-HBc Total positive patients.[11] TNF = tumour necrosis factor

Risk Level	HBV serology	Immunosuppressive or chemotherapy
High-risk (> 10% chance of reactivation)	HBsAg positive OR HBsAg negative and anti-HBc Total positive (high risk regardless of anti-HBs titre levels)	• B-cell-depleting agents such as rituximab and ofatumumab.
	HBsAg positive	• Anthracycline derivatives such as doxorubicin and epirubicin. Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent > 10–20 mg/day).
Moderate-risk (1-10% chance of reactivation)	HBsAg positive OR HBsAg negative and anti-HBc Total positive (may be lower risk and monitoring may be sufficient if high anti-HBs titres > 100 IU/L)	• TNF-α inhibitors: etanercept, adalimumab, certolizumab, infliximab. • Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab. • Tyrosine kinase inhibitors: imatinib, nilotinib, ibrutinib.
	HBsAg positive	• Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent < 10 mg/day).
	HBsAg negative and anti-HBc Total positive (may be lower risk and monitoring may be sufficient if high anti-HBs titres > 100 IU/L)	• Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent > 10–20 mg/day). • Anthracycline derivatives: doxorubicin and epirubicin.
Low-risk (< 1% chance of reactivation)	HBsAg positive OR HBsAg negative and anti-HBc Total positive (low risk especially if high anti-HBs titres > 100 IU/L)	• Traditional immunosuppressive agents: azathioprine, 6-mercaptopurine, methotrexate Intra-articular corticosteroids. • Corticosteroid therapy for ≤ 1 week.
	HBsAg negative/anti-HBc Total positive (low risk especially if high anti-HBs titres > 100 IU/L)	• Corticosteroid therapy for ≥ 4 weeks (prednisone equivalent < 10 mg/day).

[1] Coffin CS, Fung SK, Alvarez F, Cooper CL, Doucette KE, Fournier C, et al. Management of Hepatitis B Virus Infection: 2018 Guidelines from the Canadian Association for the Study of Liver Disease and Association of Medical Microbiology and Infectious Disease Canada. Can Liver J [Internet]. 2018 Dec 1 [cited 2019 Apr 18]; Available from: https://canlivj.utpjournals.press/doi/abs/10.3138/canlivj.2018-0008