

Viral Hepatitis Testing

Scope

This guideline provides recommendations for the appropriate use of laboratory tests to diagnose acute and chronic viral hepatitis in British Columbia and supplements the guidelines, *Clinical Management of Hepatitis B* and *Clinical Management of Hepatitis C*. These recommendations cover testing for hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Not considered here are the Delta or hepatitis D virus (HDV), which requires concurrent or antecedent infection with HBV for its replication and the hepatitis E virus (HEV), which manifests as acute viral hepatitis, but is uncommon in North America. Once a diagnosis of acute or chronic viral hepatitis has been made, further laboratory investigations may be indicated.

RECOMMENDATION 1 General considerations for ordering laboratory tests

Prior to ordering tests for hepatitis, the physician should consider the patient's history, age, risk factors, vaccination status and any available previous hepatitis test results. It must be recognized that an established infection with one hepatitis virus does not exclude co- or superinfection with other hepatitis viruses or other agents such as cytomegalovirus or Epstein-Barr virus, although such dual infections are considered uncommon. Other possibilities to be considered include hepatotoxic drugs including herbal medicines.

Risk factors for viral hepatitis include:

- Substance abuse (e.g. injection drug use, snorting cocaine)
- High-risk sexual activity (e.g. men who have sex with men, traumatic sex)
- Multiple sexual partners
- A sexual partner with viral hepatitis
- Travel to high-risk hepatitis endemic areas or exposure during a local outbreak
- Household contact with an infected person especially if personal items (e.g. razors, toothbrushes, nail clippers) are shared
- Attendance at daycare
- History of a transfusion-dependent illness
- Needle-stick injury or other occupational exposure (e.g. healthcare workers)
- Receipt of blood products prior to 1990
- Newborn of infected mother
- Tattoos and body piercing
- Contaminated food or water (hepatitis A only)

RECOMMENDATION 2**Workup for a patient suspected of having chronic viral hepatitis (chronic carrier)**

Both HBV and HCV can cause chronic infection. If the clinical history and risk factors are consistent with infection by these viruses, the tests indicated in Algorithm 1 and Appendix 2 permit a definitive laboratory diagnosis to be made in most cases. Chronic HBV infection is characterized by the presence of HBsAg in the blood for longer than 6 months. HCV infections are typically chronic and are characterized by the presence of anti-HCV in the blood together with the presence of HCV RNA as monitored by nucleic acid testing (e.g. HCV PCR).

To investigate chronic viral hepatitis, laboratory tests for the following markers may be considered:

- HBsAg (hepatitis B surface antigen)
- Anti-HBc-Total (total antibody to hepatitis B core antigen)
- Anti-HBs (antibody to hepatitis B surface antigen)
- Anti-HCV (antibody to hepatitis C virus antigens)
- ALT (alanine aminotransferase), the prime marker of hepatic inflammation in viral hepatitis

Selection of tests is influenced by the patient's past history of testing or vaccination. For example, if the patient is documented to be immune to HBV (i.e. a positive anti-HBs ± positive anti-HBc-total (IgM & IgG) due to vaccination or past infection), only testing for HCV should be requested.

Interpretation of Results**HBsAg**

- If negative, HBV infection is ruled out (with the rare exception of the “window period” – see Appendix 1, – comments on Anti-HBc-IgM).
- If positive, patient is infected with HBV and is infectious. If positive for longer than 6 months, then the patient has a chronic HBV infection. Once a chronic HBV diagnosis is made, testing for the presence of HBeAg (hepatitis e antigen) or HBV DNA can help identify individuals who may benefit from treatment. Interpretation of these tests is complicated and specialist input is recommended. See guideline: *Clinical Management of Hepatitis B* (<http://www.healthservices.gov.bc.ca/msp/protoguides/gps>). All household and sexual contacts of a chronic HBV carrier should be investigated for HBV infection.

Anti-HBc-total (IgM & IgG)

- If negative, past infection with HBV is ruled out.
- If positive, patient has been infected with HBV. Infection may be resolved or ongoing (HBsAg positive). If infection is resolved, the patient is considered naturally immune to HBV infection. See Appendix 1 for exceptions.

Anti-HBs

- If < 10mIU/ml, the patient has no apparent immunity to HBV (see Recommendation 4, page 4).
- If ≥10mIU/ml, the patient is considered immune to HBV (either because of resolved infection or as a result of prior vaccination). Very rarely (<1%) chronic carriers can be positive for HBsAg and anti-HBs at the same time.

Anti-HCV

- If negative, chronic HCV infection is ruled out in an immunocompetent patient.
- In immunocompromised patients, the anti-HCV response may be blunted and a qualitative test for HCV-RNA may be required to rule out occult infection.
- If positive, the patient has been infected with HCV. Most infections are chronic (mean 75%, range 50% to 85%).
- Active infection can be confirmed by a qualitative test for HCV-RNA. Treatment is indicated for those chronically infected if their serum transaminases are elevated. See guideline: *Clinical Management of Chronic Hepatitis C* (<http://www.healthservices.gov.bc.ca/msp/protoguides/gps>).

ALT

In chronic infection, levels may be consistently or intermittently elevated or even normal. Sustained elevations are typically correlated with increased hepatic inflammation and an increased risk of progression to cirrhosis. Rarely, patients with end stage liver disease may have normal ALT levels.

RECOMMENDATION 3 Workup for the patient suspected of having acute viral hepatitis

Acute viral hepatitis in North America is mainly caused by HAV, HBV and HCV. If the clinical history and risk factors are consistent with infection by these viruses, tests indicated in Algorithm 2 and Appendix 2 can be used to establish a definitive diagnosis. The patient generally presents with an abrupt onset of non-specific symptoms over several days to weeks. Typically the ALT levels are markedly elevated and jaundice may be evident.

To investigate acute viral hepatitis, laboratory tests for the following markers may be considered:

- Anti-HAV-IgM (IgM class antibody to the hepatitis A virus)
- HBsAg (hepatitis B surface antigen)
- Anti-HBs (total antibody to hepatitis B surface antigen)
- Anti-HCV (antibody to hepatitis C virus antigens)
- ALT (alanine aminotransferase), the prime marker of hepatic inflammation in viral hepatitis
- INR (International Normalized Ratio; prothrombin time) for patients clinically jaundiced

Selection of tests is influenced by the patient's past history of testing or prior vaccination. For example, if the patient is documented to be immune to HBV due to vaccination or past infection, only testing for HAV and HCV should be requested.

Interpretation of Results

Anti-HAV-IgM

- If negative, HAV infection is ruled out in immunocompetent patients.
- If positive, this is consistent with acute HAV infection. Anti-HAV-IgM may remain detectable for up to 2 years; hence its presence must be correlated with clinical presentation to establish an accurate diagnosis.

HBsAg

- If negative, HBV infection is ruled out.
- If positive, the patient is infected with HBV and is infectious.
- A repeat test at 6 months will determine if infection has resolved or if the infection has become chronic.
- All household and sexual contacts of a chronic HBV carrier should be investigated for HBV infection and offered HBV vaccination if not immune.

Anti-HBs

- If negative, patient has no apparent immunity to HBV (see Recommendation 4, page 4).
- If positive, the patient is considered immune to HBV (either because of resolved infection or prior vaccination).

Anti-HCV

- If negative, HCV infection is ruled out in most immunocompetent patients.
- If negative and no other etiology is apparent, a repeat anti-HCV test after 1-2 months is indicated since this marker only begins to become detectable 5-6 weeks after infection.
- If patient is immunocompromised, and no other cause of hepatitis is diagnosed, a qualitative test for HCV-RNA should be requested.
- If positive, patient has been infected with HCV. Infection may be acute or chronic. Active infection can be confirmed with a qualitative test for HCV-RNA. Treatment may be indicated for new infections with HCV (within 3 months of onset). See guideline: *Clinical Management of Chronic Hepatitis C* (<http://www.healthservices.gov.bc.ca/msp/protoguides/gps>).

ALT

Markedly elevated in patients with acute viral hepatitis.

INR

An elevated INR in a patient with jaundice may be a sign of fulminant hepatitis and highlights the need for specialist consultation.

RECOMMENDATION 4 Workup to determine immune status to HAV and HBV

Although immune status for HAV and HBV can be established by appropriate laboratory tests, these tests should only be requested under specific circumstances described below. When clinically appropriate, individuals who are not immune and who are at risk for HAV and/or HBV should be offered vaccination. Funded vaccine is available for most high-risk groups other than travelers to endemic areas.*

Testing for immune status for HAV is recommended for:

- People with chronic HBV or HCV infection or other liver diseases (e.g., alcoholic cirrhosis, hemochromatosis, biliary cirrhosis).
- People at high risk of acquiring HAV infection such as travelers to endemic areas* or men who have sex with men.

Testing for HAV vaccine-induced immunity is not recommended.

- HAV vaccine induces immunity in >95% of individuals and the current anti-HAV-total (IgM & IgG) test is relatively insensitive in measuring immune response post vaccination (unacceptable rate of false negative results).

Testing for immune status for HBV is recommended for:

- Individuals with chronic HCV or other chronic liver diseases
- Subjects at high-risk of HBV infection including:
 - Infants born to HBV carrier mothers (to confirm vaccine efficacy)
 - Sexual partners of HBV infected individuals
 - Immunocompromised individuals
 - Health care workers and others at risk of occupational exposure (e.g. needlestick injury).
 - Household contacts of HBV infected individuals
 - Visitors to or immigrants from regions* with high HBV endemic rates

* For information on endemic areas, refer to the Centers for Disease Control Traveler's Health Web site at: <http://www.cdc.gov/travel/diseases.htm#hepa>

To determine immunity to HAV and/or HBV, laboratory tests for the following markers may be selectively indicated:

- Anti-HAV-total (IgM & IgG antibodies to hepatitis A virus)
- Anti-HBs (antibody to hepatitis B surface antigen)

If natural HBV infection suspected, consider ordering:

- Anti-HBc-total (IgM & IgG antibodies to hepatitis B core antigen)

Interpretation of Results

Anti-HAV-total (IgM & IgG)

- If negative and not fully vaccinated, patient is not immune to HAV.
- If positive, patient is immune to HAV. Immunity may have been acquired from a previous infection or from vaccination.
- Individuals with a history of HAV vaccination may have low or undetectable antibody levels, but are still considered immune as noted above.

Anti-HBs (Anti-HBs levels are expressed in international units)

- If <10 mIU/mL, the subject is considered to be non-immune. In individuals who have received a complete course of HBV vaccine, 90-95% will respond with detectable anti-HBs. The level of anti-HBs may drop to <10 mIU/mL after 5-10 years, but these patients are generally considered to be immune.
- If ≥ 10 mIU/mL, the subject is considered to be immune. Such immunity may be due to immunization (95% response rate) or resolved natural infection. These two states can be distinguished by testing for anti-HBc-total (IgM & IgG), which is absent in immunized individuals.

Anti-HBc-total (IgM & IgG)

- If negative, past infection with HBV is ruled out.
- If positive, patient has been infected with HBV. Infection may be resolved or ongoing (HBsAg positive). If infection is resolved, the patient is considered naturally immune to HBV infection.
- Rarely a positive anti-HBc-total (IgM & IgG) will be the only detectable marker of a previous HBV infection. However, this may represent a false positive test result and vaccination is generally recommended.

RECOMMENDATION 5 Special considerations for infants and children

There are several important aspects to the presentation and laboratory evaluation of acute or chronic viral hepatitis A, B and C in pediatric patients.

Hepatitis A

Only a minority of infants (<10%) under 2 years of age with acute hepatitis A will have jaundice in association with markedly elevated ALT levels. An anti-HAV-IgM should be requested for diagnosis (see Recommendation 3). It is important to promptly institute hepatitis A prophylaxis for all household contacts (consult your local public health authority).

Hepatitis B

All infants born to hepatitis B virus carrier mothers (i.e. HBsAg positive) should have received hepatitis B immune globulin (HBIG) and the full course of HBV vaccination (0, 1 and 6 months). For these infants, the following laboratory testing is indicated approximately three months after completion of the HBV vaccination series:

- HBsAg: will be positive in the case of vaccine failure
- Anti-HBc-total (IgM & IgG): to detect infection or passively transmitted maternal antibody
- Anti-HBs: to confirm vaccine effectiveness (see Recommendation 4)

All household contacts of an individual with acute or chronic hepatitis B should be investigated for hepatitis B infection as per Recommendation 2.

Hepatitis C

Children should be screened for HCV if they are born to HCV infected women, received transfusions or other blood products prior to 1990 or have high-risk behavior(s) (see Recommendation 1). Children and adolescents with chronic HCV infection generally have no symptoms.

In newborns, anti-HCV testing is not recommended as a screening test for HCV infection, since maternal antibody can cross the placenta yielding false positive results. In 95% of cases maternal antibody will no longer be detectable in the infant by 12 months of age. In the remaining 5%, maternal antibody will no longer be detectable by 15 to 18 months. A negative anti-HCV at 12 months-of-age virtually excludes maternal-infant transmission.

A qualitative HCV RNA after six weeks of age is the recommended test to demonstrate active HCV infection in neonates. For children older than 18 months of age, the adult recommendations for hepatitis C testing apply (see Recommendations 2 and 3).

The follow up of infants and children with proven chronic hepatitis B or C infection is complex. Consultation with a pediatric specialist with expertise in viral hepatitis is recommended.

Rationale: Hepatitis Viruses - The British Columbia Perspective

Burden of Disease: In British Columbia, approximately 40,000 persons are chronically infected with HCV and another 40,000 individuals are chronically infected with HBV. Without intervention, approximately 15-30% of chronic HBV and HCV infected individuals will develop cirrhosis, end-stage liver disease, liver cancer, or require liver transplantation over the next 20-40 years [1-4]. Approximately 100 British Columbians die of end-stage liver disease each year. The cost of end-stage-liver disease, including lost income, is estimated at \$1,000,000 per person and the cost of liver transplantation is \$100,000-\$200,000 per person. From a public health perspective, the major

challenge is how to prevent new infections in at risk populations and the consequent morbidity and mortality for those already chronically infected.

HCV: No vaccine is currently available. Although blood product transmission of HCV has been virtually eliminated by effective screening of blood donors, parenteral substance abuse remains the major vehicle of ongoing transmission[6-8]. New, effective, but costly HCV treatments (interferon, pegylated interferons with and without ribavirin) can cure (eliminate HCV RNA) in 45-80% of treated individuals[3, 9, 10]. Early treatment with interferon monotherapy at the onset of acute HCV infection may prevent chronic infection in 98% of treated cases[11]. However, early treatment remains controversial[12]. The projected cost of caring for HCV, has been shown to be similar to the cost of asthma (approximately \$5.4 billion per year in the United States)[5].

HBV: A safe and effective vaccine has virtually eliminated HBV in our youth (there is a universal infant (started in 2000) and grade 6 (started in 1991) HBV vaccination program in BC), but decades of vaccination will be required before the entire population is adequately protected because of the large numbers of chronic carriers already living in BC[13]. HBV transmission continues in unvaccinated persons involved in at-risk behaviour with acute or chronically infected individuals (e.g. sexual activity). Treatment for HBV with drugs such as lamivudine and interferon is also evolving rapidly[14]. Both of these drugs can suppress HBV replication and improve the outcome of chronic HBV infection. Although 15-50% of treated HBV patients will have a sustained response, complete viral elimination may not be possible because viral DNA is typically integrated into the host genome[1].

HAV: HAV is now effectively preventable through vaccination. In BC, funded vaccination is currently available through local public health units for people already infected with chronic hepatitis B or C, injection drug users and men who have sex with men. The public health impact of HAV relates to its ease of transmission (fecal-oral), the rare occurrence of fulminant hepatitis and the fact that HAV shares some common risk factors for transmission with HBV and HCV.

Viral hepatitis is typically diagnosed in patients who present with risk factors or non-specific symptoms such as unexplained chronic fatigue or who have been identified during blood donor or insurance testing, or after maternal screening. As most cases of hepatitis remain asymptomatic, it is estimated that only approximately half of infected individuals are diagnosed. Establishing a definitive diagnosis in acute cases and follow-up testing is important to determine whether the infection has resolved or progressed to chronicity. Chronic cases need to be identified to ensure appropriate counseling and/or vaccination and follow-up of contacts. BC currently spends approximately \$10 million/year for hepatitis testing. Only by obtaining much better information on prevention and care management outcomes will we be able to truly apply evidence-based policies to enhance the quality of hepatitis services.

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Sponsors

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

APPENDIX 1

ADDITIONAL TESTS AND RARE OR UNUSUAL FINDINGS

While the above interpretations of test results are suitable for the vast majority of cases, exceptional findings may rarely be reported that require individual interpretation. Some patients may present with autoimmune hepatitis, which complicates both presentation and diagnosis.

Anti-HAV-IgM: While this antibody is typically present at presentation with acute HAV infection, it may continue to be detected in a subset of patients for up to 2 years. It can also be induced following HAV vaccination. On occasion, anti-HAV-IgM may not be detectable at the time of acute clinical presentation. If the clinical assessment is consistent with acute HAV infection, the anti-HAV-IgM should be repeated within 1 to 2 weeks to allow sufficient time for antibody to become manifest.

Anti-HBc-IgM: This antibody is generally detected in patients with acute HBV infection. However, some chronic carriers will also be anti-HBc-IgM positive. Occasionally, this antibody is present in the early convalescence “window period” when the HBsAg and anti-HBs tests are both undetectable. As current tests for HBsAg are very sensitive, testing for anti-HBc-IgM generally has limited value.

Anti-HBc-total (IgM & IgG): Rarely a positive anti-HBc-total will be the only detectable marker of a previous HBV infection. However, this may represent a false positive and vaccination is generally recommended.

Other tests to assist in clinical management of HBV and HCV

HBeAg (hepatitis B e antigen) is a viral antigen, which is correlated with high infectivity and in chronic carriers correlates with an enhanced risk of progression to cirrhosis.

Anti-HBe (antibody to hepatitis e antigen) in chronic carriers generally denotes a less infectious state and a partial resolution of HBV infection.

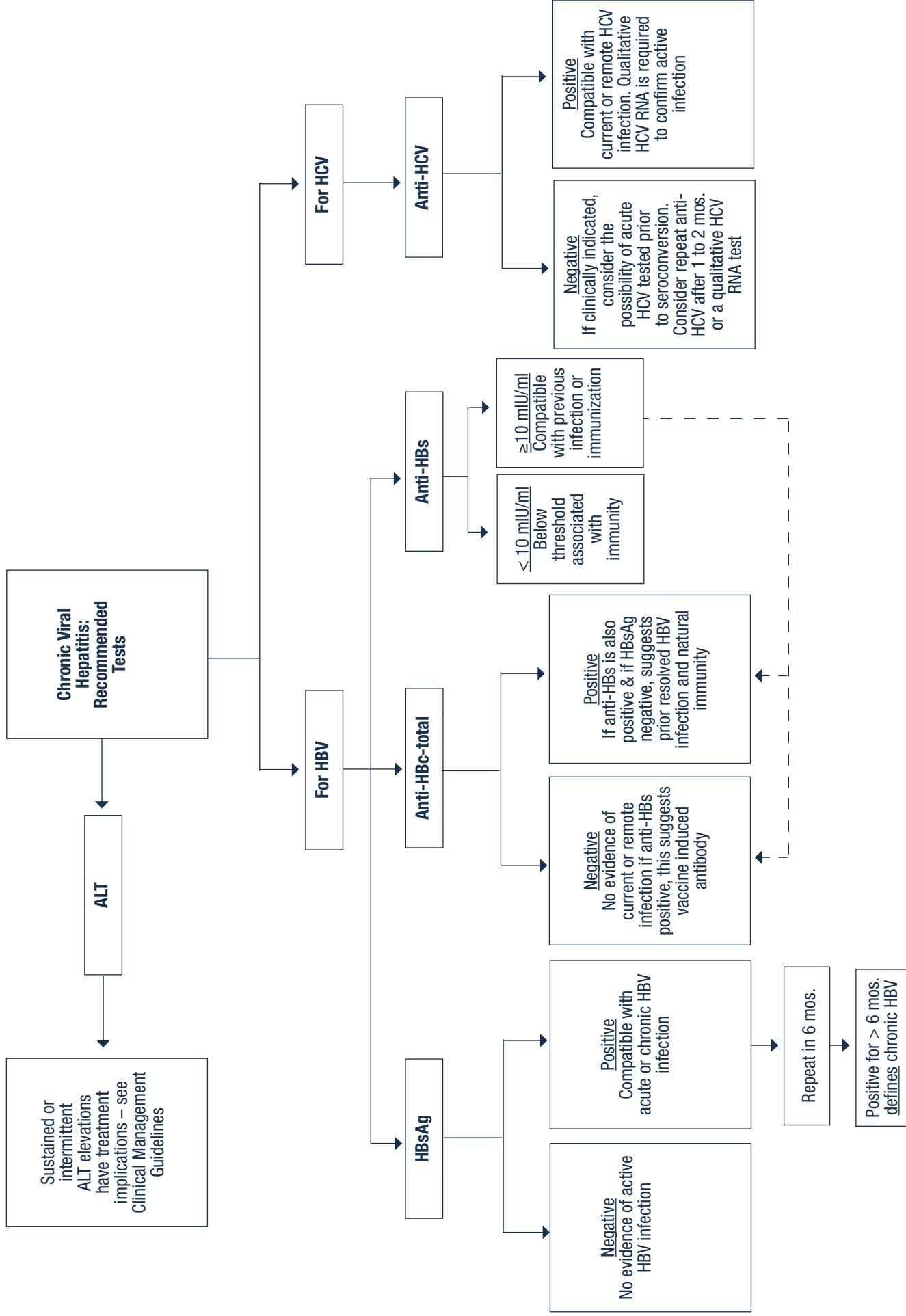
HBV DNA: The presence of HBV DNA in serum or plasma denotes active HBV infection and infectivity.

HCV-RNA: The presence of HCV-RNA in the serum or plasma denotes active infection and infectivity. HCV RNA can be detected as early as 2 weeks after infection, well before the patient presents with symptoms.

HCV antigen: A new HCV antigen test is currently being evaluated for clinical use.

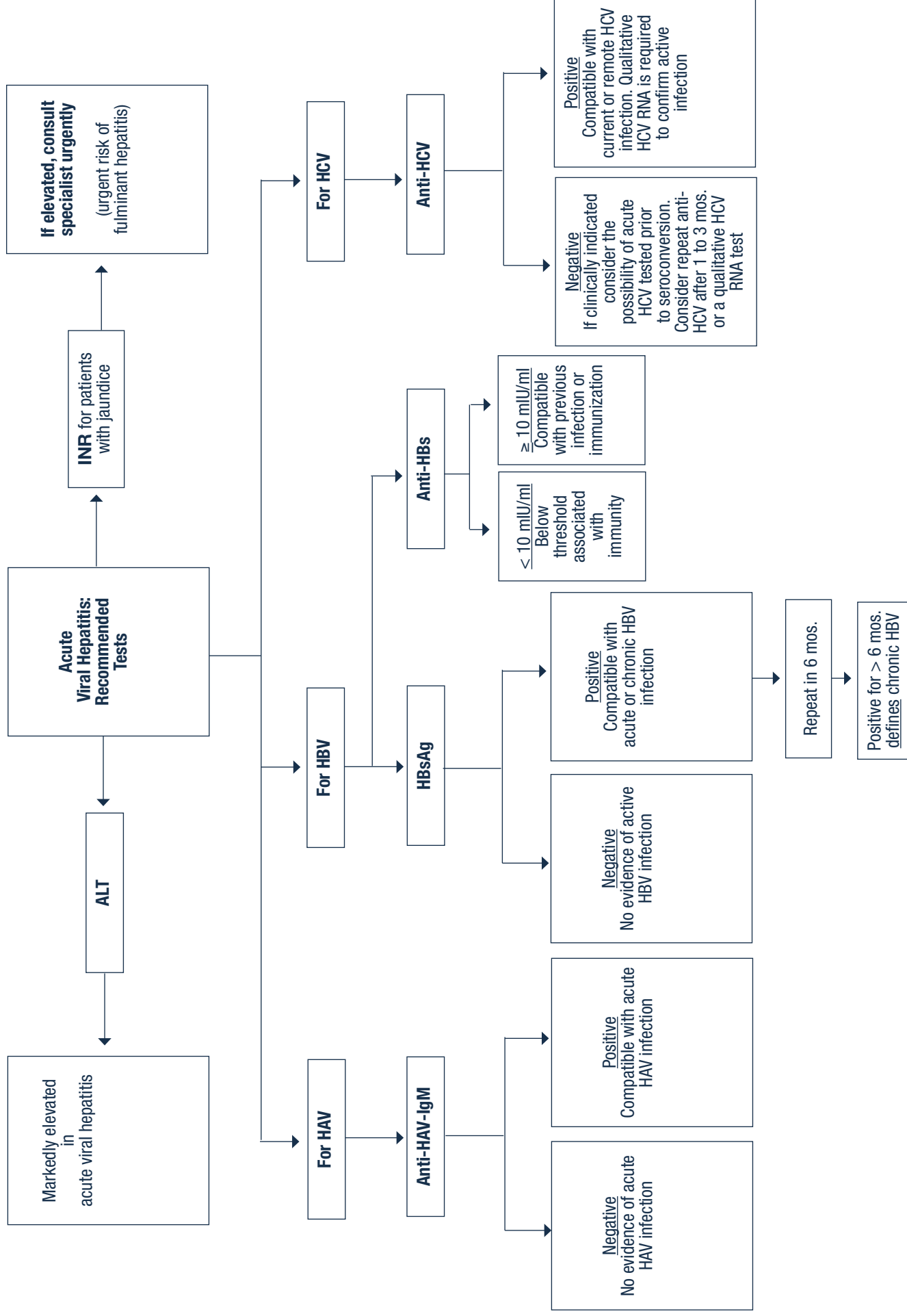
Algorithm 1

Diagnosis of Suspected Chronic Viral Hepatitis

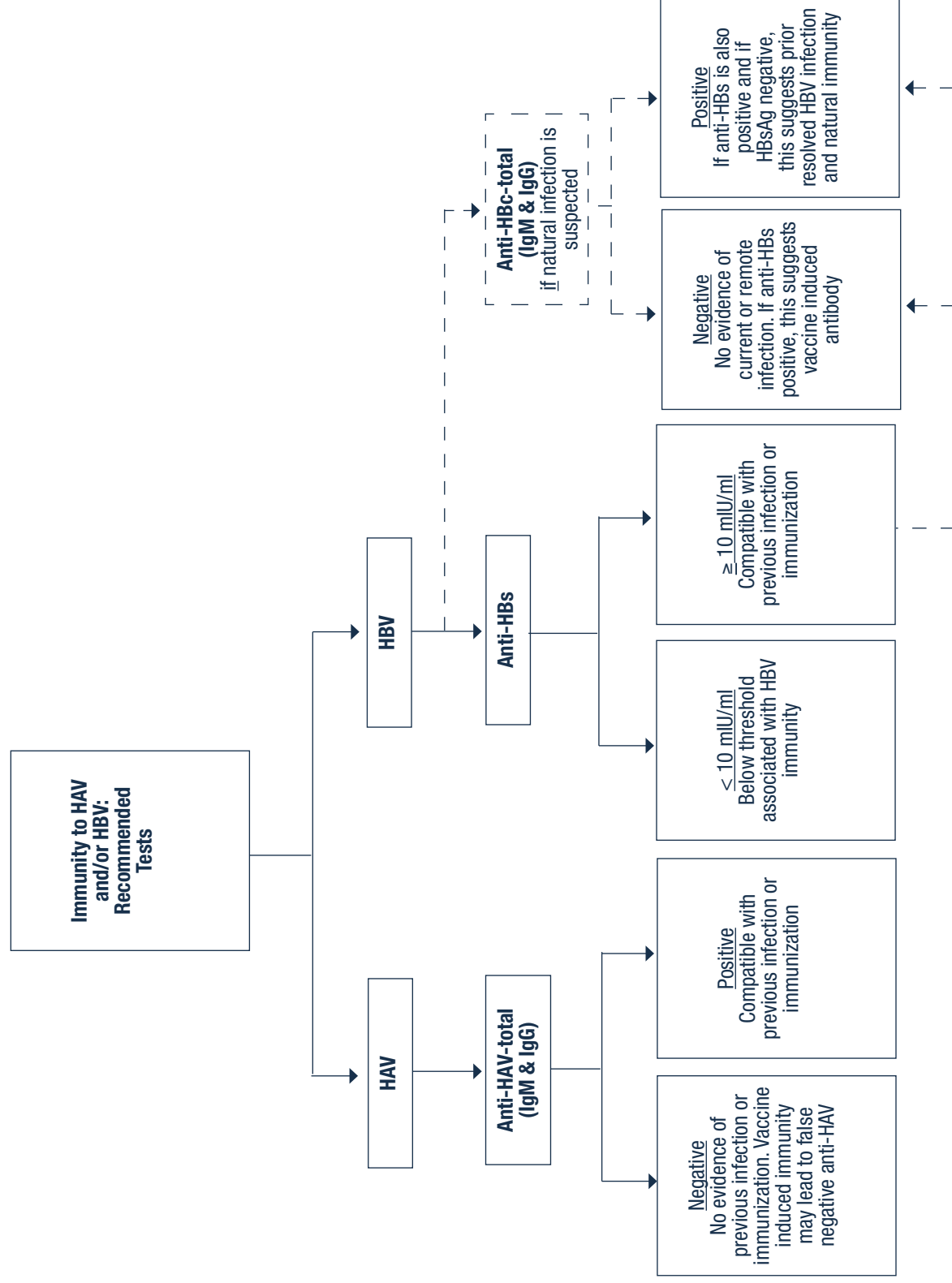


Algorithm 2

Diagnosis of Suspected Acute Viral Hepatitis



Investigation of Hepatitis Immunity



APPENDIX 2

PRIMARY AND SECONDARY TESTS TO DIAGNOSE/MONITOR HBV INFECTION

	Marker	Incubation Period	Acute Infection	Past/Resolved Infection	Chronic Infection	Vaccination
Primary Diagnostic Tests	HBsAg	±	+	-	+	- (a)
	Anti-HBs	-	-	+	-	+
	Anti-HBc-total (IgM & IgG)	-	±	+	+	-
	Anti-HBc-IgM	-	+	-	± (b)	-
Prognostic or Monitoring Tests	HBeAg	+	+	-	±	-
	Anti-HBe	-	-	±	± (c)	-
	HBV DNA (d)	± (d)	+	± (d)	+	-

+ implies positive; - implies negative; ± may be positive or negative

(a) Recent HBV vaccination within 1-2 wks can lead to a 'false' positive test. The vaccine antigen can be detected at low levels

(b) May be positive in chronically infected individuals

(c) Patients with chronic HBV infection usually have detectable HBeAg or anti-HBe. Rarely both HBeAg and anti-HBe can be detected simultaneously.

(d) Methods differ in sensitivity and standardization.