Guidelines for Ordering Diagnostic Testing for Viral Hepatitis (CLP012)

Revised September, 2010

1. Purpose

To provide clinicians and laboratory personnel with a concise reference document describing the appropriate laboratory tests for (a) assessing patients suspected of being infected with/exposed to a hepatitis virus, and (b) determining patients' immunity to hepatitis A and/or B.

Occupational exposure including needlestick presents a unique problem. Management of this type of exposure is outside the scope of this Guideline.

Interpretation of hepatitis test results is summarized in the companion document **CP012A** ***Interpretation of Viral Hepatitis Laboratory Test Results (September 2010)***.

2. Disclaimer

As is the case with any diagnostic assay, false negative and false positive results may occasionally be reported. When such a result is suspected, or if you are uncertain about which hepatitis markers are appropriate to order, contact the Laboratory Director or Medical Director of your laboratory for assistance.

Inconclusive results for any hepatitis marker are not uncommon and may require the patient to be recalled for additional or repeat testing.

Readers are reminded that OAML Guidelines cannot be applied to every clinical situation, nor can they serve as a substitute for sound clinical judgement.

3. Background

Viral hepatitis, whether acute or chronic, may be symptomatic but is more often asymptomatic. Patients exposed to, or infected with a particular hepatitis virus will usually have serological markers (antibodies and/or antigens) unique to that virus. The most common viral hepatitis agents are designated hepatitis A, B, C, D and E.

Previously, only hepatitis A and B were included in the initial laboratory investigation of acute hepatitis. Based on the advice of the OAML's Expert Panel, the acute hepatitis algorithm has been expanded to include hepatitis C.

Hepatitis D and E virus infections are rare in Canada and accordingly are not discussed in this Guideline.

4. Definitions

- **Acute Hepatitis** refers to a newly acquired infection. The term does not refer to the severity of the infection.

- **Chronic Hepatitis** refers to hepatitis B or hepatitis C infections that have been persistent for longer than 6 months.
- **Chronic Carrier State** is essentially synonymous with chronic hepatitis and infers that the patient remains infected and potentially infectious, irrespective of the clinical symptomatology.
- **IgG** refers to a class of immunoglobulins produced late in infection.
- **IgM** refers to a class of immunoglobulins produced early in infection.

5. Abbreviations

HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
anti-HAV IgG	IgG antibodies to the hepatitis A virus
anti-HAV IgM	IgM antibodies to the hepatitis A virus
anti-HAV Total	Total (IgG + IgM) antibodies to the hepatitis A virus
HBsAg	Hepatitis B surface antigen
anti-HBs	Antibodies to the hepatitis B surface antigen
anti-HBc IgM	IgM antibodies to the hepatitis B core antigen
anti-HBc Total	Total (IgG + IgM) antibodies to the hepatitis B core antigen
HBeAg	Hepatitis B 'e' antigen
anti-HBe	Antibodies to the hepatitis B 'e' antigen
anti-HCV	Antibodies to the hepatitis C virus
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
INR	International Normalized Ratio

6. Laboratory Investigation of Viral Hepatitis

a) Acute Hepatitis

Investigation of acute hepatitis should be reserved for patients who may have had recent exposure to a hepatitis virus, whether symptomatic or not, or to those who present with a syndrome of acute hepatitis (jaundice, elevated ALT, anorexia).

Clinicians investigating acute hepatitis should complete the Ontario Health Insurance Plan (OHIP) requisition as indicated below.

x	**Viral Hepatitis** *(check **one** only)*
X	Acute Hepatitis
	Chronic Hepatitis
	Immune Status / Previous Exposure *Specify:* ☐ Hepatitis A ☐ Hepatitis B ☐ Hepatitis C or order individual hepatitis tests in the "Other Tests" section below

The laboratory will perform ALT as a sentinel test to exclude or support the presence of hepatic inflammation. If the ALT value is less than or equal to 1.5 times the laboratory's upper reference limit, no further testing will be performed. Generally speaking, ALT elevations below this limit will be

due to causes other than acute viral hepatitis infections.

If the ALT value is greater than 1.5 times the laboratory's upper reference limit, the following tests will be performed:

- anti-HAV IgM
- HBsAg
- anti-HCV

If all three tests above are negative, the laboratory will automatically test for anti-HBc IgM. This test will identify those cases of acute hepatitis B where HBsAg is no longer detectable in the serum (the "core window") although the patient is still in the acute phase of the infection.

If all three tests listed above are negative, the possibility of late hepatitis C seroconversion must be considered. Accordingly, in such cases, laboratory reports will include a comment recommending that clinicians repeat the anti-HCV test in 3-4 weeks.

Follow up in the event of positive results:

Hepatitis A: In general, hepatitis A infections are self-limiting and will resolve in 8 to 10 weeks with resulting immunity. Additional serological testing is not required. Severe disease may occasionally require hospitalization.

Hepatitis B: The vast majority of acute hepatitis B infections in adults resolve completely within 6 months and result in permanent immunity. The remainder of those infected with hepatitis B progress to chronic infection. Children (1-5 years) and infants have a much higher rate of progression to chronicity (30-50% and 80-90%, respectively). Severe acute disease, as reflected clinically, may require emergent care. All patients should be retested after 6 months for HBsAg and anti-HBs to determine immune status. Persistence of HBsAg after 6 months infers chronicity (see section 6b below).

Hepatitis C: The reported spontaneous cure rate for acute hepatitis C infections ranges from 15% to 45%, with the likelihood of cure increasing the younger the age at the time of infection. Evidence indicates that early treatment (within 3 months of hepatitis C infection) dramatically increases the cure rate. Referral to a specialist (preferably with test results, including abdominal ultrasound and hepatitis C viral load; see section 7 of this Guideline) is strongly recommended irrespective of the laboratory test results.

b) Chronic Hepatitis

ALT levels are variable in chronic infection and an ALT elevation is not a requisite of active liver disease. ALT is therefore not suitable as a screening test for chronic hepatitis. Clinicians investigating chronic hepatitis should complete the OHIP requisition as indicated below.

x	**Viral Hepatitis** *(check **one** only)*
	Acute Hepatitis
X	Chronic Hepatitis
	Immune Status / Previous Exposure *Specify:* ☐ Hepatitis A ☐ Hepatitis B ☐ Hepatitis C or order individual hepatitis tests in the "Other Tests" section below

Testing for chronic hepatitis will include:

- HBsAg
- anti-HCV

There is no known incidence of chronicity associated with hepatitis A, hence no testing for this virus is performed when assessing chronic hepatitis.

Hepatitis B: Test results for hepatitis B, while usually straightforward may at times be complex. Detection of HBsAg clearly denotes infection. This serum marker may persist for up to 6 months in acute disease. If it persists longer than 6 months, the patient is considered to be a chronic carrier. From a laboratory perspective, chronic carrier status (chronic hepatitis B) is documented by at least two positive HBsAg test results performed six months or more apart. Management of chronic carriers may require measurement of HBV viral load in addition to the other markers of HBV infection, including HBeAg and anti-HBe. See section 7 for ordering instructions.

Hepatitis B is one of the few infections where antigen AND antibody may be detectable at the same time. The reason for this is likely strain variation or inadvertent immunization of an antigen positive individual. Whatever the cause, the presence of HBsAg is the overriding factor and always indicates that the patient is a carrier of the hepatitis B virus and is to be considered infectious.

Hepatitis C: The appropriate screening test for acute and/or chronic hepatitis C infection is anti-HCV. This marker appears in the serum several weeks after exposure and persists for life, even in patients who clear the infection spontaneously.

In Ontario, HCV viral load testing (HCV RNA) is not used as a diagnostic test for hepatitis C at the present time. Patients for whom antiviral treatment is being considered will require HCV RNA testing.

Please note that the anti-HCV response may be blunted in immunocompromised patients, such as those with transplants, on chemotherapy or treatment with corticosteroids, or in patients with renal failure. In these cases, HCV infection may be confirmed with an HCV RNA test. See section 7 for ordering instructions.

Practically, any patient with HCV antibody must be considered to be a chronic carrier of this virus until proven otherwise. Such patients must therefore be considered infectious.

Follow up in the event of positive results

Hepatitis B: Patients should initially have the following tests performed: ALT, ALP, bilirubin, INR, CBC, HBeAg, anti-HBe, viral load and an abdominal ultrasound. See section 7 for ordering instructions.

Referral to a specialist is recommended under the following circumstances:

- elevated ALT
- over age 40, regardless of ALT concentration
- HBeAg positive, with HBV viral load greater than 20,000 IU/mL
- anti-HBe positive, with HBV viral load greater than 2,000 IU/mL
- platelet count less than 150 $x10^9$/L
- evidence of cirrhosis, splenomegaly, hepatic mass, or portal hypertension

Patients not referred to a specialist:

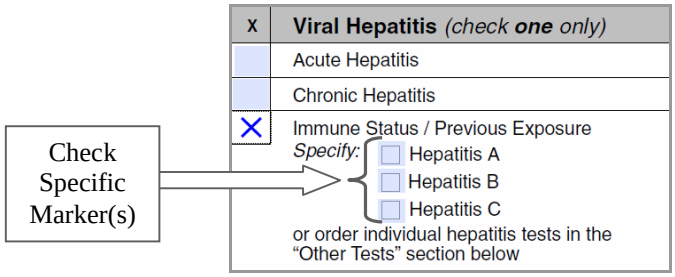
- should be followed at 6 month intervals with ALT, albumin, bilirubin, ALP, INR and CBC. Periodic measurement of HBsAg in healthy patients is warranted to determine whether the virus has been cleared.
- should have HBV viral load testing ordered if ALT levels rise. Significant deterioration of the patient's condition will necessitate a specialist referral.
- men greater than 40 years of age and women over 50, who do not require continuous specialist care, will require an abdominal ultrasound performed every 6 months to screen for hepatocellular carcinoma.

Hepatitis C : A significant proportion of hepatitis C infections respond to therapy. Referral to a specialist (preferably with results of a hepatitis C viral load measurement, liver function tests, and

hepatitis C genotyping, as well as an abdominal ultrasound scan) is recommended.

c) Immune Status (Hepatitis A and/or B) / Previous Exposure (Hepatitis A, B and/or C)

To determine a patient's immune status (naturally-acquired or post-vaccine), clinicians should check **"Immune Status/Previous Exposure"** on the OHIP requisition and specify whether the investigation is for hepatitis A, B, or both as indictated below.



Hepatitis A: If hepatitis A is checked, either anti-HAV Total or anti-HAV IgG will be performed (test choice is laboratory-specific).

A positive anti-HAV Total test indicates the presence of either IgM, or IgG, or both antibodies to hepatitis A. Therefore, considered in isolation, this test cannot distinguish between acute infection (IgM positive) and immunity (IgG positive). Only those patients at risk for acute hepatitis need to be followed up with anti-HAV IgM. A negative result for anti-HAV IgM means the antibodies detected in the anti-HAV Total test were almost certainly IgG antibodies and the patient can therefore be considered immune to hepatitis A (previous exposure or vaccine).

If the anti-HAV IgG test is offered by your laboratory and the result of this test is positive, the patient can be considered to be immune to hepatitis A (previous exposure or vaccine).

Testing for vaccine-induced immunity to HAV is not recommended because vaccination is almost universally effective.

Hepatitis B: If hepatitis B is checked, anti-HBs is performed. The presence of antibodies to hepatitis B (anti-HBs positive and HBsAg negative) denotes immunity to the disease (just as a positive anti-HAV IgG test indicates immunity to hepatitis A), unlike hepatitis C where the presence of antibodies indicates the presence of infection.

Anti-HBc Total has little application in current patient management. In the presence of anti-HBs it can help to distinguish natural immunity to hepatitis B (positive anti-HBc Total) from vaccine immunity (negative anti-HBc Total).

Please note that as stated in the "Chronic Hepatitis" section above, anti-HBs can occasionally be present in the chronic carrier state. In all anti-HBs positive patients in whom natural infection is likely to have occurred, it is advisable to test for the presence of HBsAg at least one time to ensure that they are not chronic carriers. See section 7 for ordering instructions.

Hepatitis C: If hepatitis C is checked in this section of the requisition, an anti-HCV test is performed to determine previous exposure. There is no test for immunity to hepatitis C and the immune state may not exist. There is evidence that re-infection with hepatitis C can occur after the original viral strain has been spontaneously cleared (albeit at a lower rate than seen with individuals who have never been exposed to hepatitis C).

Note: All anti-HCV positive patients are to be considered infectious until proven otherwise.

d) Laboratory Investigation of Hepatitis B Contacts

Family members and sexual contacts of known HBsAg positive patients require testing to determine if they are infected, susceptible, or immune to hepatitis B infection. Physicians should order HBsAg and anti-HBs by writing these test names in the "**Other Tests**" section of the OHIP requisition.

If HBsAg is positive, regardless of anti-HBs status, the individual is likely a chronic carrier (unless this is acute hepatitis B) and must be considered infectious. If only anti-HBs is positive, the individual is immune to hepatitis B. If the individual is neither a carrier nor immune, vaccination is recommended.

7. Ordering Instructions for Additional Tests

Viral Load (HBV DNA and HCV RNA) and genotyping for either hepatitis B or C are performed at the Ontario Agency for Health Promotion and Protection (OAHPP) Public Health Laboratories (PHL) and must be ordered on an OAHPP PHL laboratory requisition, which can be obtained from the OAHPP's website at http://www.oahpp.ca/resources/requisitions.html.

Specimens must be packaged as required by *Transportation of Dangerous Goods* regulations (details can be found at http://www.tc.gc.ca/tdg/clear/part5.htm#sec516) for shipment to the OAHPP laboratory.

For all other hepatitis tests, clinicians must write the name of the specific test required in the "Other Tests" section of the OHIP Laboratory Requisition.

8. References

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Laboratory Guidelines in Support of Clinical Practice

The OAML, through its Quality Assurance Committee, co-ordinates the development, dissemination, implementation and review of Guidelines for Clinical Laboratory Practice.

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The comments of end users are essential to the development of guidelines and will encourage adherence. You are strongly encouraged to submit your comments on this or any other OAML Guideline to:

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