CLP 012
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Guidelines for Testing for Viral Hepatitis

1. Background:

The Ontario Association of Medical Laboratories (OAML) guidelines on laboratory testing of viral hepatitis represent the consensus viewpoint of a panel of experts in the field of Virology. The guidelines have been developed to provide the ordering physician with a clear and concise reference describing appropriate testing and reporting algorithms for the diagnosis of infection, exposure and immunization.

The terms used in the algorithms are defined below.

Acute viral hepatitis refers to a newly acquired infection, which may or may not produce symptoms. The infection is often cleared within six months. The subject develops serological markers of the particular virus, which were not previously present. Certain hepatitis viruses can also cause a chronic infection.

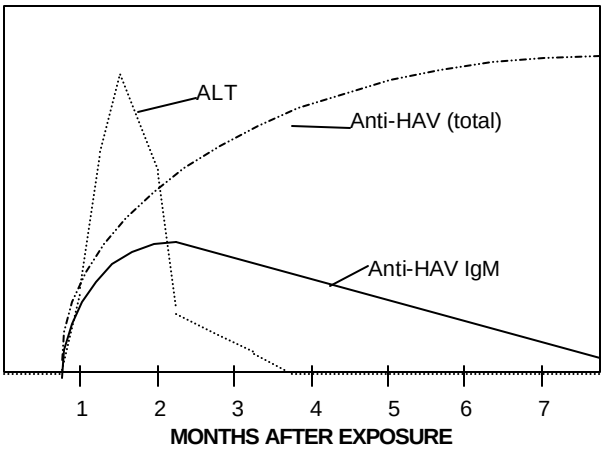
Chronic viral hepatitis is an infection, which is present for longer than six months and is usually present for many years. This infection may or may not produce symptoms.

Three viruses account for the vast majority of all viral hepatitis. These are hepatitis A, B and C. Hepatitis D, E and G are uncommon in Canada.

Hepatitis A has an incubation period of three to six weeks. It is spread by the fecal-oral route. There is no chronic form of the disease. Hepatitis A only rarely causes fulminant liver failure.

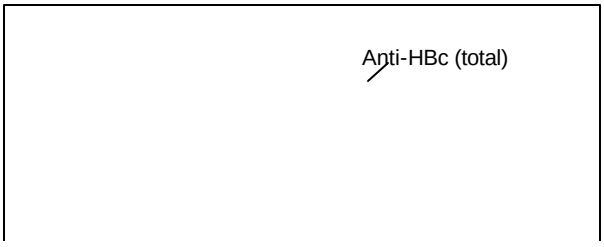
Figure 1 shows the typical course of a case of acute hepatitis A, demonstrating elevation of alanine aminotransferase (ALT).

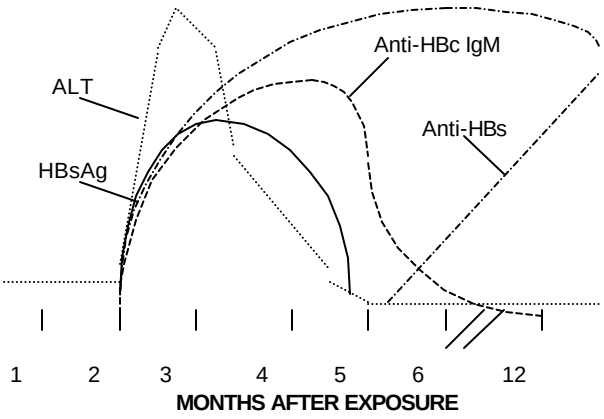
Fig. 1. Typical course of a case of hepatitis A. (Adapted from Hoofnagle & Di Bisceglie)



Hepatitis B has an incubation period of six weeks to six months. Infection in young children frequently leads to chronicity. Infection in young adults leads to chronicity in <5% of cases but, infection in older adults is associated with increased rates of chronicity.

Fig. 2. Typical course of a case of hepatitis B. (Adapted from Hoofnagle & Di Bisceglie)





Hepatitis C has an incubation period of less than three months. As many as eighty percent of infected patients develop chronic hepatitis, either mild or progressive disease. After 20 years approximately 20% develop cirrhosis.

Hepatitis D occurs only in people infected with hepatitis B. The infection may be acquired simultaneously or hepatitis D may be superimposed on a pre-existent hepatitis B infection.

Hepatitis E is not commonly found in Canada. The exception is in symptomatic patients who have recently visited an endemic area.(e.g. Mexico, India, Middle East) The disease is spread by the fecal-oral route and is an important cause of fulminant hepatic failure, particularly in pregnant women. The disease has no chronic stage.

New hepatitis viruses continue to be identified. **Hepatitis G** virus is a newly identified blood-borne agent. The clinical significance of these viruses is, as yet, unknown.

2. Limitations:

Diagnosis of acute vs. chronic hepatitis can be difficult. In both acute and chronic hepatitis, the liver enzymes may be elevated. Therefore, the pattern of elevation of liver enzymes is not a helpful measure in differentiating between acute and chronic disease. Documentation of seroconversion is useful but, rarely possible. Patients may be symptomatic or asymptomatic in the case of either acute or chronic hepatitis. Thus the differentiation between a new acute infection and a chronic infection requires a combination of clinical judgement and appropriate serological testing.

Hepatitis A To detect acute hepatitis A infection, the diagnostic test is the hepatitis A IgM antibody (anti-HAV IgM). The other available test measures total antibodies to hepatitis A (anti-HAV) and if positive, indicates immunity to hepatitis A. Anti-HAV IgM becomes positive shortly before the development of clinical hepatitis and remains positive for at least four months.

Hepatitis B The presence of hepatitis B infection is indicated by a positive hepatitis B surface antigen test (HBsAg). This is positive in both acute and chronic hepatitis B. In acute hepatitis B the HBsAg is cleared within six months and is replaced by antibodies to the surface antigen (anti-HBs). Presence of HBsAg beyond six months is consistent with chronic hepatitis B infection.

There are two assays for antibodies to the hepatitis core protein (HBcAg): for total antibodies (anti-HBc total) and for IgM antibodies (anti-HBc IgM). Anti-HBc total is positive in all patients previously or currently infected with hepatitis B. Anti-HBc IgM is found in acute infections and may be found in the earlier stages in chronic infections or sometimes during a flare of inflammatory activity. Thus this antibody cannot reliably be used to distinguish acute from chronic disease.

The hepatitis B e antigen (HBeAg) is a soluble protein produced by the virus in acute disease and in the earlier stages of chronic disease. Antibodies to this protein are produced during remission of an acute infection and in the later stages of chronic infection. The main use of these markers is in deciding whether to offer treatment to patients with chronic hepatitis B and, therefore, routine testing as part of an initial investigation is not recommended.

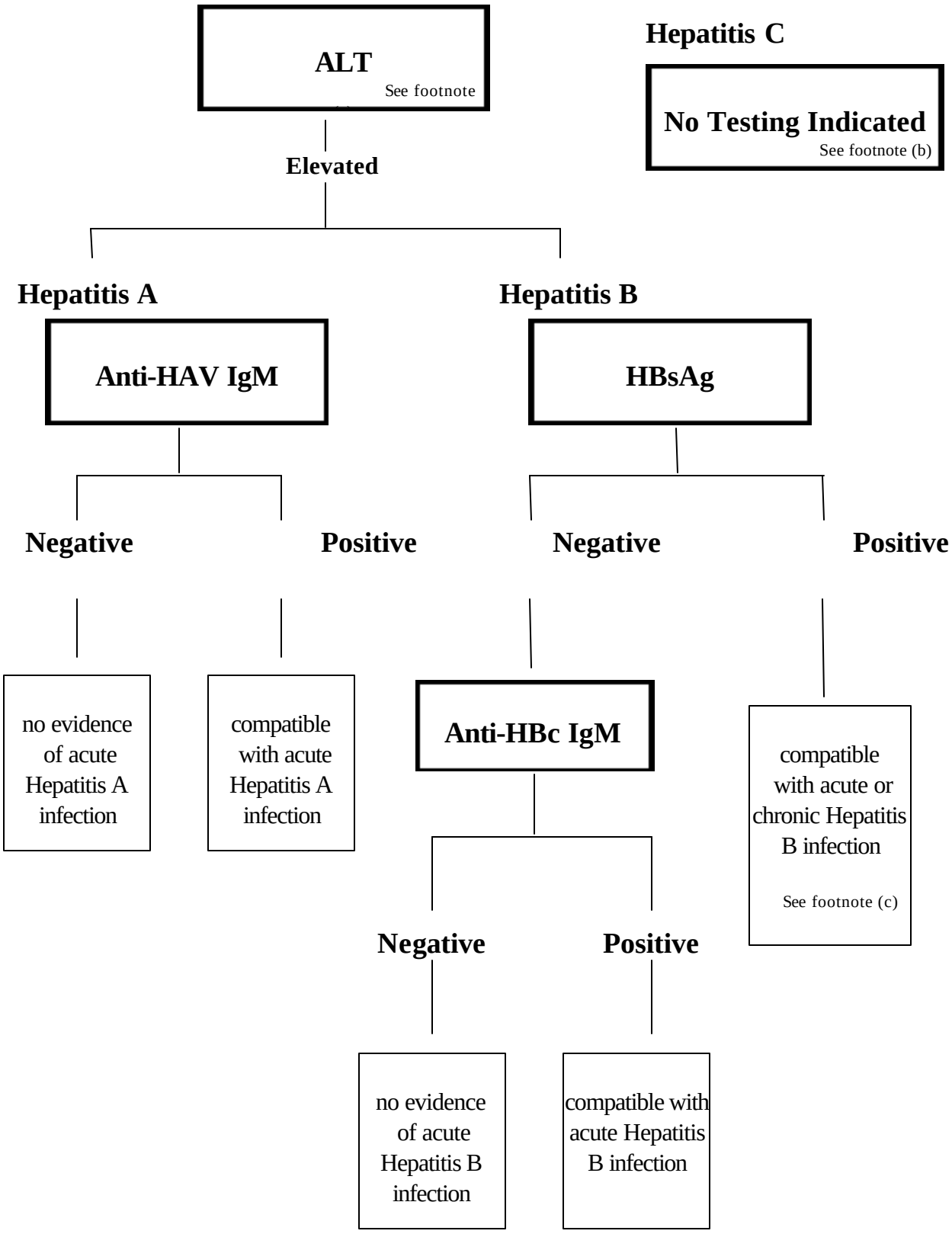
Hepatitis C The test for antibodies to hepatitis C (anti-HCV) is the only widely used marker to indicate this infection. Antibodies are present in >90% of patients who have been infected. The

antibody test generally becomes positive within between six and twelve weeks of infection. The antibody test is frequently negative at the time of onset of clinical jaundice and cannot, therefore, be used reliably to diagnose acute hepatitis C infection. The presence of the antibody is not known to be protective. There is no known clinical immunity to hepatitis C.

3. Recommendations:

The algorithms accompanying these guidelines are designed to simplify the ordering of hepatitis testing and reporting of results. The recommendations that follow are reflected in the algorithms.

Investigation for Evidence of Acute Infection:



Notes:

(a) If the ALT is elevated (> 1.5 x upper limit of normal) proceed with hepatitis testing. If ALT is not elevated, hepatitis markers will not routinely be done and the report will read, "ALT not elevated, no viral hepatitis marker testing done."

(b) Because of the prolonged period of sero-conversion, hepatitis C cannot reliably be diagnosed in the acute phase; testing should not be done for acute hepatitis C. Since antibodies to HCV may not be detectable when symptoms are present in patients for whom HAV and HBV have been ruled out, a second sample should be specifically tested for HCV one to three months later.

(c) If HBsAg is positive for a period of greater than six months, it is consistent with chronic Hepatitis B infection.

Interpretations: Acute Viral Hepatitis

The following statements are provided to assist the physician in the interpretation of test reports. As is the case with any diagnostic assay, false negative and positive results may occur.

Guidelines are appropriate at the time of writing and are applicable in most situations. However, if in doubt referral to a specialist should be considered.

Positive Anti-HAV IgM, Negative HBsAg, Negative Anti-HBc IgM

Positive anti-HAV IgM indicates acute hepatitis A infection. This will resolve spontaneously. No further serological testing is required.

Positive HBsAg, Positive Anti-HAV IgM

HAV infection in a chronic carrier of HBV can occur rarely.

Positive HBsAg, Negative Anti-HAV IgM

This pattern of markers can indicate acute hepatitis B. Testing for clearance of the infection should be performed after 6 months, using either HBsAg or anti-HBs. If HBsAg persists for more than six months, this indicates chronic infection.

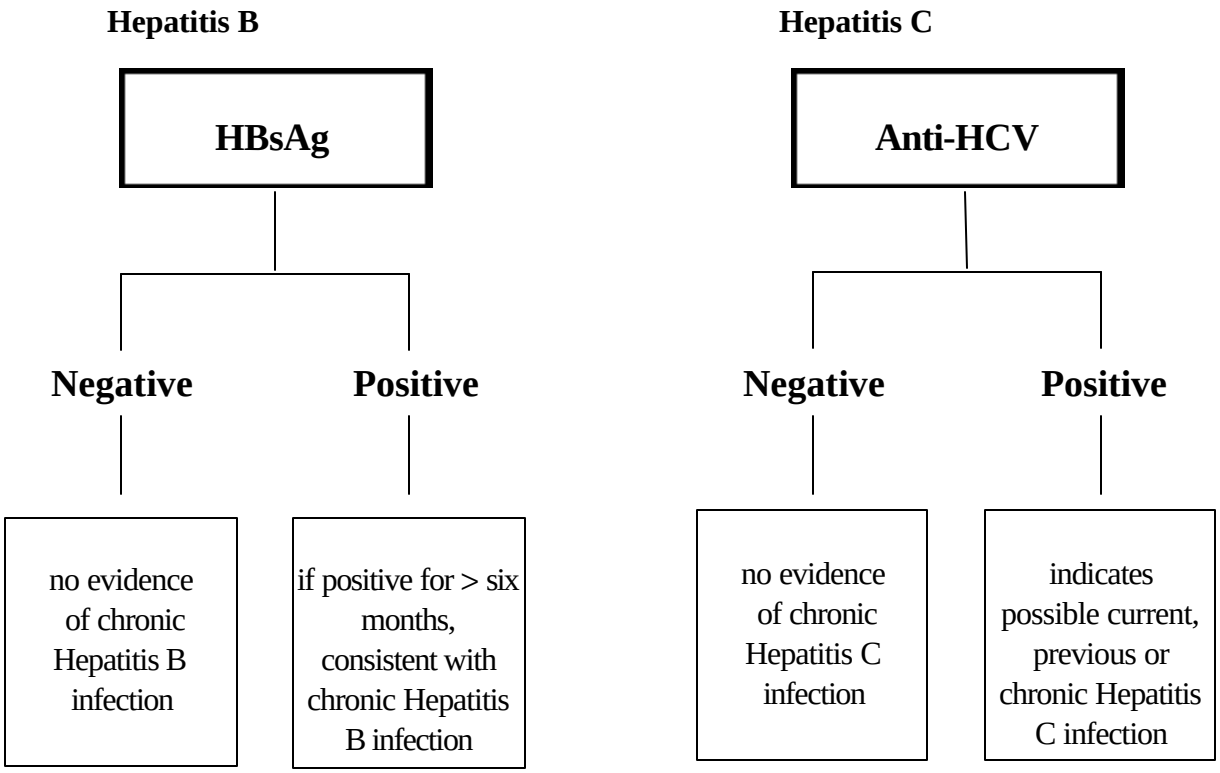
Negative Anti-HAV IgM, Negative HBsAg, Positive Anti-HBc IgM

This pattern of markers indicates acute hepatitis B. Testing for clearance of the infection should be performed after six months, using either HBsAg or anti-HBs.

Negative Anti-HAV, Negative HBsAg, Negative Anti-HBc IgM

Standard testing for acute viral hepatitis is negative. Consider acute hepatitis C. Anti-HCV usually becomes positive six weeks to three months after onset of the acute illness. Consider less common viral or non-viral illnesses.

Investigation for Evidence of Chronic Infection:



Interpretations: Chronic Viral Hepatitis

The following statements are provided to assist the physician in the interpretation of test reports. As is the case with any diagnostic assay, false negative and positive results may occur. It is preferred laboratory practice that a positive HBsAg or a positive anti-HCV be confirmed prior to the reporting of a positive result.

Guidelines are appropriate at the time of writing and are applicable in most situations. However, if in doubt referral to a specialist should be considered.

HBsAg Positive, Anti-HCV Negative

Indicates acute or chronic hepatitis B. Persistence of HBsAg for greater than 6 months is evidence of chronic HBV. If ALT is elevated in a chronic carrier, the patient may be a candidate for antiviral treatment.

Anti-HCV Positive, HBsAg Negative

A positive anti-HCV indicates exposure to the hepatitis C virus but does not distinguish current from previous infection. This requires referral to a specialist.

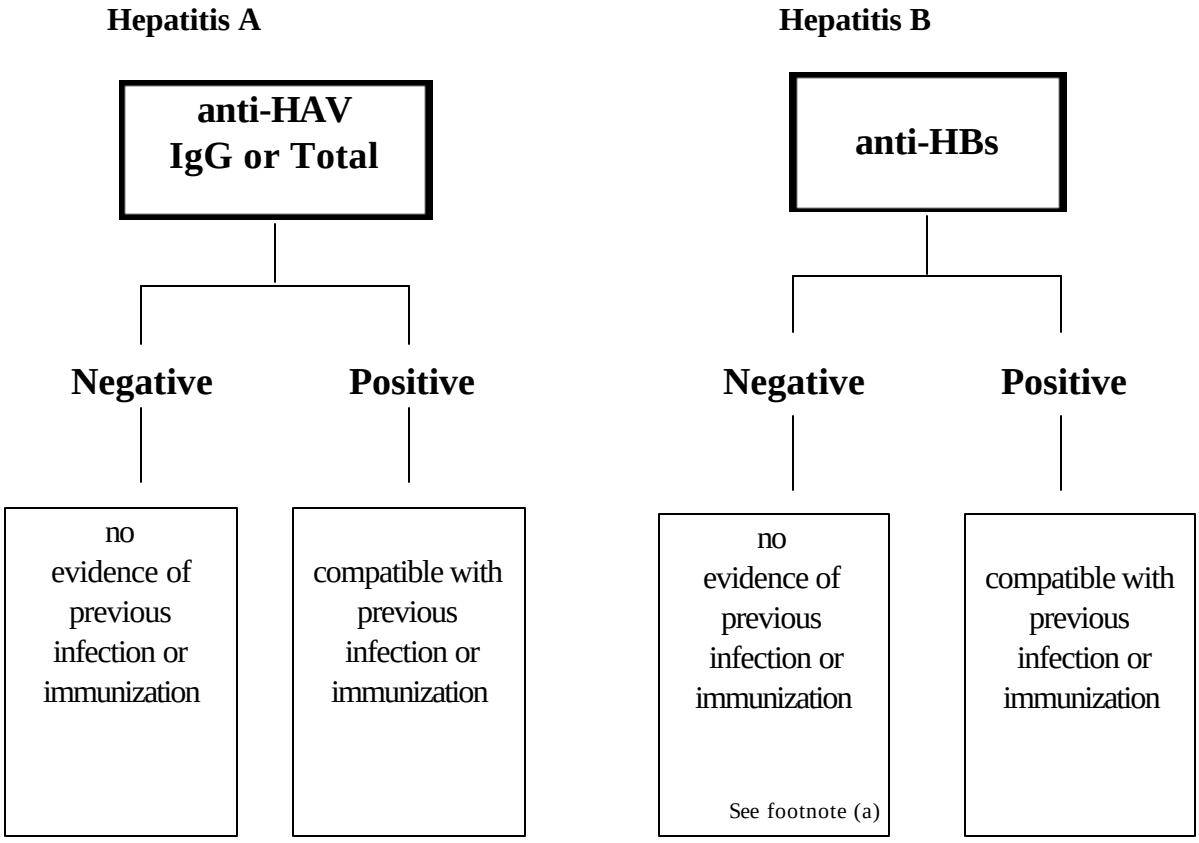
HBsAg Negative, Anti-HCV Negative

Indicates that the patient is not infected with either virus. If the liver enzymes are elevated, consider other viral or non-viral etiology. Note that anti-HCV can be falsely negative in patients infected with hepatitis C when the patient is immunocompromised, as for instance, patients on chemotherapy, corticosteroids or in renal failure.

HBsAg Positive, Anti-HCV Positive

Dual infection with both viruses. Evaluation of these patients is complex; such patients should be referred to specialists, if clinically indicated.

Investigation for Evidence of Previous infection or Immunization in Immunocompetent Individuals:



Notes:

(a) A small number of patients may be positive for anti-HBc from a previous HBV infection in the absence of anti-HBs. If there is a strong suspicion of previous infection, then order an anti-HBc.

Interpretations: Previous Exposure or Immunization

The following statements are provided to assist the physician in the interpretation of test reports. As is the case with any diagnostic assay, false negative and positive results may occur.

Guidelines are appropriate at the time of writing and are applicable in most situations. However, if in doubt referral to a specialist should be considered.

Anti-HAV (total or IgG) Positive

This test becomes positive within 2 months after vaccination against hepatitis A and six to twelve months after acute hepatitis A infection. A positive test indicates immunity to hepatitis A. After a naturally acquired infection the test generally remains positive for life.

Anti-HAV IgG Negative

A negative test indicates no exposure to either hepatitis A or to hepatitis A vaccine.

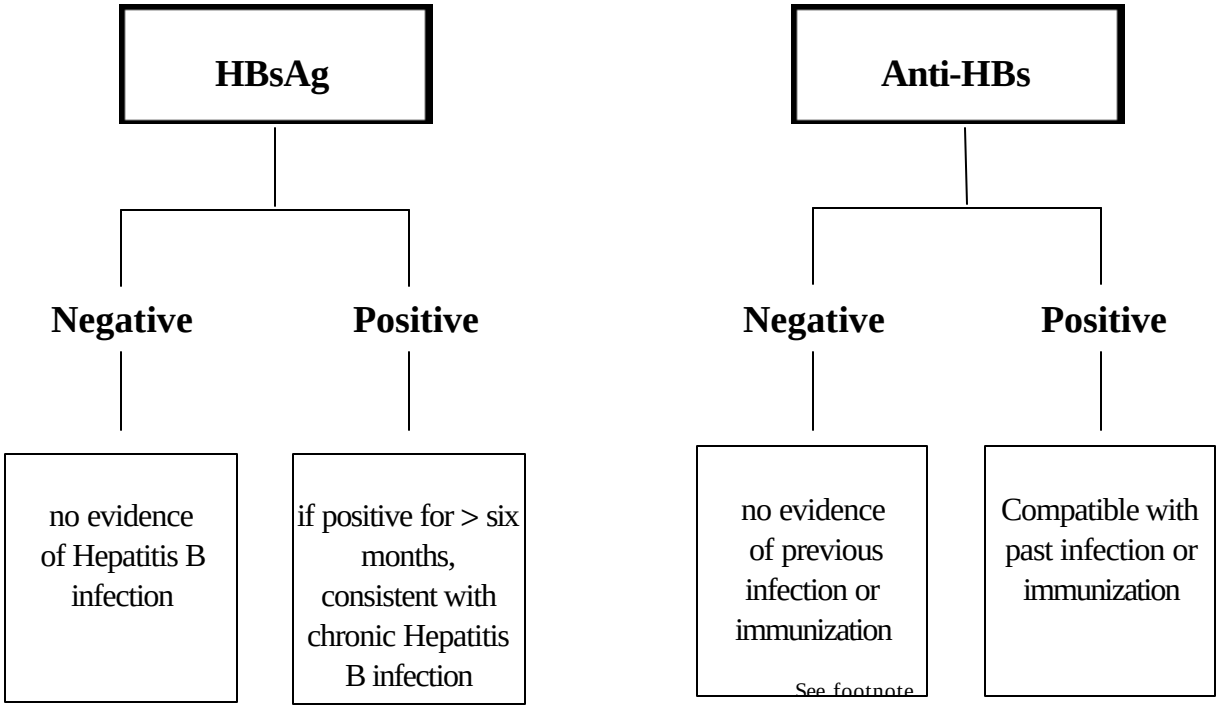
Anti-HBs Positive

A positive test is seen after naturally acquired acute hepatitis B infection or after vaccination against hepatitis B. Titres may decline below arbitrarily determined levels of antibody immunity or even become undetectable but immunity may persist for life.

Anti HBs Negative

This result most often indicates no previous exposure to hepatitis B and no immunity. However, in subjects who have been vaccinated or who have previously had acute hepatitis B, the titre of anti-HBs can decline and become undetectable and yet immunity persists. A small number of patients may be positive for anti-HBc from a previous HBV infection in the absence of anti-HBs. If there is a strong suspicion of previous infection, then order an anti-HBc.

Investigation for Hepatitis B Contacts:



Notes:

(a) A small number of patients may be positive for anti-HBc from a previous HBV contact in the absence of anti-HBs. If there is a strong suspicion of previous infection, then order an anti-HBc.

Interpretations: Hepatitis B Contacts

The following statements are provided to assist the physician in the interpretation of test reports. As is the case with any diagnostic assay, false negative and positive results may occur.

Guidelines are appropriate at the time of writing and are applicable in most situations. However, if in doubt referral to a specialist should be considered.

HBsAg Negative, Anti-HBs Negative

The result suggests there is presently no evidence of exposure to Hepatitis B. Submit a follow up specimen in 3-6 months. If still negative immunization may be appropriate.

HBsAg Negative, Anti-HBs Positive

This result indicates previous infection or immunization.

HBsAg Positive, Anti-HBs Negative

This result indicates currently infected with Hepatitis B and may become chronic carrier. Submit a follow-up serum at 6 months; if HBsAg remains positive, patient is a chronic carrier.

HBsAg, Anti-HBs positive

This result also indicates currently infected with Hepatitis B and may become a chronic carrier. Submit a follow-up serum at 6 months: if HBsAg remains positive, patient is a chronic carrier.

Acute Hepatitis

If the physician believes that the patient has acute Hepatitis, the laboratory should first assess serum levels of ALT. In the absence of elevated ALT (>1.5 x upper limit of normal), the patient does not have acute Hepatitis and further specific viral hepatitis marker testing will not normally be necessary. The report to the physician will indicate no evidence of elevated serum enzymes and that no viral Hepatitis marker testing has been done.

Hepatitis A and B are the two most common causes of acute viral Hepatitis. If the ALT levels are elevated, the laboratory should perform the anti-HAV IgM and HBsAg assays. If both are negative, the laboratory should automatically perform anti-HBc IgM. This will identify those cases of acute Hepatitis B in which anti-HBc IgM is present at an earlier stage than HBsAg.

Because of the prolonged period of sero-conversion, Hepatitis C cannot reliably be diagnosed serologically during the acute stage. Therefore testing in the acute phase is not recommended. Since antibodies to HCV may not be detectable when symptoms are present in patients for whom HAV and HBV have been ruled out, a second sample should be specifically tested for HCV one to three months later.

Chronic Hepatitis

The two most common causes of chronic viral Hepatitis are Hepatitis B and Hepatitis C.

If the physician orders testing for chronic Hepatitis, the laboratory should test for HBsAg and for anti-HCV. A positive HBsAg result is consistent with either acute or chronic infection. To diagnose chronic Hepatitis B with certainty, the HBsAg must persist for at least six months.

A positive anti-HCV result is consistent with either current, previous or chronic infection.

Previous Infection or Immunization

If knowledge of the immune status to Hepatitis A or B is required, the laboratory will test for anti-HAV IgG or total anti-HAV or for anti-HBs, as requested. The presence of antibodies indicates immunity.

Hepatitis B Contacts

Family and/or sexual contacts of newly diagnosed Hepatitis B carriers require testing to determine if they are the source of infection and/or if they are immune or susceptible to Hepatitis infection.

If the physician orders testing for Hepatitis B contacts, then the laboratory should test for HBsAg and anti-HBs.

If HBsAg is positive the individual may be a carrier. If anti-HBs is positive then the individual is immune to Hepatitis B. If the individual is neither a carrier nor immune, the individual requires vaccination.

4. Selected References:

Chernesky, M *et al.,* Diagnostic Significance of Anti-HBcIgM Prevalence Related to Symptoms in Canadian Patients Acutely or Chronically Infected With Hepatitis B Virus, *Journal of Medical Virology* 20:269-277 (1986).

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The Ontario Association of Medical Laboratories

The Ontario Association of Medical Laboratories (OAML) represents the community-based laboratory sector in Ontario.

Its mission is to promote excellence in the provision of laboratory services and, as an essential component of the health care system, to contribute to shaping the future of health care in Ontario.

The OAML encourages the highest level of professional and ethical integrity and technical excellence among laboratory owners, operators and staff in the provision of laboratory services for the benefit of the people of Ontario.

Guidelines for Clinical Laboratory Practice

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

A proposed Guideline is developed by a working group of the Committee with the participation of outside experts. The proposed guideline is then submitted to the Committee as a whole and to a Professional Advisory Group who provide an overall review of the document. The comments of the Committee and the Professional Advisory Group are incorporated into a revision of the guideline and this draft is submitted to laboratory Medical Directors, professional associations and other representatives of end users for additional comment. The document is revised in light of these comments and

There may be additional educational materials produced, if it is thought that they might be useful, and these are distributed with the guideline.

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 on any other OAML Guideline to:

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submitted to the OAML Board of Directors for approval. **Approved guidelines** are distributed to Community-based Laboratories and by them to their client physicians.	Fax: (416) 250-8464 E-mail: oaml@oaml.com Internet: http://www.oaml.com

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