The above recommendations are systematically developed statements to assist practitioner and patient decisions about testing that may be important for clinical management of specific clinical circumstances. They should be used as an adjunct to sound clinical decision making.
Chronic Viral Hepatitis

- If chronic viral hepatitis is suspected, request hepatitis B surface antigen (HbsAg) and antibody to hepatitis C (anti-HCV).

- If hepatitis B infection alone is suspected, such as after receipt of a letter of notification from the Red Cross, request hepatitis B surface antigen (HbsAg).

- If hepatitis C infection alone is suspected, such as after receipt of a letter of notification from the Red Cross, request antibody to hepatitis C (anti-HCV).

- Refer to Suspected Chronic Hepatitis Algorithm.

Immune State Determination

- Request antibody (Total or IgG) to hepatitis A virus:
  - as a pre-vaccination check for hepatitis A vaccine.
  - if immune serum globulin is required for prophylaxis.

- Request antibody to hepatitis B surface antigen (anti-HBs) to determine immunity to hepatitis B virus.

BACKGROUND

INTRODUCTION

The literature was reviewed, and the opinions of laboratory specialists, gastroenterologists, infectious disease specialists, public health physicians and family physicians within Alberta were sought during the preparation of this guideline. No adverse outcomes are foreseen by following this ordering guideline as this strategy of testing has been published in a number of studies and other guidelines.1-3

The information provided in this guideline reviews the current status of tests available and their use in assisting with a diagnosis or with patient follow-up. Ordering of tests pertinent to the stage of disease and directly relevant to clinical management should reduce unnecessary multiple tests.

The five agents most commonly associated with viral hepatitis are hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), hepatitis D (HDV), and hepatitis E (HEV), each of which has unique epidemiological features, differing sequelae and infection control measures.

One or more serological tests are routinely available for the first four hepatitis viruses. There are presently no tests routinely available for HEV. Some of these tests are appropriate for the determination of acute infection, and others for chronic infection, past exposure or immune status.

In Canada, hepatitis A and B together constitute the majority of acute viral hepatitis infections.4 In Alberta, the numbers of acute hepatitis A infections are greater than acute hepatitis B.5 The incidences of acute HAV and HBV infections in Alberta for 1995 were 8.9/100,000 and 3.8/100,000 respectively. Despite the reportedly high seroprevalence of hepatitis C, the numbers of acute infections are unknown. Some studies indicate that they may constitute at least one-fifth of the total of acute hepatitis infections.6
CLINICAL MANIFESTATIONS

The initial symptoms of acute hepatitis are nonspecific; typically malaise, weakness, followed by anorexia, intermittent nausea, vomiting, and a vague dull, right-upper-quadrant pain are noted. Alanine aminotransferase values show elevations of between 5 to 20 times normal. In the icteric phase, which is variable in duration (up to three weeks), jaundice and/or dark urine, and sometimes light stools are noted. Some patients may experience fever, rash or arthritis. Manifestations of these symptoms and signs can be quite variable and also dependent upon age. However, many patients are asymptomatic, or only mildly ill and anicteric.7-9

Patients with chronic hepatitis are commonly asymptomatic, and evidence of liver disease may be found as a result of routine medical examination or altered liver function tests for an unrelated problem, or through routine donor screening by the Red Cross. Alternatively, there may be gradual development of fatigue and a history of jaundice. Alanine aminotransferase levels may be either normal or moderately raised depending upon the extent of liver inflammation.7-8

Although there are differences in the clinical courses and risk factors for HAV, HBV, and HCV, the overlap of signs and symptoms requires a laboratory diagnosis to verify the specific agent.

Hepatitis A

The incubation period is 15 to 50 days with an average of 25 to 30 days. Transmission is mainly by the fecal-oral route and outbreaks are not uncommon. Hepatitis A infections are frequently asymptomatic, particularly in the young. In older age groups the disease can be serious and deaths from liver failure have been reported. Chronic disease and carrier states are unknown with this agent. There is now an effective vaccine against hepatitis A.2,9-11

Hepatitis B

The incubation period from onset to jaundice is generally longer than for HAV, 45 to 180 days with an average of 60 to 90 days. HBV causes both acute and chronic infections. The major routes of transmission are exposure to contaminated blood and body fluids either through injection drug use, sexual intercourse, perinatal transmission or accidental inoculation with contaminated sharp objects. Other routes are tattooing, body piercing, close household contact, institutional cases, and within renal dialysis units.1,2,8,10,11

In HBV-infected individuals, a chronic infection or carrier state occurs in 6 to 10% of adults, 25% of children aged 1 to 5 years, and 70 to 90% of infected infants. In China, southeast Asia and sub-Saharan Africa where there is a high prevalence of hepatitis B surface antigen carriers, a high incidence of hepatocellular carcinoma has also been found, suggesting a strong association. Primary liver cancer is more common in males than among females from these areas, reaching a peak in the 30 to 50 age group.8,11 In Canada, a seroepidemiological study of the inhabitants of the Northwest Territories showed a higher prevalence of HBV in First Nations’ communities, compared with other ethnic groups in this region.12 However, HBV is not considered to be a strongly contributing factor towards the incidence of hepatocellular carcinoma in this population. There are effective recombinant vaccines available against hepatitis B.

Hepatitis C

Hepatitis C, the primary etiological agent of parenterally transmitted non-A, non-B (NANB) hepatitis, is an important cause of acute and chronic hepatitis worldwide. It is only since 1988 that techniques have become available to study this virus. Consequently, the information relating to the natural history of the disease is constantly changing.1,2,6,11

Present tests can, on average, detect antibodies 8 to 12 weeks after infection. In immunosuppressed individuals, it may take up to six months or more for antibodies to become measurable.13
Hepatitis C is most commonly a subclinical infection. Less than one-third of patients have symptoms and even fewer develop jaundice. Clinical illness is uncommon in children, and is more often associated with younger and older adults. Fulminant hepatitis C is rare, and co-infection with hepatitis B has been reported in some of these cases.

Current information suggests that of patients with hepatitis C, 70% or more will have a persistent infection and some will progress to chronic hepatitis. The sequelae of chronic hepatitis C disease are potentially serious as some patients will progress to cirrhosis, and those with cirrhosis are at a higher risk for developing hepatocellular carcinoma. Preliminary data indicate that, although hepatocellular carcinoma is usually diagnosed at 30 years following initial infection, some cases have been reported to have occurred significantly earlier.

The main route of HCV transmission is injection drug use associated with the use of contaminated needles and syringes. Other less common routes are occupational/needlestick accidents and percutaneous exposure such as tattooing. Although sexual transmission has been described, it is an inefficient mode of transmission. Mother to baby transmission has also been reported to occur at a very low rate. Before April 1990, when blood and blood products were not tested for HCV, the risk of acquiring a transfusion-related hepatitis C infection was estimated to be 3%. However in many cases of HCV infections, no risk factors can be identified.

The presence of antibody to HCV solely indicates infection with the virus and does not imply immunity. Acute and chronic HCV infections cannot be distinguished by current antibody tests.

Hepatitis D

HDV is very rare in Alberta and is a result of super-infection or co-infection in those patients who are also HbsAg-positive. Infection may result in a fulminant form of hepatitis which can be rapidly fatal. Super-infection of HBV carriers almost invariably leads to chronicity and an aggressive form of hepatitis with rapid progression to cirrhosis. HDV infection is usually associated with injection drug use.

Hepatitis E

HEV is associated with fecal-oral transmission and presents as an acute infection with an incubation between 15 to 60 days, similar to HAV. Mortality is high in pregnant females (up to 20%), but considerably lower (up to 2%) in other patients. Although hepatitis E is not endemic in Canada, it is relatively common in Indian subcontinent, Middle East, North Africa, Mexico and some areas of the former United Soviet Socialist Republic. Testing for HEV is not routinely available, and the diagnosis has to be made based upon recent travel, symptoms and exclusion of other viral hepatitis agents.

Other Common Viruses Causing Acute Hepatitis

Epstein-Barr virus, the etiological agent of infectious mononucleosis, and cytomegalovirus, are two relatively common viruses which can cause an acute hepatitis-like picture. Although serum ALT levels are often mildly raised, the signs and symptoms caused by these viruses are usually distinguishable from those of HAV and HBV.

Other Emerging Viral Hepatitis Agents

In addition to hepatitis A, B, C, D, and E, there are 3 GB viruses (GBV), namely GBV-A, GBV-B and GBV-C, and hepatitis X now provisionally named HGV. All these viruses likely belong to the same family as hepatitis C.

These viruses have been found in patients with acute and chronic hepatitis and their spread appears to be mainly through the blood-borne route. However, the information regarding this group of hepatotropic viruses is still very preliminary. There are no routine tests available for these viruses at the present time.

NOTIFICATION OF POSITIVE CASES

Under present legislation, the attending physician and testing laboratory must notify Communicable Disease Control, Alberta Health and Wellness, as soon as possible if a patient is found to be positive for Hepatitis A, B, C, or D.
ADVISE TO PATIENTS

Practitioners may wish to consult the patient information material which accompanies this testing guideline.

SELECTED REFERENCES

Algorithm for Suspected Acute Viral Hepatitis

Suspected Acute Viral Hepatitis

Perform Liver Enzyme Tests (ALT)

- Elevated\(^a\)
  - Request IgM antibody to Hepatitis A\(^b\)
  - Request Hepatitis B surface antigen\(^c\)

- Normal\(^a\)

- Not Acute Viral Hepatitis

**Risk Factors for Hepatitis A**
1. Travel
2. Family & daycare contact
3. Poor hygienic circumstances

**Risk Factors for Hepatitis B**
1. Injection drug use
2. Sexual transmission
3. Percutaneous/permucosal exposure, e.g., Health Care Providers
4. Perinatal transmission
5. Renal dialysis
6. Immigration from endemic region
7. Blood transfusions & blood products
8. Close family contact

\(\text{a. Usually } \geq X5 \text{ upper limit of normal in acute viral hepatitis.}\)
\(\text{b. At the upper limit or mildly elevated.}\)
\(\text{- Consider common non-viral causes, e.g., medication, alcohol; OR}\)
\(\text{- Patient may be in the acute prodromal phase of viral hepatitis}\)
\(\text{Consider retesting ALT 2 to 3 days later when values will be significantly higher in acute viral hepatitis. Also consider requesting hepatitis serology at this point if indicated by the clinical history.}\)

\(\text{b. If hepatitis A alone is being considered, request only anti-HAV IgM.}\)

\(\text{c. If hepatitis B alone is being considered, request only HBsAg.}\)

\(\text{d. May be negative in early infection. Repeat test if sample collected within 5 to 7 days of onset of symptoms.}\)

\(\text{e. Consider requesting IgM antibody to hepatitis B core antigen ONLY if early “window period” is strongly suspected.}\)

\(\text{f. Retest at 6 months to exclude chronic hepatitis B infection.}\)
Algorithm for Suspected Chronic Viral Hepatitis

Suspected Chronic Viral Hepatitis (greater than 6 months duration)

a. If hepatitis B or C is suspected, such as after receipt of a letter of notification by the Red Cross, then request HBsAg or anti-HCV as indicated.

b. Further tests may be required to determine extent of liver inflammation and cirrhosis.

Risk Factors for Hepatitis B
1. Injection drug use
2. Sexual transmission
3. Percutaneous/permucosal exposure, e.g., Health Care Providers
4. Perinatal transmission
5. Renal dialysis
6. Immigration from endemic region
7. Blood transfusions & blood products
8. Close family contact

Risk Factors for Hepatitis C
1. Injection drug use
2. Percutaneous exposure, e.g., tattooing and needle stick exposure
3. Blood transfusions & blood products
# Viral Hepatitis Tests

## Test Abbreviation

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<th>Interpretation of Results and Comments</th>
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| **IgM Antibody to hepatitis A** (Anti-HAV IgM or HAV IgM Ab) | ✦ Positive result defines a recent HAV infection.  
✦ May be negative in early infection (if collected within 5 to 7 days after onset of symptoms).  
✦ Present for 3 to 6 months after onset of acute infection. |
| **Total Antibody to hepatitis A** (Anti-HAV or HAV Ab)  | ✦ Of extremely limited value in the diagnosis of acute infection.  
✦ Positive result indicates past infection and immunity to HAV.  
✦ Individuals given serum immune globulin for HAV prophylaxis may test as positive for at least six months. |
| **Hepatitis B surface antigen** (HBsAg)                | ✦ Used to diagnose an acute or chronic infection.  
✦ First marker to appear in an acute infection.  
✦ Disappearance indicates recovery from infection.  
✦ Persistence for > 6 months indicates chronic infection (carrier).  
✦ Individuals tested within 72 hours after administration of the vaccine may test as positive. (see anti-HBs, anti-HBc IgM and HBeAg.) |
| **Antibody to hepatitis B surface antigen** (Anti-HBs or HBs Ab) | ✦ Only test which can be used to assess presence of protective immunity after immunization with hepatitis B vaccine.  
✦ Levels of 10MIU/mL (10IU/L) are usually considered protective. Routine monitoring of levels in individuals who have received the complete course of vaccine is not considered necessary.¹  
✦ Some individuals, e.g., healthcare workers, who are believed to have been exposed to the virus by a needlestick injury, should have their anti-HBs levels tested to determine whether they require administration of hepatitis B immune globulin (HBIG) and hepatitis B vaccine booster.²  
✦ Positive result in individuals with recent acute HBV infection indicates convalescence.  
✦ Usually NOT detected when HBsAg is also present  
✦ In some cases of chronic hepatitis B infection, both HBsAg and anti-HBs can be detected. These antibodies are heterotypic and likely not protective.²  
✦ Antibody levels may decline with time. |

1. Reviewed September 2000

This accompanies the Laboratory Guideline for Serological Testing for Suspected Viral Hepatitis, March 1997
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| **IgM antibody to hepatitis B core antigen** (Anti-HBc IgM or HBe IgM Ab) | ✦ This test is expensive and should primarily be used if there is a high index of suspicion to indicate that the patient is in the early convalescence “window period” (2 to 16 weeks post infection) when HBsAg has disappeared and anti-HBs levels are not yet detectable.  
✦ Positive result in patients who are also HBsAg positive usually indicates acute infection.  
✦ Usually detectable for 3 to 12 months.  
✦ *Depending upon the threshold level of sensitivity, low levels may be detected in patients with chronic infection and reactivation.*³                                                |
| **Hepatitis B e antigen** (HBeAg)            | ✦ Marker of active HBV replication.  
✦ Also a marker of infectivity. However, *the absence of HBeAg in a person who is HBsAg-positive does not imply that the individual is NOT infectious.*  
✦ Can be used to monitor therapy of patients with chronic HBV infection.                                                                                                                                     |
| **Antibody to hepatitis B e antigen** (Anti-HBe or HBe Ab) | ✦ Appears as HBeAg disappears.  
✦ In chronic hepatitis B infection, a positive result indicates resolving or minimal liver disease.  
✦ However, individuals who are HBsAg-positive and have anti-HBe present must still be considered infectious.                                                                                           |
| **Total antibody to hepatitis B core antigen** (Anti-HBc or HBe Ab) | ✦ A positive result indicates past infection with hepatitis B virus.  
✦ Usually persists for life.  
✦ This antibody is absent in individuals who are immune solely as a result of vaccination.  
✦ Up to 10% false-positive rate has been described in individuals with no documented infection to HBV. If uncertain, presence of one other marker, e.g., anti-HBs or anti-HBe present must still be considered infectious. |
| **Hepatitis B viral DNA** (HBV DNA)           | ✦ Available by special request only. Of very limited value in the diagnosis of HBV infection.  
✦ Used to determine the presence of HBV DNA circulating in the blood which is a measure of virus replication in the liver.  
✦ Primary use is in monitoring treatment and clarifying some complex situations.                                                                                                                   |
| **Antibody to hepatitis C** (Anti-HCV or HCV Ab) | ✦ Enzyme immunoassay (EIA) tests are the most common screening test used to detect antibody.  
✦ With present EIA tests, a reactive result may be obtained after 8 to 12 weeks to several months following infection with HCV.⁴ Earlier generations of EIA tests often gave negative antibody results for up to 1 year.  
✦ False-positive results are found in patients with autoimmune chronic active hepatitis, alcoholic liver disease and other disorders relating to hypergammaglobulinemia.                                      |
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| Antibody to hepatitis C (Anti-HCV or HCV Ab)                                     | ♦ Presence of antibody can be due to *acute or chronic infection*. It may represent only evidence of an infection with HCV.  
♦ Presence of antibody does not imply immunity to HCV.  
♦ Persistently elevated ALT levels suggest chronic infection. Repeatedly normal levels do not exclude chronic infection, but suggest low grade inflammation.  
♦ ALT values in some patients with HCV infection are within normal ranges. |
| Recombinant immunoblot for antibody to hepatitis C (RIBA)                         | ♦ Supplementary test for the verification of EIA reactive results to HCV.  
♦ Indeterminate results may be found in early seroconversion, immunosuppressed patients or those unable to mount a complete antibody response. Some of the conditions which give false-positives in the EIA may well give an indeterminate or non-specific result in the RIBA. |
| Polymerase chain reaction for hepatitis C (PCR for HCV)                           | ♦ Available by special request only, as it is a research tool.  
♦ Used to determine the presence of HCV RNA circulating in the blood which is a measure of virus replication in the liver.  
♦ Can be used to assess the infectivity of the patient and monitor therapy.  
♦ May be of use in early infection when antibody to the virus is undetectable, and in immunocompromised patients who may not seroconvert.  
♦ Can be of use in resolving indeterminate RIBA results. |
| Antibody to hepatitis D virus (Anti-HDV or HBV Ab)                                | ♦ HDV occurs as a co-infection with HBV or super-infection of a chronic HBsAg carrier.  
♦ Antibodies appear late during the course of acute infection.  
♦ HDV uncommon in Alberta. |
| Antibody to hepatitis E virus (Anti-HEV or HEV Ab)                                | ♦ Routine tests not presently available for detection of this agent.  
♦ This test may be available by special request only from reference laboratories. |
| ALT (Alanine aminotransferase)                                                    | ♦ Liver enzyme test.  
♦ Used to assess extent of liver inflammation.  
♦ Can be used to monitor resolution of inflammation following acute or chronic infection. |
SELECTED REFERENCES

Refer to the Guideline for Serological Testing for Suspected Viral Hepatitis for a more detailed list of references.


Toward Optimized Practice (TOP) Program

Arising out of the 2003 Master Agreement, TOP succeeds the former Alberta Clinical Practice Guidelines program, and maintains and distributes Alberta CPGs. TOP is a health quality improvement initiative that fits within the broader health system focus on quality and complements other strategies such as Primary Care Initiative and the Physician Office System Program.

The TOP program supports physician practices, and the teams they work with, by fostering the use of evidence-based best practices and quality initiatives in medical care in Alberta. The program offers a variety of tools and out-reach services to help physicians and their colleagues meet the challenge of keeping practices current in an environment of continually emerging evidence.

TO PROVIDE FEEDBACK

The Alberta CPG Working Group for Microbiology is a multi-disciplinary team composed of microbiologists, general practitioners, and a gastroenterologist, pathologist, university representative, member of the public and representative of Alberta Health and Wellness. The team encourages your feedback. If you need more information or have difficulty applying this guideline, contact:

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