OBJECTIVE

Alberta clinicians are assisted to identify patients with suspected viral hepatitis and optimize laboratory tests for the investigation

TARGET POPULATION

Children and adults with suspected viral hepatitis

EXCLUSIONS

- Where an infectious etiology is not a consideration
- Outbreak investigations
- Pregnant women undergoing routine prenatal screening for viral hepatitis

RECOMMENDATIONS

✓ Perform clinical history

PRACTICE POINT

A clinical history and results of serum enzymes, i.e., alanine aminotransferase, should accompany the request for viral hepatitis testing

ACUTE VIRAL HEPATITIS

✓ Serum enzymes, i.e., alanine aminotransferase (ALT), *should be evaluated before* testing for specific viral serological markers. Dramatic elevations in ALT (five times or greater than the upper limit of normal) are found in patients with acute hepatitis of viral etiology. Therefore, patients with *normal* ALT values are *extremely unlikely* to have acute viral hepatitis.

✓ If acute viral hepatitis is suspected, request IgM antibody to hepatitis A virus (anti- HAV IgM) and hepatitis B surface antigen (HbsAg).

✓ If hepatitis A infection alone is suspected, request IgM antibody to hepatitis A virus (anti-HAV IgM) only.

✓ If hepatitis B infection alone is suspected, request hepatitis B surface antigen (Hb- sAg) only.

✓ Refer to Appendix A (Suspected Acute Hepatitis Algorithm)

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, e.g., after receipt of a letter of notification from the Canadian Blood Services, request hepatitis B surface antigen (HbsAg).
- ✓ If hepatitis C infection alone is suspected, such as after receipt of a letter of notification from the Canadian Blood Services, request antibody to hepatitis C (anti-HCV).
- ✓ Refer to Appendix B (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

The literature was reviewed and the opinions of laboratory specialists, gastroenterologists, infectious disease specialists, public health physicians and family physicians within Alberta were sought to prepare this guideline. No adverse outcomes are expected from this guideline as this testing approach 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 for diagnosing or patient follow-up. Ordering tests pertinent to the stage of disease and directly relevant to clinical management should reduce unnecessary and multiple test ordering.

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 having 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. These tests may be appropriate for determining acute Infection and other tests are used for chronic infection, past exposure or immune status.

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

Refer to Appendix C for an explanation of Viral Hepatitis tests.

CLINICAL MANIFESTATIONS

The initial symptoms of acute hepatitis are nonspecific. Typical reported symptoms include malaise, weakness, followed by anorexia, intermittent nausea, vomiting, and a vague dull, right- upper-

quadrant pain. Alanine aminotransferase levels are elevated between five and 20 times normal values. In the icteric phase, variable in duration and may be as long as three weeks, jaundice and/or dark urine, and sometimes light stools are reported. Some patients may experience fever, rash or arthritis. Symptom manifestation and signs can be quite variable and also depend on age of the patient. And many patients are asymptomatic, or only mildly unwell and anicteric.[7-9]

Patients with chronic hepatitis are commonly asymptomatic. Evidence of liver disease may be found as a result of a routine medical examination or altered liver function test for an unrelated problem, or through routine donor screening by Canadian Blood Services. Alternatively, fatigue may gradually develop and there may be a history of jaundice. Alanine aminotransferase levels may be normal or moderately raised depending on 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 young people. In older age groups the disease can be serious and death from liver failure has 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 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 through injection from drug use, sexual intercourse, perinatal transmission or accidental inoculation with contaminated sharp objects. Other routes are tattooing, body piercing, and close contact in households, institutional settings and on renal dialysis units.[1,2,8,10,11]

For HBV-infected individuals, a chronic infection or carrier state occurs in six to 10% of adults, 25% of children aged one to five years, and 70 to 90% of infected infants. In China, south-east 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 females from these areas, reaching a peak in the 30 to 50 age group.[8,11] In Canada, a seroepidemiological study of inhabitants living in 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 eight to 12 weeks after infection. In immunosuppressed individuals, it may take up to six months or more for antibodies to become measurable.[1]

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.[6,14] Fulminant hepatitis C is rare, and co-infection with hepatitis B has been reported in some of these cases.[15]

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/needle 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.[14]

The presence of HCV antibody only indicates virus infection and does not imply immunity. Acute and chronic HCV infections cannot be distinguished by current antibody tests.[13]

HEPATITIS D

HDV is very rare in Alberta and is a result of a super-infection or co-infection in 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.[1,2,8]

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 the Indian subcontinent, Middle East, North Africa, Mexico and some areas of the former United Soviet Socialist Republic.[2,11,16] Testing for HEV is not routinely available so the diagnosis is made based on 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 three GB viruses (GBV), namely GBV-A, GBV-B and GBV-C, and hepatitis X now provisionally named HGV. All of these viruses are thought to belong to the hepatitis C family.[17]

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 hepatotrophic viruses is still preliminary. There are no routine tests available for these viruses at this time.

Notification of Positive Cases

Under current legislation, the attending physician and testing laboratory must immediately notify Communicable Disease Control, Alberta Health Services, if a patient is positive for hepatitis A, B, C, or D.

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Appendices References

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Suggested Citation

Toward Optimized Practice (TOP) Microbiology Working Group. 2014 Apr. Serological testing for suspected viral hepatitis: clinical practice guideline. Edmonton, AB:

For more information see www.topalbertadoctors.org

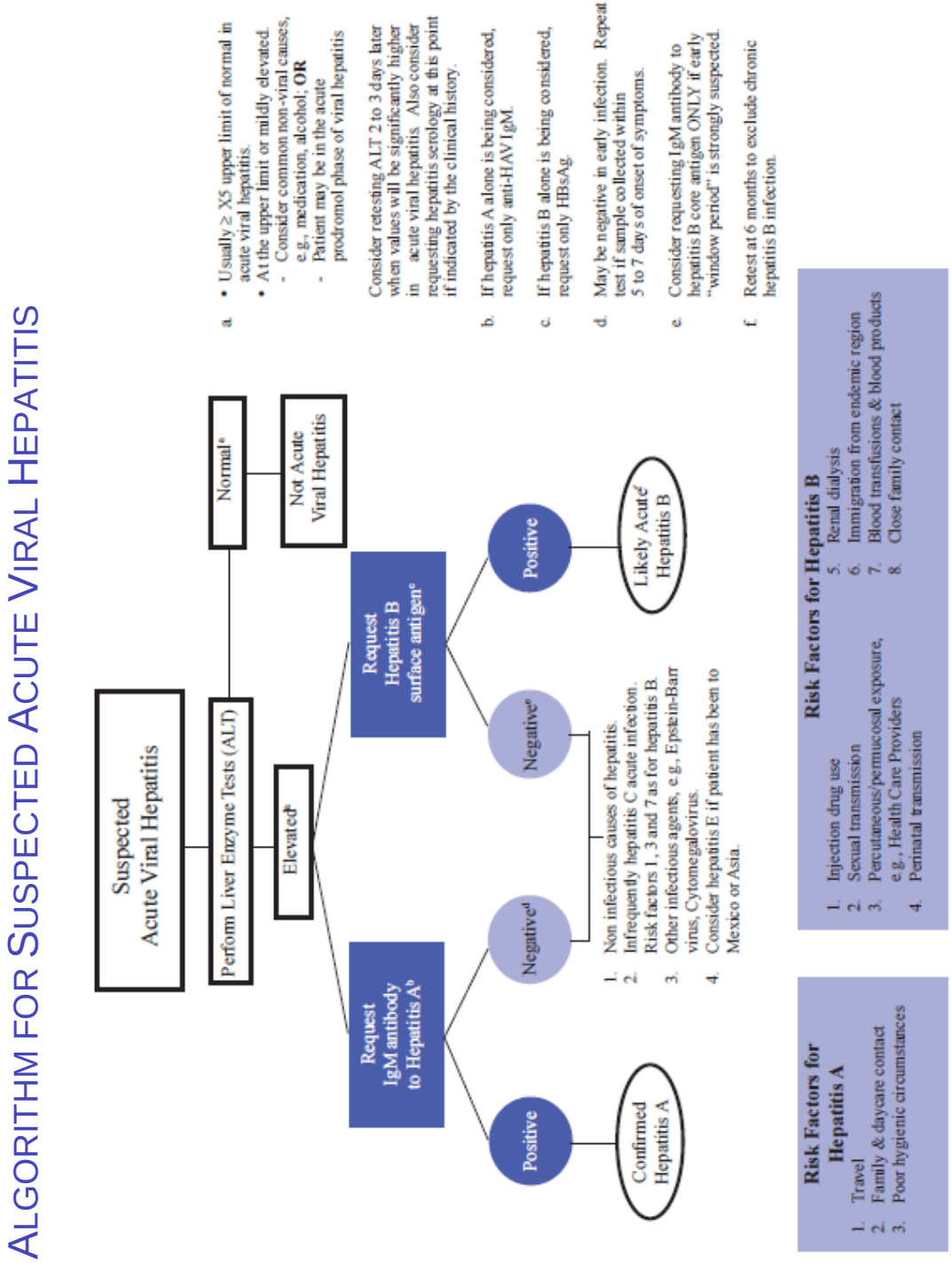
Guideline Committee

The committee consisted of representatives of microbiology, general practice, gastroenterology, pathology and the public.

March 1997
Reviewed 2000
Reviewed 2006
Reviewed April 2014

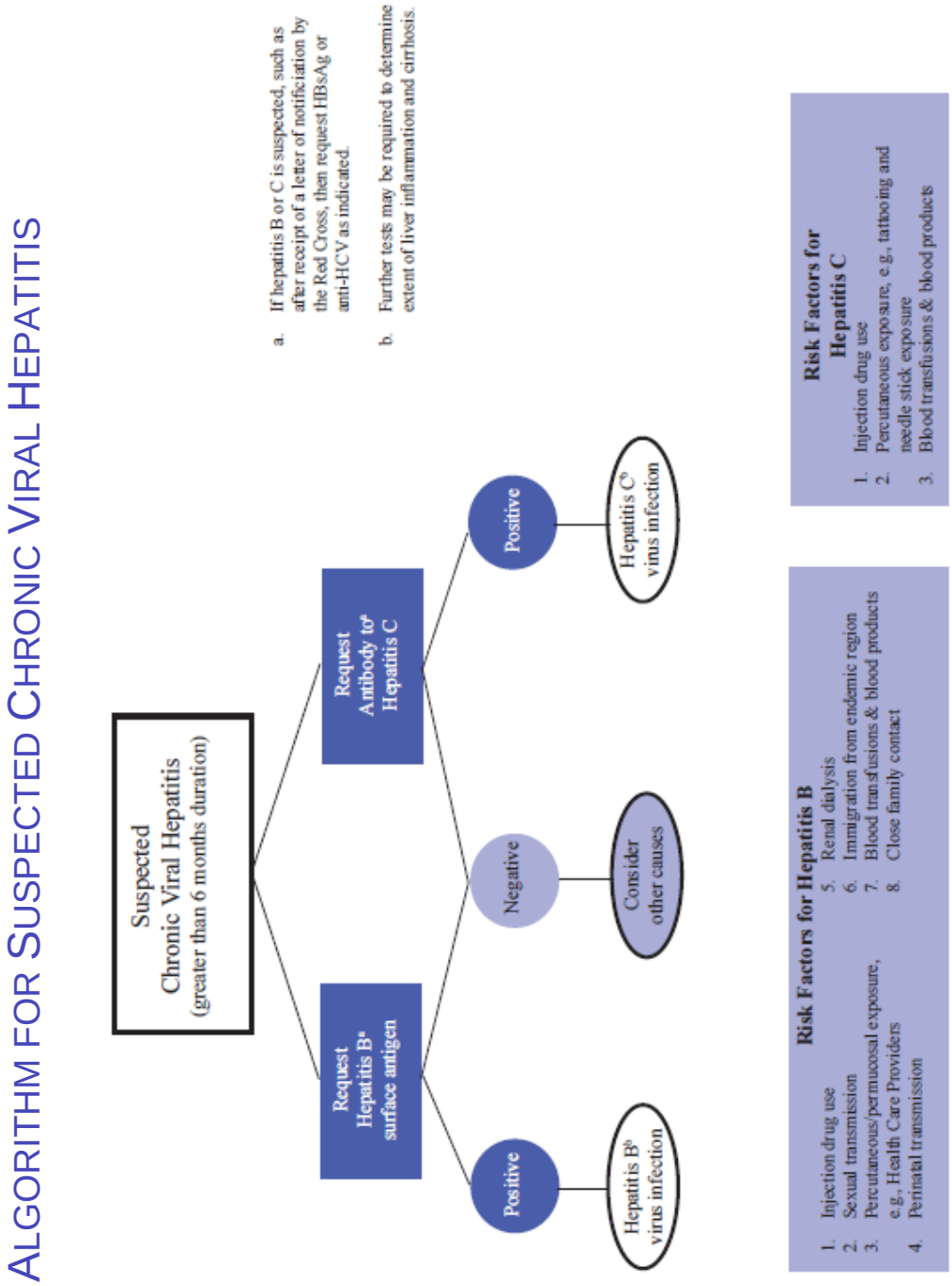
APPENDIX A

ALGORITHM FOR SUSPECTED ACUTE VIRAL HEPATITIS



APPENDIX B

ALGORITHM FOR SUSPECTED CHRONIC VIRAL HEPATITIS



APPENDIX C

EXPLANATION OF VIRAL HEPATITIS TESTS

Test Abbreviation	Interpretation of Results and Comments
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 five to seven days after onset of symptoms) • Present for three to six 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 needle 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[1] • 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
IgM antibody to hepatitis B core antigen **(Anti-HBc IgM or HBc 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" (two 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 three 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

Test Abbreviation	Interpretation of Results and Comments
	• 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 HBc 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 would confirm previous exposure with HBV. Alternatively a negative repeat test later may indicate an earlier false-positive result.
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 eight to 12 weeks to several months following infection with HCV.[4] Earlier generations of EIA tests often gave negative antibody results for up to one year. • False-positive results are found in patients with autoimmune chronic active hepatitis, alcoholic liver disease and other disorders relating to hypergammaglobulinemia • 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 completer 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

Test Abbreviation	Interpretation of Results and Comments
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 in 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