



## .. Serological Testing for Suspected Viral Hepatitis

*This guideline has been developed by an Alberta Clinical Practice Guidelines Program Working Group and is based on current scientific evidence. The opinions of laboratory specialists, gastroenterologists, infectious disease specialists, pediatricians, family physicians and public health physicians were used in the preparation of this guideline.*

### GUIDELINE GOALS

These guidelines are intended to assist practitioners with the following:

- ◆ To determine the most appropriate laboratory tests for the diagnosis of acute and chronic viral hepatitis.
- ◆ To provide information on serological tests presently available, and their value in patient management.
- ◆ To optimize the number of tests required to confirm a diagnosis of viral hepatitis while avoiding multiple tests and unnecessary patient recall.

### EXCLUSION CRITERIA

These guidelines may not apply to the following:

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

### RECOMMENDATIONS

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 the specific viral serological markers. Dramatic elevations in ALT (5 times or more 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 (HbsAg) only.
- ◆ Refer to Suspected Acute Hepatitis Algorithm.

*Recommendations continued on page 2*

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.<sup>1-3</sup>

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.<sup>4</sup> In Alberta, the numbers of acute hepatitis A infections are greater than acute hepatitis B.<sup>5</sup> 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.<sup>6</sup>

## 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.<sup>7-9</sup>

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.<sup>7-8</sup>

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.<sup>2,9-11</sup>

### 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.<sup>1,2,8,10,11</sup>

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.<sup>8,11</sup> 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.<sup>12</sup> 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.<sup>1,2,6,11</sup>

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.<sup>13</sup>

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

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.<sup>14</sup>

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.<sup>13</sup>

## 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.<sup>1,2,8</sup>

## 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.<sup>2,11,16</sup> 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.<sup>17</sup>

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.

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## THE ALBERTA CLINICAL PRACTICE GUIDELINES PROGRAM

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### 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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