GUIDELINES & PROTOCOLS

ADVISORY COMMITTEE

Abnormal Liver Chemistry - Evaluation and Interpretation

Effective Date: August 1, 2011

Scope

This guideline provides recommendations for the evaluation and interpretation of abnormal liver test results in adults (≥19 years). Use in conjunction with other guidelines (e.g., *Viral Hepatitis Testing*).

Diagnosis/Investigation

Abnormal liver tests may indicate an abnormality of the liver and provide clues as to the nature of the problem. However, in an asymptomatic patient, mild abnormalities may not be clinically significant.[1] A systematic approach to evaluating the patient and ordering further tests will help to identify underlying disease.[2] Further testing and referrals may not be necessary in many circumstances.

The term *'liver function test'* should not be used when referring to serum enzyme levels because they correlate poorly with metabolic activities of the liver.[1]

There are two broad categories of liver enzyme abnormalities: hepatocellular and cholestatic.[3,4] Usually the most marked abnormality points to the underlying category of disorder.

1. **Hepatocellular injury** *(e.g., hepatitis)*
   The membranes of liver cells can become permeable when damaged, allowing for escape of intracellular enzymes into the bloodstream. The major intracellular enzymes are alanine aminotransferase (ALT) and aspartate aminotransferase (AST).[1,2]

2. **Cholestasis** *(e.g., biliary obstruction or hepatic infiltration)*
   Obstructed/damaged intra- or extra-hepatic bile ducts cause the induction of synthesis of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT). In acute biliary obstruction, elevation of these enzyme levels often lags obstruction by approximately 24 hours. An isolated minor elevation of GGT is a relatively common finding and does not necessarily indicate significant liver disease.[2]

Note: Serum bilirubin is not a useful test for distinguishing between cholestasis and hepatocellular injury because it may be elevated in both situations.[1]

History and Physical Exam

Obtain a history to determine risk factors for liver disease (see Table 1).[5]
Perform a physical examination to look for evidence of liver disease (see Table 2).

Table 1. Risk Factors for Liver Disease[2,3]

High risk behaviour • IV drug use (past & present) • Multiple sexual partners • High-risk sexual activity • Tattoos • Nonsterile body piercing • Alcohol abuse	**Systemic illness** • Diabetes • Obesity • Hyperlipidemia • Iron overload • Autoimmune diseases • Metastatic cancer • Inflammatory bowel disease
Commonly implicated medications[3] • Acetaminophen, NSAIDs • Antibiotics (e.g., clavulinic acid-amoxicillin, nitrofurantoin, sulfonamides) • HMG-CoA reductase inhibitors (statins) • Anticonvulsant drugs (e.g., phenytoin, carbamazepine, valproic acid) • Isotretinoin (Accutane®) • Immunomodulators (e.g., methotrexate, azathioprine) • Antituberculous drugs (e.g., isoniazid) • Some herbal medications	**Other** • Travel to or residence in less developed regions or countries • Needlestick injury or other occupational exposure (e.g., razors) • Receipt of unscreened blood products, especially prior to 1990* • Hemodialysis • Contaminated food or water (hepatitis A)

*screening of donated blood products for hepatitis C (anti-HCV) began in 1990 in Canada.[6]

Table 2. Common Clues to Diagnose Liver Disease

Symptoms/signs	Level or stage of liver disease
Jaundice	Acute hepatitis, biliary obstruction, or advanced chronic liver disease
Abdominal pain, fever	Acute cholangitis, cholecystitis or liver abscess
Chronic stigmata: spider angiomata, palmar erythema, gynecomastia, testicular atrophy, asterixi	Cirrhosis
Complications: encephalopathy, ascites, acute gastrointestinal bleeding, coagulopathy, muscle wasting	Advanced liver disease (decompensated)
Chronic generalized pruritus	Cholestasis (eg., primary biliary cirrhosis)

Initial Investigations

If liver disease is suspected, but the cause is not apparent from the initial history and physical examination, direct further investigations towards determining whether the condition is predominantly hepatocellular or cholestatic.[2] Order ALT and ALP at this time.[2]

In patients with clinically overt hepatobiliary disease, it may be expeditious to include an AST and GGT with the initial blood work. Do not order GGT and lactate dehydrogenase (LDH) in isolation for initial investigation of possible liver disease.[2] Isolated elevation of GGT is nonspecific but may indicate overuse of alcohol and become a useful tool for counselling a patient where alcohol abuse or dependence is a concern.[2]

Cholestasis

If ALP elevation is the predominant abnormality, obtain GGT to confirm hepatobiliary origin.[7] If cholestasis is confirmed, then perform abdominal ultrasound to assess the biliary tree.[7] If ALP and GGT are elevated in the setting of a non-dilated biliary tree, then intra-hepatic cholestasis or hepatic infiltration is suggested. If the biliary tree is dilated, then determine the cause of obstruction.

If GGT is not elevated, then an elevated ALP may be of bone or placental origin.[7]

Hepatocellular Injury

Predominant ALT elevation points to hepatocellular damage.[2] A detailed patient history will help delineate risk factors and potential causes.

Presentation with an ALT exceeding 1000 U/L usually represents one of the following conditions: acute viral hepatitis, acute choledocholithiasis, acute vascular injury of the liver (ischemia or congestion) or ingestion of hepatotoxin (e.g., acetaminophen, poisonous mushrooms).

Test for viral causes in accordance with the *Viral Hepatitis Testing* guideline available at www.BCGuidelines.ca. Consider other causes of liver disease (see Table 3). If iron overload is being considered, refer to *Iron Overload - Investigation and Management* available at www.BCguidelines.ca.

Table 3. Enzyme Elevations in Liver Disease

	Abbreviation ***Full name***	**When is it likely to be abnormal**	**Specificity for liver disease**	**Other causes**
Hepatocellular injury (Hepatitis – all types)	ALT *Alanine aminotransferase*	Hepatitis (particularly viral, autoimmune, drug induced, non-alcoholic fatty liver disease (NAFLD), iron overload)	Sensitive and specific	Acute obstructive jaundice (within first 24h)
	AST *Aspartate aminotransferase*	Hepatitis (particularly alcoholic), hepatic fibrosis/cirrhosis	Less sensitive and specific than ALT	Cardiac or skeletal muscle injury or hemolysis
Cholestasis (Biliary obstruction, hepatic infiltration)	ALP *Alkaline phosphatase*	Cholestasis	More indicative of liver disease than GGT	Bone disease, pregnancy
	GGT *Gamma-glutamyl transpeptidase*	Cholestasis, alcohol	More sensitive than ALP May not indicate significant liver disease	Medications, hepatic congestion (CHF)

Monitoring of liver chemistry with medication use
A thorough medication history is paramount. History should include all prescribed drugs, over-the-counter drugs, as well as natural health products. Almost any medication can cause elevations of liver enzymes and possible liver injury.[3] While the majority of these reactions are idiosyncratic in nature, some are dose-related. Acetaminophen toxicity is dose-related and is the most common cause of medication-induced liver damage and liver failure.[8] For all medications, consult the product monograph for specific information.

- **Monitoring patients on a potentially hepatotoxic drug**
  Certain drugs may require specific monitoring. Please see product monographs.

- **Investigation of abnormal liver tests with medication use**
  Many hepatotoxic drugs have a "signature" toxicity.[9,10,11] In general, any recently started medication or an increased dosage of medication should be considered the primary cause of newly elevated enzymes until proven otherwise.[2] Consider withdrawing or replacing the drug if the liver chemistry abnormality is severe and it is clinically safe to do so. Repeat test in 1 to 3 months to document normalization.

Isolated test abnormality
An isolated minor abnormality (<1.5 times upper limit of normal) in an asymptomatic individual should prompt retesting in 1 to 3 months, particularly after addressing potential causes or modifiable risk factors.[3]

GGT elevation is easily induced by alcohol and medications, so an isolated elevation of this enzyme does not always imply significant liver disease.[2]

Isolated indirect (unconjugated) hyperbilirubinemia is commonly due to Gilbert's syndrome, a benign condition that occurs in approximately 2-7% of the population, and which is often unrecognised without the provocation of stress or starvation.[13] Less commonly, unconjugated hyperbilirubinemia may be due to hemolysis.

Persistent minor elevations of liver tests (≥ 6 months)
Review history for possible exposure to infectious liver disease and other risk factors such as medications or alcohol. If no obvious cause is found, further investigation is indicated (see Table 2). Refer to *Viral Hepatitis Testing* and *Iron Overload – Investigation and Management* guidelines and/or consider referral.[12]

Liver biopsy and other special tests
Disease specific tests including auto-antibodies, copper and iron studies, alpha-feto protein (AFP), and specific viral markers should only be obtained in appropriate circumstances and usually in consultation with a specialist.[2]

A liver biopsy may provide important diagnostic and prognostic information regarding the cause of liver disease. Consultation with a specialist is advisable prior to obtaining a liver biopsy.[1]

In the setting of biliary dilatation, consultation with a specialist is recommended to consider visualization of the biliary tract by computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP).

Serum ammonia levels are seldom useful and should not be obtained.

Evaluation of hepatic function
Standard measurements of liver enzymes do not reflect overall liver function. Synthetic function of the liver may be estimated by measuring serum albumin and international normalized ratio (INR).[1]

Bilirubin may be elevated in hepatitis or cholestasis.[1] In chronic liver disease a rising bilirubin may indicate deteriorating liver function.[1]

Acute presentation with right upper quadrant pain
In a patient presenting with acute right upper quadrant pain, testing is used to identify potential biliary tract disease. Perform AST, ALT, ALP and GGT testing expeditiously to differentiate between cholestasis and hepatitis. In acute biliary obstruction, levels of ALP and GGT may not be increased for approximately 24 hours.

Urgent referral for an abdominal ultrasound is recommended to identify biliary tract disease.

A patient presenting with fever and right upper quadrant pain may require urgent evaluation for possible biliary tract intervention.

Rationale

Liver disease is a common problem in primary care. Its presence and etiology may be appreciated only after blood tests are performed. Order liver enzyme tests in a directed fashion based on a suspicion of liver disease. Non-directed or routine ordering of screening panels is discouraged. Most laboratories maintain serum samples for several days allowing for further testing if required.

The approach to patients with suspected liver disease includes reviewing the history (including risk factors), performing a physical examination, and ordering selected blood tests. An asymptomatic patient with minor abnormalities of liver chemistry may be monitored by the primary care physician, with follow up. Elevated liver enzyme levels are reported in 1-4% of asymptomatic persons, most of whom will not develop clinically significant liver disease.[7]

The differentiation between hepatocellular injury and cholestasis is an important first step leading to a more efficient use of subsequent tests. The importance of alcohol, medications and obesity as causes of abnormal liver enzyme levels cannot be overstated.[2,8] Normalization of the test abnormality after withdrawal of alcohol or a medication for 1 to 3 months implicates that substance as the cause of the abnormal test.

An isolated non-progressive elevation of GGT seldom reflects significant liver disease and usually does not require specialist referral. In addition, modest ALT and/or AST elevations in obese or diabetic patients may represent non-alcoholic fatty liver disease (NAFLD), which is now a common cause of chronic liver disease.[14] Non-alcoholic steatohepatitis (NASH) is a potentially severe form of NAFLD and may lead to cirrhosis.

For investigations of viral hepatitis and iron overload refer to www.BCGuidelines.ca

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This guideline is based on scientific evidence current as of the Effective Date.

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association and adopted by the Medical Services Commission.

The principles of the Guidelines and Protocols Advisory Committee are to:

- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

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