

# GUIDELINES & PROTOCOLS

## ADVISORY COMMITTEE

### Liver Chemistry Abnormalities in Adults – Evaluation and Interpretation

Effective Date: July 1, 2004

#### Scope

This guideline provides recommendations for the interpretation and evaluation of abnormal liver test results in adults. It should be used in conjunction with other guidelines, such as *Clinical Management of Chronic Hepatitis B*, *Clinical Management of Chronic Hepatitis C*, *Investigation and Management of Iron Overload* and *Viral Hepatitis Testing*.

#### Background

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. A systematic approach to evaluating the patient and ordering further tests will help to efficiently identify any underlying disease.<sup>7</sup> 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.

There are two broad categories of liver enzyme abnormalities.<sup>7,9</sup> (see Table 2) Usually the most marked abnormality points to the underlying category of disorder.

1. Hepatocellular injury (e.g. hepatitis) – damaged liver cells develop leaky membranes, allowing for escape of intracellular enzymes into the bloodstream.<sup>1,3,10</sup> The major intracellular enzymes are aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
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 symptoms by approximately 24 hours. An isolated elevation of GGT is a relatively common finding and does not necessarily indicate significant liver disease.<sup>7</sup>

NOTE: Bilirubin is not a useful test for distinguishing between cholestasis and hepatocellular injury because it may be elevated in both situations.<sup>1,3</sup>

## RECOMMENDATION 1 History and Physical Exam

Obtain a history to determine risk factors for liver disease.<sup>9,10</sup>

### Risk Factors For Liver Disease<sup>7,9,10</sup>

#### High Risk Behaviour<sup>9</sup>

- IV drug use (past & present)
- Multiple sexual partners
- High-risk sexual activity
- Tattoos
- Nonsterile body piercing
- Alcohol abuse

#### Systemic Illness<sup>2,7</sup>

- Diabetes
- Obesity
- Hyperlipidemia
- Hemochromatosis
- Autoimmune diseases
- Possible metastatic cancer
- Chronic inflammatory bowel disease

#### Medications<sup>4,13</sup>

- Acetaminophen
- Herbal medications<sup>6,8</sup>
- HMG-CoA reductase inhibitors (statins)
- Anticonvulsant drugs
- Isotretinoin (Accutane<sup>®</sup>)
- Antibiotics
- Antituberculous drugs

#### Other<sup>9</sup>

- Travel to or residence in less developed regions or countries
- Exposure to blood or needle stick injuries
- Receipt of blood products, especially prior to 1990
- Hemodialysis
- Ingesting contaminated foods

A physical examination should be performed to look for evidence of liver disease. (see Table 1)

<b>Symptoms/Signs</b>	<b>Level or Stage of Liver Disease</b>
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 <sup>8</sup> )	Cirrhosis
Complications (encephalopathy, ascites, acute GI bleeding, coagulopathy, muscle wasting)	Advanced liver disease (decompensated)

## RECOMMENDATION 2 Initial investigations

If liver disease is suspected, but the cause is not apparent from the initial history and physical examination, then further investigations should be directed toward determining whether the condition is predominantly hepatocellular or cholestatic.<sup>7</sup> ALT and ALP should be ordered at this time.<sup>1,3</sup>

In patients with clinically overt hepatobiliary disease it may be expeditious to include an AST and GGT with the initial blood work. GGT and LDH should not be ordered in isolation for initial investigation of possible liver disease. Isolated elevation of GGT may, however, indicate evidence of overuse of alcohol and become a useful tool for counselling a patient where alcohol abuse is a concern.

## RECOMMENDATION 3 Cholestasis

If ALP elevation is the predominant abnormality, then GGT should be obtained to confirm a hepatobiliary origin.<sup>7,10</sup> If cholestasis is thus confirmed, then abdominal ultrasound should be performed to assess the biliary tree.<sup>10</sup> 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 GGT is not elevated, then an elevated ALP may be of bone or placental origin.<sup>3,9,10</sup>

## RECOMMENDATION 4 Hepatocellular Injury

Predominant ALT elevation points to hepatocellular damage. A detailed patient history will help delineate risk factors and potential causes for this inflammation. (See Recommendation 1)

Testing for viral causes should be in accordance with the guideline, *Viral Hepatitis Testing* (in progress). When appropriate, iron overload should be considered and investigated according to the guideline, *Investigation and Management of Iron Overload*.

**Table 2: Enzyme Elevations in Liver Disease**

	<b>Abbreviation Full Name</b>	<b>When it is Likely to be Abnormal</b>	<b>Specificity for Liver Disease</b>	<b>Other Causes</b>
<b>Hepatocellular Injury</b> (Hepatitis – all types)	ALT (formerly SGPT) <i>Alanine aminotransferase</i>	Hepatitis (particularly viral, autoimmune, drug induced, non-alcoholic fatty liver disease (NAFLD) <sup>11</sup> , iron overload)	Sensitive and specific	Acute obstructive jaundice (within first 24h)
	AST (formerly SGOT) <i>Aspartate aminotransferase</i>	Hepatitis (particularly alcoholic), hepatic fibrosis/cirrhosis	Less sensitive and specific than ALT	Cardiac or skeletal muscle injury
<b>Cholestasis</b> (Biliary obstruction, hepatic infiltration)	ALP <i>Alkaline phosphatase</i>	Cholestasis	More specific than GGT	Bone disease, pregnancy
	GGT <i>Gamma-glutamyl transpeptidase</i>	Cholestasis, alcohol	More sensitive than ALP  May not indicate significant liver disease	Medications, hepatic congestion (CHF)

## **RECOMMENDATION 5**    **Monitoring of liver chemistry in specific medication use**

Many medications may cause elevations of liver enzymes and possible liver damage<sup>13</sup> (see Recommendation 1). Acetaminophen toxicity is dose related and is the most common cause of drug-induced liver damage and liver failure.<sup>5,8,12</sup> Some medications cause idiosyncratic liver damage, while others are dose related. For all medications, consult the product monograph for specific information.

### **Monitoring patients on a potentially hepatotoxic drug**

ALT should be checked before starting potentially toxic drugs. As a minimum, repeat after one month, then after 6 months, and then yearly thereafter.

Note: Certain drugs may require more frequent monitoring. Examples include methotrexate, leflunomide and some drug combinations.

### **Investigation of abnormal liver tests in specific medication use**

A recently prescribed medication or an increased dosage of medication should be considered the primary cause of elevated enzymes until proven otherwise.<sup>3,4</sup> Consider withdrawing or replacing the drug if the liver chemistry abnormality is severe and it is clinically safe to do so.<sup>6</sup> The abnormal test should be repeated in six to eight weeks to document normalization.<sup>10</sup>

## **RECOMMENDATION 6**    **Isolated test abnormality**

An isolated minor abnormality (<1.5 times upper limit of normal) in an asymptomatic individual should prompt re-testing in 1 to 3 months, particularly after addressing potential causes or modifiable risk factors (See Recommendation 1).

GGT elevation is easily induced by alcohol and medications, so an isolated elevation of this enzyme does not always imply significant liver disease. Recent alcohol use is the most common cause of minor GGT elevation.<sup>7</sup>

Isolated indirect (unconjugated) hyperbilirubinemia represents the benign condition called Gilbert's syndrome and affects up to 5% of the general population although it is often unrecognised without the provocation of stress or starvation.

## **RECOMMENDATION 7**    **Minor elevations of liver tests**

Review history for possible exposure to infectious liver disease and other risk factors such as medications or alcohol. If no risk factors are present and the patient is asymptomatic the patient should be followed clinically and tests repeated in 1-3 months.

## **RECOMMENDATION 8**    **Acute presentations with right upper quadrant pain and/or jaundice**

In the patient presenting acutely, testing is used to differentiate a surgical emergency from an acute medical problem. AST/ALT and ALP/GGT should be performed to differentiate expeditiously between cholestasis and hepatitis. In acute biliary obstruction, elevation of ALP/GGT may not be apparent for approximately 24 hours.

An abdominal ultrasound should be performed urgently to identify biliary obstruction.<sup>3,7</sup>

The patient presenting with fever and right upper quadrant pain frequently has a surgical problem such as cholecystitis.<sup>9</sup>

## **RECOMMENDATION 9** 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).<sup>7</sup>

Bilirubin may be elevated in hepatitis or cholestasis. In chronic liver disease an elevated bilirubin may indicate deteriorating liver function.<sup>7</sup>

## **RECOMMENDATION 10** 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 be obtained in appropriate circumstances and usually in consultation with a specialist.<sup>7</sup>

A liver biopsy may provide information on the grade and stage of disease process and may provide further information as to etiology.<sup>9</sup> A consultation with a specialist is advisable prior to obtaining a liver biopsy.

Endoscopic retrograde cholangiopancreatography (ERCP) is useful when other tests show biliary tract dilatation because it delineates biliary anatomy and obstructing lesions of large ducts.<sup>7</sup>

Serum ammonia levels are seldom useful.

### **Rationale**

Liver disease is a common problem in primary care. Its presence and etiology may be appreciated only after blood tests are performed. Liver enzyme tests should be ordered in a directed fashion on the suspicion of liver disease. Non-directed or random ordering of screening panels should be discouraged. However, if a third party orders a screening panel and there is a surprise finding of an abnormal liver test, further investigative testing should be done in a directed manner according to the above recommendations. Most laboratories maintain serum samples for up to seven days allowing for further testing upon request.

The approach to patients with suspected liver disease should be to review the history including risk factors, to perform a physical examination, and to order selected blood tests.<sup>7</sup> An asymptomatic patient with minor abnormalities of liver chemistry can be monitored by the primary care physician, with periodic follow up (see recommendations 6 and 7).

The differentiation between hepatitis and cholestasis is an important first step leading to a more efficient use of subsequent tests.<sup>7</sup> The importance of medications<sup>8,13</sup> and alcohol in liver toxicity as a cause of abnormal tests cannot be overstated. Normalization of the test abnormality after withdrawal of the drug or alcohol for six to eight weeks implicates that substance as the cause of the abnormal test.<sup>1,3,7</sup>

An isolated non-progressive elevation of GGT seldom reflects significant liver disease and usually does not require specialist referral. In addition, modest ALT elevations in obese or diabetic patients may represent non-alcoholic fatty liver disease (NAFLD)<sup>11</sup>, formerly known as steatohepatitis (NASH).

Investigations of specific liver diseases such as viral hepatitis and hemochromatosis are covered in the guidelines, *Clinical Management of Chronic Hepatitis B*, *Clinical Management of Chronic Hepatitis C*, *Investigation and Management of Iron Overload and Viral Hepatitis Testing* [update in progress].

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## Sponsors

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# The Evaluation and Interpretation of Abnormal Liver Chemistry in Adults

