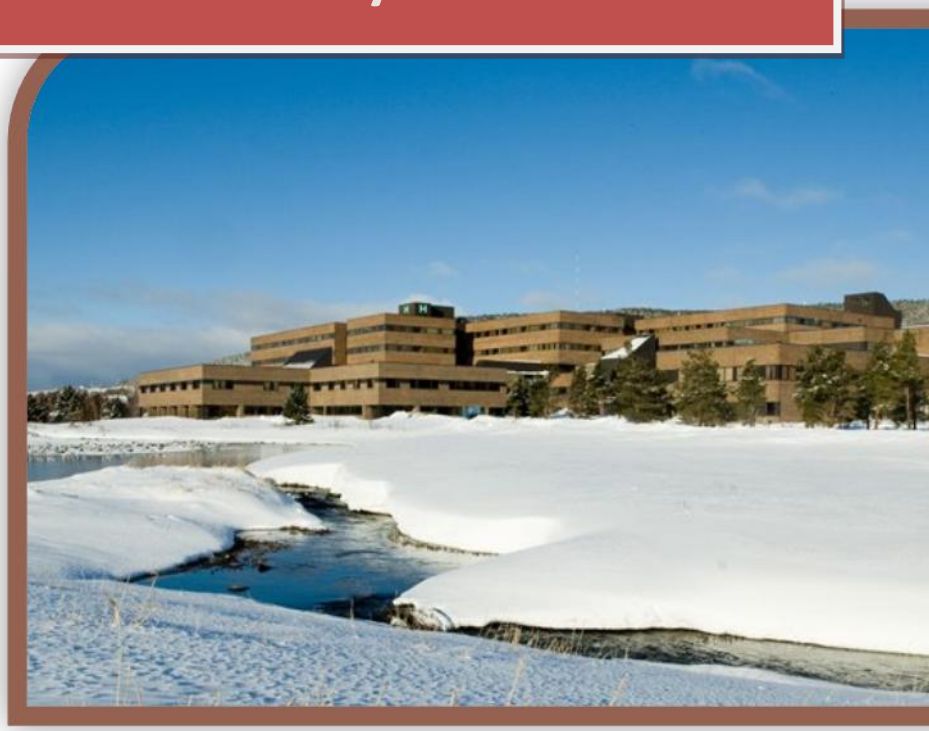
Initial investigation of liver disease using Clinical Chemistry tests.



Clinical Biochemistry Laboratory Formulary Working Group

Laboratory Medicine Program
Eastern Health
Rm 1J442 Health Sciences Centre, 300 Prince Philip Drive,
St. John's NL A1B 3V6

Office: 709-777-6375
Fax: 709-777-2442
Email: Ed.Randell@easternhealth.ca
Website: www.easternhealth.ca/Professionals.aspx?d=2&id=2010&p=1507

Executive Summary

All health professionals with test ordering privileges can order routine chemistry tests to assess liver and biliary integrity. The LFT (Liver function test) panel is defined (below) in accordance with current guidelines and best practices.

Images provided courtesy of HSIMS

The following guidelines are recommended for defining and use of LFT panels when screening for liver injury:

1. The LFT panel will consist of serum ALT and ALP levels as first line tests, with lab reflex testing of AST and total bilirubin levels if either of the first line tests is elevated.
2. ALT measurement is recommended as a first line test for screening for hepatocellular injury.
3. ALP measurement is recommended as a first line test for screening for cholestatic disease.
4. Order ALT and ALP levels in cases of suspected liver disease when there is no obvious cause identified based on history and physical exam.
5. Other tests like serum GGT and AST levels may be included for patients with evidence of overt liver disease.

Disclaimer

Contents

Scope

These recommendations apply to:

- Routine screening and investigation for suspected liver disease.
- Investigation of patients with clinical evidence of overt liver disease.

Rationale

Measurement of alanine aminotransferase (ALT) level is more sensitive and specific than aspartate aminotransferase (AST) level measurement for liver injury. Measurement of alkaline phosphatase (ALP) level offers good sensitivity for cholestatic disease. ALT and/or ALP levels are elevated in only 10 to 15% of ordered LFT panels. The measurement of other LFT panel components like AST, total bilirubin, and albumin, represent unnecessary testing in the context of liver disease screening in the remaining 85 to 90% of cases where neither ALT nor ALP levels are elevated.

Background

Few of the tests commonly referred to as liver function tests have anything to do with liver function specifically. The liver enzymes AST and ALT are released into circulation with hepatocellular injury but show poor correlation with metabolic activity of the liver. With significant hepatocellular injury increases in these typically occur together. Generally, hepatocyte injury causes increases in transaminase levels and cholestatic disease causes increased levels of ALP, gamma glutamyltransferase (GGT), and total bilirubin. Tests like albumin and protrombin time (PT)/INR measure the liver synthetic functions or functional mass.

Serum ALT level is more sensitive and specific than AST level for liver injury and there is little value in ordering both together in the absence of high clinical suspicions for liver injury. Measurement of ALT level is recommended as the primary test for investigating for hepatocellular injury. Isolated elevations in AST level can occur with injury to other tissue including liver, heart, and muscle, and commonly occurs as a result of hemolysis during blood collection and specimen processing for analysis. The most common causes of hepatocyte injury include non-alcoholic fatty liver disease; viral hepatitis; alcohol, drug or other toxic liver disease; hemochromatosis; and autoimmune disease.

The AST/ALT ratio can provide useful information to help differentiate between types of liver damage in some cases. A ratio ≤1 suggests acute hepatocellular damage. An AST/ALT ratio > 1 can occur in liver disease due to excessive alcohol use, drug-induced liver injury, malignancy, and cirrhosis. An AST/ALT ratio >2 is common in acute alcoholic liver disease. With acute injury elevations in serum AST level will be accompanied by elevations in ALT level.

Serum ALP is elevated in all forms of cholestatic liver disease. Increased ALP level and bilirubin level are typical of cholestasis, but isolated increases in ALP level can also be observed. Isolated increases in bilirubin can occur with intravascular hemolysis or in individuals with Gilbert's syndrome. The latter is a benign condition affecting 5 to 10% of individuals of western European descent.

GGT is insufficiently sensitive for population based screening for excessive alcohol consumption. Serum bilirubin cannot be used to reliably distinguish cholestasis from hepatocellular injury because it may be elevated in both situations. Elevated ALP level is not specific for liver disease but can also occur from bone (bone metastases, vitamin D deficiency, hyperparathyroidism, renal impairment, healing from fractures and Paget's disease), intestine and placenta (pregnancy). Raised GGT level with increased ALP level suggests liver as the source of the raised serum enzyme levels.

An isolated minor elevation of GGT level is a relatively common finding and does not necessarily indicate significant liver disease. An elevated ALP level without accompanying elevation in GGT level may indicate increased ALP of bone or placental origin.

Failure of the liver synthetic function is indicated by decreased albumin level and increased PT/INR measurement. This indicates loss of functional liver mass and is an indication of severe liver disease. Albumin is a long half-life protein and may require several days after severe acute liver injury to show reduction. It is not useful during the acute stages of liver injury.

It is rare to find significant abnormalities in Liver Function tests in asymptomatic individuals with no known risk factors. In this group even mild abnormalities are of no clinical significance. Elevated liver enzyme levels are reported in 1-4% of asymptomatic persons, most of whom will not develop clinically significant liver disease. An isolated minor abnormality (<1.5 times upper limit of normal) in a Liver Function test in an asymptomatic individual should prompt retesting in 1 to 3 months, particularly after addressing potential causes or modifiable risk factors.

Table 1. Recommended Usage of Tests.

ALT	•**Best test** to assess hepatocellular integrity.
AST	•Not liver specific (Liver, skeletal muscle, kidney, brain, RBCs). •AST/ALT ratio may be useful in DDx of hepatocellular injury.
ALP	•**Best test** for cholestatic disease (More specific than GGT). •Not specific for liver disease (bone, intestine, placenta).
GGT	• Helps confirm excess alcohol intake if strong clinical suspicion. •Accompanies ALP increase in biliary obstruction/lesion.
Total Bilirubin	•Commonly elevated with ALP during cholestasis. •Elevated with severe liver disease. •Elevated in non-liver disease (hemolysis).
Albumin	•Decrease may indicate severe live injury (Liver failure).
PT/INR	•Increease may indicate severe liver injury (Liver failure).

Conclusions

Investigations for liver injury should begin with measurement of ALT and ALP levels. Follow-up testing should include confirmation of the abnormality and use of other investigations including serum AST and total bilirubin levels, and possibly others given the clinical indication. Good utilization of LFTs is promoted through redefinition of LFT test panels.

The Clinical Biochemistry Laboratory Formulary Committee

The Clinical Biochemistry Laboratory Formulary Committee is a multidisciplinary group involved in improving the usage of laboratory services within Eastern Health.

The main purposes of the committee include:

1. Assisting in decision making on in-house testing menus including retiring of redundant tests and adding of new tests.
2. Reviewing and advising on issues related to laboratory utilization to promote evidence-based usage of laboratory services and best practices guidelines.

3. Advising on development of a tiered formulary for all laboratory tests available through the Clinical Biochemistry laboratory.

We acknowledge the following as committee members in development of this guideline:

- Dr. Brendan Barrett
- Dr. Paul Bonisteel
- Barry Dyer
- Dr. Christopher Kovacs
- Natasha Lee
- Peggy Manning
- Colleen Mercer
- Dr. David Parry
- Dr. Edward Randell
- Dr. Robert Woodland

References

Goessling W, Friedman LS. Increased liver chemistry in an asymptomatic patient. *Clin Gastroent and Hepatol. 2 (2005)*:852-585.

Minuk GY. Canadian Association of Gastroenterology Practice Guidelines: Evaluation of abnormal liver enzyme tests. Can J Gastroenterol. 1998;12:417-21.

Guidelines and Protocols Advisory Committee. Abnormal Liver Chemistry - Evaluation and Interpretation British Columbia Medical Association 2011. Available from: http://www.bcguidelines.ca/pdf/liver.pdf

McCurdy B. Aspartate aminotransferase testing in community-based laboratories: an expert consultation. Toronto, ON: Health Quality Ontario; 2013 June. 11 p. Available from: http://www.hqontario.ca/evidence/publications-andohtac-recommendations/expert-consultations.