Interpretation of Abnormal Liver Function Tests

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KEYWORDS

• Liver function tests • Aminotransferases • Alkaline phosphatase • Bilirubin

HOSPITAL MEDICINE CLINICS CHECKLIST

1. In the setting of abnormal liver function tests (LFTs), review history for liver disease risk factors (alcoholism, blood transfusion, intravenous drug use, current hepatotoxic medications, or family history of liver disease).
2. In patients with liver injury, review risk factors and history along with pattern of LFTs to narrow your differential.
3. For patients with abnormal LFTs, recheck alanine transaminase, aspartate transaminase, alkaline phosphatase, bilirubin, and albumin levels in 1 to 3 months.
4. Also screen for treatable causes of hepatitis if abnormal LFTs persist for more than 6 months: hemochromatosis; autoimmune hepatitis; α_1-antitrypsin deficiency; hepatitis B, C, and D; nonalcoholic fatty liver disease; and Wilson disease.
5. Check γ-glutamyl transferase level in patients with increased alkaline phosphatase levels to confirm hepatic origin of the enzyme.
6. If total bilirubin levels are increased, direct and indirect bilirubin fractions should be obtained. If indirect fraction is greater than 80% of total, then order a reticulocyte count and peripheral smear to exclude hemolysis.
7. Consider liver biopsy for any patient with abnormal LFTS of more than 6 months duration.

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Hosp Med Clin 3 (2014) e139–e148
http://dx.doi.org/10.1016/j.ehmc.2013.10.003
2211-5943/14/$ – see front matter

DEFINITIONS

1. What are the different types of LFTs?

Abnormal LFTs are defined as increased levels of static biochemical tests, which include liver tests measured in serum (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], bilirubin) and measurements of biosynthetic liver function (international normalized ratio [INR], albumin).[1,2]

2. What are normal values for LFTs?

ALT: 0 to 45 IU/L
AST: 0 to 45 IU/L
ALP: 30 to 120 IU/L
Bilirubin: 0.5 to 1.0 mg/dL
INR: 10.9 to 12.5 seconds
Albumin: 4 to 6 g/dL

3. How are normal LFTs defined?

Normal LFTs are defined as the mean distribution $\pm$ 2 standard deviations in a representative healthy population. Therefore, statistically, 5% of all healthy individuals have abnormal liver function studies, many of which may be of no clinical significance. The interpretation of all abnormal liver chemistries must be considered in the clinical context of a given patient.

4. What are the different types of liver injury?

- Hepatocellular injury: cellular injury in the liver, causing release and increase of AST and ALT levels out of proportion to increase in ALP levels.
- Cholestatic injury: stasis of bile flow from liver to the duodenum, causing increase in the ALP level out of proportion to increase in transaminase levels.
- Mixed: increase of AST/ALT and ALP levels are not mutually exclusive, and mixed-type injuries are often found. Also, bilirubin levels can be increased in either hepatocellular or cholestatic injury.

5. What is the significance of increase of the different types of LFTs?

Increased Aminotransferase (ALT/AST) Levels

Aminotransferases participate in gluconeogenesis by catalyzing the transfer of amino groups from aspartic acid or alanine to ketoglutaric acid to produce oxaloacetic acid and pyruvic acid. ALT is found in its highest concentrations in the liver and is more specific to the liver than is AST, which is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and red cells. Increased AST levels are therefore less sensitive and specific for liver injury.[3–5]

Increased ALP Levels

ALP is associated with cellular membranes, and increased levels may be caused by injury to the liver, bone, kidneys, intestines, placenta, or leukocytes. In the liver, the enzyme is located in the bile canaliculi. Biliary obstruction increases synthesis of ALP, resulting in increased plasma levels.

Increased γ-Glutamyl Transferase Levels

γ-Glutamyl transferase (GGT) is a sensitive marker of cholestasis, which is more specific to the liver than is ALP, although it is also produced in small amounts by the heart, brain, spleen, and seminal vesicles. It is often checked to confirm a biliary source of ALP increase.

Increased Bilirubin Levels

Bilirubin is formed from the lysis of red cells within the reticuloendothelial system. Unconjugated bilirubin is transported to the liver loosely bound to albumin. It is water insoluble and therefore cannot be excreted in urine. In the liver, bilirubin is then conjugated with glucuronic acid by the enzyme glucuronyltransferase, making it soluble in water. Any disruption in this process can cause the bilirubin to be increased.

Increased INR

The synthesis of coagulation factors is an important function of the liver. The INR measures the rate of conversion of prothrombin to thrombin and thus reflects a vital synthetic function of the liver. Vitamin K is required for the γ carboxylation of these factors. INR may therefore be prolonged in vitamin K deficiency, warfarin therapy, liver disease, and consumptive coagulopathy.

Decreased Albumin Levels

Albumin synthesis is an important function of the liver. With progressive liver disease, serum albumin levels decrease, reflecting decreased synthesis. Albumin levels are dependent on several other factors, such as nutritional status, catabolism, hormonal factors, and urinary and gastrointestinal losses. In the setting of liver disease, albumin concentration does correlate with overall patient prognosis.

PREVALENCE

1. How common are abnormal LFTs?

Abnormal liver biochemical and function tests are frequently detected in asymptomatic patients, because many screening blood test panels routinely include them.[5] A population-based survey in the United States conducted between 1999 and 2002[6] estimated that abnormal ALT levels were present in 8.9% of respondents.

CAUSES

1. What are the causes of increased aminotransferase levels (**Table 1**)*?*

2. What are the causes of increased hepatic ALP levels?

Increased hepatic ALP level is secondary to one of the following:

- Intrahepatic or extrahepatic biliary obstruction
  - Stones
  - Tumors
  - Strictures
  - Lymph node enlargement
  - Infection
  - Pancreatitis

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Table 1
Causes of increased aminotransferase levels

Acute Increase in AST/ALT Levels	Chronic Increase in AST/ALT Levels
Ischemic hepatitis	Alcoholic hepatitis (AST/ALT 2:1)
Drugs/toxins	Viral hepatitis
Infection	Autoimmune hepatitis
Acute viral hepatitis	Drug-induced hepatitis
Alcohol-induced liver injury	Nonalcoholic fatty liver disease
Nonalcoholic fatty liver disease	Hemochromatosis
Malignant infiltration of liver	α_1-Antitrypsin deficiency
Budd-Chiari	Wilson disease

- Cholestasis from medications (Table 2)
- Infiltrative disease
  - Cancer
  - Granulomatous disease

Table 2
Common medications that may adversely affect LFTs

Cholestatic Pattern	Hepatocellular Pattern
Amoxicillin/clavulanic acid	Acarbose
Anabolic steroids	Acetaminophen
Chlorambucil	Allopurinol
Chlorpropamide	Amiodarone
Clopidogrel	L-Asparaginase
Erythromycin estolate	Aspirin and nonsteroidal antiinflammatory drugs
Estrogen	Carbamazepine
Methimazole	HAART (highly active antiretroviral therapy) drugs
Mirtazapine	Halothane
Phenobarbital	Hydralazine
Terbinafine	Imipramine
Tolbutamide	Isoniazid
Tricyclics	Ketoconazole
	Lisinopril
	Lovastatin
	6-Mercaptopurine
	Methotrexate
	Methyldopa
	Nicotinic acid
	Nitrofurantoin
	Omeprazole
	Phenytoin
	Propylthiouracil
	Rifampin
	Risperidone
	Statins
	Sertraline
	Sulfonamides
	Tetracycline
	Trazodone
	Valproic acid

3. What are the causes of hyperbilirubinemia?

Hyperbilirubinemia may be caused by:

- Increased bilirubin production
  - Hemolysis
  - Ineffective erythropoiesis
- Extravasation of blood
  - Hematoma
- Decreased metabolism
  - Hereditary disease
  - Gilbert syndrome
  - Acquired defects in bilirubin conjugation
- Reduced bilirubin excretion
  - Bile duct obstruction

4. Which medications cause abnormal LFTs?

Medications causing hepatocellular injury or cholestasis (see **Table 2**) may result in increases in transaminase or ALP levels that are as much as 10 times normal levels.

HISTORY AND EXAMINATION

1. What are the symptoms of patients with abnormal LFTs?

- Common complaints include fatigue, malaise, nausea, hematemesis or melena/hematochezia, pruritus, jaundice, easy bruising, anorexia, weight loss, abdominal swelling or right upper quadrant discomfort, confusion, and decreased libido or erectile dysfunction.
- The severity of the complaints is often related to the acuteness and severity of the liver injury.
- Even patients with advanced liver disease may remain asymptomatic, with normal or only mildly abnormal LFTs.

2. What are the physical findings in patients with abnormal LFTs?

- Hepatomegaly or an unusually firm liver may be present.
- Jaundice, spider angiomata, palmar erythema, Terry nails, ascites, splenomegaly, dilated periumbilical veins, hemorrhoids, asterixis, edema, and testicular atrophy, gynecomastia, or loss of pubic and axillary hair may all be signs of liver disease.

DIAGNOSIS

1. What is the initial approach to patients with abnormal LFTs?

- Abnormal LFTs are often found incidentally through testing in the inpatient or outpatient setting.
- LFTs should be repeated to confirm abnormal values.
- Further history and physical examination may help determine the cause.
  - Right upper quadrant pain, fever, and nausea and vomiting suggest possible biliary tract disease.
  - Carefully document quantity/frequency of alcohol use
  - Intravenous drug use or foreign travel, especially with a viral prodrome, may suggest viral hepatitis
  - Accurate information on medication use (whether prescription, illicit, or herbal) and the time course in relation to the hepatic dysfunction is helpful.

- A hard, nodular liver may suggest cirrhosis or neoplasm; enlarged, tender liver suggests acute congestion, hepatitis, or cholangitis

2. When can further testing be delayed?

- The magnitude of liver enzyme increase may affect the decision to delay further evaluation. There are no guidelines to dictate management, but we propose immediately proceeding with further diagnostic investigation if AST/ALT levels are more than 3 times normal or if ALP levels are more than 2 times normal. Otherwise, further testing may be delayed.
- If low-level enzyme increase is discovered in the hospital setting, and further testing is to be delayed, ensure appropriate communication with the primary physician on discharge.

3. How can patterns of liver enzyme increase guide the diagnostic evaluation?

The pattern of LFT abnormality helps determine the cause and should guide further diagnostic evaluation. A diagnostic approach is outlined in **Fig. 1**.

- Hepatocellular injury pattern
  - If the magnitude or duration of transaminase increases suggests further workup is indicated,
  - Transaminase values in excess of 300 IU/L are usually caused by acute viral hepatitis (A, B), or toxic/ischemic injury
  - In chronic hepatitis, further testing should be performed to rule out the following diseases: hemochromatosis; autoimmune hepatitis; α_1-antitrypsin deficiency; hepatitis B, C, and D; nonalcoholic fatty liver disease; and Wilson disease (see **Fig. 1**)
- Cholestatic injury pattern
  - In patients with increased ALP levels, order GGT testing to confirm hepatic origin. Extrahepatic biliary tract obstruction should be differentiated from intrahepatic cholestasis with liver ultrasonography.
  - If ductal dilatation is present, endoscopic retrograde cholangiopancreaticography may be indicated. Classic biliary causes of increased ALP levels include biliary stricture, choledocholithiasis, primary sclerosing cholangitis, and cholangiocarcinoma. Causes of intrahepatic cholestasis include drug-induced causes, granulomatous disease, primary biliary cirrhosis, and malignant infiltration of the liver.[6] Increased ALP levels could also be caused by an underlying neoplastic process in the biliary system.[7]

If total bilirubin levels are increased, direct and indirect bilirubin fractions should be obtained. If the indirect (unconjugated) fraction is increased ($\geq$80% of the total), a reticulocyte count and a peripheral blood smear should be obtained to exclude hemolysis.

Prothrombin time (PT) reflects hepatic synthesis of vitamin K–dependent clotting factors (II, VII, IX, and X) and should be ordered for patients with acute or chronic liver disease or coagulopathy.

- Improvement by 30% after a 10-mg subcutaneous injection of vitamin K suggests intact hepatocellular function and makes biliary obstruction the likely cause of the abnormal PT.

If the PT fails to improve after administration of vitamin K, significant loss of hepatocellular function exists and the prognosis is by mouth.

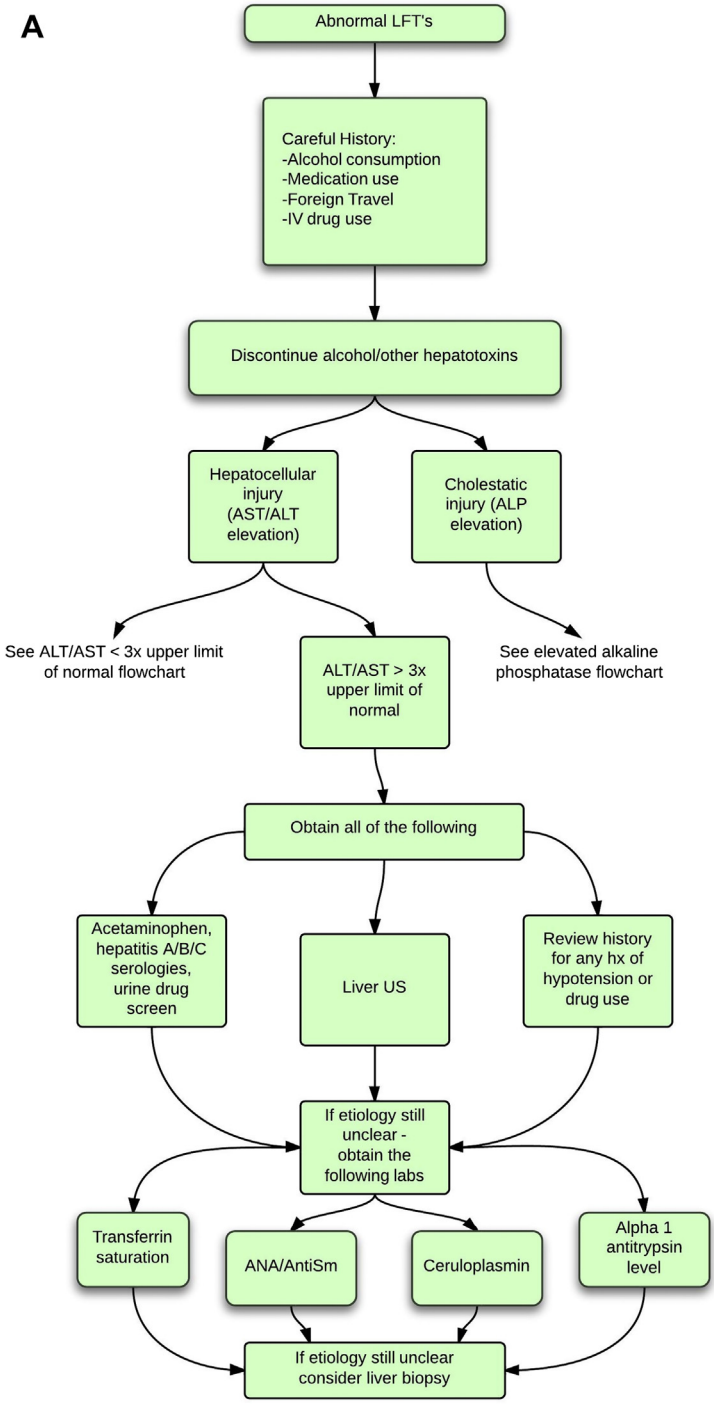

Fig. 1. Evaluation of patient with abnormal LFTs. (*From* McKenna JP. Liver function test abnormalities. In: Mengel M, Schwiebert LP, editor. Family medicine: ambulatory care and prevention. 5th edition. Philadelphia: McGraw-Hill Education; 2009. p. 297; with permission.)

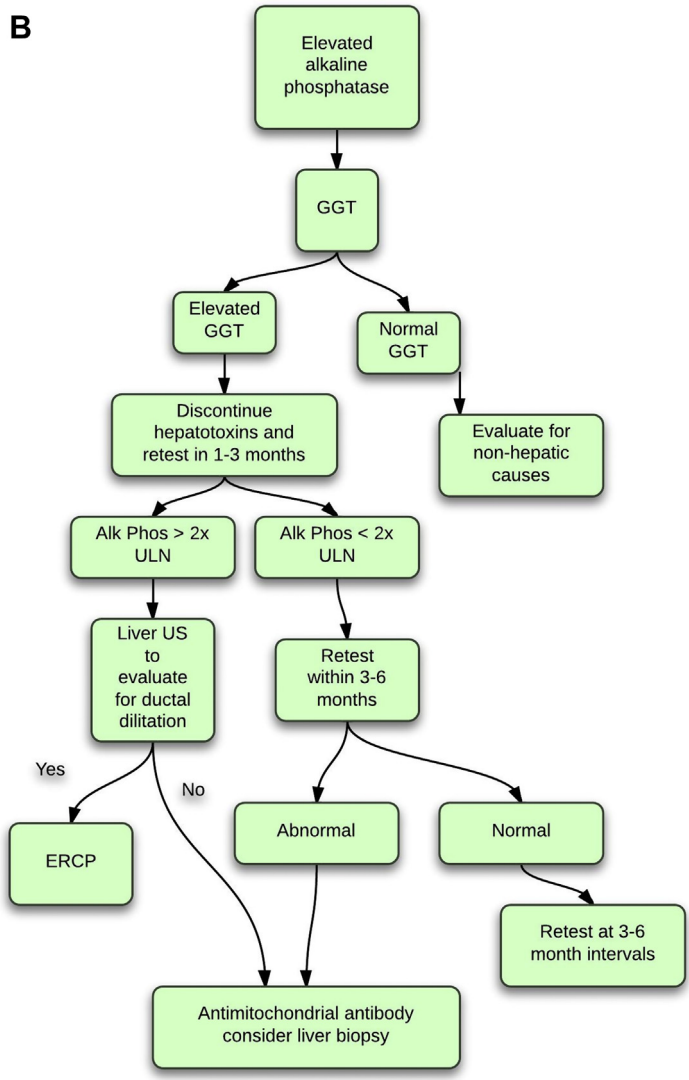

Fig. 1. (*continued*)

Liver biopsy should be considered for any patient with abnormal LFTs that persist for more than 6 months. A biopsy sample should be obtained before the end of the 6-month period if the patient's condition deteriorates. Liver biopsy is the only definitive means of establishing a diagnosis of chronic hepatitis (see **Fig. 1**).

LFT PATTERNS IN SPECIFIC DISEASE STATES

1. Alcoholic liver disease
   - Usually causes mild transaminase increase
   - ALT levels of 300 IU/L or greater are usually not consistent with alcoholic liver damage
   - AST/ALT ratio of 2:1 or greater suggests alcoholic hepatitis

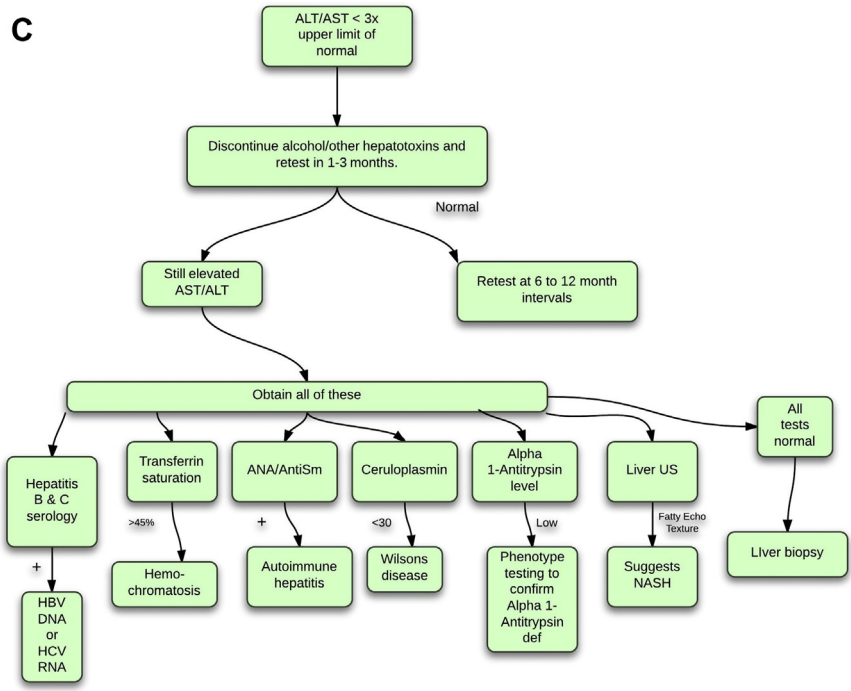

Fig. 1. (*continued*)

2. Viral hepatitis
   - Acute viral hepatitis seen in type A or B
   - Often causes significant increases of transaminases, with levels at times exceeding 1000 IU/L
   - Bilirubin level is often increased, sometimes markedly so
   - AST/ALT ratio typically 1 or less
3. Drug-induced hepatitis
   - Medications may cause severe liver injury resembling viral hepatitis, with transaminase values as high as 500 times normal levels
4. Ischemic hepatitis
   - Usually preceded by a period of hypotension
   - Transaminases often 1000 to 10,000 IU/L
   - ALP level usually normal or only mildly increased
5. Intrahepatic or extrahepatic obstruction
   - ALP level may be more than 5 times normal
   - The highest ALP values are seen in primary biliary cirrhosis
   - Bilirubin may or may not be increased
6. Infiltrative diseases
   - Neoplasms, granulomas, or amyloidosis may cause moderate to marked increases of ALP level
   - Minimal bilirubin increase
7. Hemolysis
   - Causes an increased reticulocyte count and an abnormal peripheral smear, with indirect bilirubin generally 5 mg/dL or less

8. Gilbert syndrome
   - Common, benign disorder characterized by indirect bilirubin levels of 2 to 3 mg/dL, otherwise normal LFTs, and no evidence of hemolysis
   - Fasting often increases bilirubin levels
   - Does not require any specific treatment; recommend observation and patient reassurance

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