Chapter 32
Abnormal Liver Tests

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Introduction

In general outpatient medical practice, abnormalities of liver tests are often encountered in asymptomatic patients. Different institutions may have different tests in a "liver panel", with the most common panel including assays for albumin, total and direct bilirubin, alkaline phosphatase (AP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Abnormalities in the biochemical tests may suggest various disorders, both intrahepatic and extrahepatic. This section will focus on the tests mentioned above, in addition to tests that measure liver functions in order to provide a basic approach for the evaluation of abnormal findings based on test result patterns.

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Key History and Physical Exam

Normal test result ranges are based on the range seen in 95% of healthy individuals in a studied group. By definition, 5% of abnormal test results are actually normal results that lie on the far ends of the normal spectrum [1]. Since many patients are asymptomatic, a directed history and physical exam after noting the test abnormalities is necessary to determine which results represent a clinical abnormality requiring further evaluation.

The initial approach to determining the significance of abnormal liver tests is to elicit a thorough patient history. Include a history of systemic diseases, family history of autoimmune or liver diseases, and a history of risk factors for liver disease, including alcohol history, current and prior medications, vitamins, supplements, illicit substance use, new or unknown substance or toxin ingestion or exposure, travel and occupational exposure, and risk factors for viral hepatitis. These risk factors include intravenous drug use, sexual history, tattoos, nonsterile piercings, transfusions, residence in endemic regions, or having parents from highly endemic regions [2].

In most cases, asymtomatic patients will have a normal physical exam. However, signs of a chronic process should be assessed. Examine for fever, scleral icterus or jaundice, abdominal tenderness, hepatomegaly, and muscle wasting. Signs of chronic liver disease include gynecomastia, spider angiomas, splenomegaly, palmar erythema, caput medusa, a fluid wave and bulging flanks (suggestive of ascites), and peripheral edema. Dupuytren's contractures and testicular atrophy may be seen in chronic alcoholism. Cardiopulmonary and jugular venous examination may suggest heart failure, which can cause hepatopathy.

The next step is to repeat the liver tests; only if there is persistent abnormality or the presence of risk factors should further workup be undertaken.

Decision-Making/Differential Diagnosis

The liver has various functions, including detoxification, excretion, and synthesis of albumin, serum globulins, and coagulation factors. Given the variety of these functions and the variability of sources of abnormalities, the most common liver tests may be normal in the presence of liver disease or abnormal with extrahepatic disease. Developing a complete differential diagnosis for abnormal liver tests requires an understanding of the information each study offers and what additional information further studies beyond the basic panel can provide. Identifying patterns of liver test abnormalities is helpful to establish the differential diagnosis, most commonly a cholestatic disease pattern or a hepatocellular injury pattern.

Liver Studies

Serum albumin is synthesized only in the liver. It has a half-life of approximately 18–20 days; thus it is a marker for chronic, rather than acute, liver disease [3]. Hypoalbuminemia is a result of decreased synthesis by a damaged liver and is seen most often in cirrhosis. Hypoalbuminemia may also be seen with a normal liver in cases of increased protein loss, as in nephrotic syndrome or protein losing enteropathies or with downregulation of synthesis, as with protein malnutrition or certain inflammatory conditions that increase cytokine production [4].

Almost all clotting factors are produced in the liver and have shorter half-lives than albumin. Factor VIII is the only extrahepatically produced clotting factor. Due to their short half-lives, measures of clotting factors are useful as markers of acute liver biosynthetic function failure. The prothrombin time (PT) and international normalized ratio (INR) are most commonly used as indirect measures of clotting dysfunction as the PT involves multiple clotting factors excluding factor

VIII. However, since many of these factors require vitamin K for synthesis, these measures may also be abnormal in altered vitamin K availability states, such as fat malabsorption or obstructive biliary disease. A trial of parenteral vitamin K can help to distinguish normal hepatocyte synthetic function from a state of hepatocellular dysfunction [3].

Aspartate aminotransferase (AST), also known as serum glutamic oxaloacetic transaminase (SGOT), and alanine aminotransferase (ALT), also known as serum glutamic pyruvic transaminase (SGPT), are collectively the serum aminotransferases. The ALT level is more indicative of a liver specific process as it is predominantly found in the liver, whereas AST is found in large concentrations in cardiac and skeletal muscle as well as a variety of other organs. AST and ALT can be released into the blood with hepatocellular membrane injury, although levels do not correlate with the amount of cell necrosis [1]. Given the large variety of normal ranges for transaminases between different laboratories, with no set standard [5], minimal elevations of AST and ALT may not necessarily reflect true clinically significant abnormalities. However, significant elevations, more than two times the upper limit of normal, may reflect a variety of liver conditions.

Alkaline phosphatase (AP) is an enzyme also found in various tissues: the liver, bone, intestine, kidney, and placenta are most common. Within the liver, AP is found in the bile canaliculi, specifically in the membranes of these ductules. Elevation of either the gamma-glutamyl transpeptidase (GGT) level or the 5′-nucleotidase confirms a hepatic origin of the elevated AP. Sending a fractionated AP can also aid in distinguishing the tissue of origin of the elevated AP by separating out the alkaline phosphatase isoenzymes from each distinct tissue that make up the total serum AP. An elevated AP of hepatic origin may be present with either a normal or elevated bilirubin; this association will help to establish a differential diagnosis.

Serum bilirubin levels may be a marker of the excretory function of the liver. Bilirubin is a product of the catabolism of heme proteins, predominantly hemoglobin. Unconjugated bili-

rubin is insoluble in water; once it is bound to albumin (i.e., "conjugated") by the liver, it becomes hydrophilic and can be excreted in bile and urine. The indirect fraction of bilirubin measures unconjugated bilirubin, whereas conjugated bilirubin makes up the direct fraction. Again the pattern of elevation of each fraction of bilirubin is useful to elucidate etiology [4].

Establishing Patterns of Abnormalities

The two main patterns of abnormalities encountered are of hepatocellular injury, usually with an elevation of the serum transaminases, and of cholestatic disease, with predominant AP elevation with or without hyperbilirubinemia. These patterns are important in determining the type of disease and the subsequent diagnostic evaluation and management. Isolated hyperbilirubinemia without AST, ALT, or AP elevation may also be seen. Beyond assessing the category of liver injury in suspected liver disease, it is also important to determine the level of liver function using the albumin and INR as mentioned previously. See Fig. 32.1 for an algorithm of diagnostic evaluation of abnormal liver tests.

A predominantly elevated AST and ALT pattern indicates hepatocellular injury. The serum bilirubin and alkaline phosphatase may also be elevated, but less prominently than the aminotransferases. Although ALT is more specific for the liver, both AST and ALT are sensitive for liver cell injury. A normal creatine phosphokinase (CPK) level points away from muscle as the source of elevation in aminotransferase levels, whereas if the CPK and aldolase levels are elevated, muscle disease as the source of elevated AST and ALT is more likely. A discussion of muscle conditions is outside the scope of this chapter. The levels of transaminase elevations can also aid in the differential diagnosis by degree and pattern of AST to ALT elevation. Severe elevations of AST and ALT to over 1000 units/L are most commonly seen in ischemic hepatitis, toxin-/drug-induced injury, acute viral hepatitis, and acute Budd–Chiari syndrome (occlusion of the hepatic veins).

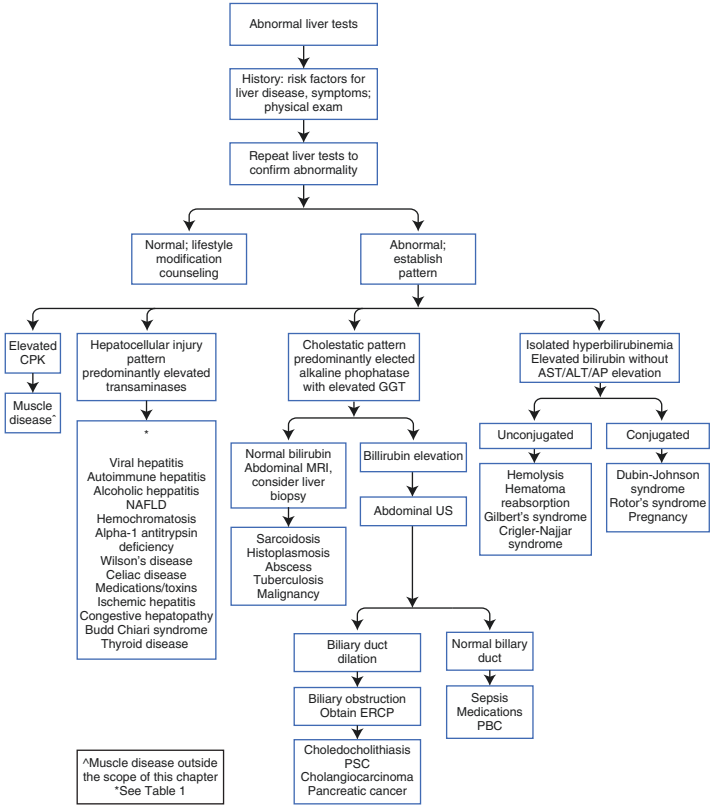

FIG. 32.1 Abnormal liver test evaluation. ^Muscle disease outside the scope of this chapter. *See Table 32.1

Obtaining a medical, drug, and toxin history; vascular imaging with doppler ultrasound; and viral serologies for hepatitis A (HAV), hepatitis B (HBV), and hepatitis C (HCV) are warranted, and further testing for Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV) can be considered, especially in immunocompromised patients. While a large number of medications have been reported to cause liver injury, a list of the more common toxins and drugs are listed in Table 32.1 [1, 3, 6–8]. Common causes of milder elevations of the AST and

TABLE 32.1 Common agents that cause elevations in liver enzyme levels

Medications	Acarbose, acetaminophen, allopurinol, amiodarone, aspirin, baclofen, bupropion, calcium-channel blockers, carbamazepine, ciprofloxacin, didanosine, fluconazole, glipizide, glucocorticoids, HMG-CoA reductase inhibitors, isoniazid, ketoconazole, methotrexate, nitrofurantoin, nonsteroidal anti-inflammatory drugs, phenytoin, pyrazinamide, rifampin, risperidone, selective serotonin reuptake inhibitors, synthetic estrogens, synthetic penicillins, tamoxifen, tetracycline, trazodone, valproic acid, zidovudine
Drugs of abuse	Anabolic steroids, cocaine, MMDA, methamphetamine, phencyclidine, toluene containing glues/solvents
Herbs and complimentary/ alternative therapies	Alchemilla, chaparral, Chinese herbs (ji bu huan, ephedra), germander, gentian, kava kava, scutellaria, senna, shark cartilage

ALT include nonalcoholic fatty liver disease (NAFLD), chronic viral hepatitis due to HBV or HCV, alcoholic liver disease, and autoimmune hepatitis (AIH). NAFLD is increasing in developed countries with increasing rates of obesity, with studies showing prevalence from 57.5 to 74% in obese patients. It can be detected as increased echogenicity on abdominal ultrasound although liver biopsy is needed to confirm the diagnosis [6]. Serologies for AIH include an antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), and anti-liver–kidney microsomal antibody (ALKM-1 Ab). Less common hepatic causes of mild, but chronically, abnormal aminotrasnferases are Wilson's disease, hemochromatosis, and alpha-1 antitrypsin deficiency. Nonhepatic causes of

milder AST and ALT elevations include celiac disease, thyroid disease, and congestive hepatopathy from congestive heart failure. An anti-tissue transglutaminase antibody can direct the diagnosis toward celiac disease in a patient with symptoms of intestinal bloating and diarrhea, as about 40% of patients have abnormal liver tests when diagnosed with celiac sprue [9]. A serum thyroid stimulating hormone assesses for thyroid abnormalities, and a transthoracic echocardiogram may be obtained to evaluate for heart failure. See Table 32.2 for further diagnostic workup of hepatocellular injury by etiology.

Table 32.2 Diagnostic evaluation of hepatocellular injury

Viral hepatitis	HAV IgM, HbsAg, HBcAb, HCV Ab; Consider CMV, EBV, HSV, VZV
Autoimmune hepatitis	ALKM-1 Ab, ANA, ASMA
Alcoholic hepatitis	History, AST:ALT ratio > 2–3:1
NAFLD	HbA1c, lipid profile, medication review, abdominal ultrasound, consider liver biopsy
Hemochromatosis	Iron studies (including transferrin saturation, ferritin), consider HFE gene testing if positive
Alpha-1 antitrypsin deficiency	Serum AAT level
Wilson's disease	Ceruloplasmin level
Celiac disease	Anti-tissue transglutaminase antibody
Medications/toxins	Review and discontinue hepatotoxic medications
Ischemic hepatitis	Assess causes of hypoperfusion
Congestive hepatopathy	Assess heart failure
Budd–Chiari syndrome	Obtain vascular imaging with doppler US of abdomen
Hypo- or hyperthyroidism	TSH

Beyond the level of elevation, the ratio of aminotransferases is also relevant for diagnosis. Most acute liver processes produce an AST:ALT ratio <1; this can be found in nonalcoholic fatty liver disease and chronic viral hepatitis, but as the injury progresses to cirrhosis, the ratio changes to >1. An AST:ALT ratio >2:1 is suggestive of alcohol as the cause of liver injury [1].

Cirrhosis is the product of a slow transformation of the injured liver into a scarred or fibrotic, nodular organ with reduced function. It is important to note that as hepatocellular injury progresses to cirrhosis, normalization of the AST and ALT is often seen. However, the various functions of the liver may be affected; it then becomes important to assess the level of biosynthetic or excretory functions of the liver, as both can be significantly reduced in cirrhosis.

In contrast to a hepatocellular injury pattern, a modest to severe elevation of alkaline phosphatase is the hallmark of cholestatic disease. As mentioned previously, it is not exclusive to the liver and can be narrowed to being of hepatic origin using 5′-nucleotidase or GGT or by fractionating the AP. The serum bilirubin may often also be elevated, both the total and direct fractions; however, it may also be normal. With an elevated serum bilirubin, the next step is to obtain an abdominal ultrasound. Biliary ductal dilation suggests biliary obstruction due to choledocholithiasis, cholangiocarcinoma, pancreatic cancer, or primary sclerosing cholangitis (PSC). Endoscopic retrograde cholangiopancreatography (ERCP) can visualize the obstruction and obtain tissue biopsy. Elevated AP and elevated bilirubin in the absence of bile duct dilation may be due to primary biliary cirrhosis (PBC), sepsis, or a medication effect: a positive anti-mitochondrial antibody (AMA) points to PBC as the diagnosis [3].

An elevated AP with normal bilirubin is most suggestive of infiltrative diseases. These may include sarcoidosis, histoplasmosis, tuberculosis, or malignancy, either primary hepatocellular carcinoma (HCC) or metastatic disease. Infectious hepatic abscesses may also follow this pattern. An abdominal magnetic resonance image (MRI) and liver biopsy may be indicated to evaluate for these disorders [3]. The level of AP is normally elevated during pregnancy, as it is produced by the placenta.

Isolated indirect bilirubinemia is most often due to hemolysis or hematoma reabsorption, Gilbert's syndrome, or less commonly Crigler–Najjar syndrome [2]. These latter two are hereditary defects of conjugation. Isolated direct bilirubinemia is usually secondary to Dubin–Johnson syndrome or Rotor's syndrome, which are inherited defects in hepatic excretion of bilirubin. Conjugated hyperbilirubinemia may also be seen in pregnancy, so a pregnancy test should be performed in women of childbearing age.

Treatment

Risk factor reduction, including substance abuse and weight reduction counseling and discontinuation of hepatotoxic substances or medications are important therapeutic measures to undertake in the general medical office. Management of diabetes and hyperlipidemia are indicated as well for NAFLD. Chronic hepatitis C infection is increasingly being managed and treated by primary care physicians. Often, very mild test abnormalities (less than three times the upper limit of normal of the aminotransferases) that are caused by medication therapy can be monitored in the primary care setting, especially when continuing the medication. A modest or severe elevation of aminotransferases should prompt discontinuation of hepatotoxic medications. With severe abnormalities and acute liver dysfunction associated with an elevated INR and often hyperbilirubinemia, patients require hospital admission to identify the cause, to initiate supportive management, or to monitor the need for transplantation. Gilbert's syndrome is often noted in the primary care setting; it is benign. Further specialty care referral is recommended for management of the other genetic disorders of bilirubin metabolism, hereditary disorders such as hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, and also for autoimmune hepatitis.

Clinical Pearls

- Not all institutions have the same liver tests in a liver panel, reference ranges vary, and 5% of abnormal tests are at the ends of the spectrum of the normal range.
- The liver's biosynthetic function is not directly measured using AST and ALT; the albumin level is a measure of chronic liver function; clotting factors are a measure of acute liver function.
- A thorough history of risk factors for liver disease helps to direct initial diagnostic evaluation and further laboratory testing.
- Identifying the pattern of liver test abnormalities helps to establish a differential diagnosis.

Don't Miss This!

- Interpretation of liver tests requires detailed knowledge of the normal ranges, variability in assays, and chronicity of abnormalities.
- Acute toxin exposure may require hospitalization for supportive care and possibly transplantation.

References

1. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. New Engl J Med. 2000;342:1266–71.
2. Limdi JK, Hyde GM. Evaluation of abnormal liver function tests. Postgrad Med. 2003;79:307–12.
3. Rochling FA. Evaluation of abnormal liver tests. Clin Cornerstone. 2001;3:1–12.
4. Pratt D. Evaluation of liver function. In: Kasper D, Fauci A, Hauser S, et al., editors. Harrison's principles of internal medicine. 19th ed. New York: McGraw Hill Medical; 2015. p. 1995–9. Chapter 358.
5. M'Kada H, Munteanu M, Perazzo H, et al. What are the best reference values for a normal serum alanine transaminase activity (ALT)? Impact on the presumed prevalence of drug induced liver injury (DILI). Regul Toxicol Pharmacol. 2011;60:290–5.

6. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346:1221–31.
7. Navarro V, Senior J. Drug-related hepatotoxicity. N Engl J Med. 2006;354:731–9.
8. Oh R, Husted T. Causes and evaluation of mildly elevated liver transaminase levels. Am Fam Physician. 2011;84:1003–8.
9. Castillo NE, Vanga RR, Theethira TG, et al. Prevalence of abnormal liver function tests in celiac disease and the effect of a gluten-free diet in the US population. Am J Gastroenterol. 2015;110:1216–22.