

The Asymptomatic Outpatient with Abnormal Liver Function Tests

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KEYWORDS

- Aminotransferases (ALT and AST) • LFT
- Alkaline phosphatase • Albumin • Prothrombin time

Traditionally, the constellation of biochemistry tests including liver enzymes, total bilirubin, and hepatic synthetic measures (prothrombin time (PT) and serum albumin level) are referred to as liver function tests (LFTs). Abnormal LFTs can be encountered during primary health care visits, routine blood donation, and insurance screening. A reported 1% to 4% of asymptomatic patients exhibit abnormal LFTs, leading to a sizeable number of annual consultations to a gastroenterology and/or hepatology practice.¹ A cost-effective and systematic approach is essential to the interpretation of abnormal LFTs.²⁻⁷ A review of pattern of abnormal LFTs, detailed medical history, and a comprehensive physical examination help establish a foundation for further individualized testing. Further investigation often involves biochemical testing for disease-specific markers, radiographic imaging, and even consideration of a liver biopsy. In the following account, markers of hepatic injury are reviewed followed by a discussion on an approach to various patterns of abnormal LFTs in an asymptomatic patient.

ABNORMAL LFTS: MARKERS OF HEPATIC INJURY

Abnormal LFTs can be found in 2 main predominant patterns of hepatic injury, hepatocellular necrosis or cholestasis. Differentiation between these 2 main patterns of hepatic injury provides clues for further testing. However, in practice, patients present with a mixed pattern of hepatic injury.

Markers of Hepatocellular Injury

Aminotransferases

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are normally intracellular enzymes with mitochondrial and cytoplasmic forms.⁸ Their names reflect

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Clin Liver Dis 13 (2009) 167-177

doi:10.1016/j.cld.2009.02.001

1089-3261/09/\$ – see front matter. Published by Elsevier Inc.

liver.theclinics.com

their role in catalyzing chemical reactions in which amino groups of alanine and aspartic acid are transferred to the alpha-keto group of ketoglutaric acid, particularly during gluconeogenesis. ALT and AST are widely distributed in cells throughout the body and are found in liver, heart, skeletal muscle, kidney, brain, and pancreas. ALT is exclusively cytoplasmic and is found primarily in the liver and kidney, with only minute amounts in heart and skeletal muscle.⁸

In addition to hepatic injury, there are many other factors that may affect aminotransferase serum levels. Hyperthyroidism has been noted to raise both AST and ALT levels. It has been postulated that excessive thyroid activity creates hepatic ischemia by increasing hepatic and splanchnic oxygen requirements.⁹ Alcohol, in addition to being hepatotoxic, also stimulates mitochondrial AST activity, resulting in the release of mitochondrial AST from cells without measurable parenchymal damage.⁸ Strenuous exercise can also raise AST values by 3-fold, and ALT has been found to be 20% lower in those who exercise regularly.⁸ Both AST and ALT levels are 40% to 50% higher in individuals with a high BMI.⁸ Muscle injury is associated with a significantly higher serum AST level (in contrast to ALT) in conditions such as rhabdomyolysis, polymyositis, and muscular dystrophy.^{10–12} ALT levels demonstrate daily variation, lowest at night and highest in the afternoon.^{8,13}

AST and ALT levels Absolute levels of aminotransferases correlate poorly with the severity or extent of hepatocellular damage and do not provide reliable prognostic information. Conversely, patients with a “burnt out” cirrhotic liver may have misleadingly low AST and ALT levels. However, the magnitude of enzyme levels categorized into mild, moderate, or markedly elevated levels can help differentiate between different causes of liver disease. Although a consensus on how to define these broad categories does not exist, many authorities would define mild elevation in aminotransferase levels as up to a 5-fold increase. A mild increase in AST or ALT levels can reflect both acute and chronic liver disease. Because of the obesity epidemic, it is likely that the most common reason for mild abnormalities in aminotransferases in the United States is nonalcoholic fatty liver disease (NAFLD).^{14,15} In addition, a mild transaminitis can also reflect medications, alcoholic liver disease, viral hepatitis, autoimmune liver disease, celiac disease, and various metabolic/genetic diseases (Wilson’s disease, alpha-1-antitrypsin deficiency, hemochromatosis, etc.). The category of high/marked elevation in aminotransferases includes a greater than 15-fold increase in levels (usually greater than 1000 U/L). When levels reach this magnitude, the differential diagnosis is narrowed to a fairly short list of conditions including acute viral hepatitis (A–E and herpes simplex virus [HSV]), ingestions (toxins/medications), and ischemic or “shock” liver. Rarely, other diagnoses to consider with marked elevations in aminotransferase levels include an acute exacerbation of autoimmune hepatitis, Budd-Chiari syndrome, HELLP (Hemolytic anemia, Elevated Liver enzymes, and Low Platelet count) syndrome, and Wilson’s disease.¹ Aminotransferases greater than 100-fold are commonly noted in toxic injections (ie, acetaminophen) and ischemic liver injury but are rare in acute viral hepatitis.⁸ Acute biliary ductal obstruction can transiently raise AST and ALT levels to greater than 15-fold, followed typically by cholestatic changes.¹⁶

AST/ALT ratio AST/ALT ratio can also provide an important diagnostic clue. The AST/ALT ratio in subjects without evidence of underlying liver disease is approximately 0.8. An AST/ALT ratio of 2.0 or greater and an absolute ALT level less than 300 U/L is suspicious of alcoholic liver disease. This distinctive pattern can be explained by 2 mechanisms. Patients with alcoholic liver disease often have a poor nutritional status

leading to shortage of pyridoxal 5'-phosphate, which is a cofactor for both AST and ALT. Pyridoxal 5'-phosphate has a greater affinity for AST than ALT, resulting in significantly depressed ALT activity relative to AST. Second, alcohol induces plasma mitochondrial AST activity and stimulates release of mitochondrial AST, leading to further increase in the AST/ALT ratio.⁸ However, patients with a history of significant alcohol use but no evidence of severe liver disease (alcoholic hepatitis or cirrhosis) will generally maintain an AST/ALT ratio less than 1.0.¹⁷ In patients with other etiologies of liver disease, such as viral hepatitis, an AST/ALT ratio greater than 1.0 can be indicative of underlying cirrhosis with a high specificity (94%–100%), but a low sensitivity (44%–75%).¹⁸ Patients with Wilson's disease can also manifest an AST/ALT ratio of greater than 4.0.^{19,20} In contrast the AST/ALT ratio is usually 1.0 or less in NAFLD.²¹

Lactate dehydrogenase

Lactate dehydrogenase (LDH) has also been used to screen for liver disease. LDH is segmented into 5 isoenzyme forms (LDH-1 to LDH-5), with the latter of hepatic origin. The diagnostic sensitivity of LDH for liver disease is poor when compared with that of aminotransferases. Currently, LDH may be useful in specific instances, such as suggesting an ischemic hepatitis and in conjunction with a rising alkaline phosphatase (AP) level in infiltrative liver disease.

Markers of Cholestasis

Alkaline phosphatase

AP is found in many organs, including the placenta, ileal mucosa, kidney, bone, leukocytes, and liver.^{22–29} AP is involved in phosphate ester hydrolysis, although its exact catalytic function is unknown. Liver and bone AP are the most abundant isoenzyme forms found in the serum and can be readily separated by electrophoretic measurements or heat treatment. Serum AP levels can rise as a result of either intrahepatic (primary biliary cirrhosis, primary sclerosing cholangitis, etc.) or extrahepatic (choledocholithiasis, biliary stricture, etc.) biliary obstruction. This rise in serum AP level reflects de novo synthesis (induced by bile acid accumulation in hepatocytes rather than impairment of bile secretion).²⁸ As bile acids accumulate intracellularly, solubilization of the hepatic plasma membranes ensues, leading to AP release. Due to this mechanism (synthesis followed by release), a rise in serum AP level is often delayed by a few days following the onset of biliary obstruction. Serum AP has a half-life of 5 to 7 days and will remain elevated for several days despite resolution of biliary ductal obstruction. In addition to obstructive processes, infiltrative granulomatous or malignant (primary or metastatic) disease can result in a rise in AP levels due to compression and/or infiltration of small intrahepatic bile ducts. A tumor causing focal, infiltrative (intrahepatic), ductal obstruction may cause an isolated increase in AP levels without a concurrent rise in bilirubin. The converse can also be true with serum AP levels remaining normal in the setting of widespread metastatic disease or large-duct extrahepatic biliary obstruction.²⁹ In addition to hepatobiliary disease, several additional factors can affect AP serum levels. High-fat food intake can increase AP levels by 30 U/L; rise in BMI can increase AP levels by 25%; tobacco use can lead to 10% rise in AP levels; during the third trimester of pregnancy, AP levels can increase by 2- to 3-fold; and oral contraceptives can increase AP levels by 20%.^{22–27} Chronic kidney disease has also been reported to raise serum levels of the intestinal AP isoenzyme.^{24,25}

Gamma glutamyl transpeptidase

Hepatic gamma glutamyl transpeptidase (GGTP) is a microsomal enzyme found on the surface of hepatocytes and biliary epithelia. As with many microsomal enzymes,

GGTP is inducible. GGTP can be induced by alcohol, phenytoin, barbiturates, and warfarin. Clinically, its main utility is suggesting a hepatic source for an elevated AP.¹⁸ However, it has a low predictive value (32%) for hepatobiliary disease, as it is present in numerous body compartments, including proximal renal tubule, pancreas (ductules and acinar cells), heart, lung, and brain.⁸ Other clinical conditions in which GGTP elevation has been reported include diabetes mellitus, hyperthyroidism, rheumatoid arthritis, and chronic obstructive pulmonary disease.³⁰ In individuals with alcohol use, a GGTP/AP ratio of greater than 2.5 has been observed. However, its clinical utility in assessing surreptitious alcohol use is questionable, as it has a half-life of 26 days and demonstrates poor correlation with alcohol bingeing.³¹ In addition, normal GGTP levels have been reported in more than one-third of subjects who consume more than 80 g of alcohol per day.

Bilirubin

Bilirubin is a catabolic end product from the breakdown of heme. The normal level is less than 1 mg/dL (18 μ mol/L).¹ Elevated serum bilirubin levels generally reflect an imbalance between production and conjugation followed by excretion. Total bilirubin can be segmented further into a water-soluble form referred to as “direct/conjugated bilirubin” or a lipid-soluble form, namely, “indirect/unconjugated bilirubin.” An elevation in direct bilirubin is highly specific for biliary tract obstruction. However, impaired biliary excretion, which is an energy-dependent process, is thought to be the reason for increased levels observed in sepsis, total parenteral nutrition, and following surgery.³² Due to its small molecular size and water-soluble properties, direct bilirubin appears in urine.

Unconjugated Hyperbilirubinemia

A rise in unconjugated serum bilirubin levels reflects 2 basic pathophysiologic mechanisms, namely, bilirubin overproduction and reduced ability to conjugate bilirubin. Overproduction of unconjugated bilirubin occurs in hemolysis, ineffective erythropoiesis, large hematoma resorption, and extensive muscle injury. A personal or family history of anemia, recent blood transfusion, and a review of the patient’s prescription medications may provide important diagnostic clues. A specific inquiry regarding the use of herbs, supplements, and other over-the-counter nutritional or medicinal agents is important. Most cases of hemolysis cause only a modest rise (<5 mg/dL) in serum unconjugated bilirubin levels. However, severe hemolytic crises, including sickle cell disease and paroxysmal nocturnal hemoglobinuria, can markedly raise serum unconjugated bilirubin levels to greater than 30 mg/dL. At a minimum, an initial diagnostic evaluation for hemolysis should include a complete blood count, reticulocyte count, and an examination of peripheral blood smear. Second-tier tests to confirm hemolysis include LDH, haptoglobin, direct Coombs test, glucose-6-phosphate dehydrogenase assay, and hemoglobin electrophoresis. A rise in the level of unconjugated bilirubin can occur under any condition impairing effective blood return (and thus proper uptake and processing) back to the liver, such as congestive heart failure or portosystemic shunting (congenital or acquired). Finally, congenital conditions with defects in bilirubin conjugation, that is, Gilbert’s or Crigler-Najjar syndrome, can cause increased unconjugated serum bilirubin levels.

Conjugated Hyperbilirubinemia

Conjugated hyperbilirubinemia is a total bilirubin with a direct bilirubin fraction greater than 50%. Etiologies causing conjugated hyperbilirubinemia are numerous but can be categorized under hepatocellular injury/necrosis and extrahepatic or intrahepatic

cholestasis. The rate-limiting step in all these conditions is the inability of hepatocyte mass to excrete conjugated bilirubin either due to acquired or inherited defects. This process leads to accumulation of conjugated bilirubin and eventual “overflow” leakage into the serum.³³ The total bilirubin level provides prognostic information in patients with alcoholic hepatitis, primary biliary cirrhosis, and acute liver failure as well as in chronic liver disease and is one of the components of the Model for End-stage Liver Disease (MELD).^{34,35}

Markers of Hepatic Synthetic Function

Prothrombin time

PT reflects the extrinsic clotting pathway involving factors II, V, VII, and X and is used to assess hepatic synthetic function. Factor VIII is the only clotting factor not synthesized by the liver but by vascular endothelium and reticuloendothelial cells. In addition to hepatic dysfunction of biliary obstruction, other explanations for a prolonged PT time include vitamin K deficiency, anticoagulation therapy, and consumption coagulopathy. In chronic liver disease, PT is generally within normal limits until progression to cirrhosis. In acute liver disease, PT is usually prolonged by at least 3 seconds in acute ischemic and toxic hepatitis, but, generally, it is not increased by more than 3 seconds in viral or alcoholic hepatitis.^{36–39} A PT value greater than 100 seconds is part of King’s College criteria for urgent liver transplantation in acute liver failure.⁴⁰ Monitoring of factor VII (half-life of 6 hours) can be useful to assess hepatic synthetic dysfunction in acute liver failure.⁴⁰ An International Normalized Ratio, a standardized measure of the patient PT to a control value, has been shown not to confer any additional prognostic advantage in the setting of acute liver failure.^{41,42}

Albumin

Up to 10 g of albumin is normally produced and secreted each day by the liver. In advanced liver disease, PT and serum albumin level can be used to assess hepatic synthetic function. However, the half-life of plasma albumin is 20 days, which significantly reduces its utility for real-time assessment of hepatic synthetic function in acute liver disease. In addition, a number of other conditions may result in decreased serum albumin levels. These include excessive loss (protein-losing enteropathy, nephrotic syndrome, burn injury), increased turnover (hormonal dysfunction, glucocorticoids), and decreased intake (malnutrition). Prealbumin is also produced by the liver with a much shorter half-life (3 days) but is unfortunately affected by several other extrahepatic factors limiting its diagnostic utility.

ABNORMAL LFTS: ANALYSIS STRATEGY

History and Physical Examination

The approach to the asymptomatic patient with abnormal LFTs should always start with a detailed history and physical examination helping to quickly parse down a large number of etiologies. During a detailed history, important diagnostic clues can be obtained, including a complete medications list (new and old medications), herbs/homeopathic treatments (ma huang, chaparral, lady’s mantle, shark cartilage, Scutellaria/skullcap, etc.), dietary agents (mushrooms, toxic ingestions, etc.), duration and amount of alcohol use, risk factors for viral hepatitis (history of blood transfusions, tattoos, intravenous drug use, etc.), sexual history, travel history, and family history. Information regarding country of origin can suggest a particular liver disease; for example, chronic hepatitis B is more prevalent in the Far East, schistosomiasis in Egypt, and malaria in Africa. During the physical examination, particular attention should be paid to stigmata of advanced liver disease including firm liver edge,

splenomegaly, ascites, asterixis, spider angiomas, palmar erythema, muscle wasting, and easy bruising.

Approach to Asymptomatic Aminotransferase Elevation

An elevation in aminotransferase levels is a sensitive indicator of active hepatocellular inflammation and necrosis. A systematic approach to abnormal AST and ALT analysis should address the following key items: the rate of rise in enzyme elevation, the magnitude (enzyme peak) of rise, the AST/ALT ratio, and any other associated clinical stigmata of liver disease. Before ordering a battery of tests, any LFT abnormality should ideally be reconfirmed after a 2- to 3-month interval. However, higher initial LFT values correspond to a lower probability for false-positive values.⁴³ In patients with persistently elevated LFTs, a first-line approach to analysis should focus on attempts to uncover any reversible or potentially treatable causes (Fig. 1). In the United States, NAFLD is the most frequent cause of a mild transaminitis (up to 250 U/L) in the asymptomatic patient^{44,45} and is suggested by uncovering risk factors or features of the metabolic syndrome. NAFLD is also prevalent in up to 10% to 15% of nonobese individuals, highlighting inherent diagnostic challenges.^{46,47} An initial ultrasound of the liver can reveal a hyperechoic (bright) liver but may be false negative. The most frequent causes for mild-moderate transaminitis (250 to 1000 U/L) include viral hepatitis and hepatotoxic drugs. Viral etiologies include both the hepatotropic viruses (hepatitis virus A to E) and herpes viruses (Epstein-Barr, cytomegalovirus, and HSV),

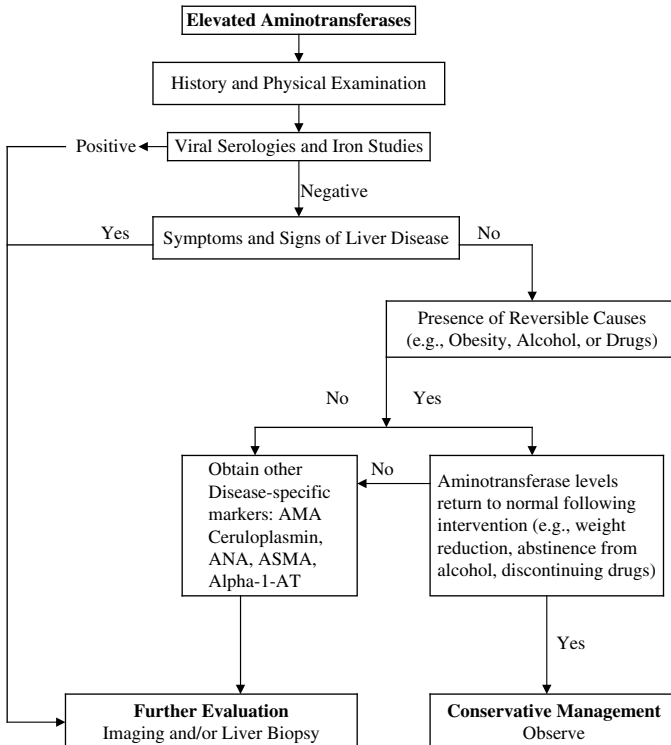


Fig. 1. Evaluation of mild but sustained aminotransferase elevation. The algorithm assumes elevation of both AST and ALT, making an extrahepatic source unlikely.

which can cause abnormal LFTs of this magnitude. The most common drug offenders include nonsteroidal anti-inflammatory agents, antiepileptics, antibiotics, statins, anabolic steroids, and recreational drugs of abuse, for example, cocaine, phencyclidine, glues, and solvents.

Hepatotoxic medications should be substituted or discontinued. An empiric trial of abstinence from alcohol should be initiated, and it can take up to several weeks to months for aminotransferases to return to normal. In patients with suspected NAFLD, sustained weight reduction should be encouraged to retard and possibly reverse fibrotic change. Further selective diagnostic testing includes serologic testing for hepatitis B and C; iron studies; checking serum ceruloplasmin in patients younger than 40 years to rule out Wilson's disease; checking serum protein electrophoresis in young females to rule out autoimmune hepatitis; obtaining thyroid-stimulating hormone levels; assessing creatine kinase levels; checking antibodies for celiac sprue; checking alpha-1-antitrypsin phenotype and levels; and searching for adrenocortical insufficiency (Addison's disease).^{48,49}

Finally, if all the above diagnostic measures have been exhausted and LFTs remain persistently abnormal for 6 to 12 months, the following approach is suggested. First, if aminotransferase values are less than 1.5 times the upper limit of normal, observation may be reasonable. Secondly, with higher elevations in LFTs, a liver biopsy can provide valuable diagnostic and prognostic information.

Approach to Isolated or Predominant Alkaline Phosphatase Elevation

Predominance of liver AP elevation in the asymptomatic patient can most often be explained by either chronic cholestasis (partial biliary obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, or drug-related cholestasis) or subtle infiltrative disease (granulomatous and malignancy). An initial step to evaluating abnormal AP levels should involve repeating the test under fasting conditions (Fig. 2). This step should be followed by organ identification, considering the lack of specificity of AP for the liver. Gel electrophoresis (isoenzyme determination) and heat separation methods are available for this purpose. However, simple measurement of a GGTP or 5'-nucleotidase is quicker and less expensive. These enzymes (GGTP or 5'-nucleotidase) parallel a rise in liver AP due to their disproportionately high concentration within liver and biliary epithelium. All suspected hepatotoxic medications should be discontinued. An ultrasound, antimitochondrial antibody, and other autoimmune markers should next be ordered to exclude extrahepatic ductal system (rare to be abnormally dilated without concomitant rise in bilirubin)/gross liver parenchymal abnormalities, primary biliary cirrhosis, overlap syndrome, or primary or secondary deposits in the liver. If no abnormalities are revealed and serum AP levels remain below 1.5-fold of normal, observation can be appropriate for these patients.⁴³ Finally, if significant AP elevation persists or if there is any further concern for the biliary structural (extra or intrahepatic) disease, a magnetic resonance cholangiopancreatography followed by an endoscopic retrograde cholangiopancreatography should be performed.

Isolated or Predominant GGTP Elevation

GGTP activity is inducible and can be elevated due to alcohol use, anticonvulsant medications, and warfarin. Age, gender, BMI, and smoking status can also influence GGTP levels.⁵⁰ However, an isolated GGTP distinctly raises the possibility of alcoholic liver disease. Alcohol avoidance for 2 to 3 months and follow-up GGTP testing is a reasonable approach in the absence of other evidence of liver disease.

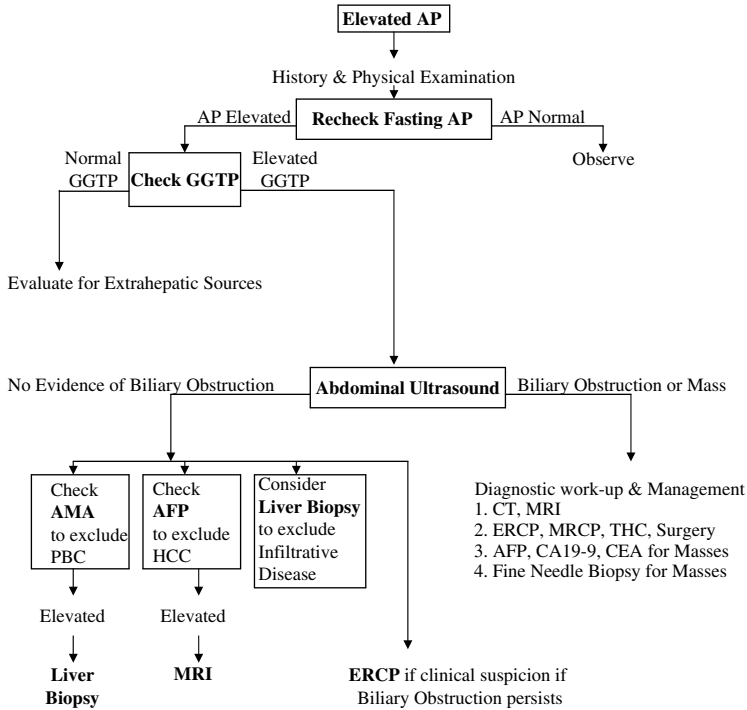


Fig. 2. Evaluation of isolated AP elevation. Clinical history taking should focus on excluding extrahepatic sources of AP (eg, symptoms of bone disease, pregnancy), medication use, symptoms of biliary colic, and cholestasis.

Drug-Induced Hepatotoxicity

Drug-induced hepatotoxicity is under-reported. It has an estimated incidence of 1:10,000 to 1:100,000.⁵¹ However, in the United States, it is the leading cause (specifically acetaminophen) of acute liver failure^{51,52} and drug withdrawal from the market.⁵³ Although many drugs are implicated in hepatotoxicity, common offenders include acetaminophen, methotrexate, and isoniazid. In addition, screening for hepatotoxicity has become a standard of care for certain medications, including statins, valproate, pyrazinamide, ketoconazole, dantrolene, tacrine, and synthetic retinoids. Clinical data on lipid-lowering agents, in particular statins, have provided assurance that mild transaminase elevations at baseline do not confer a higher risk for hepatotoxicity.⁵⁴

Screening for drug-related hepatotoxicity is limited by a number of factors, including the lack of available commercial tests to accurately measure most drug levels, non-dose-related idiosyncratic reactions and risk of progressive hepatotoxicity despite persistently normal LFTs with the use of certain drugs, for example, long-term methotrexate. A liver biopsy can provide information regarding the severity and extent of histologic damage from drug-related injury.

ABNORMAL LFTS: SUMMARY

In summary, there is no ideal test or battery of studies to evaluate abnormal LFTs in an asymptomatic patient. Abnormal LFTs should be reconfirmed. Based on diagnostic

clues obtained during clinical evaluation (detailed history, physical examination, a review of abnormally elevated LFTs, and other diagnostic data), an individualized diagnostic approach should be formulated. It may be crucial to plot a graph of duration, fluctuation, ratio, severity, and peak in LFT abnormalities and its relationship to exposure to potential hepatotoxic agents. A selective diagnostic approach appears cost effective and prudent in asymptomatic outpatients with abnormal LFTs.

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