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Analysis and Interpretation of Classic Liver Enzymes


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INTRODUCTION

Accessibility, ease of collection, and relatively low cost give serum chemistries an integral initial role in medical diagnosis. With the liver being a critical organ in the metabolism of carbohydrates, lipids and proteins as well as in first pass metabolism of exogenous medications, a great deal can be learned about hepatobiliary processes by having an appropriate grasp of specific liver chemistry tests. Liver enzymes are also commonly ordered for evaluation of other non-hepatic diagnoses and as part of health screening, which makes it imperative for all primary care physicians and specialists to have an accurate understanding of their normal values and an ability to interpret abnormal levels. Symptoms and signs of liver disease are often seen late in the disease. As a result laboratory testing helps in identifying and characterizing liver disease.

The term "liver function tests" is a misnomer, as many of these tests do not naturally reflect hepatobiliary function and are rather used as a determinant of liver injury. Furthermore, the origin of these tests may not be specific to the liver and, as such, abnormal results may be related to alternative organ injury. It is vital to use these test results in the context of patient history and physical examination in order to form an accurate diagnosis. For the purposes of this article, the liver chemistries that will be focused on will be bilirubin, alkaline phosphatase, aminotransferases and gamma-glutamyl transferase. In addition, albumin and prothrombin time will be discussed briefly. It will also provide a reference of normal laboratory values for an average adult male of individual tests based on information provided by the Mayo Clinic. Furthermore, as clinicians will be ordering these tests on a routine basis, the cost is relevant and Medicare pricing guidelines will be provided for each laboratory test. Following discussion of these tests individually, this article will focus on different patterns of abnormalities that relate to different disease processes.

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Bilirubin

Bilirubin is a product of the digestion of hemoglobin. During the catabolism of erythrocytes, an initial unconjugated or "indirect" form of bilirubin is

released into the reticuloendothelial system. As unconjugated bilirubin is water insoluble, it binds with albumin and is transported to the liver. Unconjugated bilirubin exists in majority as a component of total bilirubin when compared to direct bilirubin. In the liver, the unconjugated bilirubin enters the hepatocyte and is conjugated with glucuronic acid by the enzyme UDP-glucuronyltransferase (UGT), rendering it water soluble.[1] This conversion process, from the unconjugated form to "direct", or conjugated, form allows bilirubin to be transported through the canalicular membrane, mix with other components of bile within the biliary tree, and flow into the duodenum.[2,3,4] In the duodenum, part of the direct bilirubin is reabsorbed while the rest is converted to urobilinogen by intestinal flora and excreted in the urine and stool. In addition, there is also a delta bilirubin, which can also be referred to as biliprotein, which is produced by reaction of conjugated bilirubin with albumin.[5] It is important to note that the half-life of this product is about 17-20 days (the same as albumin) accounting for prolonged jaundice in patients recovering from hepatitis or obstruction.[6] The total bilirubin, which is a measure of both direct and indirect forms, has a normal reference range of 0.1-1.0 mg/dL.

Historically, in order to determine the serum levels of the two types of bilirubin, laboratories utilized the technique developed through the van den Bergh diazo reaction,[7] which was able to separate water soluble conjugated bilirubin from unconjugated bilirubin for individual measurement. The accuracy of the direct bilirubin levels increased as the total bilirubin rose. The direct, or conjugated, bilirubin reference range is 0.0-0.3 mg/dL in a normal individual and should be no more than 20% of the total bilirubin when the total bilirubin is elevated due to non-hepatic causes, such as hemolysis or congestive heart failure. The indirect or unconjugated bilirubin is obtained by subtracting the direct bilirubin level from the total bilirubin.

Identifying the subtype of bilirubin, which is elevated, allows for accurate diagnosis when analyzing bilirubin levels. Isolated elevation of unconjugated bilirubin occurs mainly secondary to increased bilirubin production, decreased hepatic uptake and decreased bilirubin conjugation. Elevated levels of unsuccessful erythrocyte production, hemolysis, or reabsorption of large hematomas may lead to increased unconjugated bilirubin levels. Fulminant Wilson's disease can cause isolated elevation in unconjugated bilirubin secondary to the release of copper in the blood resulting in cellular lysis [8] Unsuccessful erythrocyte production exists in the setting of rapid heme and hemoglobin turnover in the bone marrow due to premature destruction of red blood cells. There exists evidence that in these conditions there is also presence of erythroid hyperplasia of bone marrow, reticulocytosis, increased iron turnover with diminished red blood cell incorporation, and hemosiderosis of hepatic parenchymal cells and Kupffer cells. However, why this occurs in the bone marrow is not known.[8]

Isolated elevation of unconjugated bilirubin also may be due to genetically inadequate UGT production preventing conjugation in disease processes such as Gilbert's syndrome and Crigler-Najjar disease.[9] Gilbert's syndrome is a commonly seen disorder, which is relatively benign. The hyperbilirubinemia in Gilbert's syndrome is exacerbated with fasting.[10] Elevated conjugated bilirubin can be caused secondary to inherited or acquired conditions. Genetic disease processes such as Dubin-Johnson and Rotor syndrome cause an impaired hepatocellular secretion of bilirubin into the bile canaliculus causing elevated conjugated bilirubin.[11,12] As the anatomy suggests, elevations in conjugated bilirubin can occur secondary to hepatocellular dysfunction and cholestatic processes, which impair bile, flow.

Table 1. Definitions to describe the magnitude of elevations of AST and ALT

Borderline elevation in AST and ALT	<2X the upper limit of normal
Mild elevation in AST and ALT	2-5 X the upper limit of normal
Moderate elevation in AST and ALT	5-15 X the upper limit of normal
Severe elevation in AST and ALT	>15 X the upper limit of normal
Massive AST and ALT elevation	>10,000 IU/l

It has been found that despite the loss of liver function in hepatocellular disease processes, such as cirrhosis, UGT is produced at an increased rate in the remaining functioning hepatocytes forming conjugated bilirubin, such that increase in total bilirubin may not occur until late in the course of disease.[13,14] Cholestasis can occur either because of impaired secretion into a bile canaliculus or impaired transit through the biliary tree and into the duodenum. Some of the causes of intra hepatic cholestasis are drug toxicity, primary biliary cirrhosis, primary sclerosing cholangitis, viral hepatitis, cholestasis of pregnancy, benign postoperative cholestasis, infiltrative liver diseases, sepsis and total parenteral nutrition. Certain causes of extra hepatic cholestasis are choledolithiasis, malignant obstruction secondary to a mass in the pancreas, bile duct, gall bladder or ampulla, primary sclerosing cholangitis with an extra hepatic bile duct stricture, chronic pancreatitis and AIDS cholangiopathy.

Alkaline Phosphatase and gamma-glutamyltansferase

Alkaline phosphatase (ALP) is a zinc metalloenzyme and can be found in many different tissues, with most clinical relevance due to production in the bone, intestine, kidney or liver, and with more than 80% of serum ALP originating from bone or liver.[15] The average serum level of ALP in a normal adult male is 45 to 115 U/L. There are certain physiological causes that lead to increased alkaline phosphatase, examples being the during the third trimester of pregnancy secondary to the influx of alkaline phosphatate from the placenta, in adolescents secondary to increase in bone turnover, or some individuals with an increased production of intestinal alkaline phosphatase which is familial and benign.[10] Although it is generally ordered as part of routine liver chemistry, ALP abnormalities should be evaluated within the framework of hepatobiliary vs non-hepatobiliary diseases. In the liver, ALP is present in the hepatocytes on the cannalicular membrane, but is localized to the microvilli of the bile canaliculus, and elevated levels typically reflect a cholestatic disease process. The half life of ALP is one week and, as a result, even after the cholestatic process has resolved, the normalization of the ALP level may lag. In order to distinguish whether an isolated elevation of ALP is of hepatic origin, one could order ALP isozymes, which fractionate the total ALP into its tissues of origin. Alternatively, confirmation via a gamma-glutamyltransferase (GGT) level can be performed since GGT is more concentrated in hepatic tissue[1] and is not present in bone. A concurrent elevation of ALP and GGT excludes a boney origin of the enzyme. It is important to note that initially the only notable abnormality that may be seen in infiltrative diseases such as primary biliary cirrhosis, sarcoidosis, primary sclerosing cholangitis, etc. is isolated elevations in ALP.[1] Elevation in ALP is typically seen for duration of more than six months in these conditions. These cases normally require follow up with imaging or liver biopsy. ALP can also interestingly be raised in various neoplasms, which do not involve the bone or liver directly. This occurs secondary to an isozyme of ALP called the 'Regan isoenzyme'.[17]

GGT is an enzyme primarily located in hepatocytes, epithelial lining of biliary ducts, pancreas, renal tubules and the intestine. The normal GGT level in adult male ranges from 9 to 48 U/L. GGT levels may be elevated in a large variety of common diseases such as diabetes, hyperthyroidism, pancreatitis, alcoholism, COPD and rheumatoid arthritis and also as a result of various medications like coumadin, carbamazepine, phenytoin, and barbiturates. Hence the specificity for liver disease is poor. Isolated GGT elevation may be seen in alcohol abuse. Note, however, the degree of GGT elevation does not directly correlate with the amount of alcohol consumed.[11]

Aminotransferases - Alanine aminotransferase (ALT) & Aspartate aminotransferase (AST)

In 1955, serum AST and ALT elevations were first noted in patients with known viral hepatitis and other hepatic specific diseases.[18] Aminotransferases are so named as their enzymatic function is to transfer amino groups to form pyruvate via AST and form oxaloacetate via ALT. While present in several tissues including skeletal and cardiac muscle and erythrocytes, clinically relevant elevations are usually reflective of liver disease, especially with respect to ALT elevations, isolated elevations of which should be assumed to reflect liver disease

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until proven otherwise. Their location within the hepatocyte is imperative to understanding the elevation patterns seen in various liver diseases. AST has two isoenzyme forms, with 80% operating as a mitochondrial isoenzyme; however, most of the circulating serum AST is derived from the cytoplasmic isoenzyme.[19] Conversely, ALT is found only in the cytosol and is more specific to liver tissue. This makes an elevated ALT more specific for hepatocellular injury than AST. Elevated ALT levels however have also been noted in myopathic diseases.[20]

When determining a laboratory range for aminotransferases, important characteristics must be considered. Interestingly, as body mass index (BMI) increases, so does ALT; ALT is also higher in males relative to females. It is worth noting as well that AST levels may be 15% higher in African-American males.[21] As ALT has more specificity for hepatocellular injury, cutoff values are important to ensure proper inclusion of patients with liver disease and elevated aminotransferases without unnecessary evaluation of patients with potentially normal levels.[22] For the purposes of this article, we use a reference range for ALT as 7 to 55 U/L and AST as 8 to 48 U/L, with an understanding that a wide upper limit variability exists across different laboratories likely related to different reference standards.[23] The magnitude of transaminase elevation relative to the upper limit of normal may help to narrow down the differential diagnosis for the cause of hepatocellular injury. Specifically, aminotransferase levels that are 15x or more the upper limit of normal deserve to be considered separately from mild or moderate elevations.[13] Also to further classify pathologies, it is important to consider the ratio of ALT to AST.

Albumin

Albumin is a plasma protein produced solely in the liver, with a half-life of three weeks.[24] As a result, a decrease in the albumin level compared to normal (<3.5 g/L) signifies a liver disease which has been occurring for greater than three weeks. Albumin level can be influenced by other factors such as the nutritional status, catabolism, hormonal factors, and urinary and gastrointestinal losses. As a result, these factors should be taken into consideration when interpreting albumin levels. In conclusion albumin is useful to interpret chronic and progressive liver disease and is also used to predict the prognosis of liver disease.

Prothrombin Time (PT)

All coagulation factors are produced in the liver. Factor VIII is produced in endothelial cells outside the liver in addition to being produced by the sinusoidal cells in the liver. The rate of conversion of prothrombin to thrombin requiring factors II, V, VII, X and fibrinogen is the measurement of prothrombin time (PT), thus a function of the liver. Prothrombin time can be prolonged even in a severe liver disease of < 24 hours secondary to the half life of most factors being equal to or less than 24 hours.[2] It should also be noted that vitamin K is required in the production of factors II, VII IX and X. As a result, vitamin K deficiency can also cause prolonged prothrombin time. Some other factors that should be considered in cases of prolonged prothrombin time are warfarin therapy, disseminated intravascular coagulation (DIC), hypothermia and steatorrhea.

International Normalized Ratio (INR)

In order to avoid variability in laboratory values, international normalized ratio (INR) is more commonly tested instead of or in place of PT. The results are interpreted in the same way as PT would be interpreted. It is calculated according to a formula as follows:

International normalized ratio = [patient PT/mean control PT] ISI

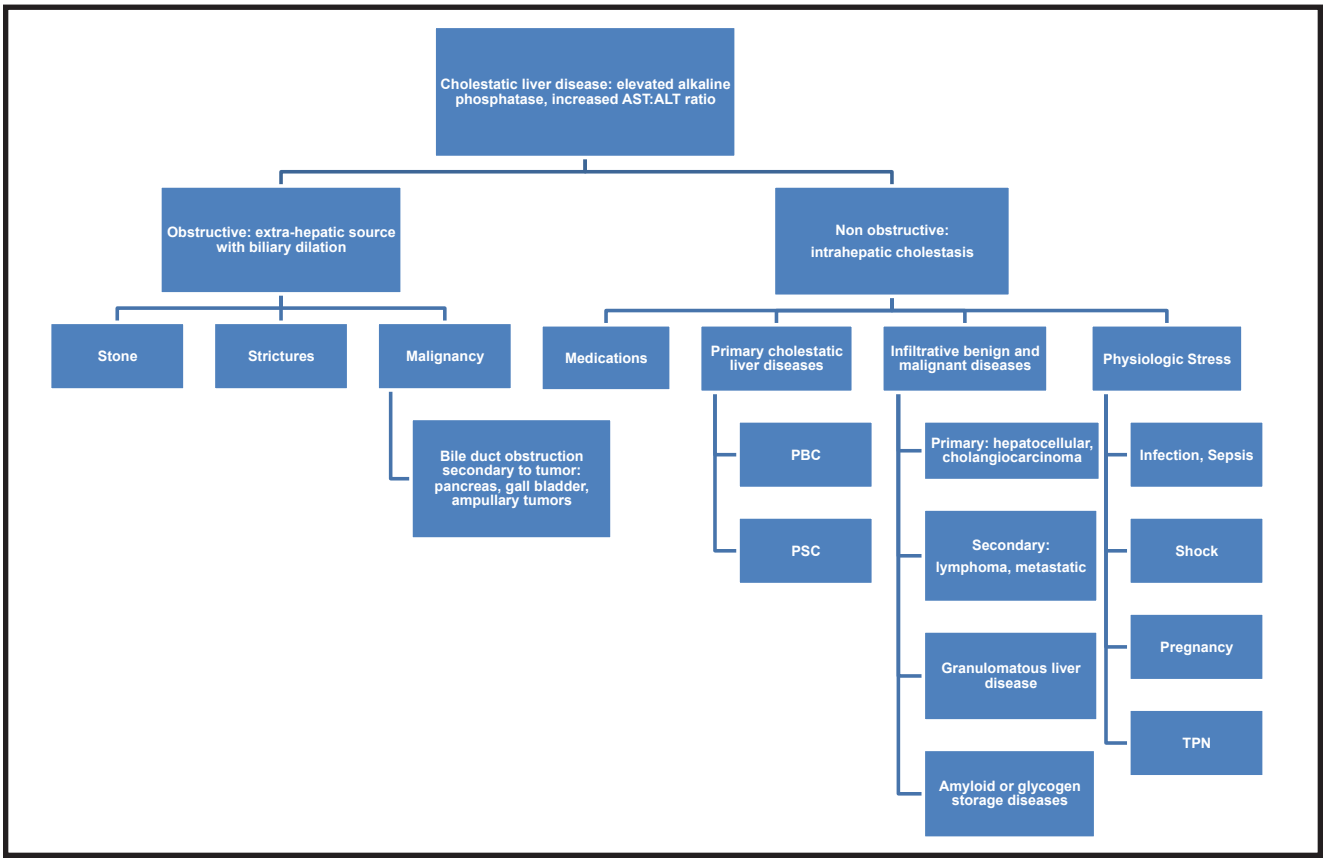
(ISI = international sensitivity index).

Patterns Of The Liver Function Tests

Once a general understanding of each individual liver enzyme has been achieved, clinicians can then use the liver enzyme panel to begin recognizing patterns. Each test is important to understand; however the elevation of each in relation to the other parts of the panel is what is most useful in interpreting disease processes. In this section we will describe the different liver enzyme patterns and their associated disease processes.

The liver enzyme panel abnormalities can be broken down into two main subgroups, which will

Figure 1. Causes of cholestatic liver disease.



be discussed individually. These subgroups are a cholestatic pattern and a hepatocellular pattern. These subgroups will then be broken down further into respective categories. The *R* ratio has been described to assess whether the pattern of liver injury is hepatocellular, cholestatic, or mixed and may be applied in drug-induced liver injury.[26] The *R* ratio is calculated by the formula *R* = (ALT value÷ALT ULN) ÷ (alkaline phosphatase value ÷ alkaline phosphatase ULN). An *R* ratio of >5 is defined as hepatocellular, <2 is cholestatic, and 2–5 is a mixed pattern. This paper will describe hepatocellar and cholestatic patterns.

Hepatocellular Disease Pattern

Hepatocellular pattern is diagnosed with a disproportionate elevation in AST and ALT relative to alkaline phosphatase. For the purpose of this paper we will use the following definitions to describe the magnitude of elevations of AST and ALT (Table 1).

It is important to identify acute liver failure or fulminant liver failure as diagnosed by hepatic encephalopathy and coagulopathy in a patient with no prior history of liver disease. For acute liver failure, it is not imperative to describe the magnitude of rise in ALT or AST. Rapid involvement of the consultancy groups and evaluation of liver transplant should be begun early on.

Causes of Aminotransferase Elevation

Massive Elevation (More than 10,000 times the upper limit)

There is an overlap for the causes of elevation in AST and ALT between the groups of severe and massive elevation in AST and ALT. Ischemic liver disease, toxin and viruses related injuries can cause a massive elevation in AST and ALT. They are described further in the section below. It is also important to note that massive AST elevations can be seen in heat stroke and rhabdomyolysis.

Severe (15 times or greater than the upper limit of normal)

The severe elevations of serum aminotransferase

levels are mainly found in the setting of excessive hepatocellular injury or necrosis in an acute setting. Although highly elevated aminotransferases can suggest an acute injury, the actual quantification of hepatocyte necrosis cannot be inferred. Furthermore, extremely elevated aminotransferases do not indicate prognosis.[11] The differential is limited and generally includes a drug or toxin induced hepatotoxicity, acute viral hepatitis, or ischemic hepatitis. Toxin-related hepatitis and acute viral hepatitis can increase the AST and ALT levels to >25 times the upper limit of normal, while ischemic hepatopathy can increase the levels to >50 times.

Many medications and toxins can cause liver injury. Some of the commonly seen medications are non-steroidal anti-inflammatory drugs, antibiotics, statins, antiepileptic drugs, and antituberculous drugs. It is also pertinent to note that certain herbal remedies and illicit drugs can cause liver injury.[10] In the United States (USA), the leading cause of acute liver failure is acetaminophen poisoning, accounting for 46% of cases.[27] Hepatotoxicity occurs when sulfate and glucuronide metabolic pathways become saturated, pushing more acetaminophen metabolism towards the cytochrome P450 pathway that results in the formation of the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQ1). Chronic alcohol abusers can be more prone to acute liver failure in the setting of acetaminophen use and caution should be taken when treating these patients.[28] Cytochrome P-450, principally cytochrome CYP2E1, metabolizes acetaminophen into a toxic metabolite, which is detoxified by glutathione under normal circumstances. CYP2E1 also detoxifies ethanol. Thus in chronic alcohol abusers, there is increase in CYP2E1 which increases the metabolism of acetaminophen into its toxic metabolites.[29] Careful attention to occupational history should be given to patients with excessive aminotransferase elevation. Occupations that could lead to aminotransferase elevation include mushroom picking (*Amanita phalloides*) and those involved in the chemical industry (vinyl chloride).[30]

Acute hepatitis can also be caused by infection with any of the primary hepatitis viruses (A-E). Hepatitis B and hepatitis C are most prevalent in the USA, with hepatitis B being the leading cause of acute viral hepatitis in the USA. Viral serological tests are important to differentiate acute from chronic hepatitis.

Hepatitis A is transmitted by the fecal oral route. It is a RNA virus, which has an incubation period of a few weeks. The IgM antibodies to hepatitis A remain in the body for a period of three to six months after the infection.[31]

Hepatitis B is mainly spread through unsafe sexual practice, parental drug use or vertical transmission. Hepatitis B surface antigen (HBSAg) is positive in either acute or chronic hepatitis B infection, while HBV core IgM antibody generally specifies the acute state. Checking for HBVsAg and HBVDNA would indicate whether there is an active infection and infectivity of the virus. In addition, checking for hepatitis B surface antibody would indicate immunity to hepatitis B either secondary to resolution of a prior infection or vaccination.

Hepatitis C is transmitted through parental drug use, cocaine inhalation, blood transfusion prior to 1992, tattoos or body piercings, needle stick injury and unsafe sexual practices. Hepatitis C antibody testing is sensitive. Presence of HCV viremia should be confirmed in the setting of a positive antibody with the HCV RNA PCR assay, which has high sensitivity and specificity. Hepatology should be consulted for patients positive for hepatitis C for evaluation of treatment, education on hepatitis C, and screening for cirrhosis and hepatocellular carcinoma.

Hepatitis D is an RNA virus that is only seen in the presence of hepatitis B surface antigen positivity. Suspicion for hepatitis D should arise when hepatitis B presents with fulminant hepatitis. Acute co-infection with hepatitis D is diagnosed when HBSAg, IgM anti-HBc, and total anti- HDV are present.

Another cause of acute hepatitis is hepatitis E virus. It is an enterically transmitted RNA virus. Another method of transmission of hepatitis E is through vertical transmission. Anti-HEV immunoglobulin IgM and IgG are used to detect hepatitis E. HEV RNA is used to confirm the presence of hepatitis E.

Occasionally, in the setting of acute hepatitis with excessively elevated AST and ALT levels, history and serology may not uncover a toxic or

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viral cause, and in these cases ischemic hepatitis should be considered. In ischemic hepatitis, the AST and ALT levels have the potential to increase to >50x the upper limit of normal. Several mechanisms can result in massive AST and ALT elevation, including decreased blood flow in instances such as hypotension, sepsis, hemorrhage, and myocardial infarctions.[13] Concurrent elevation of lactate dehydrogenase (LDH) may suggest the diagnosis of ischemic hepatitis.[32] These examples highlight the importance of a thorough history and physical examination to help stratify differential diagnoses in the setting of severe aminotransferase elevation.

Mild to Moderate (5-15 times the upper limit of normal)

Borderline and mild elevation in AST and ALT are seen in a variety of diseases. Moderate increase in AST and ALT often coincides with causes of mild and severe elevations.

The two most commonly identified non-viral entities, alcoholic liver disease and non-alcoholic fatty liver disease, will be briefly described below.

Alcoholic Liver Disease

Alcohol ingestion can cause elevation in liver chemistries. Alcohol ingestion can be an independandant cause or can attenuate transaminitis concurrent with other chronic liver diseases. Alcohol can cause a wide spectrum of liver disease from fatty liver to alcoholic hepatitis to alcoholic cirrhosis. These conditions can also be present all at once in an individual. Liver biopsy is useful to identify the stage and severity of liver disease since the liver chemistries do not always correlate with these.[33,34] The definition of significant alcohol consumption has been suggested as >210 g of alcohol per week in men and >140 g per week in women.[35] In practice, an AST:ALT ratio of 2-3:1 raises the suspicion for alcoholic liver disease. It has been demonstrated that alcohol consumption leads to decrease in plasma pyridoxal 5'-phosphate.[36] This decrease in levels results in a decrease in ALT activity. The decrease in plasma pyridoxal 5'-phosphate does not have an effect on AST leading to the ratio of AST:ALT being 3:1. Once alcohol abstinence is observed with appropriate nutritional uptake, plasma pyridoxal 5'-phosphate normalizes causing a normal ALT level.[36,37,38] When alcohol use is felt to cause liver disease, it is strongly recommended to quit alcohol use, and appropriate counseling should be given.

Non-Alcoholic Fatty Liver Disease and Nonalcoholic Steato-Hepatitis

Nonalcoholic fatty liver disease (NAFLD) is defined as (a) there is evidence of hepatic steatosis, either by imaging or by histology and (b) absence of causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of medication that could cause fatty liver injury, or hereditary disorders. NAFLD is commonly seen in individuals with the metabolic syndrome, characterized by obesity, diabetes mellitus, and dyslipidemia. Histologically, NAFLD can be characterized as non-alcoholic liver (NAFL) or non alcoholic steato-hepatitis (NASH). Differentiation of NAFL from NASH is characterized by the presence of inflammation and hepatocellular injury, in the form of ballooning of the hepatocytes, with or without fibrosis, in the setting of NASH. It is concluded that patients with NAFL have a rather benign, slow progression (if any) histologically, while NASH can rapidly progress to the cirrhotic stage.[39,40] Steatohepatitis and fibrosis as seen in NAFLD cannot be assessed accurately with serum transaminases, emphasizing the importance of further evaluation with imaging studies such as ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) and magnetic resonance elastrography (MRE) or with liver biopsy. MRE has proven to be a non-invasive, feasible and accurate modality to identify hepatic steatosis and fibrosis. MRE quantifies the extent of hepatic fibrosis with great accuracy. As compared to ultrasound, MRE is beneficial secondary to being non-technician dependant and being able to identify small amount of fibrosis. However liver biopsy continues to be the preferred modality to differentiate NAFL and NASH. The procedure related morbidity and mortality, cost and sampling error of liver biopsy has lead to interest is identifying non invasive biomarkers to identify steatohepatitis and fibrosis in NAFLD. The NAFLD fibrosis score, enhanced liver fibrosis (ELF) panel and transient elastography are identified as non-invasive

methods to identify the spectrum and stage of NAFLD. The NAFLD fibrosis score is comprised of six variables (age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio) and it is calculated using the published formula (http://nafldscore.com). Cytokeratin-18 (CK18) fragments have been investigated extensively as novel biomarkers for the presence of steatohepatitis in patients with NAFLD.[41,42] Weight loss in the form of decreased caloric intake and exercise is recommended as the primary treatment. Vitamin E (a-tocopherol) administered at daily doses of 800 IU/day improves liver histology in many non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population.[43,44]

AST/ALT Ratio

AST/ALT ratios are of great diagnostic aid. An AST:ALT ratio of 2-3:1 raises the suspicion for alcoholic liver disease as discussed previously under the section of alcoholic liver disease. ALT has a longer half life compared to AST. The half life of ALT is 47 +/- 10 hours and that of AST is 17+/- 5 hours. In cholecystitis secondary to gallstone impaction in the distal cystic duct or choledocholithiasis, there is as increase in the AST:ALT ratio initially. However once disimpaction of the stone either spontaneously or iatrogenically is achieved, there is a reversal of this ratio secondary to ALT having a longer half life as compared to AST. It is also important to note that in chronic hepatitis the AST:ALT ratio may be increased up to 1. In advanced hepatic fibrosis, there is a reversal in the AST:ALT ratio in chronic as compared to acute hepatitis. Studies have shown that this is mainly caused by to the increased catabolism of ALT. Earlier it was thought to be secondary to increased production of AST and decreased production of ALT, which has now proven to not be the cause of the ratio reversal.[45,46]

Cholestatic Liver Disease Pattern

Cholestatic injury is defined as disproportionate elevation in alkaline phosphatase level as compared with AST and ALT levels. Anatomic obstructions to bile flow (extrahepatic cholestasis) or inability to form bile by the hepatocytes (intra-hepatic cholestasis) can cause a cholestatic injury pattern.

Once the origin of alkaline phosphatase has been identified as the liver, it is recommended to evaluate with an ultrasound or other form of liver imaging to identify whether the source is intra-hepatic or extra-hepatic. An MRI/MRCP (magnetic resonance cholangiopancreatography), endoscopic retrograde cholangiopancreatography and/or endoscopic ultrasound can be ordered to better examine the bile duct morphology. In the presence of biliary dilation, the source of a cholestatic pattern is most likely extra hepatic, while the absence would indicate an intra hepatic source. Causes of cholestatic liver disease as outlined in Figure 1.

For intrahepatic cholestasis, autoimmune markers including antimitochondrial antibody, antinuclear antibody, and smooth muscle antibody should be checked to assess for PBC or autoimmune cholangiopathy. Finally, pregnancy testing in women of childbearing age should be done to assess for intrahepatic cholestasis of pregnancy. Other infiltrative disorders may raise the alkaline phosphatase and cause intrahepatic cholestasis, including sarcoidosis, atypical fungal infection, or malignancies. In these instances of infiltrative diseases, a liver biopsy may be considered to assess for primary biliary cirrhosis or other infiltrative diseases. ■

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