Jose Melendez-Rosado, MD
Ali Alsaad, MBChB
Fernando F. Stancampiano, MD
William C. Palmer, MD

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Abnormal Liver Enzymes

ABSTRACT

Abnormal liver enzymes are frequently encountered in primary care offices and hospitals and may be caused by a wide variety of conditions, from mild and nonspecific to well-defined and life-threatening. Terms such as "abnormal liver chemistries" or "abnormal liver enzymes," also referred to as transaminitis, should be reserved to describe inflammatory processes characterized by elevated alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. Although interchangeably used with abnormal liver enzymes, abnormal liver function tests specifically denote a loss of synthetic functions usually evaluated by serum albumin and prothrombin time. We discuss the entities that most commonly cause abnormal liver enzymes, specific patterns of enzyme abnormalities, diagnostic modalities, and the clinical scenarios that warrant referral to a hepatologist.

The liver is the largest solid organ in the human body, as well as one of the most versatile. It manufactures cholesterol, contributes to hormone production, stores glucose in the form of glycogen, processes drugs prior to systemic exposure, and aids in the digestion of food and production of proteins. However, the liver is also vulnerable to injury, which can be detected by abnormal liver enzymes (ALEs). Although elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) are classically referred to as elevated liver function tests (LFTs), they would more accurately describe as liver *inflammation* tests. LFTs should instead refer to serum assessments of hepatic synthetic function, such as albumin and prothrombin time. Disease categories, such as viral inflammation and injury from alcohol use, may be differentiated by following patterns and trends of enzyme elevations.

Liver tissue contains two different types of cells, hepatocytes and cholangiocytes (bile duct cells). Enzymes such as ALT and AST are found inside hepatocytes and are released into the circulation when there is hepatocellular injury. These enzymes can also be found in other organs such as kidneys, heart, muscles, pancreas, and erythrocytes. Inflammation of cholangiocytes can produce elevations in serum bilirubin, ALP, and γ-glutamyltransferase (GGT), which may be released during intrahepatic or extrahepatic bile duct inflammation or obstruction.

ALP is also found in bone and is released in diseases such as Paget's disease, hyperparathyroidism, and bone cancer. Gel electrophoresis can be used to distinguish between bone and liver sources of ALP; however, availability and cost are limiting factors. Instead, the concomitant increase of ALP and GGT suggests hepatic etiology related to elevated ALP (Raulf, Stuning, & Konig, 1985; Wei, Chen, Gao, & Tian, 2015). Isolated elevations in ALP may occur in young adults, athletes, obese individuals, and women in the third trimester of pregnancy. Familial elevation of ALP has been reported,

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About the authors: *Jose Melendez-Rosado, MD, is Gastroenterology Fellow, Cleveland Clinic Florida, Weston, Florida.*

Ali Alsaad, MBChB, is Internal Medicine Resident, Mayo Clinic, Jacksonville, Florida.

Fernando F. Stancampiano, MD, is Assistant Professor, Internal Medicine, Mayo Clinic, Jacksonville, Florida.

William C. Palmer, MD, is Assistant Professor, Gastroenterology, Mayo Clinic, Jacksonville, Florida.

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Correspondence to: *William C. Palmer, MD, Division of Gastroenterology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224 (Palmer.william@mayo.edu).*

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especially in individuals with blood types O and B (Pratt & Kaplan, 2000). GGT is very sensitive for hepatic injury but has limited specificity, as it can elevate in pancreatic disease, myocardial infarction, renal failure, diabetes, and also in association with the use of barbiturates and phenytoin (Wei et al., 2015).

Evaluation of ALEs

The first step in the evaluation of ALEs entails obtaining additional laboratory studies to evaluate for hepatic function including total and direct serum bilirubin, international normalized ratio (INR), prothrombin time, partial thromboplastin time, and serum albumin. ALEs are assessed in three parts: the pattern of elevation, degree of elevation, and clinical risk factors. Elevation patterns may give information regarding organ location. Isolated elevation of the AST and/or ALT (hepatocellular pattern) typically reflects damage to the hepatic parenchyma, whereas elevations in alkaline phosphatase and bilirubin (cholestatic pattern) tend to reflect bile duct injury or obstruction. Mixed pictures may also occur. The degree of enzyme abnormality can also provide clues to possible etiologies. Profound elevations of AST/ALT typically indicate hepatic ischemia, drug-induced injury, or acute viral hepatitis (Leise, Poterucha, & Talwalkar, 2014; Seeto, Fenn, & Rockey, 2000) (Figure 1).

Clinical risk factors including medical, family, social history (travel, alcohol, and sexual behavior), and medications are of great significance. Liver ultrasonography is a commonly available and inexpensive tool that can aid in the evaluation. Fatty infiltrate, mass lesions, or bile duct abnormalities can be observed via ultrasound with a high level of sensitivity (Khov, Sharma, & Riley, 2014; Lapis, Orlando, Mittelstaedt, & Staab, 1978). Although the common bile duct may be enlarged because of previous cholecystectomy and age, a size greater than 6 mm in diameter is considered abnormal and deserves further investigation, such as endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography (MRCP) (Perret, Sloop, & Borne, 2000).

Causes of Elevated LFTs

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is the most commonly diagnosed liver disease worldwide (Abd El-Kader & El-Den Ashmawy, 2015). Patients with NAFLD with histological and/or biochemical inflammation are deemed to have nonalcoholic steatohepatitis (NASH), which represents the most common cause of liver pathology and elevated liver enzymes in the United States (U.S.) (Rinella, 2015). Risk factors for NASH including diabetes mellitus, hyperlipidemia, and obesity (Chitturi et al., 2002; Yki-Jarvinen, 2014) are linked to insulin resistance and commonly coalesce as metabolic syndrome.

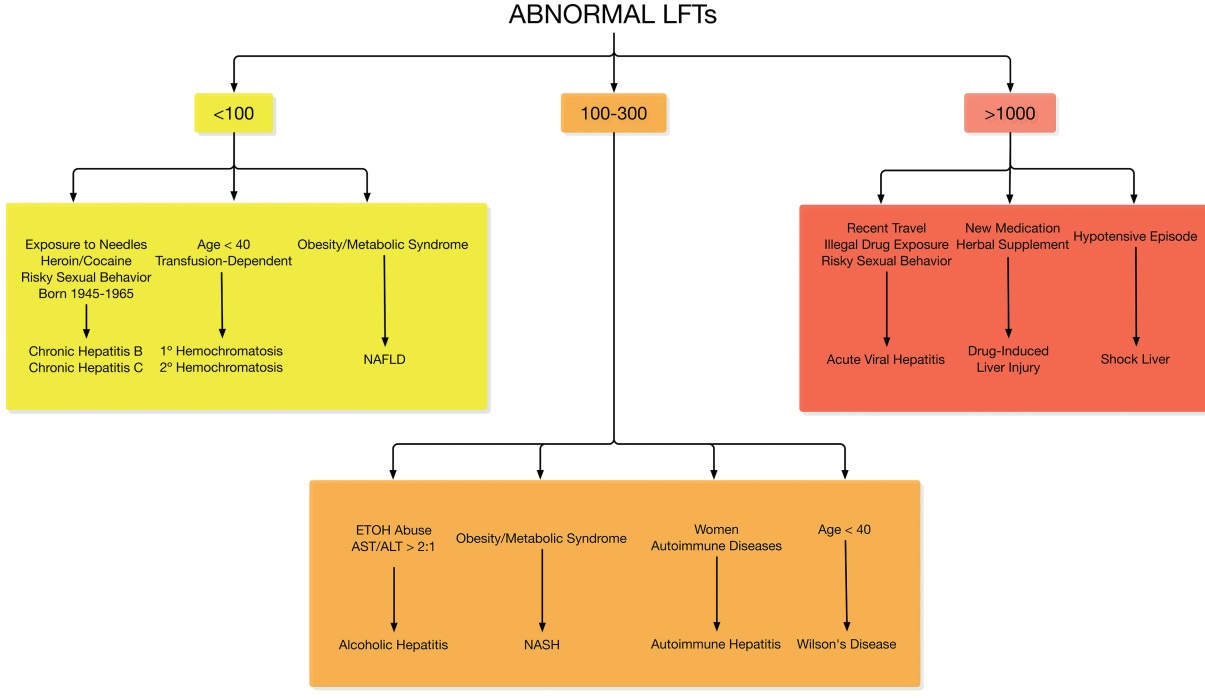

FIGURE 1. Abnormal liver function tests.

ALT is the enzyme most commonly elevated in NASH. However, normal liver enzyme levels are found in 30%–60% of biopsy-confirmed cases (Amarapurkar & Patel, 2004; Mofrad et al., 2003). ALEs are not specific in differentiating NAFLD from NASH (Afdhal, 2012). Elevated ALT only has 45% sensitivity and 85% specificity for NASH, which may lead to underdiagnosis (Nascimbeni et al., 2013; Rinella, 2015; Sebastiani et al., 2014). However, results from one study suggest that NASH progression in patients with normal ALT is comparable to those with ALEs (Ortiz-Lopez et al., 2012). Therefore, the reliability of ALEs in monitoring the progression of NAFLD is questionable. Diabetic patients with normal ALT develop NAFLD and NASH in 76% and 56% of cases, respectively (Ortiz-Lopez et al., 2012).

Elevated ALT:AST ratio greater than 1.5 times for more than 6 months is an indication for liver biopsy or hepatic elastography (Chalasani et al., 2012). An elevated AST:ALT ratio may be seen in advanced fibrosis (Afdhal, 2012). Clinicians should inform their patients that the primary driver of mortality in patients with NAFLD and NASH is cardiovascular disease, but primary liver malignancy and complications of cirrhosis remain important. No study has demonstrated ALEs as a predictor of mortality in patients with NAFLD and NASH.

Alcoholic Hepatitis

The prevalence of alcoholic liver disease is difficult to estimate, given that many patients are asymptomatic; however, the approximate prevalence of alcohol abuse and dependence in the U.S. is about 4.65% and 3.81%, respectively (Grant, et al., 2004). Excessive alcohol intake has been shown to be proportional to prognosis and mortality (Bruha, Dvorak, Dousa, Petrtyl, & Svestka, 2009). Acute alcoholic hepatitis (AH) is associated with high mortality, ranging from 30% to 50% even with appropriate therapy (Torok, 2015). Hepatorenal syndrome with an inflammatory background related to cytokine release is the leading cause of death (Gao & Shah, 2015). Relatively low ALT levels secondary to vitamin B_6 deficiency characteristically yield an elevated AST:ALT ratio (Botros & Sikaris, 2013). An AST level of less than 500 U/L and an AST:ALT ratio of more than 2:1 in the presence of alcohol consumption are suggestive of the diagnosis (Torok, 2015).

Isolated AST elevation in hemolysis and rhabdomyolysis can be confused with AH (Botros & Sikaris, 2013). Liver biopsy may be indicated in cases of diagnostic uncertainty and can help define prognosis (Casanova & Bataller, 2014; Dhanda, Collins, & McCune, 2013). Biopsy findings in AH can mimic those of NASH, thus the alcoholic-non-alcoholic index (ANI) should be applied to distinguish between the two entities (Altamirano et al., 2014; Gao and Shah, 2015; Torok, 2015). The ANI is calculated on the basis of AST:ALT ratio, mean corpuscular volume, body mass index, and gender (Altamirano et al., 2014). In addition, INR, bilirubin, and GGT levels are usually elevated in AH.

Maddrey's discriminant function is the most commonly used model to predict outcomes in AH (Maddrey et al., 1978). A score greater than 32, which is indicative of severe AH and associated with a mortality of 20%–30% within 1 month has been historically used as a threshold to administer prednisolone or pentoxifylline. Recently, the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial found no survival benefit of pentoxifylline and mild survival benefit at 28 days of prednisolone that did not reach statistical significance at 90 days or 1 year. Prednisolone was also associated with serious infections (Thursz, Forrest, & Ryder, 2015). Abstinence from alcohol consumption is the only available measure that may prolong survival.

Viral Hepatitis

Hepatitis C virus (HCV) is the most prevalent viral cause of hepatitis in the U.S., with an estimate of 2.7–3.9 million cases, followed by hepatitis B virus (HBV), with approximately 730,000 cases (Armstrong et al., 2006; Wasley et al., 2010). Risk factors associated with these viruses are intravenous and intranasal drug use, blood transfusions or organ transplantation before 1992, tattoos in unregulated settings, needle stick injuries in the healthcare setting, long-term hemodialysis, and history of incarceration. There has been a recent increase in the incidence of acute hepatitis C infection in people younger than 30 years in nonurban areas east of the Mississippi River. These cases were linked to the use of heroin preceded by narcotics by an average of 2 years (Suryaprasad et al., 2014).

Acute viral hepatitis is associated with moderate to profound elevation in liver enzyme levels, usually greater than 1,000 U/L, and hyperbilirubinemia, especially in cases of fulminant hepatic failure and those with underlying cirrhosis (Galli, Gerdes, Guasti, & Squizzato, 2014; Hoofnagle, Nelson, & Purcell, 2012). Conversely, chronic viral hepatitis can be asymptomatic and have aminotransferase levels lower than 100 U/L.

The revolutionary wave of direct-acting viral agents for HCV highlights the need to identify those subjects with chronic infection. Studies have shown that sustained virologic response in HCV may decrease chronic complications such as hepatocellular carcinoma (Morgan et al., 2013). In 2012, the Centers for Disease Control and Prevention (CDC) issued a recommendation that all individuals born between 1945 and 1965 be screened one time for the presence of HCV antibody, regardless of risk factors (CDC, 2012).

Although HCV testing lacks specificity, the presence of antibodies along with elevated liver enzymes is highly suggestive of infection (Limdi & Hyde, 2003). Quantitative HCV-RNA polymerase chain reaction (PCR) testing is required to confirm active infection, and is more sensitive in the setting of acute hepatitis C, prior to antibody formation. Acute hepatitis B infection can present similarly. Initial testing for hepatitis B infection, acute or chronic, includes surface antigen, and in certain cases, core IgM (Krajden, McNabb, & Petric, 2005).

The feco-orally transmitted hepatitis A virus (HAV) is uncommon in western countries, with only 1,239 cases reported in 2014 (CDC, 2016). Diagnosis is highly associated with a history of foreign travel to endemic areas (Klevens, Denniston, Jiles-Chapman, & Murphy, 2015). The diagnosis can be established by the presence of anti-HAV IgM antibody, which has high sensitivity and specificity (Lee et al., 2010). Immunity from previous exposure or vaccination may wane over time (Irving, Holden, Yang, & Pope, 2012; Klevens et al., 2015).

Hepatitis E virus (HEV) is also enterically transmitted and manifests as acute hepatitis (with ALT greater than 1,000 U/L) or chronic persistent hepatitis (Hoofnagle et al., 2012; Murali, Kotwal, & Chawla, 2015). Two subtypes of HEV have been recognized, with the endemic (autochthonous) form seen more commonly in developed countries (Hoofnagle et al., 2012). Because IgM anti-HEV antibody has limited accuracy, disease prevalence in the U.S. remains unknown (Hoofnagle et al., 2012; Shrestha et al., 2007). Although uncommon, cytomegalovirus, Epstein–Barr virus, varicella zoster virus, and other Herpesviridae may cause viral hepatitis, particularly in immunocompromised patients.

Hemochromatosis

Hemochromatosis is a common autosomal recessive disease that leads to abnormally increased absorption of iron from the intestine and subsequent organ deposition (Barton, Edwards, & Acton, 2015; Klevens et al., 2015). Hemochromatosis gene mutations are most prevalent in those of northern European ancestry (1:200–1:250), with 50%–90% penetrance for significant iron overload (Edwards et al., 1988). The disease tends to affect males between the ages of 40 and 60 years and may cause liver inflammation and fibrosis; yet, other organs such as the pancreas, skin, heart, and joints can be involved.

The majority of patients with hemochromatosis are asymptomatic, but nonspecific symptoms such as weakness, fatigue, and vague abdominal pain may occur (Pietrangelo, 2004). Few present with nonspecifically ALEs, hepatomegaly, cirrhosis, or hepatocellular carcinoma (HCC). Bronzed skin, impotence, hypothyroidism, diabetes, and cardiomyopathy/cardiac conduction abnormalities occur infrequently (Crownover & Covey, 2013; Pietrangelo, 2004). Elevated serum ferritin is useful but nonspecific, as it may be present in inflammatory disorders. Transferrin saturation is the most sensitive screening test and can be calculated by dividing serum iron by total iron-binding capacity. Transferrin saturation higher than 45% is highly suggestive of hemochromatosis (Limdi & Hyde, 2003; Powell, George, McDonnell, & Kowdley, 1998). The hepatic iron index, calculated by dividing the hepatic iron content by the patient's age, can confirm the diagnosis during biopsy. A ratio exceeding 1.9 is considered confirmatory of homozygous hemochromatosis (Powell et al., 1998).

HFE gene mutations play a major role in iron homeostasis by controlling hepcidin, a protein that regulates iron metabolism (Barton et al., 2015). The use of genetic testing for *HFE* and its two points of mutation *C282Y* and *H63D* has eliminated the need for a significant number of liver biopsies in patients with suspected hemochromatosis; however, it may fail to identify some uncommon mutations (Powell et al., 1998).

In patients with normal AST but no hepatomegaly, whose ferritin level is less than 1,000 ng/ml, a liver biopsy may not be necessary (Powell et al., 1998). Frequent phlebotomy is the mainstay treatment for patients with hemochromatosis. A goal serum ferritin level of 50–150 ng/ml should guide the frequency of phlebotomy (Bacon et al., 2011; Crownover & Covey, 2013).

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a complex, progressive T-cell-mediated disease characterized by damage to hepatocytes. Most common in young females, AIH is classified into main types 1, 2, and 3 on the basis of the detection of antismooth muscle antibody (ASMA), antiliver/kidney microsomal antibody-1 (anti-LKMA-1), and antisoluble liver antigen/liver-pancreas antigen antibody (anti-SLA/LP), respectively (Liberal, Vergani, & Mieli-Vergani, 2015; Sener, 2015). Hepatocellular injury is almost always evident in AIH, with markedly abnormal liver enzymes and near-normal bilirubin and ALP levels, unless the disease overlaps with other hepatobiliary or cholestatic processes (Krawitt, 2006; Liberal et al., 2015). Also, many patients with AIH present with elevated IgG. Although the diagnosis of AIH may be established with autoantibodies because of their high sensitivity and reliability, the role of liver biopsy is crucial in confirming the disease and excluding cirrhosis (Limdi & Hyde, 2003; Pratt & Kaplan, 2000).

Ischemic Hepatitis (Hypoxic Hepatitis)

Ischemic hepatitis (IH) is a serious and common cause of severe liver injury and its diagnosis is associated with a survival rate of approximately 50% (Tapper, Sengupta, & Bonder, 2015). Most commonly, IH is related to severe hypotension resulting in poor organ perfusion, but some cases are secondary to showering emboli from the left atrium in the context of myocardial infarction, atrial fibrillation, and occasionally portal vein thrombosis. IH involves centrilobular necrosis of Zone 3, the most vulnerable area in the liver lobule architecture (Ford, Book, & Spivey, 2015). An elevation of liver enzymes to greater than 20 times the upper limit of normalcy within 72 hours should raise immediate suspicion for ischemic hepatocyte injury. Bilirubin elevations commonly occur in IH, and serum lactate dehydrogenase, are typically higher than ALT (Ford et al., 2015). Rapid progression to hepatic encephalopathy and sudden INR elevation are predictors of mortality (Brosnan & Brosnan, 2009).

Congestive Hepatopathy

Contrary to IH, where insufficient amount of blood reaches the sinusoids, congestive hepatopathy occurs because of blood trapping secondary to hepatic vein outflow obstruction. Liver congestion secondary to congestive heart failure can lead to ALEs and bilirubin levels (Alvarez & Mukherjee, 2011). Increased pressure from right-sided heart failure can cause swelling of the sinusoids, hepatic hypertension, and lymphatic leak accumulation, causing ascites. Ascites because of increased right-sided cardiac pressure can be diagnosed by sampling serum and ascitic fluid albumin, and calculating the serum ascites-albumin gradient (SAAG), which should be 1.1 or more, with a total ascites protein of 2.5 g/dl or more. Hepatocardiac syndrome can be diagnosed when ALT levels correlate with right atrial pressure and hepatic venous pressure (Ford et al., 2015). Long-standing congestive hepatopathy can lead to bridging fibrosis in Zone 3 of the liver and cardiac cirrhosis (Alvarez & Mukherjee, 2011; Ford et al., 2015). Therefore, ALEs in patients with congestive heart failure mandate a careful adjustment of their medications to avoid toxicity (Alvarez & Mukherjee, 2011).

Wilson's Disease

Wilson's disease (WD) is a rare hepatolenticular syndrome caused by abnormalities in copper metabolism, in which clinical manifestations usually present before the age of 40 years. Although WD mainly involves the liver and basal ganglia, multiple organ dysfunctions may develop. A nonspecific bilirubin and liver enzyme elevation occurs in WD, with AST higher than ALT and ALP being characteristically low. The diagnosis of WD is based on a high index of suspicion (i.e., family history) and the presence of the Kayser-Fleischer (KF) ring. A positive screening test with serum ceruloplasmin less than 20 mg/dl correlates with the disease in about 90%–93% of patients. Basal 24-hour urinary excretion of copper can be performed if WD is strongly suspected in the absence of low serum ceruloplasmin and KF ring. Typically, symptomatic patients have a 24-hour urinary excretion of copper of more than 100 mcg but a level of more than 40 mcg is suggestive of the disease (Roberts & Schilsky, 2008). If the diagnosis of WD is still uncertain, liver biopsy for copper content and/or genetic testing for ATP7B is warranted (Roberts & Schilsky, 2008). A liver biopsy finding of copper more than 250 mcg/1 g dry liver tissue weight is diagnostic for WD.

Alpha-1-Antitrypsin Deficiency

Alpha-1-antitrypsin (AAT) deficiency, an uncommon cause of ALEs and liver disease in the adult population, is characterized by a significant loss of anti-inflammatory and antiproteolytic properties normally provided by the serine proteinases inhibitor AAT (Stockley, 2015). AAT deficiency leads to the accumulation of inflammatory polymers in the liver, causing fibrosis and eventually cirrhosis (Greulich & Vogelmeier, 2015). In affected individuals, concomitant liver and pulmonary disease may occur but the latter is usually more profound, with only 7%–10% of patients with AAT deficiency having ALEs (Antoury, Lopez, Zein, Stoller, & Alkhouri, 2015).

As with hereditary hemochromatosis, significant concomitant alcohol use can accelerate hepatic fibrosis. Although measurement of serum AAT level is used as a screening test, it can be falsely elevated as a response to systemic inflammation (Pratt & Kaplan, 2000; Teckman & Jain, 2014). PCR and isoelectric focusing are the most commonly used diagnostic tools (Greulich & Vogelmeier, 2015). Confirmatory diagnosis by genetic testing and gene sequencing can be performed. Although lung transplantation is crucial in patients with end-stage lung disease secondary to AAT deficiency, simultaneous liver–lung transplantation might be the best outcome for those with concomitant end-stage liver disease (Stone, Edgar, Thompson, & Stockley, 2015; Yi et al., 2014).

Hepatic Infiltration

Primary tumors (HCC and adenoma) or secondary metastatic cancers (colorectal, breast, and lung) can cause a significant elevation in liver enzymes. AST and ALT are usually modestly elevated with a significant increase in bilirubin (Limdi & Hyde 2003). ALP

elevation is dependent on the level of obstructive cholangiopathy caused by the mass (Ananthakrishnan, Gogineni, & Saeian, 2006).

Other infiltrative liver diseases such as sarcoidosis, tuberculosis, particularly the miliary type, and amyloidosis can elevate liver enzymes. Patients with celiac disease may present with asymptomatic ALEs, celiac hepatitis (cryptogenic liver disease), or chronic liver disease (Anania, De Luca, De Castro, Chiesa, & Pacifico, 2015). ALEs occur in 39%–47% of adult patients with celiac disease (Bardella et al., 1995; Jacobsen, Fausa, Elgjo, & Schrumpf, 1990). The majority of those patients have normal liver enzymes after adopting a gluten-free diet. Notably, some patients with celiac disease can have concomitant AIH Type 1 or 2. Therefore, patients with celiac disease on a strict gluten-free diet and persistent elevation of liver enzymes should be tested for ASMA and anti-LKMA-1 antibodies.

Oral Medications

Oral medications make their way into the systemic circulation via the liver, the site of a complex enzymatic interaction that affects the metabolism, pharmacokinetics, and excretion of pharmaceuticals. As the gatekeeper for orally administered drugs, it is not surprising that a wide variety of them cause elevation in liver enzymes, liver injury, and in more severe cases, liver failure (Table 1). Next, we discuss some of the most common offenders.

HMG-CoA Reductase Inhibitors (Statins)

Statins are one of the most commonly prescribed medications in the U.S. (Wolinsky, 2005). In the general population, statin-induced hepatotoxicity is extremely rare and usually presents with asymptomatic elevation in liver enzymes. A study by the National Lipid Association Safety Assessment found that elevation in LFTs of more than three times the upper limit of normal was found in less than 1% of cases, and that 70% resolved even with continuation of the same dose and type of statin. The incidence of liver failure was so rare that causality could not be established (McKenney, Davidson, Jacobson, Guyton, & National Lipid Association Statin Safety Assessment Task Force, 2006). Because most patients only have modest liver enzyme elevations, they should be tested serially, as many cases will undergo "hepatic accommodation" and eventual normalization.

TABLE 1. Medications Associated With Liver Injury

Acetaminophen	Losartan
Statins	Nonsteroidal anti-inflammatory drugs
Amiodarone	Anabolic steroids
Methotrexate	Amoxicilin/clavulanate
Allopurinol	Clindamycin
Valproic acid	Trimethoprim/sulfamethoxazole
Ketoconazole	Oral contraceptives
Lisinopril	Allopurinol

The Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study showed that the use of atorvastatin in patients with ALEs reduces cardiovascular mortality and causes a decrease in aminotransferase levels (Athyros et al., 2010). Because statin-induced ALEs are dose-dependent, lowering the dose, alternating between a statin and an intestinal cholesterol inhibitor, or discontinuing the medication could be the next step if enzymes continue to rise. Also, severity of elevation and clinical status should be taken into consideration. Currently, there is no evidence that statins cause significant hepatotoxicity.

Acetaminophen

Acetaminophen overdose remains a serious public health problem, with an annual average of 78,414 emergency department visits (Manthripragada et al., 2011). A prospective multicenter study of 275 patients with acute liver failure (coagulopathy, encephalopathy, and elevated transaminases) showed that the incidence of acetaminophen toxicity rose from 28% in 1998 to 51% in 2003, with 48% related to unintentional overdose and 44% associated with suicide attempts. Overall, 27% of patients died without transplantation and 8% underwent liver transplantation (Larson et al., 2005).

The use of alcohol, multiple acetaminophen-containing products, and narcotic abuse contribute to the problem. The transition to blister-pack-only retail sales of acetaminophen in the United Kingdom produced a dramatic decrease in the incidence of overdoses.

Acetaminophen causes hepatotoxicity by saturation of the glucuronidation and sulfation processes and production of the toxic metabolite *N*-acetyl-*p*-benzoquinoneimine, which causes oxidative damage, that leads to necrosis (James, Mayeux, & Hinson, 2003). Intoxicated patients usually experience abdominal pain, nausea, vomiting, diaphoresis, encephalopathy, and elevated liver enzymes. The pattern of elevation is strictly hepatocellular, with an average of elevated ALT into the 3,000 U/L range; however, levels higher than 5,000 U/L may be seen in intentional overdose (Larson et al., 2005).

The maximum dose of acetaminophen recommended by the Food and Drug Administration for the general population is 4 g per day. Patients with well-compensated liver conditions and no synthetic

dysfunction may metabolize the drug similarly to the general population; however, as the liver dysfunction worsens, they may experience toxicity. The highest dose of acetaminophen that would be safe for each stage of liver dysfunction is unknown, but most hepatologists believe it should be limited to 2–3 g in 24 hours (Chandok & Watt, 2010). Special attention should be paid when dosing alcoholics and malnourished patients, as glutathione stores are depleted, predisposing to hepatotoxicity (Chandok & Watt, 2010).

Amiodarone

Amiodarone is a medication commonly used to treat supraventricular and ventricular arrhythmias. Side effects affecting multiple organ systems such as the lung (pulmonary fibrosis), thyroid (hypothyroidism or hyperthyroidism), heart (cardiac arrhythmias), and liver (hepatotoxicity) are well described (Goldschlager, Epstein, Naccarelli, Olshansky, & Singh, 2000). The mechanism of liver injury is thought to be related to damage of the mitochondrial respiratory chain and inhibition of mitochondrial B-oxidation, superoxide accumulation, and lipid storage, which eventually leads to apoptosis and/or necrosis (Felser, Blum, Lindinger, Bouitbir, & Krahenbuhl, 2013).

Amiodarone is highly lipophilic and has a long elimination half-life (35–110 days), making its concentration in the liver 10–20 times higher than in plasma (Felser et al., 2013). The most common hepatic side effect is elevation in liver enzymes greater than three times the normal level in 15%–30% and hepatitis and cirrhosis in less than 3% of patients (Vassallo & Trohman, 2007). Amiodarone administered intravenously may also lead to idiosyncratic hepatic inflammation and toxicity. Fortunately, most adverse effects are reversible by dose reduction or discontinuation of the medication.

The North American Society for Pacing and Electrophysiology recommends that liver enzymes be checked prior to the initiation of amiodarone and every 6 months thereafter (Goldschlager et al., 2000). This medication should be avoided in patients with liver disease or cirrhosis. Physicians who consider prescribing this medication should consult with a cardiologist, as there is a wide variety of possible side effects and interactions.

Herbals

With the epidemic of obesity in the U.S. reaching 16.9% in ages 2–19 years and 34.9% in people older than 20 years (Ogden, Carroll, Kit, & Flegal, 2014), the advertisement of herbal weight loss supplement has increased dramatically. There is evidence that herbal supplements do not cause significant weight reduction (Onakpoya, Wider, Pittler, & Ernst, 2011) but may induce liver injury (Navarro & Seeff, 2013). Commonly advertised products include *Garcinia cambogia* and Hydroxycut, a combination of herbals that have been implicated in cases of acute hepatitis, liver failure, and death (Fong et al., 2010; Melendez-Rosado, Snipelisky, Matcha, & Stancampiano, 2015). The degree of liver enzyme elevation with herbal medications varies, with an average of 2,000 U/L. Very high liver enzymes in the absence of prescribed medications or liver disease should make the clinician suspicious of the possibility of liver toxicity secondary to herbal supplements.

Cholangiopathies and Bile Duct-Related Disease

Cholangiopathies are diseases that involve cholangiocytes, the cells that line biliary tree ducts. The term "cholangiopathy" includes primary biliary cholangitis (PBC), formally known as primary biliary cirrhosis, primary sclerosing cholangitis (PSC), cystic fibrosis, biliary atresia, polycystic liver disease, and cholangiocarcinoma (Lazaridis & LaRusso, 2015). Cholangiopathies usually present with elevated ALP and bilirubin. ALT and AST elevation is variable and depends on the extent of injury to hepatocytes and cholangiocytes. Choledocholithiasis is also commonly associated with elevated liver enzymes.

PBC is an autoimmune, cholestatic liver disease characterized by autoantibodies against the intrahepatic portion of bile ducts. PBC usually presents with nonspecific symptoms of fatigue, weight loss, and pruritus. AST and ALT are nonspecifically and infrequently elevated, but ALP, GGT, and bilirubin are moderately increased (Reshetnyak, 2015). Antimitochondrial antibodies (AMA) have a sensitivity and specificity of 84.5% and 97.8%, respectively (Hu, Zhao, Wang, & Chen, 2014). Although AMA levels do not predict outcome or disease progression, the novel autoantibody anti-sp100 seems to have a good correlation with fibrosis and cirrhosis (Carey, Ali, & Lindor, 2015; Tana et al., 2015). Bilirubin less than 1 mg/dl and ALP less than two times the normal values after a year of treatment can predict 10-year survival (Sclair, Little, & Levy, 2015). Currently, consensus guidelines propose that cholestasis (elevated ALP), positive AMA, and biopsy-proven nonsuppurative cholangitis should be present to establish the diagnosis of PBC (Lindor et al., 2009).

PSC is a chronic, progressive, granulomatous disease that involves the biliary tree and is usually associated with ulcerative colitis and Sjögren's syndrome. The pathogenesis of PSC is not fully understood, but cumulative evidence indicates a correlation between bowel microbiota and enterohepatic circulation and the development of disease (Tabibian, O'Hara, & Lindor, 2014). In addition to its potential to cause end-stage liver

disease because of fibrosis and cirrhosis, PSC is a highly premalignant condition. Therefore, periodic cancer surveillance should be performed in these patients (Folseraas & Boberg, 2016; Sclair et al., 2015).

Cancers commonly associated with PSC are hepatobiliary and colorectal neoplasms. IgG-4-related disease can cause a variant of sclerosing cholangitis and may be confused with PSC. It is recommended that IgG-4 levels be measured in patients with suspected PSC because of specific treatment modalities (Sclair et al., 2015). ALP can range from normal or near normal to massively elevated (10 times the normal values). Aminotransferases are typically elevated in the mild to moderate range. Endoscopic retrograde cholangiopancreatography, which usually reveals beaded appearance of the biliary tract, remains the best diagnostic method. No treatment has been proven to overcome the natural history of this disease, which ultimately leads to liver transplantation or death.

Referral to a Hepatologist

Certain clinical scenarios warrant referral to a hepatologist or admission to the hospital, whereas many patients with ALEs can simply be monitored. Key elements include acute liver failure, which is hallmarked by rapid elevations in INR and the presence of altered mental status, persistent ALEs greater than 10 times the upper limit of normal, ALEs with decompensated cirrhosis, and ALEs with positive autoimmune markers, chronic viral hepatitis, or unexplained persistent elevations for greater than 6 months. In these cases, the subspecialist may choose to outline a plan of care and refer the patient to the primary provider or follow the patient clinically in the outpatient setting in the short or long term. Prompt recognition of acute liver failure or decompensated cirrhosis should lead to referral to a liver transplant center for evaluation.

Conclusions

Abnormal liver enzymes can provide a sensitive marker of liver inflammation. They range from self-limited to chronic (>6 months). Further imaging or laboratory tests are indicated for very elevated levels and/or chronic elevations. Novel markers are needed to improve specificity for certain liver diseases. Prompt referral to a subspecialist or transplant center is needed in certain cases. ✪

Take-Home Points

1. ALEs should prompt assessment of serum prothrombin time, bilirubin, and albumin. Abdominal ultrasonography can also be beneficial.
2. ALEs should be characterized by the pattern and degree of elevations, as well as by clinical risk factors.
3. Alarming signs such as the development of acute liver failure or altered mental status should prompt hospitalization.
4. Referral to a hepatologist is warranted if no clear etiology of ALEs is found or the abnormalities persist.

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