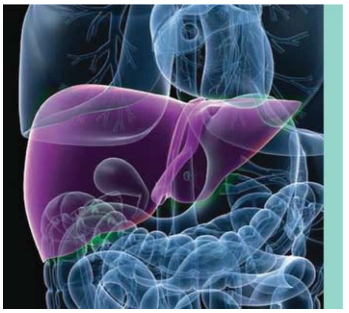

Interpretation of Abnormal Liver Chemistries in the Hospitalized Patient

Jorge E. Sanchez, M.D., M.P.H., and Kathleen E. Corey, M.D., M.P.H., M.M.Sc.

Abnormalities of liver chemistry tests (LCTs) in hospitalized patients are common and their evaluation is different from that performed in outpatient settings. This review focuses on the evaluation of new-onset liver chemistry abnormalities in the hospitalized patient.

INITIAL EVALUATION

The first step in the evaluation of LCT abnormalities in the hospitalized patient is to obtain a thorough history of presenting illness and to perform a physical examination. The history should focus on determining whether the onset of abnormal tests was gradual or sudden and whether they preceded or occurred after the hospitalization because the timing of the LCT abnormalities is critical to determining the differential diagnoses. A careful inventory of all inpatient and outpatient medications, herbal or dietaries supplements, and over-the-counter medications dating back at least 6 months is essential. Evaluation for evidence of immunosuppression (recent chemotherapeutics, corticosteroids, transplantation, or critical illness) is also necessary. The physical examination often provides clues about the cause (right upper quadrant tenderness, jaundice in hepatitis, or biliary obstruction), chronicity (sequelae of chronic liver disease), or severity (altered mental status in encephalopathy) of disease.

Early in the evaluation it is important to identify individuals with acute liver failure (ALF) defined by findings of liver injury of less than 26 weeks in duration, an international normalized ratio equal to or greater than 1.5, and encephalopathy.[1] It is imperative to identify those patients with ALF or impending ALF expeditiously because this population benefits from transfer to a facility capable of liver transplantation.

After a history and physical examination, the liver chemistries should be evaluated to elucidate the pattern

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; HSV, herpes simplex virus; LCT, liver chemistry test; NAC, *N*-acetylcysteine.

From the Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA.

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TABLE 1. DIFFERENTIAL DIAGNOSIS BY PATTERN OF INJURY IN HOSPITALIZED PATIENT

Hepatocellular	Cholestatic
DILI (including acetaminophen)	DILI
Viral hepatitis (A, B, C, D, E, CMV, EBV, HSV)	Obstruction: choledocholithiasis, malignancy
Alcohol hepatitis	Biliary strictures
AIH	Primary sclerosing cholangitis
Ischemic hepatitis	Primary biliary cirrhosis

TABLE 2. COMMON DRUGS AND THEIR PATTERN OF LIVER INJURY

Hepatocellular		Cholestatic
Acetaminophen	Lamotrigine	Amoxicillin-clavulanate
Alpha-methyldopa	Methimazole	Androgens and estrogens (oral contraceptives)
Amiodarone	Methotrexate	Azathioprine
Allopurinol	Minocycline	Azithromycin, erythromycin
Azathioprine	Naproxen	Captopril
Carbamazepine	Nevirapine	Carbamazepine
Cocaine	Niacin	Chlorpromazine
Dapsone	Nitrofurantoin	Cimetidine
Diclofenac	Phenytoin	Ciprofloxacin
Ecstasy	Propylthiouracil	Dicloxacillin
Ferrous sulfate	Quinidine	Naproxen
Fluconazole	Salicylate	Parenteral nutrition
Green tea extract (catechin)	Sertraline	Phenytoin
Halothane	Statins	Tolbutamide
Hydralazine	Sulfonamides	Trimethoprim-sulfamethoxazole
Isoniazid	Sulfonylureas	
Kava Kava	Thiazolidinediones	
Ketoconazole	Valproate acid	

of injury: hepatocellular or cholestatic.[2] A hepatocellular pattern is often manifested by predominant elevations of aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and most often represents injury to the hepatocytes. A cholestatic pattern is often manifested by predominant elevation of alkaline phosphatase and gamma-glutamyltransferase, and most often represents injury to the bile ducts or infiltrative disease. Serum total bilirubin can be elevated in both patterns, especially in those with cholestatic injury for which conjugated bilirubin is usually predominant. Identification of the predominant pattern of liver injury is helpful because it narrows the differential diagnoses (Table 1); however, such distinction is not always absolute and substantial overlap often exists.

DRUG-INDUCED LIVER INJURY

In a hospitalized patient in whom liver chemistry abnormalities develop suddenly, the most common culprit is drug-induced liver injury (DILI). Various agents can result in liver or bile duct injury, or both, with a pattern that is hepatocellular, cholestatic, or mixed[3] (Table 2). Antibiotics and antiepileptics account for more than 60% of DILI cases in the hospitalized patient.[4] Medications can cause liver injury in a predictable timely and dose-dependent manner (e.g., high doses of acetaminophen within 1-2 days of ingestion), whereas others do so more unpredictably or in an ''idiosyncratic'' manner (e.g., isoniazid). The diagnosis of DILI is one of exclusion, and therefore when an offending drug is suspected, other causes should be excluded. Liver biopsy is not required to make the diagnoses of DILI but may help in excluding competing causative factors, such as autoimmune hepatitis (AIH), and should be pursued when LCTs fail to improve with discontinuation of the likely culprit of DILI.

If a patient has liver injury and acetaminophen overdose or therapeutic misadventure is suspected, *N*-acetylcysteine (NAC) should be initiated early using the Rumack-Matthew monogram. For other DILI, removal of the offending agent is the most important part of the management. Recent data demonstrate that NAC results in longer transplant-free survival in patients with nonacetaminophen ALF with low-grade encephalopathy.[5] In the same study, patients with DILI had longer overall survival and transplant-free survival with the use of NAC.

HEPATOCELLULAR LIVER INJURY

The differential diagnosis for hepatocellular injury is broad and includes viral hepatitis (hepatitis A virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus [EBV], herpes simplex virus [HSV], and cytomegalovirus [CMV]), acute AIH, alcoholic hepatitis, and ischemic hepatitis.

Recent high-risk behaviors including intravenous drug use or travel to endemic areas should raise suspicion for viral hepatitis. Immunosuppression should raise the possibility of reactivation hepatitis B, or infection with CMV/HSV, whereas hypercoagulability should raise suspicion for thrombosis (e.g., Budd-Chiari syndrome). History of recent cardiovascular compromise (cardiac arrest, decompensated heart failure, hypotension) can cause ischemic hepatitis, which usually resolves supportively with improvement in hemodynamics. Although rare, AIH can occur spontaneously or be induced by medications. For patients with recent new medication exposures (minocycline, nitrofurantoin, methyldopa, hydralazine) or at high risk for AIH, evaluation should be pursued with IgG immunoglobulin levels and anti-nuclear/anti-smooth antibodies.

Finally, it is important to inquire about alcohol habits to assess for alcoholic hepatitis, which usually results in injury with an AST:ALT ratio greater than 2. The Maddrey's discriminant function, which uses serum prothrombin time, reference prothrombin time, and total bilirubin, can be used to identify those patients with alcohol hepatitis who have poor prognosis and might benefit from prednisolone.[7]

CHOLESTATIC LIVER INJURY

Common causes of cholestatic injury (aside from DILI) include biliary obstruction from choledocholithiasis, biliary strictures (primary sclerosing cholangitis) or destruction of the ducts (primary biliary cirrhosis), or malignancy. Diagnostic workup usually begins with a right upper quadrant ultrasound to evaluate the diameter of the common and intrahepatic bile ducts, and gallbladder for the presence of stones. If this fails to reveal abnormalities and biliary disease is still suspected, a magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography can allow for more sensitive evaluation of biliary structures. If these studies are negative, consideration of infiltrative diseases such as sarcoidosis, lymphoma, or amyloidosis (especially if lactate dehydrogenase is increased) should be considered with further imaging and consideration of biopsy.

CONCLUSION

Abnormalities of liver chemistries occur frequently in hospitalized patients. It is important to take a careful history, examine the patient, and review all medications, including over-the-counter or herbal supplements, for the preceding 6 months. With the help of the predominant pattern of liver chemistry injury (hepatocellular, cholestatic, or mixed), the clinician can narrow the differential diagnoses and rapidly initiate appropriate treatment.

CORRESPONDENCE

Kathleen E. Corey, M.D., M.P.H., M.M.Sc., Massachusetts General Hospital, Gastroenterology Associates, 55 Fruit Street, Boston, MA. E-mail: kcorey@partners.org

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