Laboratory Recognition of Hepatic Injury

Hepatic injury is defined by damage to hepatocytes. Traditionally, two main patterns of hepatic injury are recognized, acute and chronic. These are often termed "hepatitis", indicating the presence of inflammation in the liver. With some causes of hepatic injury, however, inflammation is minimal or absent; the more specific term hepatic injury will thus be used in this document. Acute hepatic injury refers to hepatocyte damage that occurs abruptly and over a short period of time. The most consistent feature of acute hepatic injury is significant elevation of aminotransferases (usually more than eight times the upper reference limit), often accompanied by increased bilirubin. Protein synthesis is affected in some cases, particularly those due to direct injury to hepatocytes by ischemia or toxin ingestion. Chronic hepatic injury refers to continuing hepatocyte damage over long periods of time, usually defined as a period greater than 6 months. Chronic hepatocyte injury is usually recognized by slight elevation of aminotransferases (usually less than 4 times the upper reference limit), although activities may be intermittently elevated and, in a small percentage of cases, persistently within reference limits. Bilirubin excretion and protein synthesis are generally normal. Alkaline phosphatase is generally within reference limits in most cases of acute and chronic hepatic injury; measurement is generally used to recognize hepatic disorders with obstruction of biliary drainage, which may otherwise resemble acute or chronic hepatic injury. Total protein, often included in hepatic panels, is generally not useful in evaluating hepatic function, since it is affected by changes in immunoglobulin levels as well as by changes in liver synthesis. An increase in globulins is helpful in patients with acute or chronic hepatic injury in suggesting the possibility of autoimmune disease as a cause of injury.

Recommendation

A liver panel that contains the following tests should be used to evaluate patients with known or suspected liver disease: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, total protein, and albumin. Such a panel is currently approved by the Health Care Financing Administration for Medicare reimbursement.

Acute Hepatic Injury

Acute hepatic injury can be recognized by the presence of jaundice or non-specific symptoms of acute illness accompanied by elevation of AST and/or ALT activities. An estimated 80% of individuals with acute viral hepatitis are never diagnosed clinically, although some may be detected by elevated aminotransferases in the face of non-specific or absent clinical symptoms. AST and ALT activities are seldom greater than 10x the upper reference limit in liver diseases other than acute hepatic injury. ALP is over 3x the upper reference limit in less than 10% of cases of acute hepatic injury. (174, 175) Hepatitis A occurs in Over the past decade, there has been a significant decline in the incidence of acute viral hepatitis; in the Centers for Disease Control and Prevention

Sentinel Counties Study, hepatitis B declined by 55% and non-A, non-B hepatitis (most of which are hepatitis C) by 80%. (175a) Other liver diseases are now more commonly encountered as causes of increased AST or ALT activities; in a recent study, 25% of those with AST more than ten times the upper reference limit had obstruction as a cause. (176) Overall, about 1-2% of patients with bile duct obstruction have transient increases in AST and/or ALT activities of greater than 2000 U/L (177, 178); aminotransferase activities usually fall to within reference limits by 10 days even if obstruction persists (174, 176, 177).

The best discriminant values for recognizing acute hepatic injury appear to be 200 U/L for AST (sensitivity 91%, specificity 95%) and 300 U/L for ALT (sensitivity 96%, specificity 94%). (175) AST is over ten times the upper reference limit in slightly over half of patients at the time of presentation. (175) In uncomplicated alcoholic hepatitis, AST and ALT values are almost never over 10x the upper reference limit, AST/ALT ratio is over 2 in 80%, and elevated alkaline phosphatase is present in 20% of cases. (98, 179, 180) Jaundice occurs in 60-70% of cases of alcoholic hepatitis. (179, 180) The frequency of jaundice in patients with acute viral hepatitis differs both by age and etiologic agent. Jaundice is rare in children with viral hepatitis, and when present less severe than in adults. In one study, only 1% of children with acute hepatitis had peak bilirubin over 171 μmol/L (10 mg/dL), while 27% of adults did. (181) In adults, jaundice develops in 70% of cases of acute hepatitis A (182), 33-50% of cases of acute hepatitis B (183, 184) and 20-33% of cases of acute hepatitis C (185, 186). There is a direct correlation between age and peak serum bilirubin in children; an increase of 10 years in age was associated with an average increase of 85 μmol/L (5 mg/dL) in bilirubin. In adults, there is no relationship between age and peak bilirubin. (187) The distribution of direct bilirubin as a percentage of total bilirubin is similar in acute hepatic injury and obstructive jaundice: only 16% of those with acute hepatic injury have direct bilirubin < 50% of total bilirubin. Lower percentages of direct bilirubin suggest another cause for jaundice such as hemolysis. (187)

Recommendations

Acute hepatic injury can be diagnosed by ALT more than 10x upper reference limits and alkaline phosphatase less than 3x the appropriate upper reference limit (IIB).

Direct bilirubin is needed to rule out other causes of increased total bilirubin such as hemolysis, but does not differentiate hepatic injury from obstructive jaundice (IIB).

Markers of Severity

Acute viral hepatitis A or B is usually a self-limited illness, and most patients recover completely. In those with acute hepatitis C infection, approximately 80-85% develop chronic hepatitis, although the percentage appears to be lower in children or in young women receiving Rh immune globulin. (154, 188, 189) Rarely, acute hepatic injury causes severe liver damage and acute liver failure. Testing should identify patients at highest risk for liver failure. Aminotransferase activities are more related to the cause of

hepatic injury, rather than to severity. There is weak correlation between aminotransferase activities and bilirubin in viral hepatitis (175) and none in ischemic or toxic hepatic injury (190). Peak aminotransferase activities bear no relationship to prognosis, and may fall with worsening of the patient's condition; in all causes of hepatic injury, aminotransferase activities begin to fall before peak bilirubin occur regardless of whether recovery or deterioration occurs. (175, 191) Prothrombin time (PT) is the most important predictor of prognosis; cutoff times > 4 seconds beyond control, > 20 seconds, or INR > 6.5 have been used to identify patients at high risk of death. (99, 191) In ischemic or toxic hepatic injury, prolongation of PT is common early after injury, with peak abnormality occurring by 24-36 hours and then rapidly returning to normal. In acetaminophen injury, marked prolongation of PT does not by itself indicate likelihood of liver failure (94, 96), but persistent elevation or rising PT 4 days after acetaminophen ingestion does. (192) Other tests may be prognostically helpful with specific causes of hepatic injury. (191) In viral hepatitis, total bilirubin > 257 μmol/L (15 mg/dL) indicates severe liver injury and mandates close monitoring for encephalopathy. (193) In alcoholic hepatitis, bilirubin > 428 μmol/L (> 25 mg/dL), or albumin < 25 g/L (2.5 g/dL) predicts a high likelihood of death. (91, 180)

Recommendations

Total bilirubin > 257 μmol/L (15 mg/dL) or PT > 4 seconds above the upper reference limit in an individual with viral hepatitis, in the absence of other factors affecting results, indicates severe liver injury (IIB).

With acetaminophen toxicity, persistent elevation or rising prothrombin time more than 4 days after ingestion indicates severe liver injury (IIB)

Differential Diagnosis

Table 12. Patterns of Laboratory Tests in Types of Acute Hepatic Injury

Disease	Peak ALT (x URL)	AST/ALT Ratio	Peak Bilirubin (mg/dL)	Prothrombin Time Prolongation (s)
Viral Hepatitis	10-40	< 1	< 15	< 3
Alcoholic Hepatitis	2-8	> 2	< 15	1-3
Toxic injury	> 40	> 1 early	< 5	> 5 (transient)
Ischemic injury	> 40	> 1 early	< 5	> 5 (transient)

x- times; URL- upper reference limit

The pattern of laboratory abnormalities varies with different causes of acute hepatic injury (Table 12); it is often possible to suspect the type of agent causing hepatic injury from the pattern seen. Initial evaluation of patients with the most common (immunologic) pattern of acute hepatic injury should include a drug history and testing for antibodies to hepatitis A, B, and C viruses (HAV, HBV, and HCV). Most hepatic drug reactions occur within 3 to 4 months of initiating treatment. However, in some instances, hepatic injury may become manifest as late as 12 months after beginning treatment and in a few instances injury may become evident days to weeks after stopping the responsible drug. (198) Hence, it is important to ask about all drugs the patient may have received or has continued to receive during the past year or so. Evaluation for viral hepatitis should use the Health Care Financing Administration approved acute hepatitis

panel (IgM anti-HAV, IgM anti-HBc, HBsAg, and anti-HCV) (Figure 8). IgM anti-HAV, the diagnostic test of choice for acute HAV infection, disappears by 4-6 months (194), while total HAV antibodies persist for life (129) and are found in a high percentage of the population (130). Because of its brief period of transmissibility, diagnosis of acute HAV infection should be made as soon as possible after presentation, ideally within 48 hours, to allow immune globulin treatment of exposed individuals. IgM anti-HBc and HBsAg are the most reliable tests for acute HBV infection (134, 193); IgG (and thus total) anti-HBc persists for years, and is not helpful in diagnosis of acute hepatitis B infection. (136) Other HBV viral markers and antibodies are not of use in the diagnosis of acute HBV infection. There is currently no test to definitively diagnose acute hepatitis C, since anti-HCV and HCV RNA can be present in both acute and chronic HCV infection. Anti-HCV is detectable with EIA-2 in only 57% of acute HCV cases at the time of initial enzyme elevation, while HCV RNA is positive in essentially all cases (195), although it is intermittently present in 15%. (157, 196) By the time of clinical presentation, 80-90% have detectable anti-HCV. (196) Patterns that would support a diagnosis of acute hepatitis C are negative anti-HCV but positive HCV RNA, or (if HCV RNA was not tested) anti-HCV results that convert from negative to positive within a short time period. Use of anti-HDV to detect delta (HDV) infection should be limited to patients with positive HBsAg, particularly if accompanied by severe acute hepatitis, high risk factors (IV drug abuse, hemophilia) or a biphasic pattern of illness. (197) If a patient with chronic hepatitis B becomes superinfected with HDV, a clinical picture resembling severe acute hepatic injury and hepatic failure may evolve. (197)

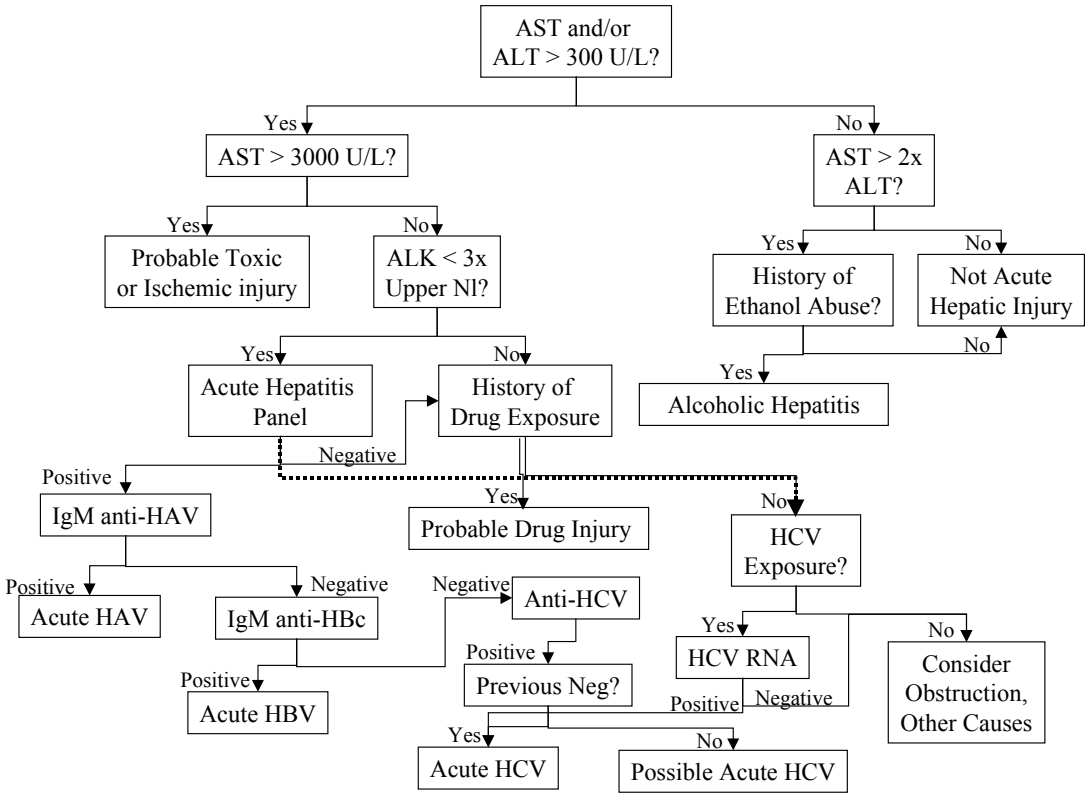

Figure 8 – Approach to acute hepatitis – In a patient with signs or symptoms of acute liver injury (fever, loss of appetite, dark urine, light stools, jaundice), initial evaluation includes measurement of AST and ALT activities. Slight elevations in AST (< 10x the upper reference limit), particularly with AST > ALT, suggest acute alcoholic hepatitis, while marked elevations (> 1,000x the upper reference limit) strongly suggest ischemic or toxic liver injury. In those with intermediate values, and acute hepatitis panel (see text) is the initial test for evaluation. Presence of IgM anti-HAV or IgM anti-HBc are considered diagnostic for acute hepatitis A and B, respectively. Acute hepatitis C cannot be definitively diagnosed by serologic tests, but can be suspected by appearance of anti-HCV in a patient with jaundice (when previously negative), or positive HCV RNA in a patient lacking anti-HCV. In patients with negative results for viral markers, another cause of acute liver injury such as obstruction, other infectious agents, Wilson's disease, or autoimmune hepatitis should be considered (see Table 13).

Recommendations

Initial evaluation of acute hepatic injury should include a detailed drug history and viral markers (IgM anti-HAV, IgM anti-HBc, HBsAg, and anti-HCV) (IIB).

Because of the need for post-exposure prophylaxis, turnaround time of IgM anti-HAV should be < 48 hours (IIIC, E).

If cost-effective (based on prevalence), laboratories may use total antibody to HAV and anti-HBc initially, performing IgM antibodies only if one or both is positive, if the turnaround time needs can be met (IIIE).

Diagnosis of acute HCV infection (in a patient with a clinical picture of acute hepatic injury) can be presumptively made by negative HAV and HBV markers, recent

exposure, and either negative anti-HCV and positive HCV RNA or negative anti-HCV at initial presentation with development of positive anti-HCV within 1-3 months. (IIIB)

Testing for HDV should be limited to patients with positive HBsAg, atypical clinical course, and high risk for HDV infection (IIB, E)

Workup of Patients without Obvious Cause for Acute Hepatic Injury (Table 13)

Table 13 – Uncommon Causes of Acute Hepatic Injury

Disorder	Key Feature	Laboratory Tests	Associated findings
Wilson's disease	Young individuals, low alkaline phosphatase, high bilirubin.	Low ceruloplasmin in only 40%. Abnormal gene on chromosome 13	Urine, serum copper not reliable in acute Wilson's. Often associated with hemolysis, renal insufficiency
Autoimmune hepatitis	Young individuals; increased gamma globulins; low albumin, ascites often present	Positive ANA and/or ASMA	Other autoimmune disorders in some cases
Hepatitis E	Travel to endemic area	Anti-HEV	Similar to hepatitis A
Other viruses	Clinical features of mononucleosis often present	Anti-CMV, anti-EBV	Elevated alkaline phosphatase

ANA – antinuclear antibody; ASMA – anti-smooth muscle antibody; HEV – hepatitis E virus; CMV – cytomegalovirus; EBV – Epstein-Barr virus

Ischemic and Toxic Hepatic injury - Values of AST or ALT over 100x normal are rare in viral hepatitis (174, 175), but common in both toxin ingestion, especially acetaminophen (96, 199, 200), and ischemic hepatic injury. (94, 95, 190) In acetaminophen-induced hepatic injury, peak AST is over 3,000 U/L in 90% of cases. (200) Toxic or ischemic hepatic injury cause over 90% of cases of acute hepatic injury with AST activity > 3,000 U/L. (200a) In both ischemic and toxic hepatic injury, AST and ALT activity typically peak early (often in the first 24 hours after admission) with AST activity initially higher than that of ALT. After peaking, activities of both fall rapidly; AST may fall by 50% or more in the first 24 hours, (199, 200) and declines more rapidly than ALT due to its shorter half-life (175); AST activity reaches near normal values an average of 7 days after injury. (174) Prothrombin time is more than 4 seconds above the reference limits in 90% of cases (94, 96), and rapidly falls after peak AST is reached. (94) Bilirubin is less than 34 μmol/L (2 mg/dL) in 80% of cases of toxic or ischemic injury. (94, 95, 96) Lactate dehydrogenase (LDH) activity is often higher than that of AST at presentation in toxic or ischemic hepatic injury (94, 199, 200), while it is increased on initial determination in only 55% of cases of viral hepatitis, with average values being only slightly above the upper reference limit. (175)

Other Causes - Rarely, Wilson's disease and autoimmune hepatitis (discussed in more detail under chronic hepatic injury) can present as acute hepatic injury (Table 13). Hepatitis E is endemic in parts of the world; individuals with acute hepatic injury who have traveled to or reside in endemic areas should be tested for anti-HEV. Several viruses other than the classical agents (HAV, HBV, HCV, HEV) have been associated with hepatitis, including herpesvirus, cytomegalovirus (CMV), enterovirus, coronavirus, reovirus (in neonates), adenovirus, parvovirus B6 (in pediatric populations), varicella-

zoster virus, and Epstein-Barr virus. Syphilis, leptospirosis, and toxoplasmosis also may cause hepatic injury, as may other less common infectious agents. Rarely, other disorders including lymphoma, Budd-Chiari syndrome, and venoocclusive disease may present with a picture of acute hepatic injury. In general, hepatic injury associated with these etiologies is either unusual, or is associated with a specific syndrome (chicken pox with varicella-zoster virus, mononucleosis with Epstein-Barr virus or cytomegalovirus). Most patients with other infectious causes of hepatic injury have signs and symptoms that suggest a particular agent as the cause. Specific diagnosis of infection by other agents should be pursued when the etiology remains unknown after more common causes are excluded, and when establishment of a specific diagnosis appears clinically indicated. Superinfection with other hepatitis viruses may occur in a patient with other forms of hepatic injury; for example, patients with chronic HCV or alcoholic hepatitis may become infected with either HAV or HBV and develop an acute hepatitis due to the superimposed infection. In chronic hepatitis, an acute rise in aminotransferases mimicking acute hepatic injury can occur with clearance of HBeAg (208) or with emergence of quasispecies of HCV. (209)

Recommendations

In patients with negative viral markers and initial AST > 100x upper reference limit, toxic exposure or ischemia should be suspected (IIB).

In patients with negative viral markers and enzyme levels 8-100 times the upper reference limit, testing must exclude the possibility of Wilson's disease and autoimmune hepatitis (IIB).

Testing for antibody to hepatitis E is recommended in those with negative serologies for other viruses and history of recent travel to or residence in an endemic area (IIIE).

Tests for other infectious agents (Epstein-Barr and cytomegalovirus, syphilis, toxoplasmosis) may be used if no other causes are evident (IIB).

Monitoring

Aminotransferases - Aminotransferase activities tend to rise before and peak near onset of jaundice in viral hepatitis, falling gradually from that point on. (191). Activities tend to fall slowly in viral hepatitis and alcoholic hepatitis, AST and ALT decrease, on average, 11.7% and 10.5% per day, respectively, and remain elevated 22 ± 16 and 27 ± 16 days, respectively. (175) In hepatitis A, a secondary rise in enzymes occurs in 5-10% of cases before activities return to baseline, associated with circulating HAV RNA and viral particles in stool, indicating potential for transmission of infection. (210). As discussed above, AST and ALT fall rapidly after reaching peak activities in ischemic and toxic hepatic injury. Once aminotransferases have shown a consistent pattern of decrease, they need not be checked again until the patient has clinically recovered. Return of aminotransferases to normal is not a reliable sign of recovery in hepatitis B or C. In patients with chronic HCV infection, 49% with normal ALT on

initial visit after seroconversion developed elevated ALT on subsequent follow-up. (211) In hepatitis B, AST and ALT may return to normal despite persistence of infection. (212)

Bilirubin - Bilirubin peaks later than aminotransferases, often by a week or so, and then gradually decreases. Peak bilirubin over 257-342 μmol/L (15-20 mg/dL) is unusual in viral hepatitis. Only 10-12% of patients with viral hepatitis have peak values over 257 μmol/L (15 mg/dL) and only 4% have peak values over 342 μmol/L (20 mg/dL); higher bilirubin is more common in HBV infection. (175, 181) As total bilirubin declines, the proportion of δ-bilirubin increases, often reaching 70-80% of total bilirubin (213, 214). In adults with viral hepatitis, bilirubin remains elevated 30.3 ± 19.7 days after peak levels are reached (175), but clears more quickly in children (181); jaundice remains more than 6 weeks in 34% of adult HBV cases but in only 15% of other forms of viral hepatitis. (181) Prolonged elevation of conjugated bilirubin occasionally occurs with viral hepatitis, particularly with HAV, but does not signify a poor prognosis if synthetic function remains intact. (215) Significant elevation of bilirubin is uncommon in toxic and ischemic hepatic injury. Once serum bilirubin has begun to decline, there is no reason to measure it again unless jaundice worsens clinically.

Coagulation Tests – Elevated prothrombin time is a common finding in ischemic and toxic hepatic injury, often with results > 15 seconds or 4 seconds above the reference limit before rapidly returning to normal. There are no data on the degree of elevation affecting prognosis in ischemic hepatic injury. Elevation of prothrombin time > 15 seconds or more than 4 seconds above reference limits in viral or alcoholic hepatitis is a marker of more severe disease. (98, 99, 180)

Serologic Markers – In individuals with acute hepatitis B, HBsAg is the best indicator of viral clearance. Patients who lose HBsAg and develop anti-HBs virtually never develop recurrence of liver injury, and can be considered to have recovered from HBV infection. In acute HCV infection, most individuals never develop a clinical picture of acute hepatic injury. (154, 211) The only reliable marker of clearance of HCV is repeatedly (on at least two occasions) negative HCV RNA, using sensitive qualitative tests.

Recommendations

Prothrombin time > 4 seconds above reference limits, bilirubin > 15 mg/dL (257 μmol/L), or development of encephalopathy identify high risk patients that require close monitoring and consideration of referral to a gastroenterologist or hepatologist. (IIB)

In patients with acute hepatitis B, repeat HBsAg should be performed within 6-12 months; if negative and anti-HBs is positive, no further follow-up is needed. (IIE)

In patients with acute hepatitis C, ALT should be repeated periodically over the next 1-2 years to assure continued normal results. Clearance of virus should be confirmed with qualitative HCV RNA measurement (IIB).