Elevated liver enzymes

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- **Hepatocellular injury is defined as disproportionate elevation of AST and ALT levels compared with alkaline phosphatase levels.**

- **Cholestatic injury is defined as disproportionate elevation of alkaline phosphatase level as compared with AST and ALT levels**
- **An elevated conjugated bilirubin implies hepatocellular disease or cholestasis.**

The evaluation of hepatocellular injury includes

- **testing for viral hepatitis A, B, and C,**
- **assessment for nonalcoholic fatty liver disease and alcoholic liver disease,**
- **screening for hereditary hemochromatosis,**
- **autoimmune hepatitis,**
- **Wilson’s disease, and alpha-1 antitrypsin deficiency**
- **history of prescribed and over-the-counter medicines should be sought**

evaluation of an alkaline phosphatase elevation determined to be of hepatic origin

- **evaluation of an alkaline phosphatase elevation determined to be of hepatic origin, testing for primary biliary cholangitis and primary sclerosing cholangitis should be undertaken.**

1. Before initiation of evaluation of abnormal liver chemistries, one should repeat the lab panel and/or perform a clarifying test (e.g., GGT if serum alkaline phosphate is elevated) to confirm that the liver chemistry is actually abnormal. (Strong recommendation, very low level of evidence).

2. Testing for chronic hepatitis C is conducted with anti-HCV and confirmation is performed with HCV-RNA by nucleic acid testing. Risk factors for hepatitis C include history of intranasal or intravenous drug use, tattoos, body piercings, blood transfusions, high risk sexual conduct, and those born between 1945 and 1965. Testing for acute hepatitis C is with anti-HCV and HCV RNA by nucleic acid testing. (Strong recommendation, very low level of evidence).

3. Testing for chronic hepatitis B is conducted with HBsAg testing. Testing for acute hepatitis B is with HBsAg and IgM anti-HBc. The following groups are at highest risk: persons born in endemic or hyperendemic areas (HBsAg prevalence >2%), men who have sex with men, persons who have ever used injection drugs, dialysis patients, HIV-infected individuals, pregnant women, and family members, household members, and sexual contacts of HBV-infected persons. (Strong recommendation, very low level of evidence).

4. Testing for acute Hepatitis A (IgM HAV) should occur in patients presenting with acute hepatitis and possible fecal-oral exposure. Testing for acute hepatitis E (IgM HEV) should also be considered in those returning from endemic areas and whose tests for acute hepatitis A, B, and C are negative. (Strong recommendation, very low level of evidence).

5. Patients with elevated BMI and other features of metabolic syndrome including diabetes mellitus, overweight or obesity, hyperlipidemia, or hypertension with mild elevations of ALT should undergo screening for NAFLD with ultrasound. (Strong recommendation, very low level of evidence).

6. Women consuming more than 140g per week or men consuming more than 210g per week who present with AST>ALT should be considered at risk for alcoholic liver disease and should be counseled for alcohol cessation. (Strong recommendation, very low level of evidence).

7. All patients with abnormal liver chemistries in the absence of acute hepatitis should undergo testing for hereditary hemochromatosis with an iron level, transferrin saturation, and serum ferritin. HFE gene mutation analysis should be performed in patients with transferrin saturation ≥45% and/or elevated serum ferritin. (Strong recommendation, very low level of evidence).

8. Patients with abnormal AST and ALT levels, particularly patients with other autoimmune conditions, should undergo testing for autoimmune liver disease including ANA, ASMA, and globulin level. (Strong recommendation, very low level of evidence).

9. Patients with persistently elevated AST and ALT levels, especially patients <55 years of age, should undergo screening for Wilson's disease with serum ceruloplasmin testing. In the setting of low ceruloplasmin, confirmatory testing with 24-h urinary copper and slit-lamp eye examination to identify pathognomonic Kayser–Fleischer rings should occur. (Strong recommendation, very low level of evidence).

10. Patients with persistently elevated AST or ALT should undergo screening for alpha-1 anti-trypsin (A1AT) deficiency with alpha-1 anti-trypsin phenotype. (Strong recommendation, very low level of evidence).

11. Physicians should ask patients with abnormal liver chemistries about prescribed and over-the-counter medications, non-prescribed complementary or alternative medicines, and dietary or herbal supplements which may be associated with DILI. (Strong recommendation, very low level of evidence).

12. A liver biopsy may be considered when serologic testing and imaging fails to elucidate a diagnosis, to stage a condition, or when multiple diagnoses are possible. (Strong recommendation, very low level of evidence).

13. An elevation of alkaline phosphatase should be confirmed with an elevation in GGT. Given its lack of specificity for liver disease, GGT should not be used as a screening test for underlying liver disease in the absence of other abnormal liver chemistries. (Strong recommendation, very low level of evidence).

14. Patients with alkaline phosphatase elevation with or without elevation of bilirubin should undergo testing for PBC (formerly named primary biliary cirrhosis) with testing for anti-mitochondrial antibody. (Strong recommendation, very low level of evidence).

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14. Patients with alkaline phosphatase elevation with or without elevation of bilirubin should undergo testing for PBC (formerly named primary biliary cirrhosis) with testing for anti-mitochondrial antibody. (Strong recommendation, very low level of evidence).

15. Patients with alkaline phosphatase elevation with or without elevation of bilirubin should undergo testing for PSC with MR cholangiography or ERCP in conjunction with IgG4. (Strong recommendation, very low level of evidence).

16. In those with ALT and/or AST levels <5X ULN, the history and laboratory testing should assess for viral hepatitis B and C, alcoholic and NAFLD, hemochromatosis, Wilson's disease, alpha-1-anti-trypsin deficiency, autoimmune hepatitis and consider drugs/supplement related injury. (Strong recommendation, very low level of evidence).

17. In those with ALT and/or AST levels 5–15X ULN, evaluation should also assess for acute hepatitis A, B, and C in addition to all etiologies for AST/ALT elevation less than 5x ULN. (strong recommendation, very low level of evidence).

18. In those with ALT and/or AST levels >15X ULN, or massive elevation ALT of >10,000IU/l, evaluation should also assess for acetaminophen toxicity and ischemic hepatopathy (shock liver). (Strong recommendation, very low level of evidence).

19. A patient presenting with acute hepatitis with an elevated prothrombin time, and/or encephalopathy requires immediate referral to liver specialist. (Strong recommendation, very low level of evidence).


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