Differential Diagnosis of Transaminase Elevation >5 times normal (ALT Predominant)

Disease	Notes
Chronic hepatitis C infection	Highly prevalent disease and a common cause of elevated liver enzymes. Diagnosed by obtaining a positive HCV antibody test and viremia can be confirmed with HCV-RNA for at least 6 months.
Chronic hepatitis B infection	Highly prevalent infection. Test for HBsAg and anti-HBc. Positive hepatitis B surface antigen or the immunoglobulin (Ig) M-fraction of the hepatitis B core antibody indicates infection and chronic infection is defined by HBV positivity for ≥6 months.
Drug-induced chronic hepatitis	Most medications have been reported to be associated with serum liver enzyme elevations. History of drug consumption and improvement with discontinuation.
Hepatic steatosis/ steatohepatitis	Most common cause of mild liver enzyme elevations. Obesity, weight gain, hyperlipidemia, or diabetes mellitus usually present.
Hemochromatosis	Common genetic diseases; consider in patients with mildly elevated ALT or AST levels. Check for elevated serum ferritin levels, serum iron, and iron saturation (serum iron/iron binding capacity). Quantitative hepatic iron index on liver biopsy and HFE genotyping assist diagnosis. Elevated risk of hepatocellular carcinoma and cirrhosis.
Autoimmune hepatitis	Female predisposition. Often associated with thyroid disease and other autoimmune disorders. Check anti-nuclear antibodies, anti-smooth muscle antibodies, and liver-kidney microsomal antibodies. Liver biopsy is recommended to confirm diagnosis.
Wilson's disease	Check serum ceruloplasmin (low), serum and urinary copper levels (elevated), slit-lamp examination for Kayser-Fleischer rings, and liver biopsy for quantitative copper measurement. Family history, neuro-psychiatric or ophthalmologic manifestations are suggestive.
α-1-Antitrypsin deficiency	Check protease inhibitor phenotype analysis (Pi-type) and confirmatory liver biopsy. Family history is suggestive.
Celiac disease	Usually presents with steatorrhea, positive gliadin, endomysial serum

	antibodies; endoscopy with small bowel biopsy is gold standard
Acute viral hepatitis (A, B, C, D, or E, Epstein-Barr virus (EBV), adenovirus or cytomegalovirus)	Can cause variable elevations of the serum ALT, which may exceed a level of 5 times normal. Diagnosis of acute hepatitis A, D, or E can be made by virus-specific IgM antibody assays, and acute HBV infection can be diagnosed by obtaining a detectable HBsAg and Hep B core IgM antibody. Acute HCV infection may be diagnosed by measuring the serum HCV-RNA. Other hepatotropic viruses diagnosed by serologic measurement of antibody titers, detection of viral antigen in the serum and clinical context (i.e. EBV can cause pharyngitis, lymphadenopathy, atypical lymphocytes, splenomegaly). Tissue involvement can be verified by liver biopsy if indicated.

Transaminase Elevation <5 times normal (AST Predominant)

Alcohol use	Commonly associated with an AST:ALT ratio of approximately 2:1, and the AST rarely exceeds 300 IU/dL. Liver injury includes hepatic steatosis, hepatitis, and cirrhosis. Quantity of alcohol and the length of time that alcohol has been consumed are important factors for the development of disease. Significantly higher enzymes should prompt investigation for additional or other cause.
Non-alcoholic hepatic steatosis/ steatohepatitis (NASH)	NASH may present similarly to alcohol-related liver injury, and biopsy findings are often similar.
Drug-induced liver injury	Most medications have been reported to be associated with serum liver enzyme elevations. History of drug consumption and improvement with discontinuation.
Non hepatic diseases	Hemolytic anemia, myositis, muscular dystrophy, and macro-AST.

Transaminase Elevation >15 times normal

Drug-induced Hepatotoxicity	Acetaminophen overdose is the most common cause of drug induced fulminant hepatic failure. Patients with significant alcohol consumption may be particularly susceptible acetaminophen.
Acute viral hepatitis (A, B, C, D, or E)	Diagnosed with serologic markers. Initial HCV antibody testing may be negative during acute viral hepatitis C. Hepatitis A virus (HAV) may be acquired from oral-fecal contact, often in an institutional setting, from contaminated food, and HAV is particularly prevalent in many third-world nations. Hepatitis D occurs due to blood-blood contact in concert with hepatitis B. Hepatitis E is acquired by contaminated food or water in endemic areas, and may be particularly fulminant in pregnant females.
Wilson's disease	Check serum ceruloplasmin (low), serum and urinary copper levels (elevated), slit-lamp examination for Kayser-Fleischer rings, and liver biopsy for quantitative copper measurement. Family history, neuro-psychiatric or ophthalmologic manifestations are suggestive.
Autoimmune hepatitis	Female predisposition. Often associated with thyroid disease and other

	autoimmune disorders. Check anti-nuclear antibodies, anti-smooth muscle antibodies, and liver-kidney microsomal antibodies. Liver biopsy is recommended to confirm diagnosis.
Ischemic hepatitis	Preceded by an episode of hypotension followed by an acute and rapid rise of liver enzymes.
Acute bile duct obstruction	Transient elevations with the passing of gallstones via the common bile duct. Enzymes typically decline rapidly when a stone passes. Check Ultrasound.
Acute vascular events	Budd-Chiari syndrome (characterized by the development of ascites and jaundice) diagnosed by imaging the hepatic vein and parenchyma. Surgical ligation or thrombosis of the hepatic artery (can occur after surgical procedures of the biliary tree or liver) visualized by Doppler evaluation or angiography.

ALT = alanine aminotransferase; ANA = antinuclear antibodies; AST = aspartate aminotransferase; ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; PCR = polymerase chain reaction; RNA = ribonucleic acid.