TABLE 34. Other Viral Causes of Hepatitis[a]

Infection	Symptoms/Laboratory Findings	Diagnosis	Treatment/Outcome
Cytomegalovirus	Mimics EBV-related mononucleosis Mild aminotransferase elevations	CMV serologies in immunocompetent host	Supportive; spontaneous recovery is norm
Primary herpes simplex virus in women in third trimester of pregnancy	Fever, altered mental status, right-upper-quadrant pain, hepatomegaly, presentation similar to sepsis Aminotransferase levels ≥5000 U/L, disproportionately low bilirubin level, coagulopathy	PCR; herpes simplex virus testing; liver biopsy showing intranuclear inclusions, multinucleated giant cells, and coagulative necrosis with minimal inflammation	IV acyclovir; 80% case-fatality rate in untreated patients
Primary varicella zoster virus (rare)	Primary infection in organ transplant recipients can cause acute liver failure	Biopsy of skin or affected organ	IV acyclovir
Parvovirus B19	Fever, rash, arthralgias Transiently elevated aminotransferase levels	Serologic tests demonstrating positivity for parvovirus B19-specific IgM antibody	Supportive; rarely associated with fulminant hepatic failure

CMV = cytomegalovirus; EBV = Epstein-Barr virus; IV = intravenous; PCR = polymerase chain reaction.

[a]Other viruses associated with elevated liver chemistries: human herpes virus 6, 7, and 8 and adenoviruses.

Autoimmune Hepatitis

Autoimmune hepatitis is a chronic inflammatory hepatitis that is four times more common in women than men and can be associated with other autoimmune diseases (autoimmune thyroiditis, rheumatoid arthritis, or ulcerative colitis). It can affect individuals at any age but most frequently occurs in middle-aged adults. Presentation of autoimmune hepatitis varies from asymptomatic elevation of aminotransferase levels to extrahepatic symptoms, such as myalgia and malaise, to acute liver failure. Diagnosis is based on laboratory results (including positivity for antinuclear and smooth-muscle antibodies and elevated IgG levels), exclusion of other diagnoses (e.g., Wilson disease, viral hepatitis, and drug-induced liver injury), and liver histology.

Treatment includes a combination of prednisone and azathioprine for most patients. Prednisone monotherapy may be less preferable because of adverse effects, although azathioprine requires monitoring for cytopenia and may cause drug-induced hepatitis. Biochemical response occurs in 3 to 8 months for the 85% of patients whose disease responds to standard treatment, but histologic response can lag by many months. Duration of treatment should be 2 to 3 years before consideration of withdrawal. Liver biopsy is recommended to determine histologic response before consideration of drug withdrawal. High relapse rates after discontinuation of treatment underscore the need for serial monitoring of liver tests. Patients with severe acute autoimmune hepatitis presenting with jaundice should be managed by a hepatologist, and patients with features of acute liver failure require urgent transfer to a transplant center.

KEY POINTS

- Diagnosis of autoimmune hepatitis is based on elevated aminotransferase levels, positivity for antinuclear antibody and smooth-muscle antibody, elevated levels of IgG, and liver histology.
- Treatment of autoimmune hepatitis includes a combination of prednisone and azathioprine for most patients; duration of treatment should be 2 to 3 years before consideration of withdrawal.

Alcohol-Induced Liver Disease

Alcohol injury to the liver may take the form of steatosis, steatohepatitis, fibrosis, or cirrhosis. A history of alcohol use is the most important component in making the diagnosis, although not all patients are forthcoming about alcohol use. See MKSAP 19 General Internal Medicine 2 for more information about screening for alcohol use disorder. Most patients with alcoholic liver disease have consumed more than 100 g of alcohol daily for 20 years. Alcoholic hepatitis is a distinct clinical syndrome of severe steatohepatitis on a background of chronic alcoholic liver disease, often presenting with fever, jaundice, tender hepatomegaly, and leukocytosis. Approximately 25% of heavy drinkers develop cirrhosis. Differentiating alcoholic hepatitis from decompensated cirrhosis in patients with underlying cirrhosis can be difficult.

Physical examination may show evidence of hepatomegaly in patients with steatosis or steatohepatitis. In patients with alcoholic hepatitis or cirrhosis, findings of advanced liver disease may be present, including muscle wasting, scleral icterus, jaundice (including sublingual jaundice), spider

angiomata, gynecomastia, testicular atrophy, or palmar erythema. Laboratory evaluation of alcohol-induced liver disease may show an elevated mean corpuscular volume, AST-to-ALT ratio greater than 2, elevated γ-glutamyl transferase level, elevated phosphatidyl ethanol level, and, in advanced cases, elevated INR and thrombocytopenia. The IgA level may be elevated. The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/alcoholic-liver-disease-nonalcoholic-fatty-liver-disease-index) can help distinguish alcoholic liver disease from nonalcoholic fatty liver disease. The predictive model is based on AST, ALT, mean corpuscular volume, age, height, weight, and sex.

Alcoholic hepatitis is most often diagnosed clinically, with liver biopsy reserved for diagnostic uncertainty. Severity of alcoholic hepatitis can be determined by the Maddrey discriminant function (MDF) score, which is calculated as follows:

MDF score = 4.6 (prothrombin time [s]
- control prothrombin time [s])
+ total bilirubin (mg/dL)

The Model for End-Stage Liver Disease (MELD) score (https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/) can also be used to assess severity, with a MELD score greater than 20 suggesting moderate to severe disease. (See Classification of Liver Disease Severity for additional details on components of this score.)

In severe cases (MDF score ≥32, MELD score >20, or hepatic encephalopathy), treatment with prednisolone (which does not require hepatic metabolism, unlike prednisone) is recommended. Contraindications to prednisolone include active infection, upper gastrointestinal bleeding, acute kidney injury, concomitant liver disease (especially HCV and HBV), and multiorgan failure. The STOPAH trial showed a trend toward improvement in 28-day mortality with prednisolone, but results were not statistically significant. However, a meta-analysis of randomized studies (including STOPAH) showed that glucocorticoids reduced short-term mortality by 46%. Pentoxifylline is no longer recommended for treatment of alcoholic hepatitis and is not effective in patients whose symptoms do not respond to prednisolone.

Response to glucocorticoids can be assessed on day 7 with the Lille score (www.mdcalc.com/lille-model-alcoholic-hepatitis). Because of risk for infection, prednisolone should be discontinued in patients with no response (Lille score ≥0.45). A Lille scores below 0.45 supports prednisolone continuation for 28 days.

Nonsevere alcoholic hepatitis (MDF score <32; MELD score ≤20) requires supportive measures and should not be treated with prednisolone. All patients require assessment for nutritional deficiencies, nutritional management, thiamine replacement, and alcohol treatment, with a goal of abstinence.

Alcoholic cirrhosis can be diagnosed on clinical and radiologic grounds in patients with obvious evidence of portal hypertension and a history of consistent alcohol intake. Liver biopsy is sometimes necessary in cases with diagnostic ambiguity. In patients who drink alcohol, liver inflammation increases stiffness, making elastography inaccurate. Nutritional assessments and alcohol treatment are required. Alcohol abstinence can result in significant stabilization of liver function and reversal of portal hypertension. Patients with alcoholic liver disease and evidence of cirrhosis with or without portal hypertension should be referred to hepatology for further management and consideration of liver transplantation, regardless of duration of alcohol abstinence. Alcohol-induced liver disease is the second most common reason for liver transplantation in the United States, behind HCV.

KEY POINTS

- The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index can help distinguish alcoholic liver disease from nonalcoholic fatty liver disease.
- Manifestations of alcoholic hepatitis include fever, jaundice, tender hepatomegaly, and leukocytosis.
- Severity of alcoholic hepatitis is determined by the Maddrey discriminant function (MDF) score and Modified End Stage Liver Disease (MELD) score; patients with an MDF score of 32 or greater, MELD score greater than 20, or hepatic encephalopathy may be considered for prednisolone therapy.
- Pentoxifylline is no longer recommended for treatment of alcoholic hepatitis.
- All patients with advanced alcoholic liver disease should be referred to hepatology for further management and consideration of liver transplantation, regardless of duration of alcohol abstinence.

Drug-Induced Liver Injury

Drug-induced liver injury encompasses a spectrum of liver injury and can be induced by prescription, over-the-counter, and herbal medications. Patients should be asked about exposure to medications in the past 6 months, both prescription and nonprescription, including supplements. Use of the National Institute of Health's Web-based tool LiverTox (www.livertox.nih.gov) can help assess risk for hepatotoxicity.

Acetaminophen is the medication most recognized to have intrinsic hepatotoxicity. People who chronically drink alcohol can develop acetaminophen hepatotoxicity even when taking therapeutic doses of acetaminophen. The early recognition of acetaminophen-induced liver injury is critical so that *N*-acetylcysteine can be administered promptly to prevent liver failure.

Antibiotics (particularly amoxicillin-clavulanate) and antiepileptics (phenytoin and valproate) are also commonly associated with drug-induced liver injury, representing 60% of cases. Other than acetaminophen, the drugs most often causing acute liver failure in the United States are antituberculosis