Nonviral or Drug-Induced Etiologies of Acute Liver Failure

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KEYWORDS

• Acute liver failure • Autoimmune hepatitis • Budd-Chiari syndrome • Wilson disease
• Fulminant hepatic failure

KEY POINTS

- When viral hepatitis and drug-induced liver injury are ruled out as etiologies of acute liver failure, Budd-Chiari, autoimmune hepatitis, and Wilson disease need to be evaluated as possible underlying etiologies.
- If no infection is present in a patient with acute liver failure from autoimmune hepatitis, consider corticosteroid therapy if MELD-Na is less than 28 and reassess for improvement within 1 week.
- Following an algorithm in patients presenting with acute Budd-Chiari syndrome is associated with improved outcomes and can lead to reversal of acute liver failure.
- Acute liver failure in patients with Wilson disease requires urgent liver transplantation evaluation because spontaneous survival is unlikely.
- In patients with acute liver failure and pregnancy, prompt delivery is recommended.

INTRODUCTION

Acute liver failure (ALF) is a highly fatal but rare condition with approximately 2000 cases occurring annually in the United States.[1] ALF is diagnosed by the following criteria: absence of pre-existing liver disease, acute onset less than 26 weeks, coagulopathy defined as international normalized ratio greater than 1.5, and the presence of encephalopathy.[2] Patients can present with a wide range of symptoms including fatigue, jaundice, and confusion. In the pre–liver transplant era, outcomes were poor with survival of 15% but now are steadily improving to more than 65% and climbing with increased liver transplantation (LT) success rates.[3] Patients with ALF are listed as United Network for Organ Sharing status 1a and given top priority over all forms

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of chronic liver disease in adults because their expected survival is thought to be less than 7 days, requiring urgent prioritization.[4]

There are a wide range of causes of ALF and regional differences that affect health behaviors, exposures, and genetics.[5] Drug-induced liver injury, more specifically acetaminophen, is the most common cause of ALF and has a high likelihood of spontaneous survival.[6] Although the most common causes of ALF are drug-induced liver injury and viral hepatitis, other causes of ALF can account for up to 48% of cases, with indeterminate causes making up 17% to 38% (**Fig. 1**).[3,5] Diagnosis is complicated because biopsy is often not possible given the presence of severe coagulopathy. Identification of the cause as early as possible in the clinical course is essential because certain disease processes are potentially reversible and prognosis can help drive transplant decision-making. This article reviews nonviral and nondrug-induced causes of ALF.

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis (AIH) is an inflammatory disorder of the liver with a prevalence of 11 to 17 per 100,000 persons[7] and accounts for up to 6% of patients presenting with ALF.[8] Classically, patients present in the third to sixth decade of life and are female.[7] The severity of presenting symptoms can range from asymptomatic to acute, which accounts for approximately 25% to 40% of patients with AIH.[7,9] AIH is frequently associated with other autoimmune diseases including thyroiditis, synovitis, ulcerative colitis, and celiac disease.[7]

Diagnosis revolves around laboratory testing and biopsy results.[10] Along with a hepatocellular injury pattern, patients frequently have elevated serum globulin levels. AIH type 1 is associated with positive antinuclear antibody (ANA) and anti–smooth muscle antibody, whereas anti-liver cytosol type 1 and antiliver/kidney microsome type 1 are present in AIH type 2.[11] The International Autoimmune Hepatitis Group created criteria for diagnosis for AIH in 1999[10] and a simplified version in 2008.[12] Classic biopsy findings for AIH are the presence of interface hepatitis along with plasma cell infiltrate.[13] The diagnosis of AIH in ALF is more complicated because the histology is similar to that of a drug-induced liver injury.[9] Additionally, serum immunoglobulin G levels are normal in 25% to 39% of patients with acute presentation of AIH, whereas ANA is weakly positive or absent in 39% of patients.[14] Furthermore, in patients with ALF, only 50% and 60% of those clinically diagnosed to have AIH were diagnosed by the simplified 2008 and 1999 criteria, respectively.[15] Therefore, AIH is likely a frequent cause of indeterminate ALF, and in a study of 72 patients

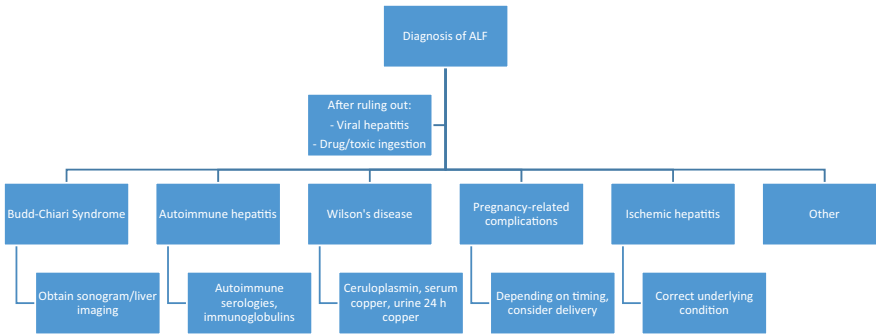

Fig. 1. Differential diagnosis of acute liver failure.