The Clinical Spectrum and Manifestations of Acute Liver Failure

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KEYWORDS

• Acute liver failure • Acetaminophen toxicity • Cerebral edema
• Hepatic encephalopathy

KEY POINTS

- Acute liver failure is a rare condition defined by the onset of hepatic encephalopathy and coagulopathy in patients without preexisting cirrhosis or liver disease.
- Management includes early recognition and administration of cause-specific therapy preferably in an intensive care unit setting as well as transfer to a liver transplantation center.
- Complications can be life threatening and include metabolic and acid-base disturbances, renal failure, cardiopulmonary complications, bleeding, and coagulopathy.
- Cerebral edema and intracranial hypertension are complications of acute liver failure that result in high morbidity and mortality.

INTRODUCTION

Acute liver failure (ALF) is a rare, life-threatening condition that is defined by the onset of hepatic encephalopathy (HE) and coagulopathy (international normalized ratio [INR] $\geq$1.5) in patients without cirrhosis or preexisting liver disease of less than 26 weeks.[1,2] In addition, patients can develop acute on chronic liver disease with autoimmune hepatitis, Wilson disease, and alcohol-induced liver injury (ie, severe alcoholic hepatitis). The time frame of ALF is classified as hyperacute (<7 days), acute (7–21 days), or subacute (22 days to <26 weeks) based on the onset of encephalopathy and jaundice.[3,4] The most common causes of ALF in the United States include acetaminophen (acetyl-p-aminophenol) toxicity, idiosyncratic drug-induced liver failure, viral hepatitis, and indeterminate causes. Early recognition of ALF and initiation of cause-specific therapy and immediate contact with a liver transplant center have led to improved outcomes

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over the past few decades.[5,6] In this article the authors discuss the clinical spectrum and manifestations of ALF.

PATHOPHYSIOLOGY

ALF occurs when the rate of hepatocyte death, characterized by apoptosis or necrosis, exceeds the rate of hepatocyte regeneration. The cellular damage that occurs varies by disease process. For example, acetaminophen toxicity results in apoptosis, whereas ischemia results in necrosis. The end result, however, is the same, in that hepatocyte death leads to multi-organ failure.[7]

CAUSE

ALF results from a wide variety of causes and varies by country. The causes of ALF have also changed over the past few decades. In the United States and Western Europe, there has been a decline in viral hepatitis and an increase in acetaminophen-induced ALF, which, along with idiosyncratic drug-induced liver failure, accounts for 60% of cases of ALF. In contrast, Asian countries have a higher incidence of hepatitis viruses leading to ALF with hepatitis E virus in India and Pakistan and hepatitis B virus (HBV) in Japan, China, and Thailand.[8–10] Determining the specific cause of ALF can help practitioners manage the condition and predict its prognosis. Knowing the cause also helps predict how certain manifestations will present. For example, acetaminophen-induced ALF and mushroom poisoning both have a rapid presentation, whereas other forms of drug-induced liver failure tend to have a more insidious onset. Causes of ALF are listed in **Table 1** and briefly discussed later.

DIAGNOSIS AND INITIAL EVALUATION

A thorough history and physical examination helps aid in the diagnosis. Specifically, it is important to illicit potential exposures, including drugs, herbs, toxins, and viruses, to help determine the cause of ALF and to initiate cause-specific treatment.

The most widely accepted definition of ALF includes the onset of encephalopathy as well as evidence of coagulation abnormalities (prolonged prothrombin time, INR $\geq$1.5) in patients without preexisting cirrhosis and with an illness of less than 26 weeks of duration. This definition includes patients with Wilson disease, autoimmune hepatitis, or a viral hepatitis, as long as the duration of illness has only been recognized for less than 26 weeks. Patients with severe alcoholic hepatitis, however, are considered to have acute-on-chronic liver failure as most patients have a long-standing history of heavy alcohol use.

Initial laboratory tests should include routine chemistries, complete blood count, coagulation panel, and an arterial blood gas. It is also important to evaluate for complications, including an arterial lactate, ammonia, amylase, and lipase, as well as monitoring urinary output. Depending on the cause of ALF, variations in laboratory testing can be seen, which is discussed in detail in the following section. The following laboratory abnormalities can be seen in most patients with ALF[4,11]:

- Prolonged prothrombin time, INR greater than 1.5
- Elevated aminotransferase levels
- Elevated bilirubin
- Anemia and thrombocytopenia
- Elevated serum creatinine and blood urea nitrogen