Acute Liver Failure

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KEYWORDS

• Acute liver failure • Cerebral edema • Encephalopathy • *N*-acetylcysteine
• Liver transplantation • Extracorporeal liver support system • Liver dialysis

KEY POINTS

- Acute liver failure is a life-threatening condition of heterogeneous etiology.
- Outcomes are better with early recognition and prompt initiation of etiology-specific therapy, complex intensive care protocols, and urgent liver transplantation.
- Cerebral edema and intracranial hypertension (ICH) are reasons for high morbidity and mortality.
- Hypertonic saline is suggested for patients with high-risk for developing ICH and, when ICH develops, mannitol is recommended as a first-line therapy.

INTRODUCTION

Acute liver failure (ALF) is a rare but life-threatening condition. The most widely accepted definition includes the evidence of hepatic necrosis, coagulation abnormality (International Normalized Ratio $\geq$1.5), and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with a duration of illness of less than 26 weeks. Patients with Wilson disease, perinatally acquired hepatitis B virus (HBV), or autoimmune hepatitis may be included, despite the presence of underlying cirrhosis, if their disease has only been recognized for less than 26 weeks. It is important to appreciate that ALF is a distinct entity from an acute exacerbation of chronic liver disease (or acute-on-chronic liver failure). For instance, acute alcoholic hepatitis is not considered to be ALF. ALF can be further classified based on the time interval between the development of jaundice and encephalopathy[1–4] (**Table 1**). It should be noted that the onset of encephalopathy is often sudden, may precede jaundice, asterixis may be transient, and, unlike chronic liver disease, may be associated with agitation, changes in personality, delusions, and restlessness.[5]

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Table 1
Classification of acute liver failure

	Interval Between Onset of Encephalopathy from Jaundice	Common Etiologies	Clinical Presentation	Prognosis
Hyperacute	<7 d	APAP, HAV, ischemic	Cerebral edema common	Fair (survival without LT ~36%)
Acute	7–21 d	HBV, drugs	Cerebral edema less common	Poor (survival without LT ~14%)
Subacute	22 d to <26 wk	drugs, indeterminate	Cerebral edema rare; ascites, peripheral edema and renal failure more common	Very poor (survival without LT ~7%)

Abbreviations: APAP, acetaminophen; HAV, hepatitis A virus; HBV, hepatitis B virus; LT, liver transplantation.

Over the last 3 decades, ALF has evolved from a poorly understood condition with a near entirely fatal outcome, to one with a relatively well-characterized phenotype and disease course.[6,7] Complex intensive care protocols and urgent liver transplantation (LT), as well as specific therapy according to the etiology, have been used promptly as a standard of care for ALF. Accordingly, the overall and LT-free survival rates of patients with ALF have been improving through the past few decades and the majority of patients may now be expected to survive, particularly where LT is available.[6,8]

ETIOLOGY

The etiology of ALF varies greatly by country and also has changed over time.[9–11] Over the past few decades, the most common etiology of ALF has evolved, with hepatitis A and B on the decline in incidence, while acetaminophen (APAP) and other medications related ALF have been on the increase, at least in the United States and Western Europe.[6,9–11] In the United States and the UK, APAP overdose currently accounts for 45% to 60% of cases of ALF, with viral hepatitis and idiosyncratic drug reactions each accounting for 10% to 12% of cases.[6,9–11] Notably, the incidence of APAP overdose also varies among developed countries, because it accounts for only 3% to 9% of ALF in Spain and Germany, reflecting the differences in behavior and perhaps in the national regulatory system with regard to access to large doses of APAP.[12,13] By contrast, Asia Pacific countries have a higher incidence of ALF owing to hepatitis viruses, specifically hepatitis E virus in India and Pakistan, and HBV in Japan, Hong Kong, Thailand, as well as Australia, with fewer cases of APAP overdose being observed.[6,10,11,14]

Common and uncommon etiologies of ALF are listed in **Table 2**. Apart from the well-known causes of drug-induced ALF, several recently introduced agents (eg, tyrosine kinase inhibitors, monoclonal antibodies, dabigatran, rivaroxaban, lamotrigine, levetiracetam, pregabalin, venlafaxine, duloxetine, sertraline, darunavir, and maraviroc) and herbal supplements (eg, black cohosh, germander, chaparral, kava kava, Chinese herbs, and anthraquinones) have also been reported to cause ALF.[15,16] Important clinical characteristics, prognosis, and specific therapies of selected etiologies of ALF, including viruses,[17–24] medications,[25–27] autoimmune,[28,29] Wilson disease,[30]