Chapter 6
The Clinical Spectrum and Manifestations of Acute and Acute on Chronic Liver Failure

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Key Concepts
ALF is a rare, heterogeneous and life-threatening clinical syndrome that occurs in patients without known existing liver disease, unlike ACLF which is more common and occurs in patients with liver disease.

The clinical presentation includes liver dysfunction that may lead to multiple organ failure and death.

Survival has improved substantially through advances in critical care management and liver transplantation.

Introduction

Both patients with a previously healthy or diseased liver can develop acute liver failure. In the former case it is termed acute liver failure (ALF) or Fulminant Hepatic Failure (FHF) and in the latter case it is termed acute on chronic liver failure (ACLF). Both ALF and ACLF share common clinical features, however, they also differ in some other features. In this chapter, we will discuss the definitions, causes, clinical manifestations and special features relating to both ALF and ACLF. It is important
to understand that some features can be ascribed to the liver failure itself, whereas others (such as Kayser Fleischer ring in Wilson’s disease) are present as a result of the particular cause of the liver failure. Patients with ACLF may display clinical features relating to chronic liver disease, for example, stigmata of portal hypertension such as variceal bleeding and ascites.

**Acute Liver Failure (ALF)**

ALF has an unpredictable and dramatic clinical course. According to the American Association for the Study of Liver Diseases (AASLD), ALF is defined as severe liver injury accompanied by a loss of synthetic function (International Normalized Ratio, INR ≥1.5) and any degree of encephalopathy occurring in a patient without existing liver disease over a period of <26 weeks [1, 2]. Some patients with newly diagnosed liver disease such as Wilson’s disease, hepatitis B or autoimmune hepatitis can still be considered as having ALF even if they show evidence of cirrhosis at presentation if their disease has been recognized for <26 weeks. Although its value has been questioned, some authors further categorize ALF into hyperacute (<7 days), acute (7–21 days) and subacute (22 days–26 weeks) [1]. Acetaminophen toxicity, idiosyncratic drug reactions, and hepatotropic viruses are the most common causes of ALF. A typical constellation of non-specific symptoms develops in the patient with ALF which may precede the distinctive features. These symptoms at first can be confused for common illnesses until severe symptoms develop. The first symptoms of ALF generally include fatigue, malaise, nausea, vomiting, and subtle mental changes [3, 4]. Eventually, jaundice develops along with physical signs of liver disease such as hepatic dullness to percussion, and abdominal pain [3, 4].

Complications of ALF include cerebral edema, sepsis, acute respiratory distress syndrome, hypoglycemia, coagulopathy, gastrointestinal bleeding, pancreatitis, and acute kidney injury. Supportive care is the hallmark of management. However, Liver transplantations remains the only definitive treatment for patients who do not recover spontaneously [4].

**Specific Findings Based on Etiology**

Whereas liver failure itself causes symptoms as described above, some patients with ALF also display unique manifestations of their particular etiology [1] for example:

- Mushroom Poisoning such as from Amanita phalloides is characterized by severe gastrointestinal symptoms such as nausea, vomiting, diarrhea and abdominal cramping.
- Herpes Simplex Infection causes skin lesions in half the cases.
- Wilson’s Disease causes Coombs negative hemolytic anemia, Keyser-Fleischer rings and is characterized by high urine and hepatic copper levels. Serum ceruloplasmin is
reduced in about half the cases of ALF not related to Wilson’s so is not helpful in the diagnosis of Wilson induced ALF. The renal failure of Wilson’s disease is partially due to direct renal tubular damage from copper.
– Acute Fatty Liver of Pregnancy and HELLP syndrome occurs in a small number of women towards the end (or just after) their pregnancy. Its unique features include hypertension and proteinuria (pre-eclampsia), hemolytic anemia, thrombocytopenia and steatosis and can in rare occurrences be complicated by hepatic hemorrhage or rupture.
– Budd-Chiari Syndrome, or acute hepatic venous outlet obstruction, will often cause hepatomegaly, abdominal pain and ascites as the venous blood leaving the sinusoids get backed up.

**Acute on Chronic Liver Failure (ACLF)**

ACLF is an acute deterioration of liver function in patients with chronic liver disease. Although several definitions by different liver societies exists (Table 6.1) [5–7], controversy remains regarding the most inclusive and practical definition [8]. In clinical practice, we generally use the criteria developed by the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) which was based on the infection related ACLF score [5]. These criteria defined ACLF as two or more extrahepatic organ failures [5]. Organ failures include brain (grade III and IV HE), cardiovascular (shock), respiratory (need for mechanical ventilation) and renal (need for renal failure)

| Criteria                              | Asian Pacific Association for the Study of Liver (APASL)                                      | European Association for the Study of Liver-Chronic Failure (EASL-CLIF) | North American Consortium for the Study of End-Stage Liver Disease (NACSELD) |
|---------------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Severity score                        | Liver failure defined as jaundice (serum Bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5 or prothrombin activity of ≤40%) ascites or encephalopathy develops within 4 weeks | Hepatic and extrahepatic organ failure                                | Extrahepatic organ failure                                                   |
| Requirement for diagnosis             | Ascites, HE                                                                                        | Organ failure (hepatic failure not essential for diagnosis)            | Extrahepatic organ failure                                                  |
| Underlying liver disease              | Noncirrhotic chronic liver disease or compensated cirrhosis                                        | Compensated and decompensated cirrhosis                               | Decompensated cirrhosis                                                     |
| Common precipitating events           | Reactivation hepatitis B Superimposed hepatitis E Alcoholic hepatitis                              | Alcoholic hepatitis Bacterial infections Unknown in ≥40%               | Not specified, but only patients with infection included                    |
replacement therapy). ACLF can develop at any stage from compensated to decompensated cirrhosis [9]. However, in approximately 25% there is no prior history of acute decompensation of liver cirrhosis [9]. ACLF frequently develops in the setting of an acute event that acts as a precipitating factor [7]. The most frequent precipitating events of ACLF in Europe and North America are bacterial infections and acute alcoholic hepatitis. In Asia, ACLF often occurs due to acute viral hepatitis type A, B, and E superimposed to cirrhosis [9, 10]. Approximately 44% of patients, however, do not have any identifiable precipitating event [6]. In these cases, ACLF might result from undetected infections, unrecognized drug-induced liver injury, or subclinical intestinal translocation of bacterial pathogen-associated molecular patterns (PAMPs) and increased damage associated molecular patterns (DAMPs) release. The clinical course and prognosis of ACLF depends partially on the presence and type of precipitating event. ACLF caused or complicated by infection shows a worse prognosis than that observed in ACLF subjects without infection. ACLF in subjects with no prior history of acute decompensation is more severe than in those with prior history of acute decompensation [9]. Clinical features of ACLF include jaundice, abdominal pain, nausea, vomiting and depressed mental status and these may deteriorate to multiple organ failure and death. In addition to supportive care, management of ACLF involves early recognition and treatment of the precipitating event. Liver transplantation represents the only definitive therapeutic option for patients with ACLF. However, less than half of the patients with ACLF are listed and of these, transplant is feasible in only 10–25%, as more that 50–70% of the listed patients die [11].

**Laboratory Abnormalities**

Patients with ALF and ACLF have an INR $\geq 1.5$. They also display abnormalities in both liver specific (elevated transaminases and direct bilirubin) and in non-liver specific tests such as lactic acidosis, hypoglycemia, hyperammonemia, electrolyte deficiencies, elevations in amylase and lipase, elevated creatinine and thrombocytopenia. Falling transaminases are not a marker for hepatic recovery in the face of rising INR and bilirubin as they may fall due to a loss of functional liver mass [4, 12].

Some etiologies of ALF and ACLF display unique patterns of lab abnormalities [1, 12].

- Acetaminophen (APAP) hepatotoxicity is characterized by extremely high transaminase levels, sometimes exceeding 3500 IU/L with relatively low bilirubin levels.
- Wilson’s disease, when it causes ALF is characterized by very high serum bilirubin (>20 mg/dl) with very low alkaline phosphatase. A ratio of total bilirubin (mg/dl) to alkaline phosphatase (IU/L) of greater than 2 is highly specific to Wilson’s disease.
- Ischemic hepatitis is characterized by markedly elevated transaminases that rise quickly and improve rapidly with stabilization of the extrahepatic pathology. Lactic dehydrogenase may also rise quickly as an indicator of cell necrosis.
- Viral Hepatitis is characterized by markedly elevated transaminases that take longer to trend down than in ischemic hepatitis. AST/ALT ratio is typically <1.
- Acute Alcoholic Hepatitis is characterized by a high AST/ALT ratio (>1.5) but only moderate elevations (to the hundreds) [13].
- Reye’s syndrome and linezolid induced hepatitis are characterized by severe lactic acidosis with only moderate transaminase and bilirubin elevations [14].

Many organs systems are affected in ALF and ACLF, summarized below:

### Neurological

Hepatic encephalopathy (HE) is generally graded on a scale from I-IV based on the West Haven criteria and summarized in Table 6.2 [3, 4]. The onset of encephalopathy can be gradual or abrupt and it may precede the appearance of jaundice. Agitation, delusional ideas, and hyperkinesis are common but short-lived symptoms; coma rapidly ensues. The overall prognosis for those with stable grade I–II encephalopathy is good, whereas the prognosis for patients with grade III–IV encephalopathy is much poorer. In cases of acetaminophen overdose, encephalopathy usually occurs on the third or fourth day after ingestion and rapidly progresses to grade IV within 24–48 h.

In ALF, cerebral edema occurs in some patients with grade III HE and in 70–80% of patients with grade IV [15] although in early stages it may go unrecognized barring a high level of suspicion. Cerebral edema may be marked by the Cushing Triad (bradycardia, hypertension and abnormal respirations), posturing, abnormal brainstem reflexes including sluggish or unresponsive pupils, seizures and death [4, 15]

| Grade | Behavior/arousal                                      | Abnormal movement | EEG/seizure     | Pupillary changes | Cerebral edema  |
|-------|------------------------------------------------------|-------------------|-----------------|-------------------|-----------------|
| I     | Alert with subtle irritability, sleep disturbances, mild confusion | Asterixis mild | Usually normal | None | Uncommon |
| II    | Lethargy, disorientation, inappropriate behavior      | Asterixis easily elicited | Slowing | None or hyperresponsive | Uncommon |
| III   | Sleeping most of the time but arousable, incoherent speech, marked confusion | Asterixis present if patient cooperative | Possible subclinical or convulsive seizure | Hyperresponsive to sluggish | Possible |
| IV    | Unarousable, possibly responds to pain                | Asterixis usually absent, posturing may be present | Possible subclinical or convulsive seizure | Sluggish to fixed and dilated | Likely |

Table 6.2  Manifestations of hepatic encephalopathy by grade
Arterial ammonia level above 200 μg/dL in grade III and grade IV encephalopathy is a strong predictor of brain herniation [16]. The mechanism(s) responsible for cerebral edema are not completely understood, but likely include cerebral hyperemia, vasogenic edema due to disruption of the blood-brain barrier, cytotoxicity due to the osmotic effects of ammonia, glutamine, and other amino acids, as well as the deleterious effects of proinflammatory cytokines and dysfunction of the sodium-potassium ATPase pump with loss of autoregulation of cerebral blood flow [4]. Late clinical stages of cerebral edema include systemic hypertension, decerebrate rigidity, hyperventilation, pupillary dilation, seizures, and brainstem herniation.

The significance of HE in ACLF has been investigated [17, 18]. Indeed, grade III-IV HE was associated with 30-day mortality independent of other organ failures, indicating that HE is an important independent prognostic factor in patients with ACLF [18].

**Cardiovascular**

Patients with ALF or ACLF may have hemodynamic compromise caused by several factors such as hypovolemia (poor oral intake, vomiting, gastrointestinal bleeding), significant vasodilatation due to Systemic inflammatory response or sepsis. Structural and functional cardiac abnormalities such as cirrhotic cardiomyopathy which occurs in approximately 40–50% patients with liver cirrhosis [19] can certainly contribute to the hyperdynamic circulation. Adrenal insufficiency and hepatoadrenal syndrome occurs in up to 60% of cases of ALF [2]. Unlike patients with compensated cirrhosis, patients with ALF and ACLF may present in shock leading to multiple organ failure [4, 20]. Lactic acidosis in ALF and ACLF may be caused by poor hepatic clearance, hepatic necrosis and tissue hypoperfusion [20].

**Pulmonary**

Patients with ALF and ACLF commonly have respiratory compromise, often leading to acute respiratory failure. Patients are at risk for pneumonia, either due to aspiration or immune dysfunction. Inadequate ventilation in the setting of HE may also lead to atelectasis [4, 20]. Excessive intravenous fluid use may also contribute to respiratory compromise [2], especially in the setting of acute kidney injury and fluid overload that leads to pulmonary edema. The severe inflammatory state of ALF can lead to the acute respiratory distress syndrome (ARDS). Patients with grade III and IV HE are at high risk of respiratory failure and often require endotracheal intubation to protect their airway thus securing the airway in patients with grade III-VI HE is important. Patients with ACLF have additional causes of
respiratory compromise as a result of their chronic liver disease such as massive ascites which impairs the movement of the diaphragm, pleural effusions (hepatic hydrothorax) and pulmonary vascular shunting (hepatopulmonary syndrome).

Coagulation

Although an INR $\geq 1.5$ is part of the definition of ALF, this represents the failing liver’s poor synthetic function and does not necessarily indicate a bleeding tendency. Patients with ALF have a decrease in factors II, V, VII, IX and X [2] but also a decrease in anticoagulation factors such as protein C and protein S [4]. Additionally, inflammation in ALF may raise the level of factor VIII leading to hypercoagulability [2]. Patients with ALF and ACLF may also suffer from disseminated intravascular coagulation and multiple organ failure leading to thrombocytopenia which is a marker of poor outcome [2, 3], unlike thrombocytopenia in chronic liver disease which is caused by splenic sequestration. As a result of these various factors, patients may fall anywhere on the spectrum between hypo- and hyper-coagulable. It is noteworthy that when studied in a series of ALF patients who had a mean INR of 3.4, mean Thromboelastography (TEG) parameters were normal [21]. The majority of patients had normal TEGs, 34% had TEGs compatible with hypocoagulability and 8% had TEGs compatible with hypercoagulability [21]. Although it is challenging, patients need to be characterized as having a bleeding or thrombosis phenotype and management of coagulopathy should be guided based on global coagulation assessment. The application of global viscoelastic testing requires more data [22].

Renal

Almost 50% of patients with ALF develop variable degree of acute kidney injury (AKI) [3] and many will require renal replacement therapy [4, 23]. Mechanisms include renal hypoperfusion (due to intravascular volume depletion and reduced mean arterial pressure), acute tubular necrosis (ATN) due to systemic inflammatory response syndrome (SIRS), hepatorenal syndrome (HRS), and direct toxic effects of the etiologic agent responsible for liver injury such as acetaminophen (APAP). Patients who required renal replacement therapy recover their kidney function within 4 weeks unless multiorgan dysfunction syndrome was present [3].

In ACLF, the spectrum of AKI extends from purely functional to or varying degree of parenchymal damage, collectively called hepatorenal disorders (HRD) [24]. AKI is often precipitated by hepatic (alcohol abuse, drugs) and/or extrahepatic (sepsis) events. The pathogenesis include macrovascular dysfunction (systemic vasodilatation, inadequate cardiac output), microvascular dysfunction, danger or inflammation signals from either pathogen- associated molecular
patterns (PAMPs) or damage-associated molecular patterns (DAMPs), and finally direct tubular damage [25].

**Infectious**

Patients with ALF and ACLF are at high risk for sepsis due to multiple defects in the immune system including impairments in the function of system monocytes, neutrophils and compliment [2] as well as hepatic reticuloendothelial dysfunction [20]. However, detecting an infection may not be as straightforward as in the general population. The liver failure itself can cause alterations of consciousness, a septic-like hemodynamic profile, elevated lactic acidosis, fever, leukocytosis etc. Furthermore, although ACLF can lead to infections, infections can be a trigger to cause ACLF [7]. Infections can cause direct organ and systemic damage as well as exacerbate the liver failure. Common infections include pneumonia (including due to aspiration), bacteremia, urinary tract infections and spontaneous bacterial peritonitis [4, 20]. Of course, like all critically ill patients, healthcare associated infections are common.

**ALF Vs ACLF**

ALF and ACLF share much in common but do have important differences summarized in Table 6.3.

| Table 6.3 Differences between ALF and ACLF |
|------------------------------------------|
| **Acute liver failure** | **Acute on chronic liver failure** |
| **Most common etiologies/triggers** | Drug reaction including APAP, viral hepatitis, autoimmune hepatitis and many others | In West: Extrahepatic bacterial infections, alcohol abuse, gastrointestinal hemorrhage, unknown. In East: Reactivation of hepatitis B, A or E |
| **Presence of portal hypertension** | Absent | Often present |
| **Gastrointestinal bleeding** | Usually absent | Often present |
| **Coagulopathy** | Present | Present |
| **Encephalopathy** | Present | Present |
| **Prognosis** | Poor without transplant, but 65% 1 year survival when transplant patients included | Short- and medium-term mortality is 50–90% |
| **Liver recovery after acute illness** | If immediate transplant not needed, usually make a full recovery | If immediate transplant not needed, half resolve to prior chronic disease, 30% stabilize to the “new normal” of the exacerbation and 20% continue to progress |
Summary
Both ALF and ACLF are potentially devastating diseases whose clinical manifestations span nearly all organ systems. Although many common features such as coagulopathy, encephalopathy and jaundice are a direct result of the liver injury, a particular patient’s clinical course and outcome is also dependent on the etiology or trigger of the liver failure.

Self Study

Questions
1. What events can precipitate ACLF?
2. What is the maximum duration of alcohol abstinence permitted for alcohol consumption to be considered a trigger?
3. Can clinicians prognosticate patients with ALF?

Answers
1. In the West, the most common precipitating factors are bacterial infection, excessive alcohol use and gastrointestinal bleeding. In contrast, the most frequent precipitating insult in Asia is Hepatitis B virus reactivation and, less frequently, Hepatitis E virus and Hepatitis A virus infection. In the CANONIC study, 44% of patients developed ACLF without a clear precipitating factor.
2. Controversies remain regarding the maximum duration of alcohol abstinence permitted for alcohol consumption to be considered a trigger of ACLF. In the CANONIC study, excessive alcohol use in the past three months was one of the precipitating events leading to ACLF. A large multicenter study from the APASL ACLF research consortium (AARC) reported that alcohol consumption within four weeks of illness represented nearly half of precipitating hepatic events [26].
3. Various prognostic evaluation systems, most of which have features derived from analyses of historical patient cohorts that were treated without transplantation, are in use worldwide [3]. The presence of encephalopathy is a key indicator, with further consideration given to the patient’s age and the severity of liver injury, as assessed by the presence of coagulopathy or jaundice. The most well characterized evaluation system is the King’s College Criteria, that has a clinically acceptable specificity but a limited sensitivity [3].
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