# Liver Failure

## Acute and Acute on Chronic

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# Preface

Acute liver failure (ALF) and acute on chronic liver failure (ACLF) is a syndrome characterized by acute decompensation with potentially lethal complications. Acute liver failure represents a rather rare but highly fatal condition, while ACLF represents approximately 5% of all hospitalizations with a mortality rate of approximately 50% in the USA.

With the advent of new antivirals in our therapeutic armamentarium, it has been noted that ACLF due to viral hepatitis has declined; perhaps, it has been traded for the upcoming entity—non-alcoholic steatohepatitis-induced end-stage liver disease—and the usual suspect—alcoholic liver disease or the combination of those two together.

We are excited as a number of causes that induce liver disease can be controlled nowadays, viral in particular, but the way we treat late stages of ALF and ACLF still remains the same: liver transplantation. A number or trials utilizing new compounds or even noncellular and cellular assisted devices have been addressed, but the survival benefit has not been proven or it is equivocal.

*Liver Failure: Acute and Acute on Chronic* provides a comprehensive multidisciplinary approach to epidemiologic aspects, pathophysiology of the diseases and syndromes in a state-of-the-art review of the literature, diagnostic modalities, clinical manifestations, management, and potential future directions.

A highly regarded international panel of scientists, pioneers in their field, have contributed a significant number of chapters written in a superb didactic fashion. The textbook *Liver Failure: Acute and Acute on Chronic* provides a panoramic view of these complex entities and provides very thoughtful insights on how to resolve some of the uncertainties while encountering these entities and outlines a better approach strategy.

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# Chapter 1
# Classification and Epidemiologic Aspects of Acute and Acute on Chronic Liver Failure


**Zaid H. Tafesh and Nikolaos Pyrsopoulos**

## Introduction

Acute liver failure (ALF) is a dreaded outcome of injury to the liver, caused either by direct hepatotoxicity or secondary liver injury related to an extra-hepatic process. It is a clinical entity that has been recognized by various names, definitions, and classifications across different decades and continents [1]. Although there is some inconsistency in defining and classifying ALF, these variations are reflective of the wide spectrum in clinical presentations that characterize this disorder.

Regardless of which definition or classification is adopted to describe ALF, there are a few overlapping themes that are central to the diagnosis. The absence of chronic liver disease (with a few exceptions that will be discussed later) is paramount and a loss of synthetic function of the liver must be present. Universally, coagulopathy and an altered sensorium related to hepatic encephalopathy are the two accepted markers of ALF, regardless of which definition is customary, as they are markers of decreasing synthetic function of liver [2, 3]. While coagulopathy can be seen with acute liver injury (ALI) [4], a potential perquisite to ALF, the presence of hepatic encephalopathy of any grade differentiates the two and is a marker of more advanced liver injury and a poorer prognosis.

The major differences in definitions and classifications of ALF are often related to the duration of illness and the speed in which the clinical presentation progresses in severity. Although overall management of ALF will often depend more on

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etiology, classifying the disease has both prognostic value and aides in narrowing the differential diagnosis.

From an epidemiologic angle, there is also variability depending on the ALF population of interest. While there is a long list of possible etiologies of ALF, each region of the world has a handful of diagnosis that are more common than others [5]. A strong understanding of ALF epidemiology is vital for quick recognition of this potentially devastating illness and allows for appropriate targeted treatment when indicated in a timely fashion.

This chapter will focus on the definitions, classifications and epidemiologic aspects of ALF. The most common definitions and classifications will be introduced and their clinical relevance will be discussed thereafter. A brief review of the epidemiology of ALF will also be presented, noting important distinctions between different patient populations. Finally, a brief comment on the differences in classification and epidemiology of acute on chronic liver failure (ACLF) will also be discussed.

**Definition of Acute Liver Failure** The original description of ALF by Charles and Davidson in 1970 introduced the defining characteristics of the disease, namely a condition secondary to liver injury without any background of chronic liver disease leading to encephalopathy. At the time, the accepted duration between the onset of any symptom and the development of encephalopathy was no greater than an 8-week time frame [6]. More recently, the accepted definition by American Association for the Study of Liver Diseases (AASLD) includes the presence of any degree of encephalopathy and coagulopathy defined by an International Normalized Ratio (INR) $\geq 1.5$ with no evidence of prior liver disease [7]. In contrast to the original description in the 1970s, the AASLD allows ALF to include an illness of up to 26 weeks in duration, resulting in a more inclusive definition that represents the wide variation in the natural history of this condition. European guidelines consider liver injury meeting the above criteria but lasting longer than 28 weeks as chronic liver disease, and not ALF [2]. However, the most notable difference in the ALF definition comes from Japan. In contrast to the advice set by the majority of other countries, the Japanese societies have elected to include both patients with and without hepatic encephalopathy (or hepatic coma) in the diagnosis of ALF [8]. Yet, consistent with other descriptions of this condition, the prognostic concerns related to the development of HE are strongly emphasized.

Collectively, these definitions illustrate ALF as a disease process that is generally short in duration (no longer than 26–28 weeks from the onset of symptoms to encephalopathy) but with various rates of progression to coagulopathy and encephalopathy, the characteristic hallmarks of the condition.

## Classification of Acute Liver Failure

Over the past several decades, there have been regular attempts at developing a classification system for ALF based on the timeline of symptomatology. While the AASLD has been hesitant to endorse the merit of these classification schemes in

predicting patient prognosis or altering the overall management of ALF [3], guidelines from Europe on the management of ALF have favored these classification structures as potentially clinically useful and thus merit future investigation [2].

There are four commonly referenced sub-classification systems (Table 1.1), which includes the O'Grady system [9], the Bernuau classification [10], the International Association for the Study of the Liver classification [11], and the Japanese system [8]. The observation that time from jaundice to encephalopathy may have bearing on the likelihood of survival has been central to the development of these models.

The oldest of the four classification schemes is the Bernuau system, developed based on observations of the clinical presentation of patients with ALF in Paris. The

**Table 1.1** Classification systems for acute liver failure

| Classification Scheme | Subclassification terms | Term definitions | Criticisms | Reference |
|---|---|---|---|---|
| Bernuau[a] | Fulminant<br>Subfulminant | **Fulminant:**<br><2 weeks from jaundice to HE<br>**Subfulminant:**<br>2–12 weeks to HE | Not inclusive of ALF with HE onset between 12–26 weeks<br>Under diagnosis ALF | [10] |
| O'Grady[b] | Hyperacute<br>Acute<br>Subacute | **Hyperacute:**<br>Jaundice to HE in 7 days or less<br>**Acute:**<br>HE in 1–4 weeks<br>**Subacute:**<br>HE in 4–12 weeks | Not inclusive of ALF with HE onset between 12–26 weeks<br>Under diagnosis ALF | [9] |
| IASL[a] | Acute<br>Subacute | **Acute:**<br>Symptom onset to HE within 4 weeks *(hyperacute in first 10 days)*<br>**Subacute:**<br>HE and/or ascites between 5–24 weeks | Diagnosis can be made without HE if ascites is present<br>Some with decompensated cirrhosis could be included in definition | [11] |
| Japanese[a] | ALF with hepatic coma<br>ALF without hepatic coma | **With hepatic coma:**<br>*Acute Type*-grade II or greater HE within 10 days<br>*Subacute type*- grade II or greater HE between 11–56 days<br>**Without hepatic coma:**<br>No or grade I HE in 8 week timeframe | Includes patients without HE.<br>Inclusive of diseases otherwise classified as acute liver injury, which may have a different prognosis compared to ALF | [8] |

*ALF* Acute Liver Failure, *HE* Hepatic Encephalopathy, *IASL* International Association for the Study of the Liver

[a]Classification assumes presence of coagulopathy

[b]Classification places less emphasis on the presence of coagulopathy. Suggests need to lower threshold in using prothrombin time for transplant selection

authors proposed adding the term "fulminant" to ALF to represent the development of hepatic encephalopathy [10]. Under this classification system, the presentation is defined as fulminant liver failure when no more than 2 weeks have passed between the onset of jaundice and HE. Alternatively, if the timeframe to HE is between 2 and 12 weeks, then the episode is classified as subfulminant.

Two years prior to the publication of the O'Grady ALF classification system, the incremental improvement in survival associated with a shorter timeframe of jaundice to encephalopathy was recognized in a Japanese cohort of 236 patients. The investigators noted that patients with fulminant liver failure related to viral hepatitis who developed encephalopathy in 10 days or less from the time of jaundice were significantly more likely to survive than those who had a longer delay between the two symptoms [12]. This finding was mirrored by observations of Bernuau and colleagues [13], where patients with a more indolent course characterized as subfulminant liver failure had poorer survival than patients with fulminant liver failure. These findings consequently lead to ongoing efforts towards developing a common nomenclature to describe these sub-classifications.

The O'Grady classification system was introduced in 1993 in the Lancet and has since been favorably adopted and cited in the management of ALF [9], both in Europe and North America. O'Grady recognized the "clinical spectrum" with regards to the ALF phenotype and thus proposed *acute liver failure* as the core term with *hyper* or *sub* as the relevant prefixes to portray the differences at opposite ends of the spectrum. Time from jaundice to encephalopathy of 7 days or less was classified as hyperacute liver failure, 8–28 days as ALF, while changes in mental status after 4 weeks but before 12 weeks would be classified as subacute liver failure. Consistent with observations within other cohorts, O'Grady noted that in 228 patients with ALF, survivors were clustered within those who developed HE within the first week of the illness (assuming jaundice represented the start of the illness), despite having the highest rate of cerebral edema (69%). The worst outcomes were seen in patients who developed HE between 8 and 28 days, with rates of cerebral edema as high as 56% and a survival rate of only 7%. Patients within the subacute liver failure group also had very poor overall prognosis with a 14% survival rate, but were less likely to develop cerebral edema. Although modern advances in critical care medicine have led to lower rates of cerebral edema and mortality overall, these differences between each subclassification of ALF remain relevant.

In 1999, the International Association for the Study of the Liver formed a subcommittee to address what was felt at the time to be several inconsistencies in the nomenclature of fulminant hepatic failure/ALF and the adoption of this nomenclature. They proposed differentiating between acute hepatic failure and subacute hepatic failure [11]. Under this classification scheme, HE remained the most important diagnostic criterion for ALF, defined as the development of HE within 4 weeks of symptom onset. Subacute liver failure included the development of HE and/or ascites between 5 and 24 weeks. Utilizing symptom onset rather than the onset of jaundice and allowing a subset of subacute liver failure patients to include those

who develop ascites without encephalopathy are the most notable differences of this classification system. One potential criticism of this approach is the concern that this definition of subacute liver failure may capture a subset of patients that would otherwise be classified as having decompensated cirrhosis, especially in the absence of HE. The choice to pursue liver transplantation in the short run for these patients may differ, although it may be an appropriate option in some regardless of the presence of HE.

Overall, despite these various classification proposals, some central themes resonate. A shorter timeframe from the onset of jaundice/symptoms to HE (usually 7–10 days) represents a subgroup of ALF patients at high risk for cerebral edema, profound coagulopathy, and a rapidly progressive illness, but overall better transplant-free survival and spontaneous recovery. In contrast, those individuals with more indolent ALF courses with a delay in HE development are less likely to survive without transplant, although their initial clinical presentation may be less dramatic.

## Epidemiology of Acute Liver Failure

Given the morbidity and mortality associated with ALF, it is fortunate that the disease remains a rare entity overall. Although accurate approximations of incidence and prevalence rates in the developing world are limited and likely underestimated, ALF incidence is reported at 1–6 cases per million people annually in developed countries [14]. Historically, the outcome of ALF was predominantly fatal. However, with transformations in patient care including improvements in critical care management and the utilization of early liver transplantation, survival in ALF has dramatically increased to 75% in countries like the United Kingdom. Moreover, there has been an equally promising drop in the proportion of ALF patients who develop intracranial hypertension, the most devastating morbidity related to this illness [15]. The etiology of ALF seems to be the principal determinant of sub-classification (Fig. 1.1) and therefore overall prognosis [3]. Consequently, a careful review of the etiology and distribution by region is essential to developing an appropriate differential diagnosis.

Differences in the epidemiology of ALF globally are predominantly linked to variations in the risk for viral hepatitis infection and local patterns of drug/medication use [16]. ALF in Western and developed countries is predominantly related to drug induced liver injury (DILI), while developing countries continue to struggle with high rates of viral hepatitis A, B, and E as predominant culprits [14]. Although there is significant overlap in patient presentation regardless of etiology of ALF, quickly determining the etiology, if possible, may allow healthcare providers to offer the few therapies available to a select few diagnosis in hopes of avoiding liver transplantation or death. Moreover, as mentioned earlier, the cause of ALF is the best predictor of prognosis and may guide how aggressive care should be upfront.

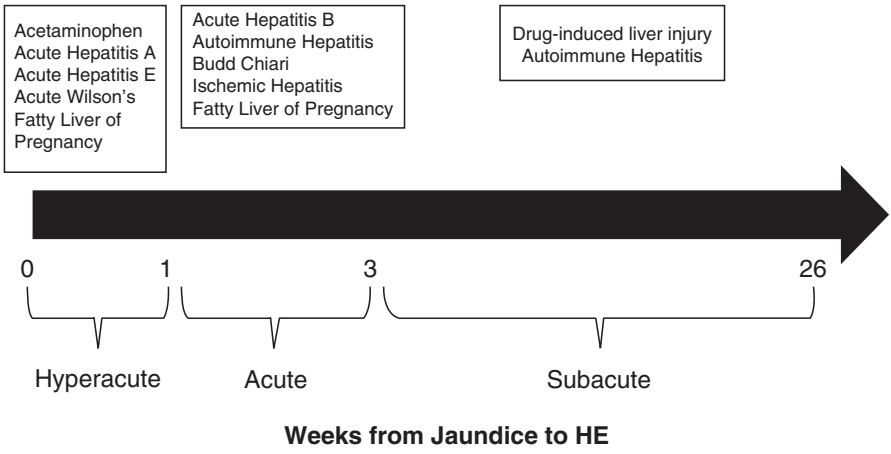


**Fig. 1.1** Common causes of acute liver failure by subclassification

## Drug-Induced Liver Injury (DILI)

Countless drugs are introduced into the market annually, and a significant portion carry the risk for hepatotoxicity [17]. The recent explosion in immunotherapy, namely checkpoint inhibitors aimed at suppressing the "brakes" of the immune system are likely to contribute even further in the near future to this ongoing concern [18]. To promote research and collaboration in this field, the National Institute of Diabetes and Digestive and Kidney Diseases created the LiverTox website, which now serves as an excellent tool for healthcare providers to rapidly review reported hepatotoxicity for a particular drug or supplement [19]. While around 90% of non-acetaminophen related drug induced liver injury does not progress to ALF [4], there is much higher concern for ALF when acetaminophen overdose is suspected. Therefore, it is reasonable to divide ALF related to DILI into events that are acetaminophen and non-acetaminophen related.

### *Acetaminophen-Related Acute Liver Failure*

Acetaminophen (or parecetamol) is one of most widely available and commonly utilized analgesics around the world. In many countries, including large portions of Europe and the entire United States, it can be purchased over the counter without a prescription, and in the US, in almost unlimited quantities. Acetaminophen-induced ALF is characterized by profound aminotransferases elevation (>3500 IU/mL) [3] and a hyperacute presentation [2, 3, 14]. Multi-organ failure is common, but unlike other etiologies of ALF with similar levels of illness severity, the chance spontaneous recovery and survival is as high as 70% without liver transplantation and 86% with LT [15].

Hepatotoxicity can result from either intentional overdose (such as a suicide attempt) or an unintentional overdose in predisposed hosts or individuals taking other analgesics that also contain acetaminophen [20]. Glutathione stores are essential in shifting the metabolic pathway towards non-toxic byproducts of acetaminophen. Alcoholics are at particular risk for developing hepatotoxicity from acetaminophen even at doses under the maximum recommended (4 g daily) and especially with long-term acetaminophen use over days to weeks. This is primarily due to the depletion of glutathione stores related to chronic alcohol abuse, and thus increased production of N-acetyl-p-benzoquinoneimine, the toxin implicated in DILI related to acetaminophen [21, 22]. Thus, alcoholics and individuals on chronic opioids containing acetaminophen are more likely to have an accidental overdose leading to ALF.

In contrast to many developing countries, acetaminophen overdose is the most common identifiable cause of ALF overall and DILI-related ALF in the US, the majority of Europe, and Australia [14]. In the United States, acetaminophen accounted for 39% of ALF cases, and the majority is felt to be accidental [23]. Similar to the US, ALF in the UK is primarily related to acetaminophen overdose, with rates as high as 73% historically [1]. More patients were reported to have an intentional rather than unintentional overdose, raising high enough concerns within the country that major legislation was passed limiting the over the counter sale of the drug [24]. However, despite these efforts, between 1999–2008, 57% of ALF cases in the UK were still attributed to acetaminophen [25]. In contrast, DILI, and thus acetaminophen, as an etiology for ALF in developing countries is less common, with some studies reporting a 0% incidence in Pakistan and Sudan in the early 2000s [26, 27].

A study evaluating adult patients with ALF admitted to the Liver Intensive Therapy Unit in King's College London from 1973–2008 found that those with acetaminophen identified as the etiology were more likely to be female and young (mean age of 30 years) [15]. Similar to the UK, data from the Acute Liver Failure Study Group (ALFSG) also found that women were more likely to develop ALF related to acetaminophen overdose, and were predominantly non-Hispanic whites. Luckily, this demographic was also more likely to have spontaneous survival [28, 29]. Thus, this etiology of ALF is more likely to be seen in young, white women in developed countries with a hyperacute presentation of liver failure characterized by significant transaminase elevation and often multi-organ system failure.

## *DILI (Non-acetaminophen) Related Acute Liver Failure*

DILI related to a drug other than acetaminophen (which will be termed DILI going forward) is the second leading cause of ALF in developed countries. It accounts for 11–17% of ALF cases in the US, UK, Germany, Sweden and Spain [25, 30–32]. Of

these countries, Spain has the highest reported incidence of DILI related ALF, accounting for 17% of all ALF admissions in a Spanish study between 1992–2000, while acetaminophen-related ALF resulted in only 2% of cases [30]. It can result from the ingestion of prescription medications, over the counter drugs, herbal remedies, nutritional supplements, or weightloss agents amongst other substances, even at the intended doses. Global variations in the most common offending drug class exist, with herbal and nutritional supplements more commonly implicated in Asia [33]. However, the estimated number of Americans on some type of supplement has increased through the years, and is now estimated to be over 50% of the adult population [34].

Unlike acetaminophen related ALF, DILI is predominantly seen in older individuals, often above the age of 60 years [2]. This is significant because mortality related to ALF from DILI is associated with increased age, [4] which may explain the poorer outcomes observed in patients diagnosed with this cause of ALF. In both the US and Spain, women were more likely to develop ALF from DILI than men, similar to patterns seen in acetaminophen related liver failure [4, 35]. However, the ethnic disparities seen in DILI differed from acetaminophen related ALF, with Asians and blacks more commonly affected than whites in the US. Furthermore, Hispanic whites rather than non-Hispanic whites are more likely to present with this disease, possibly owing to the wider use of anti-tuberculosis therapies, which are common causes of DILI. Asians in the US are five times more likely than blacks or whites to develop DILI related to supplements, which has been associated with higher morbidity and mortality [29].

Although only 1 in 10 patients who developed DILI progress to ALF, those that do progress have only a 20% chance of recovering without LT [4]. The remaining 80% of patients with ALF either undergo transplantation or do not receive one in time and die. The clinical presentation is more commonly subacute in nature and poorer outcomes are associated with deep jaundice and higher aminotransferases [4, 14]. Drug discontinuation, though advised, does not always reverse liver injury and a hypersensitivity clinical presentation, such as DRESS, is infrequent [2, 36]. The most common classes of drugs leading to DILI include antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), anti-tuberculosis drugs, and anti-epileptics.

## *Viral Hepatitis*

Acute viral hepatitis remains the most common etiology of ALF in the developing world, accounting for as high as 80% of documented cases in endemic regions [27]. Although there is a long list of viruses with the potential to cause acute hepatitis and thus ALF, Hepatitis A (HAV), B (HBV), and E (HEV) are the most commonly implicated [16]. The survival rate primarily depends on the health characteristics of the infected host [37], and specifically for ALF related to acute HBV, to the time to anti-viral therapy initiation [38].

The subclassification of ALF in the first few days of the illness can suggest an increased likelihood for one viral infection over another. ALF related to acute HBV is often acute in symptomatology [2] and therefore, is associated with higher mortality rates than HAV and HEV. In contrast, ALF related to either HAV or HEV is often hyperacute with a higher rate of spontaneous recovery and survival. However, older patients and those with underlying chronic liver disease are at particular risk for poor outcomes from any acute viral hepatitis leading to ALF, regardless of the underlying viral etiology [37].

Acute HBV is a common viral-cause of ALF globally, with predominance in Asia and sub-Saharan Africa [14, 39, 40], where the infection is more prevalent. In the US, HBV is much more common in immigrant communities. Asian Americans are more likely to develop ALF from acute HBV as compared to black or white Americans [29]. In Europe, the proportion of ALF from HBV is highly variable, with rates as low as 4% in Sweden, and as high as 32% in Spain [30, 32]. Luckily, less than 5% of patients who acquire acute HBV go on to develop ALF, [1, 41] although those who do progress to ALF are at high risk for death without LT. Those who develop ALF from denovo acute HBV infection have higher rates of survival when compared to cases of HBV reactivation. Reactivation of HBV can occur in the setting of chemotherapy or severe immunosuppression such as in the setting of a solid organ transplant in patients with chronic HBV or prior exposure to HBV and persistent hepatitis B core antibody positivity [42, 43]. Thus, it is vital to screen anyone for hepatitis B exposure or infection prior to the initiation of immunosuppressive regimens known to increase the risk for HBV reactivation, such as chemotherapy for lymphoma or post-transplant anti-rejection therapy.

Acute HAV has a highly variable presentation, from asymptomatic in many children, to an acute hepatitis with gastrointestinal symptoms such as diarrhea, and rarely, ALF [41, 44]. The virus is transmitted in a fecal-oral manner and is more common in areas with lower standards of hygiene. Overall, it is a less common cause of ALF globally, with higher rates in countries such as Pakistan (7% of ALF cases) and much lower rates in the UK (as low as 2%) [25, 27]. Data from 2006 published by the ALFSG noted that acute HAV accounted for 3.1% of enrolled patients. From 1988–2005, the annual frequency of LT for acute HAV remained under 1% within the ALFSG, decreasing significantly from 0.7% to 0.1% during the study period [45]. In fact, despite the fact that 1.5 million cases of acute HAV are estimated annually, less than 1% result in ALF [46].

ALF secondary to acute HEV is a rare entity in developed countries, with estimated rates as low as 0.4% of ALF cases in the US [47] and 1% of cases in the UK [25]. However, some reports place HEV as one of the most common causes of ALF in countries like Pakistan, China, and India [48]. Most cases in developed countries are thought to be related to international travel to endemic areas, although sporadic cases have also been documented as well. Analysis of the ALFSG suggested that prior HEV infection based on antibody presence was seen in a large number of patients with ALF from other causes (>40%) [47]. However, the clinical significance of this finding remains unknown. Thankfully, because of it's hyperacute presentation, many patients will recover without the need for transplantation. Patients

who are older and with multiple other comorbidities tend to have the worst outcomes [2]. Historically, pregnant women where also thought to be at increased risk for poor outcomes from ALF related to HEV, although newer data questions the validity of this belief [49]. Regardless, ALF related to HEV is much more common globally than in North America and Europe, and should be considered on the differential diagnosis in endemic regions and in patients who have returned from recent travel to these regions as well.

The epidemiology of ALF related to viral hepatitis has seen a dramatic shift over the past few decades, mainly related to the introduction of the hepatitis A and B vaccines, and the widespread implementation of childhood vaccination programs [5]. Efforts to promote vaccination in endemic regions is key, and addressing barriers to access is essential in decreasing the morbidity and mortality of ALF related to viral hepatitis.

## *Other Causes of Acute Liver Failure*

As detailed previously, the majority of ALF cases globally are related to acetaminophen overdose, other DILI-related causes, and viral hepatitis, but there remains a long list of other potential etiologies that should always be considered, especially when the diagnosis is unclear. While 7–38% [5] of causes for ALF remain unknown, autoimmune hepatitis (AIH), ischemic hepatitis, Wilson's Disease, Budd-Chiari Syndrome, and pregnancy-related ALF are other potential etiologies that are worth mentioning.

AIH has been described in up to 4% of ALF cases in the US and is predominantly seen in young (~40 years of age) Caucasian women. Although autoimmune markers may be helpful in the diagnosis, biopsy may be necessary as rates of positive autoimmune markers have been reported in as little as 50% of cases. Even when present, positive autoimmune markers do not always confirm a diagnosis of AIH. An acute presentation of AIH is seen in up to 25% of individuals with the disease, although only a smaller subset progress to ALF [23, 50]. Of note, similar to chronic hepatitis B, previously unrecognized AIH leading to an acute flare with coagulopathy and encephalopathy is still considered ALF, despite the chronicity of the underlying disease.

Acute Wilson's Disease accounts for around 3% of ALF presentations in the US [23], is more common in younger patients, and is universally fatal without LT [2, 7]. The presence of previously unrecognized chronic Wilson's Disease does not exclude Acute Wilson's Disease as a form of ALF. It can be recognized by several pathognomonic features, included a characteristically low alkaline phosphatase level, the presence of a hemolytic anemia (sometimes leading to an indirect hyperbilirubinemia) and the presence of Kaiser Fletcher Rings.

Ischemic hepatitis as a cause of ALF is often secondary to another insult. Potential causes of ischemic hepatitis include sepsis or the use of drugs such as cocaine that may induce an ischemic insult in the liver. It has been reported to cause

up to 6% of ALF cases in the US and is managed with supportive care and treatment of the underlying insult [1, 23].

## Acute on Chronic Liver Failure

The progression from compensated cirrhosis to decompensated cirrhosis is a well-defined event characterized by the development of ascites, esophageal variceal bleeding, hepatic encephalopathy or other complications of portal hypertension [51]. It pertains to an increased short-term mortality and is thus an indication for liver transplant evaluation in the appropriate patient. However, a subset of patients with underlying liver disease can present with a condition that mimics the acuity and critical illness of ALF, now termed as acute on chronic liver failure (ACLF). In contrast to decompensated cirrhosis, ACLF represents a different syndrome in which severe hepatic dysfunction is associated with extrahepatic organ failures and can occur rapidly in an individual with known chronic liver disease [52–54]. This is thought to occur secondary to a trigger including direct hepatic or extra-hepatic insults and present in 24–40% of patients with cirrhosis admitted to the hospital [53]. The hallmark characteristic of ACLF is the associated high short-term mortality, which is consistently cited in attempts to define the syndrome and is measured typically in weeks rather than longer periods of time [55–57]. With a threshold of at least 15% mortality within 4 weeks [56], it is clear that the various definitions of ACLF all carry significant prognostic weight and are therefore important to properly understand.

The process of defining, classifying and describing the epidemiology of ACLF has suffered from various inconsistencies, likely related to cohort studies with dissimilar inclusion and exclusion criteria and subtle differences in definitions for extrahepatic organ failure (Table 1.2) [58, 59]. The two commonly sited long-term studies are the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) and the EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study [55, 56]. However, the first large consensus on ACLF was published in 2009 by the Asian Pacific Association for the study of the Liver

**Table 1.2** Comparing CLIF-SOFA vs. NACSELD-ACLF organ failure definitions

| Organ failure | CLIF-SOFA [56] | NACSELD-ACLF [55] |
|---|---|---|
| *Circulatory* | +Vasopressors | MAP <60 mmHg |
| *Respiratory* | PaO2/FiO2 ≤ 200 or SpO2/FiO2 ≤ 214 | Mechanical ventilation |
| *Renal* | Creatinine ≥ 2 mg/dL or RRT | RRT |
| *Cerebral* (West Haven HE) | Grade III or IV | Grade III or IV |
| *Liver* | Total bilirubin ≥12 mg/dL | Not included |
| *Coagulation* | INR ≥ 2.5 | Not included |

*HE* Hepatic Encephalopathy, *RRT* Renal Replacement Therapy

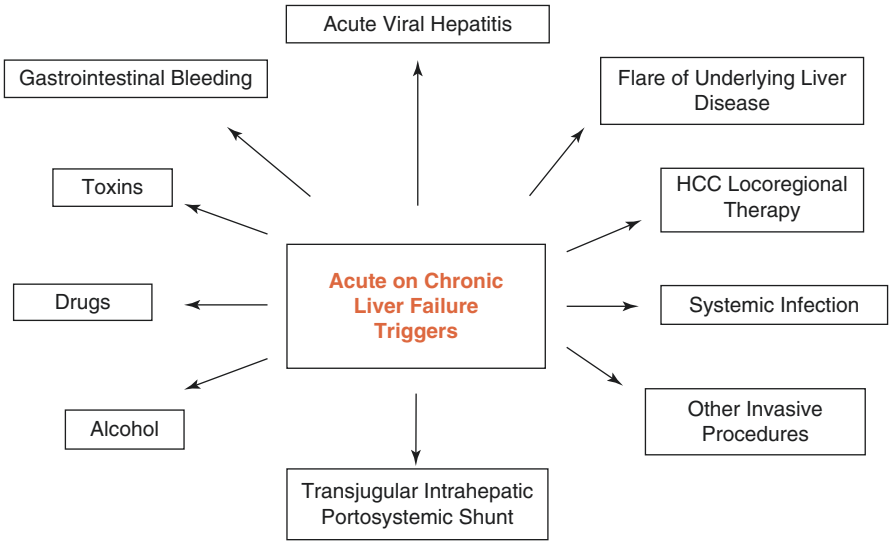


**Fig. 1.2** Common triggers of acute on chronic liver failure

(APASL), which has since been revised both in 2014 and 2019 [57]. All three study groups focus not only on defining ACLF, but also identifying the triggers of this condition which serve as primary drivers of its epidemiology (Fig. 1.2). Examples of triggers include heavy alcohol ingestion, acute viral hepatitis or reactivation of HBV, bacterial or fungal infections, gastrointestinal hemorrhage, or flare of the underlying liver disease [54]. To better understand the differential effect of these triggers on patients with underlying liver disease in both the Eastern and Western hemispheres, a closer look at how each society has studied and defined ACLF is necessary.

## *ACLF in the East*

The APASL characterizes ACLF as an "acute hepatic insult" leading to liver failure and its complications including ascites and encephalopathy in a patient with chronic liver disease or cirrhosis that leads to high 28-day mortality [57]. Although at first glance there are concerns that such a definition may include many patients who merely transition from compensated to decompensated cirrhosis, the threshold for 28-day mortality in studies used to develop this definition was at least 33%. Thus, in Asia, only patients with decompensated liver disease with an extraordinarily high short-term mortality are recognized as having ACLF. Interestingly, unlike the West, patients in the Eastern hemisphere can be diagnosed with ACLF in the absence of cirrhosis, so long as they have some underlying chronic liver disease diagnosis [57, 59]. The presence of liver failure manifested by a serum bilirubin $\geq$5 mg/dL and

coagulopathy however is an absolute requirement to make the diagnosis, while extrahepatic organ failure is seen as a consequence of ACLF, rather than a defining characteristic, which is felt to be often related to subsequent sepsis developing after ACLF is recognized [57].

The acute insult or trigger for ACLF in Asia centers primarily on direct hepatic insults given the nature of the current ACLF definition. Observations and trends from research using the APASL ACLF Research Consortium (AARC) has been instrumental in determining the major causes of this clinical entity, which includes data from 5228 patients in 43 centers from 15 countries that have been added since 2014 [57]. Acute viral hepatitis, mostly HBV reactivation, remains the most common cause of ACLF in Asia [54, 60]. Moreover, a study of Chinese patients using the European definition of ACLF based on both the presence of intra or extrahepatic organ dysfunction (determined by the CLIF-SOFA score) also revealed that the majority of ACLF triggers were related to an HBV flare or exacerbation (35.8%). Within the same cohort, the second most common insult leading to ACLF was bacterial infections (nearly 35%) followed by less common triggers including upper GI bleeding (9.9%), superimposed HAV or HEV infection (6.4%) or heavy alcohol use (6.2%) [54]. Yet, similar to other observational research done in the field, a large portion of patients diagnosed with ACLF did not have an identifiable trigger (20.5%), a particular concern for efforts in preventing ACLF in future patients with chronic liver disease [53, 55, 59]. Patients with hepatic insults (such a viral hepatitis or alcoholic hepatitis) tended to be younger in age and overwhelmingly with a diagnosis of HBV related cirrhosis (>90%) [54]. In addition to HBV, other common etiologies of underlying chronic liver disease in patients enrolled in the AARC included NAFLD, HCV, and alcohol-related liver disease [57], similar to other parts of the world. Surprisingly, some reports have even put underlying alcohol related liver disease as the most common etiology of chronic liver disease in Asian patients with ACLF (47% alcohol vs. 25% viral) [53]. Additionally, underlying metabolic comorbidities such as obesity, type 2 diabetes, hypertension and dyslipidemia were associated with a more severe disease course in those with alcohol related chronic liver disease [57].

In addition to these common ACLF triggers, studies out of Asia have also identified DILI as a cause of ACLF in as high as 1 in 10 patients with the condition. The most common culprits are anti-tuberculosis therapies (predominantly in India) and herbal remedies (predominantly in China) [61, 62].

## *ACLF in Europe*

In 2013, the initial findings of the CANONIC study were published and introduced the European definition of ACLF. It was considered a syndrome that occurs in hospitalized patients with acute decompensation (AD) of their underlying cirrhosis and has a high mortality related to associated organ failure. The aim of this study was to define ACLF based on a predicted 28-day mortality of at least 15% and only in a

subset of patients with underlying cirrhosis who are hospitalized with an AD of their liver disease [56], thus excluding non-cirrhotic chronic liver disease patients who are considered in the APASL definition. A cohort of 1343 patients with cirrhosis admitted with AD were enrolled from 12 European countries in the CANONIC study. By comparing rates of 28-day mortality on the basis of the presence of hepatic, cerebral, coagulation, circulatory and kidney failure as well as the total number of organ failures, a definition for ACLF and corresponding ACLF grades were developed. Each type of organ failure was graded using a modifying sequential organ failure assessment (SOFA) score (CLIF-SOFA). Ultimately, the strong correlation between kidney failure and 28-day mortality was noted, and ACLF was therefore defined by one of three possibilities in this patient population: (1) A single organ failure if that organ failure was the kidney (2) Two organ failures (3) a single non-kidney organ failure in the presence of kidney dysfunction, defined by a serum creatinine of 1.5–1.9 mg/dL with or without moderate hepatic encephalopathy [56].

In the European cohort, patients with ACLF were more likely to be younger than those without (mean age 56 years) and predominantly male. Underlying chronic liver disease was overwhelming related to alcohol (60% of the ACLF population) and the most common triggers were bacterial infections (32.6%) and active alcoholism (24.5%). Similar to the Asian cohort, a large portion of patients who developed ACLF did not have an identifiable trigger (43.6%) and gastrointestinal bleeding, although assumed to be the insult in 13.2% of ACLF patients, was not more common than in those without significant organ failure [56]. Although alcohol related liver disease is a common backdrop for ACLF in both Europe and Asia, unlike the Asian population, viral hepatitis is less prevalent and ranges from 12 to 14% of ACLF cases [56, 63].

The CANONIC study was also successful in formulating a grading scheme for ACLF based on the type and number of organ failures and the associated 28-day mortality. ACLF grade 1 is associated with a 22.1% 28-day mortality and includes patients with kidney failure alone, those with liver, coagulation, respiratory or circulatory failure with underlying renal dysfunction, or patients with cerebral failure with underlying renal dysfunction. ACLF grade 2 is simply defined by the presence of 2 organ failures and is associated with a 32% 28-day mortality. ACLF grade 3 occurs in the sickest patients, is characterized by a 76.7% 28-day mortality, and includes only patients with 3 or more organ failures [56]. Not surprisingly, the more organ failures present, the higher the mortality rate. However, what is most important to note is the significance of renal dysfunction or failure in patients with ACLF, which is well characterized by both this ACLF definition and grading scheme.

## *ACLF in North America*

In North America, ACLF has been primarily investigated in hospitalized patients with cirrhosis who suffer from an infectious episode as well [55, 59], although the NACSELD ACLF definition has also been validated in patients without infection

[64]. Similar to Europe, the definition of ACLF within NACSELD was based on the presence of organ failure, although only extrahepatic organ failure is included in the definition. Renal, brain, circulatory, and respiratory failure are the four organ systems assessed when determining the presence of ACLF within this cohort. Aside from the presence of advanced hepatic encephalopathy (West Haven grade 3–4), the presence of each organ failure is defined somewhat differently. Respiratory failure is present when there is a need for mechanical ventilation, the presence of shock based on blood pressure thresholds is used to describe circulatory failure, and the need for dialysis is necessary before kidney failure is recognized. ACLF is present when two or more organ systems fail and mortality was defined at 30 days [55].

The underlying etiology of chronic liver disease included only patients with cirrhosis, with coexisting alcohol and viral associated liver disease being the most common underlying diagnosis (27%), followed closely by viral hepatitis alone (25%) [53, 55]. Triggers for ACLF episodes were harder to elucidate, especially given the focus on infected patients with cirrhosis. Although this focus on infected individuals has been cited as a potential limitation, it has shed some light on key aspects of this common trigger for ACLF. Urinary tract infections were the most prevalent type of infection in this cohort, comprising over a quarter of all infectious episodes. Even more surprising was the fact that more gram-positive organisms were isolated than gram-negative, and the rate of isolated fungal infections was as high as 17.6% [55].

One major concern of the Western ACLF definitions (both CANONIC and NACSELD) is the heavy reliance of the presence of organ failure as a way to make a diagnosis of ACLF. This may lead to late recognition of this syndrome [52, 57, 59] at a point where even the best intensive care may not dramatically alter the natural history of the disease. A definition such as that used by the APASL that identifies ACLF in patients prior to resulting extrahepatic organ dysfunction may allow for early intervention and hopefully better outcomes, although this has yet to be proven.

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# Chapter 2
# Acute and Acute on Chronic Liver Failure: Mechanisms of Disease and Multi-systemic Involvement

**Vivek Lingiah, Mumtaz Niazi, and Nikolaos Pyrsopoulos**

**Key Concepts**
- ALF and ACLF are conditions where an initial liver injury results in multi-organ involvement and dysfunction
- ALF and ACLF are mediated by systemic inflammation
- Unopposed systemic inflammation leads to increased risk of multi-organ failure

## Introduction

Traditionally, liver failure (LF) has been subdivided into acute liver failure (ALF) or chronic liver failure (CLF). In the last few years, the concept of acute on chronic liver failure (ACLF) has gained significant attention. Liver failure is a syndrome which causes significant hepatic injury, liver synthetic dysfunction, as well as extensive multi-organ failure. The mechanism, how acute liver injury leads to complex, multi-systemic consequences is incompletely understood and remains elusive. The PIRO concept (Predisposition, Insult, Response and Organ Failure) has been suggested as a method to better define the underlying mechanism in ACLF. Further knowledge about this lethal syndrome can be attained as the underlying pathophysiology is deciphered, organ by organ.

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## Liver

Pathological changes resulting in LF can be divided into two main categories—acute, severe liver necrosis and chronic, progressive liver cell damage. Since hepatocytes have the ability to regenerate, in ALF, severe and acute insult to hepatocytes initiates a race between hepatocyte cell death and regeneration. The injured hepatocytes attract inflammatory cells with subsequent release of inflammatory cytokines into the circulation, which inhibits mitosis. The aftermath of hepatocyte injury is the buildup of waste products, systemic inflammatory response, and impairment of regenerative capabilities.

Apoptosis and necrosis are the two fundamental pathways by which liver cell death occurs [1]. Mechanisms of hepatic apoptosis are complicated by multiple signaling pathways. The severity of hepatic apoptosis is varied due to different etiologic factors which can cause apoptotic cell death through membrane receptors and intracellular stress [2]. Apoptosis is often silent, resulting in minimal inflammation. Necrosis, on the other hand, is an acute and severe response, in which the depletion of adenosine triphosphate (ATP) results in intracellular swelling and eventually cell rupture, producing a substantial inflammatory response [3]. Cell death is caused by many interrelated processes such as caspases, oxidative stress and anti-oxidants, transcription factors, cytokines, and kinases [2, 4]. The nature and duration of cellular injury determines if cell death would be by apoptosis or necrosis.

Necrosis is the premature death of a cell. In the necrotic pathway, severe liver damage involves oxidative stress, ATP depletion, cellular swelling and subsequently blebbing of membrane integrity. Mitochondrial depolarization, along with breakdown of lysosomes and rapid ion changes result in a vicious cycle with further volume shifts, cellular swelling and bleb formation, ending in membrane rupture [5]. This membrane rupture eventually leads to cell death. Other major features include significant energy loss, reactive oxygen species (ROS) generation, as well as triggering non-apoptotic proteases. Moreover, there is a robust increase of intracellular calcium cations during necrosis. These high cytosolic calcium levels activate mitochondrial calcium overload and subsequent inner mitochondrial membrane depolarization, resulting in a cessation of ATP production. Calcium shifts, loss of ATP, and oxidative stress are linked via intricate feedback loops, which augment each other, resulting in massive cell death [6, 7, 8]. Secondary inflammation also occurs as a result of cellular rupture, resulting in release of intracellular contents.

Hepatic apoptosis, the programmed form of cell death, is present in nearly all forms of hepatocyte injury. Factors such as viruses and hepatotoxins can mediate significant apoptosis through ligands and membrane receptors [9]. The apoptotic pathway in ALF follows a cascade of several steps. Apoptosis is composed of both an extrinsic and intrinsic pathway. The extrinsic pathway causes a direct activation of caspases and is started with the collaboration of apoptosis-causing factors and their respected ligands. The cleavage of procaspase eight to active form is the end result of specific ligands (TNF-α, FasL) binding to their respective transmembrane proteins (TNF-R1, Fas). Inflammatory cytokines such as TNFα can constantly

induce the activation of caspase-8, caspase-3, and DNA fragmentation via membrane receptors [10, 11]. The indirect or intrinsic pathway involves mitochondrion-mediated activation of caspases. Mitochondrial damage occurs secondary to excess reactive oxygen species. This results in cytochrome c release and caspase-9 activation, which in turn triggers caspase-3 activation and apoptosis [12]. The concept of necro-apoptosis, the aptly named overlap between the apoptotic and necrotic pathway, have also been more recently described.

Inappropriate activation of death receptors may result in liver failure. This has been described in animal models [9, 13] and HCV infected patients [14]. Liver dysfunction reflects the severity of liver damage that includes both apoptosis and necrosis. Liver cell death via apoptosis develops as a key component of nearly all acute and chronic liver disease. Apoptosis affects liver tissue repair, regeneration and fibrosis. It also mediates the mechanisms of hepatic fibrosis/cirrhosis. Liver failure will develop if there is a severe enough liver injury, and the regenerative capabilities of the liver are outmatched by an increased rate of cell death. With this critical loss of hepatocytes, liver synthetic function decreases, with a breakdown of intra-hepatic metabolism, affecting other organ systems. The necrotic component of hepatocyte death results in increased systemic inflammation, which is augmented by a reduction in hepatocyte capacity to remove circulating cytokines. The ultimate result of these two processes is severe liver injury that results in ALF, which has multi-organ repercussions with poor prognosis.

Liver failure in ACLF is characterized primarily by coagulopathy and hyperbilirubinemia. The type of hepatic insult dictates the mechanism of LF. For example, apoptosis occurs in alcohol related ACLF but sub massive hepatic necrosis occurs in case of flare of hepatitis B (HBV) related ACLF. Injured hepatocytes have reduced ability to secrete bile salts and inflammation secondary to tissue damage or pathogen, causes reduced bile transporters in hepatocyte and subsequently cholestasis [15].

## Immune System

The liver is rich in innate immune cells and immunosuppressive cytokines. It is the first organ that comes into contact with bacterial products arriving from the gut, through the portal circulation. Activation of systemic immune response plays a crucial role in the pathogenesis of syndrome of liver failure (ALF or ACLF). Both the systemic inflammatory response and the compensatory anti-inflammatory response are more pronounced in cirrhosis compared to normal individuals and markedly pronounced in ACLF. Gut dysbiosis and increased gut permeability is associated with increased endotoxemia in cirrhosis and ACLF. Cirrhosis affects innate immunity by impairment in the synthesis and function of patterns recognition receptors (PRRs) and various proteins, hence decreasing the bactericidal capacity of the body.

In LF, innate immune-induced liver injury occurs initially with subsequent adaptive immune response-related injury. Innate immune activation can be due to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular

**Table 2.1** Criteria that make up the systemic inflammatory response syndrome [17]. To have SIRS, one must meet 2 or more of the above criteria

- Temperature > 38 °C or < 36 °C
- Heart rate > 90 beats per minute
- Respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mmHg
- White blood cell count >12,000/$mm^3$ or < 4000/$mm^3$ or < 10% immature neutrophils

patterns (DAMPs), endogenous signals derived from injured cells. In ALF or ACLF, hepatocellular damage may result from sterile Inflammation (e.g. alcohol, surgery, acetaminophen) driven initially by DAMPs, or septic inflammation which is driven by PAMPs. Various cells take part in the innate immune response, expressing receptors that can identify both PAMPs and DAMPs. The Toll-like receptors (TLRs) can detect both PAMPs and DAMPS and are key in sensing foreign bio-materials and triggering intracellular defense mechanisms. However, this initiation of inflammatory mechanisms can lead to more cell injury than repair [16].

The clinical picture of ALF and ACLF, shares many similarities with severe sepsis or systemic inflammatory response syndrome (SIRS) with multi-organ failure (Table 2.1) [17–20]. Sepsis like immune paralysis has been demonstrated in LF. The importance of SIRS in the outcome of LF has been well-established and has been associated with multi-organ failure and increased mortality [18–20]. SIRS occurs as a result of the release of pro-inflammatory cytokines such as TNF-ά, interleukin (IL)-1, and IL-6 [21]. Simultaneously, there exists a compensatory anti-inflammatory response syndrome (known as CARS), mediated by anti-inflammatory cytokines like IL-4, IL-10, and transforming growth factor-ß, which works to reduce the SIRS. However, persistent CARS may not be beneficial as it can result in sepsis and high mortality. Despite having a vigorous inflammatory immune response, the patients with ALF and ACLF are more susceptible to infection, with high morbidity and mortality [22–24]. The relationship between the SIRS response and high susceptibility to infection in LF patients could be secondary to inflammatory response causing immune dysregulation [25].

Monocytes, macrophages/Kupffer cells are important players in both the innate and the adaptive immune systems. Their activation results in significant cytokines production augmenting both pro-inflammatory and anti-inflammatory responses along with T cell activation. Many changes in monocyte function and secretion have been demonstrated in both ALF and ACLF, such as increased IL-6 and CRP levels. In ALF, monocytes have shown decreased ability to secrete TNF-ά when challenged, a finding linked with worse outcomes. In LF, with reduced TNF-ά secretion, there is amplified release of IL-10 (an anti-inflammatory/immunosuppressive cytokine), and decreased HLA-DR expression—these changes result in an impaired ability of monocyte antigen presentation [26–29].

The production of fibronectin and complement synthesis principally occurs in the liver. Fibronectin is a key glycoprotein in the process of opsonization, helping to clear pathogens through Kupffer cells and the reticuloendothelial system. Significantly decreased fibronectin levels have been noted in ALF patients, a finding associated with increased mortality [30]. The liver failure not only causes

decrease production of complement levels, particularly C3 and C5, but also causes qualitative changes both in classical and alternative pathways, leading to defective opsonization [31].

Neutrophils are a crucial component of the innate immune system. Evidence supports that neutrophils in cirrhosis exhibit high resting reactive oxygen species (ROS) production but impaired neutrophil endothelial adhesion and neutrophil chemotaxis [29]. In ALF, other functions of neutrophils are noted to be reduced, such as superoxide/hydrogen peroxide production and complement receptor expression [32]. Neutrophil dysfunction in cirrhosis may be reversible. Granulocyte colony stimulating factor (G-CSF), an immunomodulator glycoprotein which stimulates neutrophil cell growth, differentiation and function, has been shown in small studies to have survival benefit in ACLF. This observed benefit is likely related to liver regeneration, improved immune response and the improvement in neutrophil activity causes reversal of the significant immune dysfunction, with subsequent prevention of sepsis and reduced mortality [33].

LF is therefore, a clinical syndrome that results from activation of the systemic immune response both pro- and anti-inflammatory cytokines spilling into the systemic circulation and DAMPs as a result of massive hepatocyte necrosis. Dysregulation between pro and anti-inflammatory factors causes immune dysfunction in ALF and ACLF, contributing to grave outcomes in this population. This underlines that the patient's immune system may cause collateral tissue damage and can be a double-edge sword for the host, resulting in multi-organ failure (Fig. 2.1).

## Brain

One of the most important components of ALF is neurologic deterioration. The evolution of hepatic encephalopathy (HE) can be quick, with progression of slight confusion or agitation, to delirium, seizures, and coma being associated with reduced survival (Table 2.2) [34, 35]. In the advanced phases, complications such as cerebral edema and increased intracranial pressure can occur, which have been associated with decreased spontaneous liver recovery rates <20%, compared to 70% in grades 1 + 2 HE [36].

In ALF, DAMPs are released from necrotic liver cells. This results in production and release of pro-inflammatory cytokines from the portal circulation which enter the systemic circulation [37, 38]. This leads to decreased systemic vascular resistance with decreased systemic blood pressure and an increased cardiac output, that culminates in a decreased cerebral perfusion pressure (CPP) [37]. However, even with a reduced CPP, cerebral blood flow can be immensely increased secondary to dysfunctional autoregulation with drastically reduced cerebrovascular resistance (CVR). This results in increased delivery of potentially harmful products, like ammonia and cytokines, to the brain [39].

Cytokines are formed by means of the systemic inflammatory response syndrome, the clinical manifestation of the release of pro-inflammatory cytokines

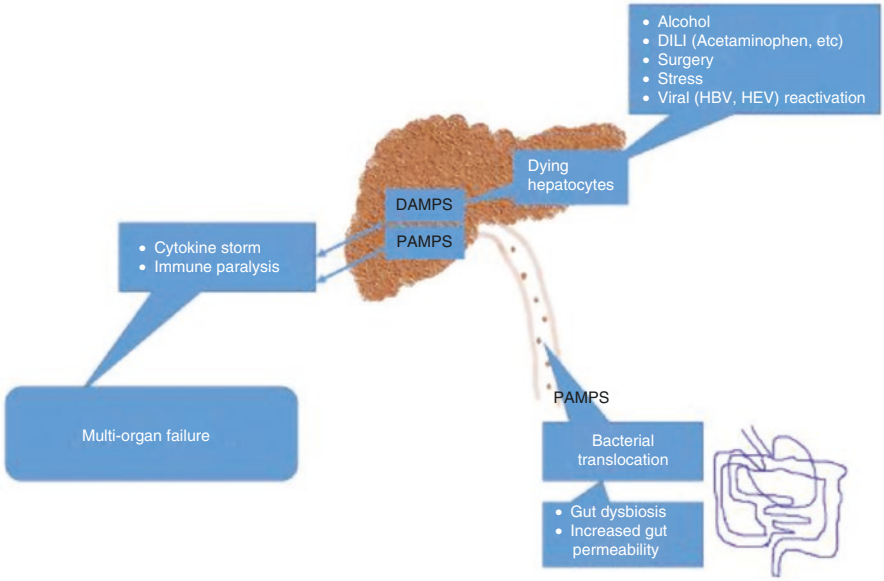


**Fig. 2.1** Pathogenesis of Immune Activation in ACLF. Gut dysbiosis and increased gut permeability lead to increased rates of bacterial translocation and endotoxemia in ACLF. Immune activation can occur through this and other septic pathways via pathogen-associated molecular patterns (PAMPs). It can also occur via 'sterile' inflammatory pathways, like alcohol, surgery, acetaminophen toxicity, viral hepatitis reactivation, etc. that cause hepatocyte necrosis and release damage-associated molecular patterns (DAMPs). The subsequent cytokine storm and eventual immune paralysis can lead to multi-organ failure and increased susceptibility to bacterial infections

**Table 2.2** West Haven criteria grades of hepatic encephalopathy and associated signs/symptoms [34]

| Grade | Signs/symptoms |
|---|---|
| 1 | Mild lack of awareness, shortened attention span, sleep disturbance |
| 2 | Lethargy, minimal disorientation for time/place, asterixis |
| 3 | Stuporous, incoherent speech, sleeping but wakes with stimulation |
| 4 | Comatose |

(TNF-alpha, IL-1, IL-6, IL-8, and IL-12) [40]. Prior studies have shown the presence of SIRS to predict the evolution of hepatic encephalopathy, increase of intracranial pressure (ICP), or development of multi-organ dysfunction syndrome (MODS) [41, 42]. Aside from entering the brain through the systemic circulation, the pro-inflammatory cascade can be initiated in the brain itself by means of microglia [43]. In 2009, Jiang et al. were able to demonstrate microglial activation in mouse models of ALF [44]. Microglia are the resident macrophage of the brain, which can be activated in response to tissue damage, vascular changes, as well as impending energy failure [38]. In mouse models of ALF, high cytokine levels in the

brain were complemented by increases in the gene expression that they encoded, supporting the hypothesis that these cytokines were produced in the brain itself [43].

In ALF, mild HE (grades 1–2) is associated with lower rates of cerebral edema, compared to grades 3 and 4 HE, where it has been reported in 50–80% of cases [45, 46]. Two mechanisms have been suggested for the pathophysiology of cerebral edema, vasogenic and cytotoxic. Vasogenic edema suggests that there is a loss of blood-brain barrier (BBB) function resulting in water and solutes accumulating extracellularly. Cytotoxic edema conversely postulates that there is an intact BBB and that the brain cell swelling is taking place intracellularly [47]. There is more evidence in the literature to support cytotoxic edema and this review will focus upon the pathophysiology of cytotoxic edema.

The astrocyte is the principal brain cell that experiences swelling in ALF, a fact that has been demonstrated via experimental models and in ALF patients [48, 49]. Astrocytes occupy one third of the cerebral volume. In patient with ALF, MRI diffusion-weighted images revealed a decreased extracellular space, signifying an intracellular fluid buildup [50]. While the precise process of astrocyte swelling remains incompletely understood, ample evidence exists to show ammonia plays a large role. Ammonia is produced in the gut by the enzyme glutaminase as well as by urease-producing bacteria. Ammonia is delivered to the liver via the hepatic portal circulation, where it is processed principally through the urea cycle [40]. This pathway is compromised in ALF due hepatocyte injury, resulting in elevated serum ammonia levels [47]. Clemmeson et al. showed that high arterial ammonia levels were associated with increased brain uptake of ammonia, development of cerebral edema and herniation [51]. Comparable conclusions were demonstrated in children with urea cycle disorders like ornithine carbamoyl transferase deficiency, suggesting that hyperammonemia alone could be responsible for radiologic findings of cerebral edema [52]. In the brain, ammonia detoxification occurs solely within astrocytes. This is done via glutamine synthetase, which works intracellularly to combine ammonia and glutamate to form glutamine [35]. Previous studies have demonstrated raised glutamine levels within brain tissues of ALF patients, leading to the hypothesis that elevated ammonia levels resulted in enhanced generation and accumulation of glutamine within astrocytes, causing swelling in those cells [47].

This theory is known as the osmotic gliopathy hypothesis, where elevated glutamine levels function as an osmotic stressor, leading to water being drawn into the cell. This hypothesis has received validation based on the effects of methionine-s-sulfoximine (MSO), a glutamine synthetase inhibitor. In both in vivo and in vitro studies, MSO lowered glutamine levels not only in normal brains but also significantly reduced astrocyte swelling [47]. A variation of the osmotic gliopathy theory proposes that instead of elevated glutamine production within the astrocyte, in ALF there is an error or abnormal expression in SNAT5, the glutamine export transporter, resulting in intracellular glutamine accumulation. Glutamine's inability to leave the astrocyte causes a decrease in the pool of releasable glutamate, resulting in a decline in glutamatergic neurotransmission with extreme neuroinhibition, distinctive of the HE of ALF [43, 53].

An alternate concept, the 'Trojan Horse' hypothesis, has risen to explain the roles of ammonia and glutamine in astrocyte swelling. In this scenario, surplus glutamine created within astrocytes is transited into the mitochondria, where it is processed by phosphate-activated glutaminase (PAG) to glutamate and ammonia. The 'Trojan horse' is glutamine, which transports ammonia into mitochondria. Ammonia accrual results in oxidative stress, cerebral astrocyte swelling, with subsequent cellular degeneration [54].

Oxidative and nitrosative stress are critical factors in the development of ammonia-related neurologic changes. O'Connor et al. showed significant elevations in lipid peroxidation in hyperammonemic mice [55]. Ammonia has also been observed to result in free radical formation in both rat models and cultured astrocytes [56, 57]. Hyperammonemic mice were also noted to have reduced antioxidant enzyme activity like glutathione peroxide, superoxide dismutase, and catalase, with increased brain superoxide production [58]. Studies have shown oxidative stress causing astrocyte swelling in vivo and in vitro [35]. Furthermore, inhibition of ammonia-induced astrocyte swelling has been observed with the utilization of antioxidants such as superoxide dismutase, catalase, and vitamin E [59]. Also, nitrosative stress has been shown to lead to ammonia—induced encephalopathy. Using nitroarginine to inhibit nitric oxide synthase resulted in significantly decreased deaths in hyperammonemic mice. Similarly, nitric oxide levels were noted to be elevated in animal models with porto-systemic shunts receiving ammonia infusions [47].

Both cytokine release or oxidative/nitrosative stress can lead to mitochondrial permeability transition (MPT) induction. This is a calcium-based phenomenon that results in the exposure of the permeability transition pore that is within the inner mitochondrial membrane. When opened, there is increased protons/ion/solute permeability, lowering the potential of the inner mitochondrial membrane. This causes impaired oxidative phosphorylation with diminished ATP generation. Secondary oxidative stress and free radicals formation occur via the MPT, resulting in a vicious cycle [35, 47]. The MPT is associated with astrocyte swelling as MPT inhibitors such as cyclosporin have been demonstrated to impede astrocyte swelling in culture. Other compounds that inhibit the MPT, like trifluoparazome, magnesium, pyruvate, and L-histidine inhibit ammonia-related astrocyte swelling to varying degrees [35]. Could MPT induction be occurring as a result of ammonia entering the mitochondria via the Trojan Horse mechanism? 6-diazo-5-oxo-L-norleucine (DON), an agent that blocks PAG, prevents free radical production, induction of the MPT, and astrocyte swelling [47]. Therefore, while the process is still not fully understood, MPT induction plays a part in the development of brain edema. This may be due to free radical generation, leading to oxidative stress. Another possibility is that there are energy failure issues caused by the decreases in oxidative phosphorylation and ATP generation, resulting in dysfunction of the ion transporters involved in cell volume regulation [35].

The Na/K/Cl cotransporter-1 (NKCC1) has also been linked to swelling of astrocytes. Jayakumar et al. demonstrated that ammonia exposure lead to over-activation of this channel via increased oxidation/nitration, resulting in an intracellular influx

of these ions along with water and eventually cell swelling [60]. The ATP-dependent, non-selective cation channel (NCCa-ATP channel) has also been implicated in astrocyte swelling. The same group noted that ammonia-infused astrocytes had significant increased activation in the NCCa-ATP channel. This was recorded via the channel's regulatory protein, sulfonylurea receptor 1 protein (SUR1). Elevated levels of SUR1 correlated to astrocyte swelling, with activation of SUR1 levels occurring only during lower ATP situations [61].

More evidence is being found to suggest that aquaporin (AQP) water channels are activated in ALF, allowing water entry into the astrocytes via upregulated AQP-4 channels. Increased AQP-4 expression in astrocytes was noted in regular mice subjected to ALF, but not in AQP-4 knockout mice. This was shown as well in astrocyte cell cultures exposed to ammonia, with AQP-4 upregulation stopped with L-Histidine, a compound that blocks glutamine transport into the mitochondria. This suggests that glutamine uptake by astrocyte mitochondria may result in AQP-4 activation, resulting in astrocyte swelling [62].

In acute-on-chronic liver failure, the development of hepatic encephalopathy is associated with worse outcomes [63]. The pathophysiology of HE involves hyperammonemia, systemic inflammation, and issues with cerebral bloodflow.

The role of ammonia is similar to that mentioned in the ALF section, with ammonia being processed into glutamine in astrocytes, either acting as an osmotic stressor within the cell, or causing ammonia production in the mitochondria, leading to oxidative stress [63, 64]. Sawhney et al. showed that hyperammonemia was significantly associated with HE in patients with ACLF. They found that there was a significant correlation between increasing ammonia levels and increasing severity of HE, as well as the fact that improving levels of HE were significantly linked to decreasing ammonia levels [65].

Against this hyperammonemia, an added hepatic insult with systemic inflammation occurs, causing cerebral edema. This implies an additive connection between ammonia and inflammation, which has been shown in murine models of ACLF, where cirrhotic rats given endotoxin showed similar findings to patients with ACLF who developed cerebral edema [64]. Patients with cirrhosis are relatively immunosuppressed and are at higher risk for infection (sepsis and/or SIRS occurs in 40% of hospitalized cirrhotic patients), which is a frequent trigger for the development of hepatic encephalopathy [66]. Shawcross et al. looked at 100 cirrhotic patients admitted for grade 3–4 HE and were able to show that 46% of patients had evidence of (+) cultures, with another 22% having evidence of SIRS. SIRS was found to be significantly higher in patients with Grade 4 HE compared to grade 3 HE [66]. Beyond systemic inflammation, neuroinflammation initiated by microglial cells, releasing TNF alpha and IL-6, may also enhance neuropsychological injury initiated by elevated ammonia levels [63].

As mentioned earlier, cerebral blood flow has been noted to be increased in ALF and is traditionally seen in HE occurring in ALF patients. While CBF has been shown to be reduced in cirrhosis, there is evidence that ACLF may also have increased CBF. In a recent study, transjugular intrahepatic portosystemic shunt placement was evaluated in cirrhotic patients. The acute placement of a TIPS (which

has been shown to cause endotoxemia), led to increases in nitric oxide and associated endothelial dysfunction, resulting in increased CBF [64, 65]. Cerebral oxygenation as assessed via jugular venous O2 (JVO2, thought to be representative of cerebral oxygen usage and linked to alterations in CBF) has also been reviewed. Sawhney et al. showed that abnormal baseline JVO2 was significantly associated with both the presence and severity of HE, as well as slower recovery from HE [65].

In ACLF, overt increases in ICP and cerebral edema-related deaths have been described, however these are less in frequency to ALF. Prior studies have found that overt cerebral edema occurs in about 5% of patients with ACLF. The low incidence of death from cerebral herniation may be related to cerebral atrophy or decreased cerebral perfusion [63].

There has been some controversy in ACLF as to the cause of cerebral edema. In ALF, glutamine production within astrocytes with cytotoxic edema seems established. In chronic liver failure (CLF), this process occurs more slowly, with enough time for the brain to compensate by shifting other organic osmolytes like myo-inositol and choline to counteract imbalances caused by intra-astrocyte glutamine buildup [67, 68].

MRI studies have been used to better understand intracranial fluid shifts. Mean diffusivity (MD) refers to the water transit index across cell membranes. Kale et al. found an association between interstitial edema and elevated MD in CLF patients as opposed to controls [69]. Nath et al. studied MD in ACLF patients compared to CLF patients and found that MD and CS (spherical isotropy) were significantly increased in patients with CLF, though the MD was non-significantly decreased and CS was significantly increased in ACLF. They posited that increases in CS were related to increased extracellular water. In CLF, both CS and MD were increased, resulting in interstitial edema (due to decreased glial fibrillary acid protein expression in astrocytes). In ACLF, the initial precipitating insult was thought to lead to a decrease in MD (thought to be associated to intracellular, cytotoxic edema) and the increased CS resulted in elevated extracellular, interstitial edema. Nath interpreted from this that both interstitial and cytotoxic edema were present in ACLF, but that interstitial edema was more predominant given the non-significant change in MD [67].

Gupta et al. also assessed cerebral edema in patients with ACLF via MRI. They divided ACLF patients into 1 group with cerebral failure (all ACLF grade 3) and 1 group without cerebral failure (with no ACLF, and grades 1,2, and 3 ACLF). Cerebral failure encompassed all patients with grade 3 and 4 hepatic encephalopathy. They noted that patients with ACLF had MRI evidence (via MD scores) of cerebral edema, which was elevated in severity with higher levels of ACLF. Levels of IL-6 were also substantially elevated in grade 3 ACLF versus controls. All patients with grade 3 ACLF had similar degrees of ACLF, regardless of the presence or absence of clinical hepatic failure. The increased MD scores with increasing severity of ACLF suggest that ACLF has increasing amounts of vasogenic/interstitial edema, rather than cytotoxic edema. This is thought to be related to blood-brain barrier dysfunction and neuroinflammation from SIRS and cytokine release in ACLF, which correlates with the increased IL-6 levels seen in more severe ACLF, corresponding to higher MD values. This posits that higher IL-6 levels were related with higher levels of cerebral edema [70].

## Kidney

Another common manifestation of ALF is acute kidney injury (AKI). AKI has a high incidence, with a range between 40–85%, which primarily depends on the etiology (more often seen with acetaminophen-induced ALF) [71]. There are many causes of AKI in ALF (Table 2.3). Prerenal azotemia often occurs as a result of systemic vasodilatation, gastrointestinal bleeding, volume loss from vomiting or aggressive lactulose therapy, and poor volume resuscitation [72]. As to the cause of systemic vasodilatation, many studies had previously hypothesized that the 'functional renal failure' occurring in ALF has a comparable pathophysiology to hepatorenal syndrome, with splanchnic vasodilatation and eventual systemic vasodilatation resulting in a decreased effective arterial circulating blood volume. As renal blood flow decreases, there is activation of multiple vasoactive systems, including the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), as well as arginine vasopressin. These systems are incapable of normalizing renal blood flow, and so this cycle continues to activate, decreasing renal blood flow and worsening kidney injury [73, 74]. However, there are issues with making this comparison. Patients with ALF and renal failure do not always have clinically significant portal hypertension (CSPH). If it is present, it is not as severe as that seen with hepatorenal syndrome in cirrhotic patients. Also, the vasodilation in ALF seems more generalized as opposed to cirrhosis, where its seen primarily in the splanchnic circulation. Patients with sub-fulminant ALF have a higher likelihood of having CSPH, and therefore it is in these patients that there may be more overlap with hepatorenal syndrome of cirrhosis [75].

Systemic vasodilatation and hypotension, with consequent SNS/RAAS stimulation are more in line with the mechanisms of sepsis and SIRS. Both bland SIRS and sepsis have been shown to be active in patients with ALF, with early studies showing an association of SIRS with progression of encephalopathy [19, 75]. One of the earliest studies highlighting the association of SIRS and kidney injury was a study done by Leithead et al. Their retrospective study of 308 patients in ALF found that

**Table 2.3** Causes of acute kidney injury in acute liver failure

| |
|---|
| • Hypotension<br>– Prerenal azotemia<br>– GI losses (GI bleeding, vomiting, diarrhea from increased lactulose)<br>– Volume reduction/poor volume resuscitation |
| • DAMPs/PAMPs<br>– Cyclophilin A<br>– HMBG1<br>– Bacterial sepsis |
| • SIRS/cytokines<br>– TNF alpha, IL-1, and IL-6 |
| • ATN<br>– Ischemic<br>– Toxic (acetaminophen, amanita poisoning, trimethoprim-sulfamethoxazole, etc.) |
| • Renal hypoperfusion |

renal dysfunction was independently associated with age, ALF severity, circulatory dysfunction, paracetamol-induced ALF, infection, and SIRS. 70% of patients developed SIRS and 67% met AKI criteria in the study. The presence of infection did not affect the frequency of SIRS, however patients with AKI had significantly higher rates of SIRS development compared to those without AKI (78% vs. 58%, $P < 0.001$). There was also noted to be a parallel association between increasing number of SIRS components and increased risk of kidney dysfunction, with 47, 60, 69, 79, and 81% of patients with 0, 1, 2, 3, and 4 components of SIRS respectively developing AKI ($P = 0.047$). Importantly, when ALF etiology was further subdivided into acetaminophen and non-acetaminophen-related ALF, a statistically significant association was still observed between SIRS and AKI in the non-acetaminophen group ($P < 0.001$), removing the possible confound of acetaminophen-related drug nephrotoxicity causing AKI [75].

SIRS is the byproduct of a substantial inflammatory cascade occurring as a result of systemic cytokine release. In ALF, non-infected patients show similarly elevated cytokine levels compared to infected patients. These cytokines may arise from breakdown of hepatocytes from an apoptotic/necrotic liver, endotoxemia, or impaired hepatic cytokine metabolism [76–78]. These elevated cytokines, like TNF alpha, IL-1, and IL-6, induce renal parenchymal inflammation as well as renal tubule apoptosis, with further consequent inflammation [79, 80]. Renal and hepatocyte cell necrosis causes the release of DAMPs, resulting in activation of the renal innate immune system. Increased levels of cyclophilin A, a pro-inflammatory DAMP, have been seen in patients with acetaminophen-related ALF. Murine studies have also shown that mice lacking cyclophilin A were resistant to acetaminophen-related injury. Release of other DAMPs, like HMBG1, have also been noted in ALF patients. These DAMPs work by acting as ligands and activating toll-like receptors, in particular TLR-4. This method of renal inflammation can be augmented if infection is present, with release of pathogen-associated molecular patterns (PAMPs) [79]. Indeed, even HRS is now being linked to SIRS, with studies showing significant numbers of patients with cirrhosis and HRS developing SIRS (with only 50% of those cases being associated with infection) [81].

ATN occurs often in ALF (22–50% of cases) and is divided into ischemic and toxic ATN [72, 79]. Ischemic ATN occurs secondary to extended periods of decreased perfusion of the kidneys, with breakdown of proximal tubule cell cytoskeletal integrity. This process can occur when renal blood flow decreases significantly enough due to various etiologies. Toxic ATN occurs after exposure to substances like acetaminophen, amanita poisoning, trimethoprim-sulfamethoxazole, etc., that cause both direct nephro- and hepatotoxicity [79, 82]. Acetaminophen, in particular, has been shown to cause renal failure even with a lack of significant liver injury, suggesting that the toxic metabolites, N-acetyl-p-benzoquinone-imine, are causing direct renal toxicity [75, 83]. Rhabdomyolysis, whether related to shock, trauma, or drugs/toxins can also contribute to ATN in ALF [84].

AKI is a complication also seen very frequently in ACLF. The EASL-CLIF consortium defined kidney dysfunction as a creatinine between 1.5 and 1.9 mg/dL, kidney failure as a creatinine greater than 2 mg/dL, and the CANONIC study group

including AKI in all categories of ACLF 1 [85]. Studies have shown that rates of AKI in patients with ACLF range from 22.8 to 51%, which is higher than the prevalence in hospitalized cirrhotic patients [86].

Similar to ALF, sepsis and SIRS have a role in ACLF-related AKI. This was shown in a study measuring different inflammatory cytokines and human nonmercaptalbumin 2 (an oxidized form of albumin that is an indicator of oxidative stress) in ACLF and non-ACLF patients. Patients with ACLF had significantly higher levels of inflammatory markers, with the degree of ACLF being correlated with the degree of systemic inflammation. Evidence of AKI in ACLF was associated with IL-6, IL-8, and human nonmercaptalbumin 2, but not with plasma renin levels, suggesting that the systemic inflammation contributing to the pathogenesis of ACLF is occurring via non-hemodynamic processes [87]. Cirrhotic mice given lipopolysaccharide (LPS) have also shown renal tubular injury, including rises in renal expression of TLR4 and caspase 3. Inflammatory cytokines and LPS can initiate direct kidney tubular cell destruction via caspase-mediated pathways. It shouldn't be surprising then that norfloxacin for SBP prophylaxis and rifaximin decrease the incidence of AKI [88].

The most common causes of AKI range from functional kidney injury, like prerenal azotemia and HRS, to structural kidney disease like ATN [89]. Studies have shown that in patients with decompensated cirrhosis, nearly two-thirds of cases were related to functional AKI, with structural AKI making up the other one-third [90]. Given that patients with ACLF have chronic liver disease or cirrhosis, one might think to discover similar findings.

However, studies have not shown this to be the case. Maiwall et al. evaluated the presence and etiology of AKI in hospitalized ACLF patients in comparison to those with acutely decompensated cirrhosis (ADC) [91]. While both categories of liver disease had similar amounts of AKI, patients with ACLF had significant less frequency of volume responsive AKI (21 vs. 34%, $p = 0.02$) and significantly higher prevalence of structural AKI compared to ADC (32 vs. 18%, $p = 0.013$). ACLF patients also had significantly elevated bilirubin levels, inflammatory markers (WBC and platelet counts), as well as significantly higher MELD and CTP scores compared to decompensated cirrhotic patients. Granular casts were also seen more commonly in ACLF patients, signifying structural damage to renal tubules [91]. This finding of structural kidney disease being more prevalent in ACLF AKI was reproduced by Jiang et al. with the use of urinary tubule injury biomarkers. They also showed that patients with ACLF-related AKI had a significantly lower response rate to terlipressin than in patients with ADC-related AKI (32.6 vs. 57.9%, $P = 0.018$), reinforcing that functional kidney disease related to splanchnic vasodilatation was not the major cause of AKI in ACLF [89]. Indeed, resolution of HRS-AKI with albumin and splanchnic vasoconstrictors may not occur in up to 40% of patients, suggesting other pathophysiologic processes at play or the development of tubular injury [88].

Maiwall's group also looked at post-mortem kidney biopsies of patients with ACLF and ADC and noted that bile pigment nephropathy was seen more commonly in ACLF patients, with elevated serum bilirubin levels being the only significant

predictor on multivariate analysis [91]. Elevated bilirubin levels have been shown to cause 'cholemic nephrosis', a bilirubin toxicity shown in animal studies to correlate with increased histologic kidney damage [92]. Bile acids can cause direct toxic effects on the kidneys as well as lead to tubular obstruction. In another study looking at cirrhotic patients, tubular bile casts were observed on kidney biopsy in 11 of 13 patients with HRS-AKI, with the thought that these bile casts were involved with the cause of renal injury [93].

Kidney biopsy to diagnose structural disease in cirrhotic patients has bleeding risks given clotting cascade defects and is infrequently done. Trawale et al. performed kidney biopsies on 65 patients with cirrhosis and AKI (Cr > 1.5 mg/dL). Of these patients, 18 showed proteinuria of <0.5 mg/day and no hematuria, yet had evidence of glomerular injury, as well as acute and chronic tubulointerstitial lesions showing that patients suspected of having functional kidney disease may also have structural disease [94]. Likely there is overlap in the pathogenic mechanisms with AKI in ACLF, with HRS-AKI possibly progressing into non-HRS-AKI, as evidenced by the duration of HRS increases the non-response rates to terlipressin and albumin over time [88].

## Hemostasis

To prevent blood loss in event of blood vessel injury, normal hemostasis involves 3 complicated and complex sequence of phases. (1) primary hemostasis: initial sealing of the blood vessel wall breach by activated platelet; (2) secondary hemostasis: blood coagulation, fibrin mesh formation and clot stabilization by plasma procoagulant proteins; (3) fibrinolysis: fibrin mesh/clot dissolution by plasma anticoagulant proteins (Table 2.4) [95].

The liver synthesizes the majority of plasma protein involved in Hemostasis. Liver failure is often accompanied by substantial changes in all components of hemostasis including thrombocytopenia, platelets dysfunction, procoagulant factors and anticoagulant factors secondary to hepatic synthetic dysfunction and portal hypertension. Decreased plasma concentration of procoagulant factors except factors VIII (which is produced in endothelium) are commonly observed in LF secondary to impaired synthesis. However, production of naturally occurring anticoagulants

**Table 2.4** Phases of hemostasis and abnormalities seen in liver failure

| Phase of hemostasis | Abnormalities |
|---|---|
| Platelets/primary hemostasis | • Thrombocytopenia<br>• Elevated vWF |
| Coagulation/secondary hemostasis | • Elevated factor 8<br>• Decreased pro- and anticoagulant proteins |
| Fibrin dissolution/fibrinolysis | • Decreased plasminogen<br>• Decreased antiplasmin<br>• Increased plasminogen activator inhibitor-1 |

(antithrombin and protein C, S) also decreases. Hemostasis is the end result of interactions of coagulation and fibrinolysis. Literature supports the concept of rebalanced hemostasis in liver disease.

Primary hemostasis is a result of platelets adhesion and aggregation at the site of endothelial injury. Mild to moderate thrombocytopenia have been seen both in ALF and ACLF but the mechanism of thrombocytopenia in patients with ALF has been poorly understood. Thrombocytopenia is liver failure seems to be multifactorial. It could be secondary to decreased production (myelotoxic agents such as alcohol), splenic sequestration (from hypersplenism) and increased destruction. The principal regulatory protein for platelet synthesis, thrombopoietin (TPO) is manufactured in the liver. TPO level has been reported normal, decreased or elevated in CLD and ALF [96, 97]. In one study of ALF patients, TPO was described as normal levels to high levels even in the presence of thrombocytopenia. Therefore, even though TPO is primarily synthesized in the liver, its production remains intact and does not contribute to reduced platelet counts in ALF [98]. Since, the clinical picture of ALF and ACLF, shares many similarities with SIRS with multi-organ failure. A recent study in patients with ALF concluded, microparticles production secondary to SIRS-induced platelets activation, resulting in platelet remnants clearance and subsequent thrombocytopenia, was correlated with multi-organ failure and high mortality [99]. Patient's with ALF also have elevated Von Willebrand factor (vWF), and may restore platelets adhesions despite thrombocytopenia [100]. Elevated vWF have been reported in cirrhosis and has been established as a predictor of hepatic decompensation and mortality [101]. Elevated vWF levels also have been correlated with organ failure, and predicted in-hospital survival in ACLF [102]. Increased risk of bleeding secondary to thrombocytopenia may be balanced by elevated vWF both in ALF and ACLF.

Coagulopathy has been included in prognostic models for both ALF and ACLF. Acute liver injury both in ALF and ACLF, causes early and substantial decrease production of procoagulant proteins II, VII, IX, X as well as factor V and factor XI. Significant factor deficiencies occur secondary to short half-life and reduced production with rapid development of coagulopathy, manifested as elevated prothrombin time (PT) and international normalized ratio (INR). However, INR is not calibrated for use in patients with cirrhosis. An increase bleeding tendency has been historically attributed to the degree of abnormalities of these tests but spontaneously and significant bleeding in ALF is rare about 5% [103]. A recent study by Acute Liver Failure Study Group, including 1770 patients with ALF, determined that despite median INR of 2.7, clinically significant bleeding was uncommon. Bleeding complications in ALF patients were indicators of severe systemic inflammation instead of coagulopathy and so are bad prognostic factors [104]. Bleeding secondary to portal hypertension is more commons in ACLF. However, ALF is linked with minimal mucosal bleeding or hematoma production, even though, ALF has been known to cause portal hypertension due to sinusoidal collapse [105]. In patients with ALF, PT/INR do not correlate well, when assessment of coagulation was done with thromboelastography (TEG). TEG results among 20 ALF patients revealed a hypocoagulable profile, normal profile, and hypercoagulable profile in

20%, 45%, and 35% respectively [106]. In most ALF patients, in spite of INR elevations, there appears to be only marginal global hemostatic effects as accessed with TEG. The mechanisms behind this are secondary to an increase in clot strength with rising severity of liver injury, higher factor VIII levels, and a proportionate drop in pro- and anticoagulant proteins [107].

Hemostasis is the end result of interactions of fibrinolysis and coagulation. Fibrinolysis is the natural breakdown of the fibrin clot. The liver is the principal organ involved with production and removal of proteins involved in fibrinolysis such as plasminogen, ȧ2-antiplasmin, thrombin activatable fibrinolysis inhibitor (TAFI) and fibrinogen. Disruption of the fibrinolytic system is one possible cause for increased bleeding in liver failure. In ALF, profound alterations in many vital fibrinolytic proteins are present. Plasminogen as well as ȧ2-antiplasmin levels are reduced in ALF patients in comparison to healthy volunteers [108]. Tissue plasminogen activator levels remained unchanged, but plasminogen activator inhibitor-1 levels (derived from endothelial cells) were increased, consistent with fibrinolytic state. Even with reduced central protein activity in the fibrinolytic pathway, sufficient inhibitor presence limits bleeding tendencies.

Even though all patients in ALF and ACLF develop coagulopathy, PT/INR inadequately estimate the hemostasis in this setting since it is only sensitive to procoagulant. Coagulopathy may or may not be associated with bleeding diathesis. Literature supports the concept of a rebalanced hemostatic state in liver diseases secondary to decrease production of both pro and anticoagulant factors.

## Pulmonary

Central hyperventilation is often the first pulmonary manifestation of ALF, leading to a respiratory alkalosis [72]. This hyperventilation can increase as ICP rises, as hyperventilation results in precapillary vasoconstriction that leads to decreases in cerebral blood flow and ICP [72, 109]. Hypoxemia due to lung injury is a serious complication of ALF. The etiologies to this can be multifactorial, related to hydrothorax, atelectasis, impaired compliance related to increased intra-abdominal pressure, intrapulmonary arteriovenous shunting, or acute respiratory distress syndrome (Table 2.5). Refractory hypoxemia is considered a contraindication to transplantation in some centers [110].

**Table 2.5** Causes of hypoxemia due to lung injury in acute liver failure

- Hydrothorax
- Atelectasis
- Impaired compliance from increased intra-abdominal pressure
- Intrapulmonary A-V shunting
- Acute respiratory distress syndrome
- Pulmonary edema

In patients with advancing ALF, pulmonary edema is more prevalent, with studies showing it to be more frequent in patients with cerebral edema. Early studies posited a central or neurologic basis to pulmonary edema versus other common factors like increased capillary pressure or increased capillary permeability. Positive end-expiratory pressure (PEEP) has also been implicated, as high levels of PEEP can hamper venous return, increase intracerebral capillary pressure, and prompt the development of cerebral edema. Another possible cause of pulmonary edema is intrapulmonary vasodilatation, as evidenced by increased intrapulmonary shunting [111]. Morphometric studies on inflated lungs of autopsied ALF patients showed diffuse dilatation of the pulmonary vascular bed, similar to cirrhosis, though not as severe [112].This abnormal arteriolar dilatation could cause increased capillary hydrostatic pressure and lead to pulmonary edema, despite normal pulmonary artery and left atrial pressures [111].

More modern theories suggest that oxidative stress (causing production of toxic oxygen free radicals) and cytokine release are main factors for lung injury in ALF. Given that ALF results in pro-inflammatory cytokine generation and oxidative stress in multiple organs, this was thought to be a cause of lung injury [110, 113]. This was tested in a study that gave the iron chelating agent, desferrioxamine (DFX), which inhibits hydroxyl radical formation and theoretically decreases oxidative stress, to swine receiving surgical liver devascularization to simulate ALF. Postoperative lung injury was assessed via tissue diagnosis and bronchioalveolar lavage fluid (BALF) assessment. Pigs that received DFX had profoundly decreased BALF protein and nitric oxide product (nitrite/nitrate) concentrations and higher levels of catalase than controls. Nitric oxide is a known oxidative molecule which can induce apoptosis and catalase conversely augments antioxidant capacity. Histology in the DFX group showed significantly less alveolar epithelial cell necrosis, alveolar collapse, as well as total lung injury. Together, the results demonstrated that oxidative cells at least partially mediated lung injury in ALF, and that blocking these iron-dependent oxidative phenomena ameliorated lung injury [113]. Decreased nitric oxide production also helped avoid vasodilatation and microvascular leak, decreasing the risk for pulmonary edema [113, 114]. Other inflammatory substances have also been noted to be released in during ALF and SIRS, like hyaluronic acid. Low molecular weight HA has been shown to cause acute lung injury via toll-like receptors 2 and 4 [115].

A PaO2/FiO2 ratio < 200 mmHg is indicative of acute respiratory distress syndrome (ARDS), while a PaO2/FiO2 ratio between 200–300 mmHg reflects acute lung injury [116]. The CANONIC trial defined pulmonary failure of ACLF as a PaO2/FiO2 ratio < 200, which was noted in 9% of patients [85]. Pulmonary failure in ACLF has often been found to be related to respiratory infections. Intubation and mechanical ventilation, whether for respiratory failure from infection or shock, or airway protection from hepatic encephalopathy or gastrointestinal bleeding, increases the risk for pulmonary infection [116]. Cirrhosis changes certain pulmonary cellular functions, with decreased alveolar macrophage activity, changes in the proportions of T-lymphocyte subsets, and increased capillary permeability. Increased amounts of pulmonary macrophages have also been noted to be present,

increasing LPS-related lung edema [15]. Levesque et al. looked at 246 cirrhotic patients requiring mechanical ventilation during hospitalization. 209 patients met criteria for ACLF at admission. 75% of patients met criteria for infection, with 50% of those infections being pneumonia (16% on admission, 34% during hospitalization, with 29% being ventilator—associated pneumonia). Having ACLF also impacted mortality, with the ICU mortality for patients without ACLF being 16% versus 75% for those with ACLF [117].

## Conclusion

Both acute and acute on chronic liver failure are disorders with significant systemic effects. The dysregulated inflammatory response initiated by severe liver injury results in multi-organ involvement. Better understanding of the mechanisms of acute/acute on chronic liver failure can hopefully lead to new treatment protocols that can improve survival outcomes.

## Self Study

**Questions**

1. Which statement is true?
   (a) The production of fibronectin and complement synthesis occurs primarily in the liver
   (b) Fibronectin levels are increased in ALF
   (c) Cytokine production is decreased in ALF/ACLF
   (d) Patients with ALF and ACLF are less susceptible to infection
2. Which statement is true?
   (a) In the brain, ammonia detoxification occurs primarily within astrocytes
   (b) Grade 3 + 4 hepatic encephalopathy are less commonly associated with cerebral edema compared to Grade 1 + 2
   (c) Cytotoxic edema is associated with impaired blood brain barrier function
   (d) In ACLF, the development of hepatic encephalopathy is associated with improved outcomes

**Answers**

1. –

   (a) CORRECT ANSWER. The production of fibronectin and complement synthesis occurs primarily in the liver
   (b) Fibronectin levels are significantly decreased in ALF
   (c) Cytokine production is increased in ALF/ACLF
   (d) Patients with ALF and ACLF are have a higher susceptibility to infection

2. –

   (a) CORRECT ANSWER. In the brain, ammonia detoxification occurs primarily within astrocytes
   (b) Grade 3 + 4 hepatic encephalopathy are more commonly associated with cerebral edema compared to Grade 1 + 2
   (c) Cytotoxic edema is associated with an intact blood brain barrier function, whereas vasogenic edema is associated with impaired blood brain barrier function
   (d) In ACLF, the development of hepatic encephalopathy is associated with worse outcomes

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# Chapter 3
# The Pathology of Acute and Acute on Chronic Liver Failure

**Rachel Hudacko, Ryan Cristelli, and Billie Fyfe**

**Key Concepts**
- Acute liver failure and acute on chronic liver failure are clinical, not pathologic, diagnoses.
- Literature on the pathology of these entities is scarce, and there is no consensus for pathologic classification of either condition.
- The presence of certain histologic features may be helpful in establishing etiology and perhaps offering prognostic information.
- Liver biopsy in these settings has limitations, and clinicopathologic correlation is essential in managing these patients.

## Introduction

The diagnoses of acute liver failure (ALF) and acute on chronic liver failure (ACLF) are based on clinical, not pathologic data. Both are due to a variety of etiologies with a wide range of pathologic features. While some etiologies of ALF and the acute insult of ACLF have specific histologic features and patterns of injury, the end result is often submassive or massive necrosis which show similar histologic changes regardless of etiology. Histologic findings may be heterogeneous throughout the liver and may differ depending on the timing of the pathologic examination to the initiating event [1].

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Literature on the pathology of ALF is scarce due to the rarity of the condition and the limited amount of pathologic material available for examination. Although there are older studies [2–4] and recent reviews [1, 5] that describe distinct patterns of hepatic injury, necrosis, and regeneration in ALF, there is no published consensus for a pathologic classification system. Literature on the pathology of ACLF is even sparser with only a few studies attempting to correlate histologic and clinical findings [6–8]. Neither a classification system nor a standardized description of the histologic features of ACLF exists at this time. In this chapter, the gross and microscopic pathologic features as well as the pathology of specific etiologies of both ALF and ACLF will be reviewed. Usefulness and limitations of liver biopsy examination for these conditions will also be discussed.

## Acute Liver Failure

**Definition of Acute Liver Failure** According to the American Association for the Study of Liver Disease (AASLD), the definition of ALF in adults is a severe liver injury with evidence of coagulation abnormality and encephalopathy in a patient WITHOUT preexisting chronic liver disease/cirrhosis, presenting within 26 weeks of symptom onset [9].

### *Gross Findings*

Gross examination findings in the liver in ALF vary depending on the underlying etiology, the severity of necrosis, and the timing and extent of injury. When necrosis is massive (>90% of the parenchyma), the liver weight is decreased by one half to two thirds, and the capsule is usually wrinkled due to this decrease in volume [1] (Fig. 3.1). The cut surface may be diffusely congested or show a "nutmeg appearance" with mottled red-brown parenchyma, as typically seen in cases of ischemic and some drug and toxin-induced injuries (Fig. 3.2). "Map-like" areas of necrosis comprised of dark-red soft parenchyma may also be present [2]. When necrosis is submassive (<90% of the parenchyma) and/or the clinical course is prolonged, areas of necrosis may alternate with regenerative nodules of tan-green viable parenchyma resulting in an irregular nodular capsular surface [1]. This may mimic cirrhosis on imaging studies. Rarely, the liver may be grossly enlarged in cases of ALF secondary to malignancy (Fig. 3.3).

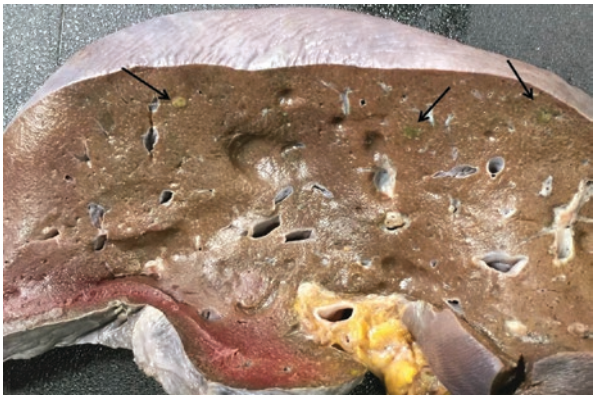

**Fig. 3.1** This section of liver is from a patient who died of acute liver failure with massive hepatic necrosis due to acetaminophen toxicity. The capsular surface is wrinkled, and the consistency of the parenchyma is very soft. The only viable remaining hepatocytes are seen as small yellow-green nodules (arrows). (Courtesy of Joshua Hendrix, DO, Rutgers Robert Wood Johnson Medical School)

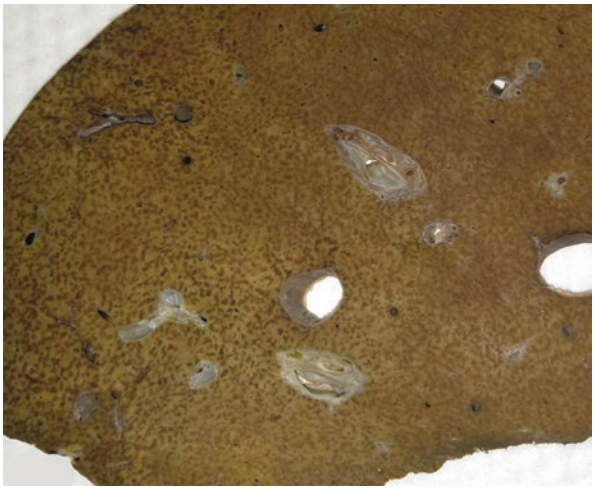

**Fig. 3.2** Section of liver after formalin fixation from a patient who died of multiorgan failure secondary to cardiogenic shock has a "nutmeg" appearance with areas of tan viable parenchyma alternating with red-brown congested and necrotic parenchyma

## *Histologic Findings*

Although no consensus for the pathologic classification of ALF exists, there are several published classifications and descriptions of the histologic findings in ALF. A recent review by Lefkowitch describes the basic patterns of necrosis in ALF

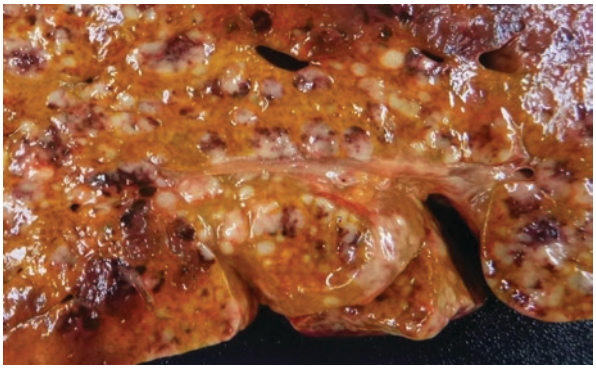

**Fig. 3.3** This liver is from a patient who died of acute liver failure secondary to metastatic small cell carcinoma of the lung. The cut surface shows innumerable white metastatic tumor deposits of varying sizes with areas of peri- and intratumoral hemorrhage occupying the majority of the parenchyma. (Courtesy of Gina Prochilo, DO, Rutgers Robert Wood Johnson Medical School)

[1]. Massive hepatic necrosis, the most severe lesion in ALF, shows diffuse loss of hepatocytes with sinusoidal congestion and varying degrees of inflammation and periportal ductular reaction, depending on the etiology and duration of the disease. The reticulin framework may remain intact if the onset of necrosis is very rapid or may collapse and show condensation of the framework on reticulin stain in subacute cases [1]. Any surviving hepatocytes may show steatosis and/or cholestasis. With a more protracted clinical course, nodules of regenerating hepatocytes may alternate with zones of necrosis, which may be confused radiologically and histologically with cirrhosis.

**Definition of Ductular Reaction** Ductular reaction or ductular proliferation results from activation of progenitor cells during hepatic regeneration. These cells form a periportal network of small tubular structures that resemble native bile ducts but have irregular contours, sometimes multiple or no lumens, and flattened epithelium with mild atypia [1].

When necrosis is submassive, distinct patterns may be distinguishable on histologic examination and are subdivided into zonal and non-zonal patterns [1]. Zonal patterns of necrosis involve specific acinar zones of the parenchyma (i.e. periportal-zone 1, midzonal-zone 2, and perivenular/centrilobular-zone 3). The perivenular/centrilobular necrosis pattern is the most common of the three. It is typically seen in drug/toxin-induced injury including acetaminophen toxicity and mushroom poisoning, in ischemic/hypoxic injury including heat stroke, shock, and hepatic artery thrombosis, and occasionally in some patients with autoimmune hepatitis [1]. Midzonal necrosis, which involves zone 2 hepatocytes with sparing of periportal and perivenular hepatocytes, is rare and is typically associated with dengue fever and yellow fever viral infections. Periportal necrosis is the least common pattern and is associated with phosphorous and ferrous sulfate toxicity [1]. Nonzonal

necrosis involves any acinar zone and is typically described as confluent necrosis in a "geographic" pattern. This type of necrosis may be seen in ALF due to herpesvirus or adenovirus infections. In the absence of massive/submassive necrosis, a diffuse hepatitis pattern of injury may be present in patients with acute viral hepatitis or drug-induced liver injury (DILI) [1]. This pattern is characterized by diffuse lobular +/− portal inflammation with acidophil bodies and spotty (small foci) necrosis that may progress to confluent necrosis.

**Definition of Confluent Necrosis** Confluent necrosis refers groups of necrotic hepatocytes with resultant collapse of the normal reticulin architecture. When confluent necrosis links central veins to central veins or portal tracts, it is referred to as bridging necrosis.

One histologic classification system for necrosis and regeneration described in a retrospective autopsy study divided the findings into four categories: (1) extensive multiacinar confluent necrosis without regeneration, (2) multiacinar confluent necrosis with regeneration, (3) bridging necrosis with regeneration, and (4) differential pathology characterized by an admixture of the first three categories. This study did not correlate these categories with the etiology or prognosis of ALF [2].

A study performed by the King's College group evaluated liver specimens in a serial fashion from patients receiving auxiliary transplantation in order to assess regeneration after ALF [3]. Specimens included portions of resected native livers, biopsies of the residual in situ native liver, and native livers removed at orthotopic transplantation after auxiliary transplantation failure. The authors classified patterns of injury into three categories: (1) diffuse injury when there was a uniform, but incomplete, distribution of cell loss from lobule to lobule, (2) map-like injury when there were broad regions of complete loss with architectural collapse alternating with areas of regeneration in an uneven distribution, and (3) complete loss of hepatocytes [3]. This study offers a unique perspective on regeneration after ALF and reports that 62.5% of native livers regenerated to full recovery after auxiliary transplantation, including 100% of patients with ALF due to acetaminophen toxicity. Map-like patterns of injury showed variable regeneration, and histological recovery was minimal in livers with complete hepatocyte loss [3]. Another study correlated clinical parameters with severity of hepatocyte loss and histologic features of regeneration on liver biopsy in patients with ALF and found that >50% hepatocyte loss, low proliferative activity of remaining viable hepatocytes, and high hepatic progenitor cell activation were indicators of poor outcome [4].

**Definition of Auxiliary Liver Transplantation** Auxiliary liver transplantation is a technique of transplantation that implants a partial liver graft in an orthotopic (natural anatomic) location after resection of part of the native liver or in a heterotopic (non-anatomical) location with minimal or no handling of the native liver. This technique is used in patients with ALF to act as a reliable bridge to adequate native liver regeneration, thus avoiding the need for lifelong immunosuppression [10].

## Acute on Chronic Liver Failure

**Definition of Acute on Chronic Liver Failure** No consistent definition of ACLF exists in the literature. The Asian Pacific Association for the Study of Liver (APASL) consensus definition is an acute hepatic insult resulting in jaundice and coagulopathy complicated within 4 weeks by ascites and/or encephalopathy in a patient WITH chronic liver disease/cirrhosis. It is associated with a high 28-day mortality rate [11].

Acute hepatic insults may be hepatotropic (i.e. viral hepatitis, DILI, alcohol consumption, etc.) or non-hepatotropic (i.e. systemic infection, trauma, shock) if they produce a direct hepatic insult. Both cirrhotic and non-cirrhotic chronic liver diseases (i.e. chronic hepatitis, nonalcoholic steatohepatitis without cirrhosis) qualify as "chronic liver diseases". Acute decompensation of cirrhosis is a completely different entity and is a result of parenchymal extinction and loss of regenerative potential [11].

### *Gross Findings*

Although few studies describe the histologic features of ACLF, only one study briefly illustrates the gross findings of explanted livers from patients with underlying hepatitis B virus-associated cirrhosis undergoing transplantation for ACLF [7]. They describe livers showing few residual green nodules of viable parenchyma separated by collapsed necrotic areas, which is in contrast to cirrhotic livers that show many discrete nodules. A review of autopsy cases with ACLF from one of our institutions showed similar changes with areas of parenchymal necrosis within and between cirrhotic nodules (Fig. 3.4).

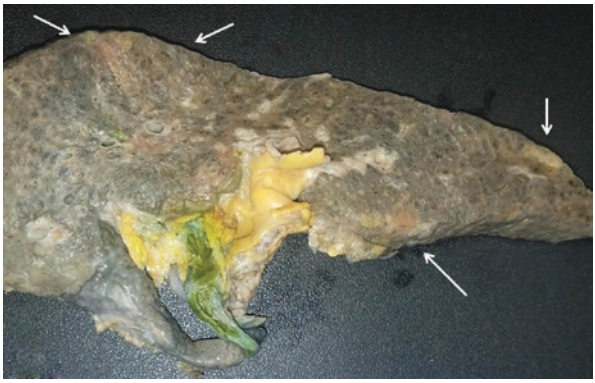

**Fig. 3.4** This section of liver after formalin fixation is from a patient who died of acute on chronic liver failure. The underlying chronic disease was alcoholic cirrhosis, and the acute insult was septic shock secondary to Aspergillus fumigatus pneumonia. The cut surface shows areas of pale tan-yellow necrotic parenchyma (arrows) in a background of well-established cirrhotic nodules

## *Histologic Findings*

Three reports describe histologic features of ACLF and attempt to correlate them with clinical and prognostic data [6–8]. One prospective study of 102 patients with histologically proven alcoholic cirrhosis compared transjugular liver biopsy findings of those presenting with ACLF to those with chronic decompensated cirrhosis [6]. Precipitating events of the ACLF included excessive alcohol intake, infection, and variceal bleeding. The group assessed a wide spectrum of histologic features and found that infectious parameters (defined in the study as ductular bilirubinostasis/cholestasis and cholangiolitis), Mallory bodies, and features of alcoholic steatohepatitis (steatosis and hepatocyte ballooning) were significantly more frequent in patients with ACLF as opposed to those with chronic decompensated cirrhosis. They also found a positive correlation between infection and ductular bilirubinostasis. They suggested that the presence of ductular bilirubinostasis on biopsy was an early characteristic feature of ACLF, and recognizing this may allow for more rapid identification of high-risk patients [6].

**Definition of Ductular Cholestasis** Ductular bilirubinostasis or ductular cholestasis refers to bile plugs present in the lumens of dilated ductules located at the interface between the portal tract and hepatic parenchyma [6] (Fig. 3.5).

Another prospective study evaluating a homogeneous cohort of 174 patients with histologically confirmed cirrhosis secondary to chronic viral hepatitis B infection (HBV) examined total hepatectomy specimens after liver transplantation and divided the cohort into two groups: with or without submassive necrosis defined as necrosis involving 15–90% of the entire liver [7]. No livers showed massive necrosis (>90%). Cirrhotic livers without submassive necrosis demonstrated the usual regenerative nodules, while livers with submassive necrosis had histologic features similar to those seen in ALF, including variable degrees of necrosis and inflammation within cirrhotic nodules and ductular reaction expanding from periportal regions. Residual viable cirrhotic nodules showed considerable cholestasis, including ductular cholestasis. They suggested that the presence of these remaining viable cirrhotic nodules is essential in distinguishing ACLF from ALF. In patients with submassive necrosis, the precipitating events were more often HBV reactivation, infection/sepsis, and physiological exhaustion (defined as excessive physical activity), while the precipitating events in those without submassive necrosis were more often variceal bleeding and portal vein thrombosis. The study concluded that submassive necrosis is a critical feature of HBV-associated ACLF, and its presence supports the notion that ACLF is a separate entity from cirrhosis [7].

The third study was a retrospective review of liver biopsies from 50 patients with ACLF [8]. This group semiquantitatively graded 14 histologic parameters, correlated them with clinical outcomes, and compared them amongst three major etiological groups: group (1) acute viral hepatitis superimposed on any chronic liver disease, group (2) reactivation of HBV infection, and group (3) alcoholic hepatitis superimposed on chronic alcoholic liver disease [8]. They observed two distinct histologic patterns. Pattern I showed marked ductular proliferation, ductular bile plugs,

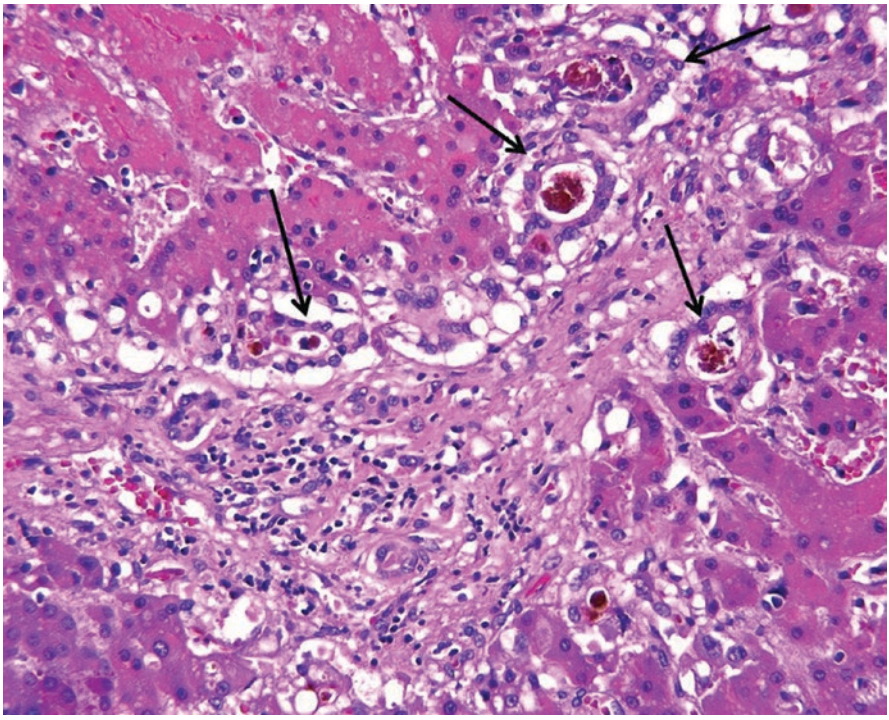

**Fig. 3.5** Section of the liver at autopsy from a patient who died of septic shock shows bile plugs present in ductules at the periphery of this portal tract, which is referred to as ductular cholestasis (arrows). A focus of necrotic hepatocytes is present in the top left corner. H&E stain, 20X

eosinophilic degeneration of hepatocytes, confluent or bridging necrosis, apoptosis, Mallory's hyaline, pericellular fibrosis, and higher stage of fibrosis and was associated with a poor outcome. Pattern II showed hepatocyte ballooning with lesser involvement by fibrosis and necrosis and was associated with a good outcome. Pericellular fibrosis and Mallory's hyaline were significantly more common in the alcoholic group.

The first two studies evaluated rather homogeneous cohorts, while the third study was retrospective and only reviewed 50 cases. These studies have opened the door to the pathology of ACLF. However, more standardized studies focusing on etiology are needed before a consensus for a pathologic classification is attained.

## Specific Histologic Features of ALF/ACLF

### *Perivenular/Centrilobular Necrosis Pattern*

When necrosis is less than massive, it may be possible to distinguish certain etiologies of ALF and the acute insult of ACLF, or at least provide a differential diagnosis on histologic examination. For specimens with perivenular/centrilobular necrosis, the differential diagnosis includes ischemic/hypoxic injury, shock, heat stroke,

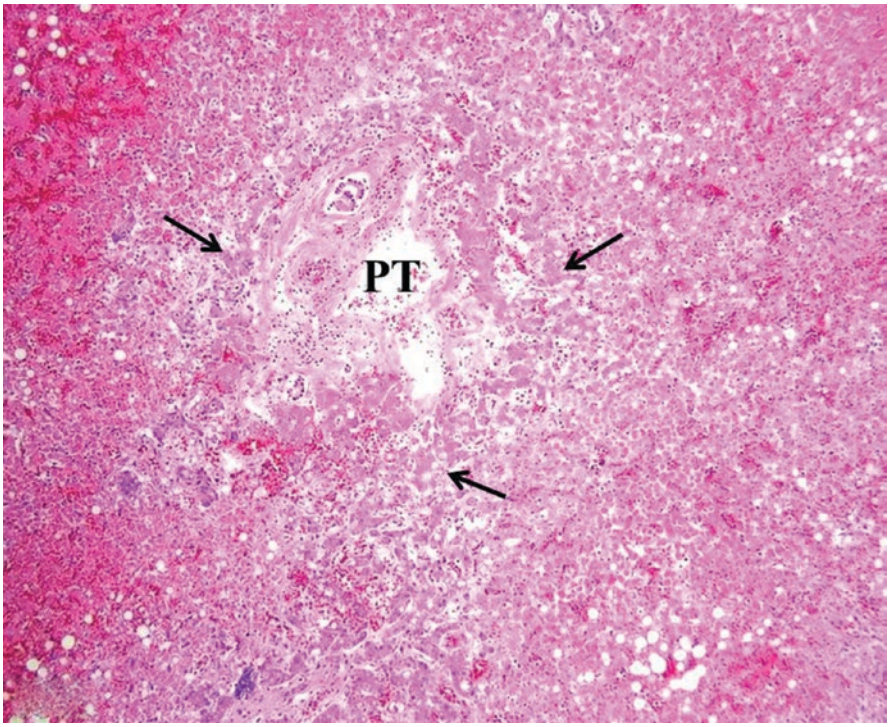


**Fig. 3.6** Liver from a patient who died of cardiogenic shock shows submassive necrosis with marked congestion involving zones 2 and 3 and a thin rim of remaining viable hepatocytes in zone 1 (arrow). PT indicates portal tract. H&E stain, 4X

acetaminophen toxicity, and mushroom poisoning. The necrosis in all of these entities is of coagulative type usually without associated inflammation (Fig. 3.6). There may be an accompanying mild inflammatory infiltrate in cases of heat stroke and in patients subsequently treated with vasopressors [1].

Budd-Chiari syndrome may also result in centrilobular hepatocyte necrosis but is typically associated with sinusoidal congestion and dilatation. Perivenular confluent necrosis may occasionally be present in autoimmune hepatitis. In these cases, the necrosis is associated with inflammation including Kupffer cells, lymphocytes, eosinophils, and increased numbers of plasma cells (Fig. 3.7). Specimens may also demonstrate central (peri)venulitis [1]. The presence of other features of autoimmune hepatitis including lymphoplasmacytic interface activity and portal tract lymphoid aggregates is helpful in supporting an autoimmune etiology.

## *Midzonal and Periportal Necrosis Patterns*

Midzonal and periportal necrosis patterns of injury are uncommon and are associated with specific etiologies. Midzonal necrosis with sparing of zones 1 and 3 is associated with dengue and yellow fever viral infections [1]. This pattern has also

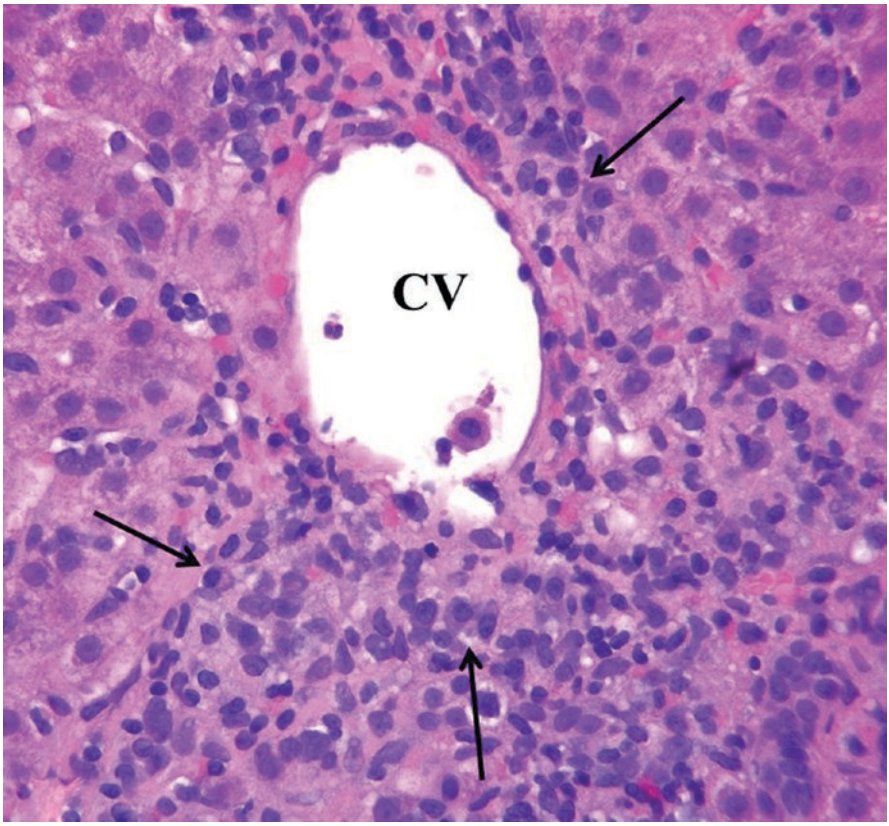


**Fig. 3.7** Liver biopsy from a patient with acute liver failure secondary to autoimmune hepatitis. The biopsy shows perivenular confluent necrosis with loss of hepatocytes in zone 3 around the central vein (CV). The hepatocytes are replaced by an inflammatory infiltrate with prominent plasma cells (arrows). H&E stain, 40X

been described in autopsies from patients with shock and was either associated with centrilobular hepatocyte regeneration or rarely with centrilobular sparing in some regions of the liver [12]. Periportal necrosis is associated with ferrous sulfate and phosphorous toxicity [1]. Prussian blue stain for iron deposition and quantitative iron analysis may help support a diagnosis of ferrous sulfate toxicity.

## *Nonzonal Necrosis Pattern*

A "geographic" nonzonal necrosis pattern of injury is typically seen with herpesvirus and adenovirus infections. In herpes family virus infections including herpes simplex virus (HSV) and varicella zoster virus (VZV), typical Cowdry A eosinophilic and Cowdry B basophilic inclusions may be seen in hepatocytes at the

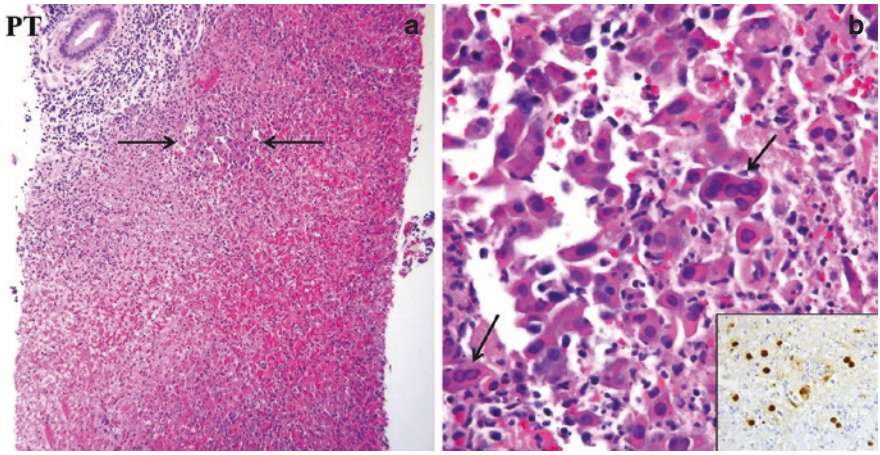


**Fig. 3.8** (**a**) Liver biopsy from a patient who presented with acute liver failure and a history of lung transplantation. The biopsy showed submassive necrosis (80%) with associated inflammatory debris and congestion. Arrows denote a group of residual viable hepatocytes. PT indicates a portal tract. H&E stain, 10X. (**b**) Hepatocytes with glassy nuclei, chromatin margination, and foci of multinucleation (arrows) were present at the periphery of the necrotic areas. H&E stain, 40X. Immunostain for HSV1 was positive in infected hepatocyte nuclei (inset)

periphery of necrotic areas. The infected hepatocyte nuclei may have a ground-glass appearance with chromatin margination and occasional multinucleation (Fig. 3.8) [5, 13]. Human herpesvirus 6 (HHV6) infection may also result in nonzonal necrosis, but viral inclusions are not usually identified on histologic examination [14]. Immunohistochemical staining for HSV1/2 and VZV will highlight infected hepatocytes, while immunostaining for HHV6 may show positivity in biliary epithelium, hepatocytes, endothelial cells, and/or inflammatory cells [14].

The necrosis in adenovirus infection may be focal or confluent in a nonzonal pattern, often with a "punched out" appearance. Viable hepatocytes at the periphery may show typical basophilic "smudged" nuclear inclusions with or without cytoplasmic aggregates of basophilic material representing viral products (Fig. 3.9) [15, 16]. Immunostaining or in situ hybridization can highlight these infected hepatocytes. Polymerase chain reaction (PCR) for specific viruses performed on liver tissue may also be helpful in attaining the diagnosis.

## *Diffuse Hepatitis Pattern*

The diffuse hepatitis pattern of injury appears as diffuse lobular inflammation with or without portal inflammation, features of hepatocyte injury including ballooning degeneration and apoptosis/acidophil bodies, and varying degrees of cholestasis. Necrosis may be focal or confluent and may bridge from lobule to lobule with

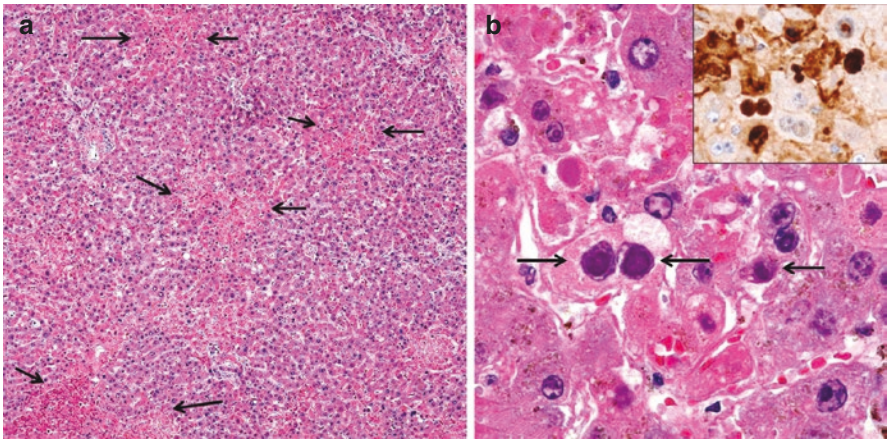


**Fig. 3.9** (**a**) Section of the liver at autopsy from a patient with a history of acute myeloid leukemia status post stem cell transplant who presented with acute liver failure. Low power view (H&E stain, 4X) shows irregular punched out areas of necrosis demarcated by arrows. (**b**) On higher power (40X), the hepatocyte nuclei contain basophilic "smudgy" inclusions typical of adenovirus. Immunostain for adenovirus was positive in infected hepatocytes (inset). (Courtesy of Jeanine Chiaffarano, DO, Jefferson Health New Jersey)

collapse of the reticulin framework [5]. This pattern is seen most commonly in acute viral hepatitis A, B with or without hepatitis D, and E infections, DILI, toxin/herbals/supplement-induced injury, autoimmune hepatitis, and rarely in metabolic diseases such as Wilson disease. While certain features such as increased numbers of plasma cells and lymphoplasmacytic portal and interface activity are characteristic of autoimmune hepatitis, these features are nonspecific and may be seen in acute viral hepatitis A and E, as well as DILI [16, 17].

Interestingly, ground-glass hepatocytes and sanded nuclei which are characteristics of chronic viral hepatitis B infection are not seen in acute infection. Immunohistochemical stains for hepatitis B surface antigen and core antibody are also negative in the acute phase due to ongoing immune clearance of the virus, thus making it difficult to distinguish acute viral hepatitis B infection from other acute viral hepatitides [16]. However, the presence of these features would be particularly helpful in establishing chronic viral hepatitis B infection as the underlying etiology of cirrhosis in ACLF (Fig. 3.10).

## *Alcohol-Induced Injury*

While alcohol use alone may not induce ALF, alcoholic hepatitis is an acute event that can incite ACLF. It is more often superimposed on alcoholic cirrhosis but may be the acute insult for ACLF with underlying chronic liver disease of any etiology [6, 8]. Histologically, steatosis and steatohepatitis (i.e. ballooning degeneration of

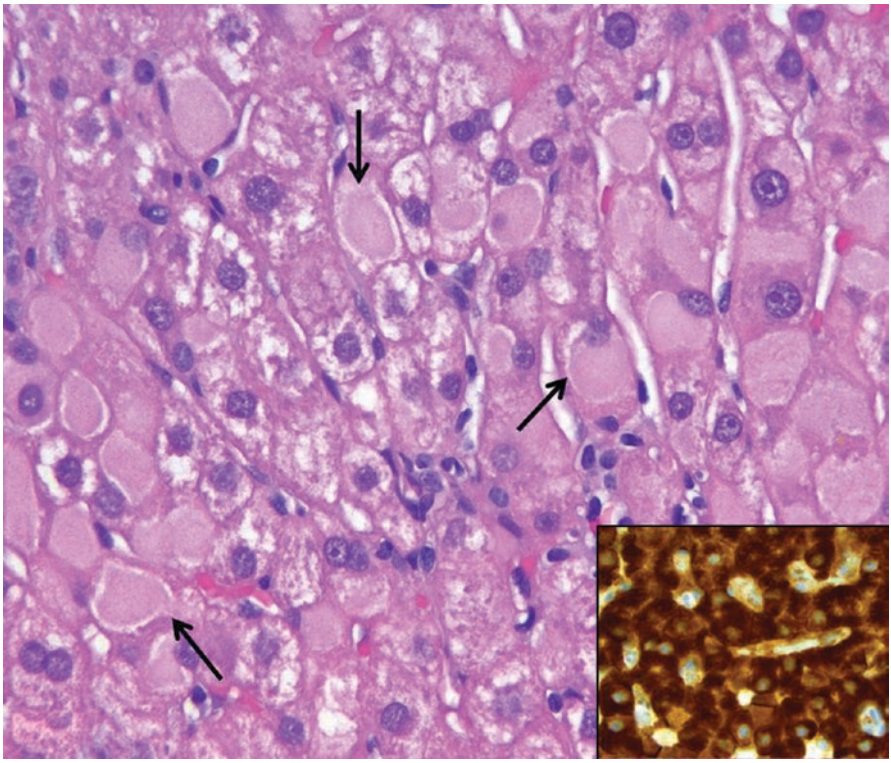

**Fig. 3.10** Liver biopsy from a patient with chronic viral hepatitis B infection shows hepatocytes with "ground glass" cytoplasm, some of which demonstrate a halo of cytoplasmic clearing (arrows). H&E stain, 40X. Immunostain for hepatitis B surface antigen highlights the infected "ground glass" hepatocytes brown (inset)

hepatocytes, pericellular/lobular inflammation) are the main findings. The presence of marked ballooning, Mallory-Denk bodies, neutrophilic infiltrates, and central vein sclerosis favors alcoholic over nonalcoholic steatohepatitis (Fig. 3.11). In the study examining features of acute on chronic alcoholic liver failure by Katoonizadh, et al., Mallory-Denk bodies and hepatocyte ballooning were more common in patients with ACLF as opposed to those with chronic hepatic decompensation [6].

## *ALF Versus ACLF* (Table 3.1)

One of the hallmarks of diagnosing ACLF is to establish the presence of underlying chronic liver disease or cirrhosis. Areas of bridging necrosis may mimic bridging fibrosis, and special stains may be helpful in distinguishing the two. Well-established cirrhotic nodules are probably the easiest to recognize as there is diffuse

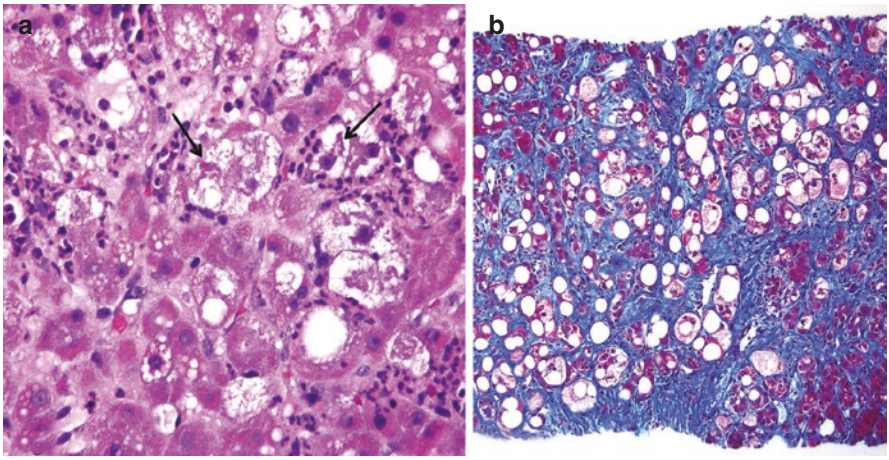


**Fig. 3.11** (**a**) Liver biopsy from a patient with alcohol-induced acute on chronic liver failure shows ballooning degeneration of hepatocytes with pericellular neutrophilic inflammation. Macrovesicular steatosis is seen as clear vacuoles in the hepatocyte cytoplasm. Arrows denote Mallory-Denk bodies which appear as thick "ropy" bright magenta material in the cytoplasm. H&E stain, 40X. (**b**) Masson trichrome stain at 10X highlights extensive pericellular/perisinusoidal fibrosis, supporting steatohepatitis as the underlying chronic liver disease

**Table 3.1** Useful immunohistochemical and special stains for evaluating livers with *ALF* and *ACLF*

| Stain | ALF | ACLF |
|---|---|---|
| Trichrome | Pale blue-gray in areas of necrosis/parenchymal collapse | Bright blue in fibrous scars<br>Used to stage the degree of fibrosis in chronic liver disease<br>Highlights pericellular fibrosis in chronic alcoholic and nonalcoholic steatohepatitis |
| Reticulin | Black in areas of necrosis/parenchymal collapse | Gray-brown in fibrous scars of chronic liver disease |
| van Gieson/orcein | Negative or few sparse elastic fibers | Abundant elastic fibers in chronic scarring |
| IHC for HBsAg/HBcAb | Negative in acute viral hepatitis B infection | Positive in chronic viral hepatitis B infection |
| IHC for HSV/VZV/HHV6/adenovirus | Positive in infectious causes of ALF | Positive in infectious causes of acute insult in ACLF |

*IHC* indicates immunohistochemical stain, *HBsAg* indicates hepatitis B surface antigen, *HBcAb* indicates hepatitis B core antibody, *HSV* indicates herpes simplex virus, *VZV* indicates varicella zoster virus, *HHV6* indicates human herpesvirus-6

circumferential fibrous scarring composed of type 1 collagen fibers surrounding nodules of hepatocytes. This type 1 collagen, which is also found in normal portal tracts, stains bright blue with a Masson trichrome stain [1]. In contrast, the newly formed fibrous tissue that develops in submassive hepatic necrosis with regeneration has a paler light blue-gray appearance on Masson trichrome stain due to the

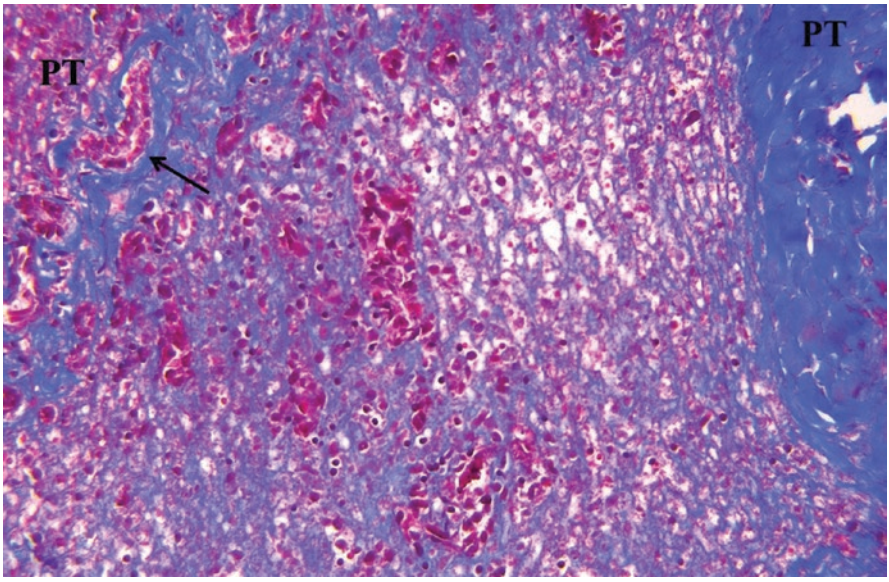


**Fig. 3.12** Masson trichrome stain performed on an autopsy liver with massive necrosis due to acetaminophen toxicity shows pale blue staining in areas of parenchymal necrosis, due to an admixture of collagens with other matrix proteins present in newly formed fibrous tissue. This is in contrast to the dense bright blue staining of type 1 collagen present in normal portal tracts (PT) and fibrous scars of cirrhosis. Arrow denotes bile duct. Masson trichrome stain, 20X

admixture of different types of collagens and other proteins (Fig. 3.12). The fibrous scars of cirrhosis also contain elastic fibers, which can be highlighted by a van Gieson or orcein stain. Few or no elastic fibers are present in the early fibrosis of parenchymal collapse due to submassive necrosis [1].

Reticulin stain can also be helpful in differentiating cirrhosis from parenchymal collapse in necrosis. Reticulin (type III collagen) fibers are narrow and black on reticulin stain and normally delineate cords or plates of hepatocytes. Necrosis leads to collapse of the normal reticulin framework and approximation of reticulin fibers (Fig. 3.13). Areas of complete parenchymal collapse appear black. Type I collagen that is present in normal portal tracts and in fibrous scars of chronic liver disease appear gray-brown on reticulin stain [16].

In patients with chronic liver disease without cirrhosis, evaluation of the stage of fibrosis should be performed with the aid of the above special stains. If the etiology of the underlying chronic liver disease is not clinically known, the pathologist can look for histologic clues that may help suggest the diagnosis. For instance, pericellular/perisinusoidal fibrosis is a pattern of fibrosis appreciated in both alcoholic and nonalcoholic steatohepatitis, and its presence may help support this as the underlying liver disease even in the absence of significant steatosis ("burnt out steatohepatitis") (Fig. 3.11b). Extensive lymphoplasmacytic portal and interface inflammatory activity can suggest autoimmune hepatitis or immune-mediated DILI as the

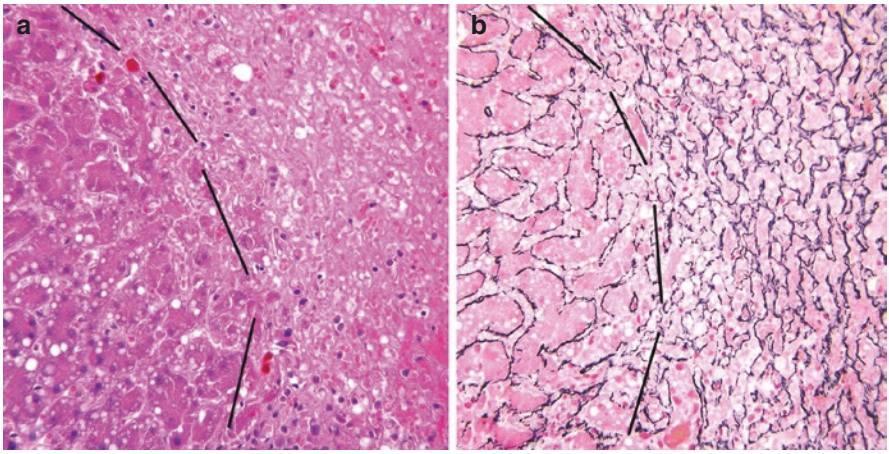


**Fig. 3.13** (**a**) In this case of acute liver failure due to acetaminophen toxicity, there was massive necrosis of the liver (right) at autopsy with only few small nodules of remaining viable hepatocytes. Surviving hepatocytes contain small fat droplets in the cytoplasm which appear as clear vacuoles (left). H&E stain, 20X. (**b**) Reticulin stain delineates the hepatic cords in the remaining viable parenchyma (left) and shows compression of the reticulin fibers in areas of necrosis (right). Reticulin stain, 20X

underlying etiology of chronic liver disease. Residual hepatocytes with ground-glass cytoplasm and sanded nuclei that stain positive for hepatitis B surface antigen and core antibody immunostains respectively would confirm a diagnosis of chronic viral hepatitis B infection. Staining for copper accumulation with a rhodanine stain or performing quantitative copper analysis may be helpful in the diagnosis of Wilson disease.

## Utility and Limitations of Liver Biopsy in ALF/ACLF

As previously stated, ALF and ACLF are not histologic diagnoses. Pathologic examination of liver biopsies can potentially assist in establishing the cause of acute liver failure, confirm or exclude underlying chronic liver disease, stage the fibrosis of chronic liver disease, shed light on the acute insult in a patient with ACLF, and perhaps offer prognostic information.

In ALF, regional variations in degree of inflammation and necrosis throughout the liver may be considerable, and a small transjugular core biopsy may over or underestimate the overall extent of necrosis. Nonetheless, it has been proposed that >50% of hepatocyte loss on a liver biopsy is critical and warrants discussion for the possibility of liver transplantation [1, 4]. The AASLD recommends performing a liver biopsy in specific situations of ALF: when autoimmune hepatitis is suspected as the cause and autoantibodies are negative, when malignancy is suspected, and if

the etiology remains unknown after extensive clinical evaluation in attempts to identify an etiology that might influence treatment [9].

Sampling error also limits the usefulness of liver biopsy in ACLF. Staging of fibrosis may be inaccurate in small biopsies, especially when taken from the subcapsular region where there is naturally more fibrous tissue. Differentiating between parenchymal collapse with regenerative nodules and established fibrosis of chronic liver disease/cirrhosis can be difficult on small biopsy samples, especially in diseases that are known for having heterogeneous patterns of injury such as autoimmune hepatitis [18]. Also, the precise histologic features of the dynamics of acute injury, regeneration, and remodeling of hepatic parenchyma are unknown, which limits the accuracy of the above-mentioned special stains in assisting in the determination of age of injury [18]. The APASL advocates that the need for liver biopsy in ACLF should be individualized and that a standardized biopsy assessment, which does not currently exist, would facilitate a more uniform approach to diagnosis and treatment [11].

## Future Perspectives

Liver biopsy can play a diagnostic and prognostic role in the evaluation of ALF and ACLF in certain situations. Limitations of core biopsy need to be taken into consideration in the clinical decision-making process. Clinicopathologic correlation and open communication between the clinical team and the pathologist are essential when evaluating these patients. Controversies regarding terminology and diagnostic criteria still exist, more so for ACLF than ALF. More clinicopathologic studies with focus on etiology, especially for ACLF, are needed to further address these controversies.

## Self Study

**Questions**

1. Which statement is false?
   (a) Zone 3 necrosis is typically seen in association with acetaminophen toxicity and shock.
   (b) Autoimmune hepatitis is never associated with zone 3 necrosis.
   (c) Midzonal necrosis is associated with dengue and yellow fever viral infections.
   (d) Periportal zone 1 necrosis can be due to ferrous sulfate or phosphorous toxicity.

2. Which statement is false?

   (a) Masson trichrome stain highlights type 1 collagen surrounding cirrhotic nodules a bright blue color.
   (b) Elastic fibers are present in fibrous scars of cirrhosis.
   (c) Reticulin stain highlights type 1 collagen fibers black in areas of parenchymal collapse.
   (d) Rhodanine stain can be used to highlight copper accumulation within hepatocytes in Wilson disease.

3. Which statement is false?

   (a) The presence of a periportal ductular reaction implies infection/sepsis in patients with acute on chronic liver failure.
   (b) The presence of >50% hepatocyte loss on biopsy is critical and warrants discussion of the possibility of transplantation.
   (c) Ballooning degeneration of hepatocytes and pericellular inflammation are features of steatohepatitis.
   (d) Cowdry A and B inclusions may be seen in hepatocytes infected with herpes simplex and varicella zoster viruses.

**Answers**

1. –

   (a) Zone 3 perivenular/centrilobular necrosis is seen in association with acetaminophen toxicity, mushroom poisoning, shock, heat stroke, and ischemic/hypoxic injury.
   (b) CORRECT ANSWER. Zone 3 confluent necrosis with inflammatory infiltrates including plasma cells may occasionally be seen in autoimmune hepatitis.
   (c) Midzonal (zone 2) necrosis is seen in dengue and yellow fever viral infections and rarely in patients with shock.
   (d) Periportal zone 1 necrosis is rare and is seen in association with ferrous sulfate and phosphorous toxicity.

2. –

   (a) Masson trichrome stain highlights type 1 collagen bright blue. This type of collagen is normally present in portal tracts and is the main type of collagen present in fibrous scars of cirrhosis.
   (b) Elastic fibers are present in the fibrous scars of cirrhosis but are typically not present in newly formed fibrous tissue present in areas of necrosis and parenchymal collapse.

(c) CORRECT ANSWER. Reticulin stain highlights type III collagen black. Necrosis leads to collapse of the normal reticulin framework, and therefore, areas of parenchymal collapse will appear black on reticulin stain. Type 1 collagen that is present in portal tracts and fibrous scars of cirrhosis will appear gray-brown on reticulin stain.
(d) Rhodanine stain will highlight copper granules that have accumulated in hepatocyte cytoplasm in patients with Wilson disease.

3. –

(a) CORRECT ANSWER. The presence of ductular bilirubinostasis/cholestasis in ductules at the periphery of portal tracts implies infection/sepsis. Periportal ductular reaction results from activation of progenitor cells during hepatic regeneration.
(b) It has been proposed that >50% hepatocyte loss on a liver biopsy is critical and warrants discussion for the possibility of liver transplantation.
(c) Ballooning degeneration of hepatocytes and pericellular/lobular inflammation are features of both alcoholic and nonalcoholic steatohepatitis.
(d) Cowdry A eosinophilic and Cowdry B basophilic inclusions may be present in hepatocytes that are infected with herpes simplex virus and varicella zoster virus. They are typically not seen in human herpesvirus 6 infections.

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# Chapter 4
# Liver Regeneration in Acute and Acute-on-Chronic Liver Failure


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**Key Concepts**

- Liver regeneration is a tightly regulated process of coordinating cytokines, growth factors, inflammation, and cell fate.
- Emerging pathophysiologic mechanisms of this process, or processes include the gut-liver axis, microRNAs, the Hippo-YAP pathway, and stem cell function.
- Promising therapeutics include immunomodulation, microRNA technology, and stem cell therapy.

## Introduction

The study of liver regeneration has evolved dramatically over the past century, and our understanding stems from early experimental models of liver injury by partial hepatectomy [1] and carbon tetrachloride [2] to the modern discovery of liver progenitor cells. Similarly, there has been an evolution in understanding of liver

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regeneration in liver disease as relates to its temporal course—from chronic liver injury to acute liver failure (ALF), as well as the recently defined unique entity of acute-on-chronic liver failure (ACLF). Our goal in this review is to clearly describe liver regeneration in the acute injury setting (such as ischemic, toxic, and surgical insults), as well as in acute on chronic liver injury (additional insult in those already with chronic hepatic fibrosis and cirrhosis). It is beneficial for the reader to understand modern concepts in liver regeneration in the setting of ALF and the preclinical and animal models developed in its study. Historically, the 2/3 partial hepatectomy (PHx) model has been used as the apical model for liver injury—an acute insult which under certain circumstances can lead to liver failure in its host and does not cause persistent injury in remaining hepatocytes. This is referenced throughout as a means of understanding pathways of liver regeneration.

## *Background*

The liver is the organ in the body whose purpose is to maintain homeostasis of essential functions involving (i) proteins, cholesterol, and hormone metabolism and synthesis; (ii) biotransformation of bilirubin and medications, bile salt synthesis for nutritional utilization, immune regulation via the reticuloendothelial system; and (iii) storage of glycogen, lipids, and essential vitamins and minerals. Given the complexity of function, it follows that the liver has complex and unique mechanisms to maintain normal cell function and repair of injured cells. These unique characteristics include rapid initiation of mitosis from quiescent hepatocytes, the ability to synchronize this process between varying hepatic cell types, and an astonishing ability to regulate an essential hepatic mass.

Early models first suggested the presence of an extra-hepatic "humoral" factor(s) that initiated the regeneration process. Early studies in PHx models demonstrated restoration of liver mass to preoperative weight, and that irreversible necrosis ensued and regeneration failed after a greater degree of hepatic resection [1, 3]. These investigators found a significant increase in mitotic activity and DNA synthesis in rat hepatocytes from the normal partner induced by cross circulation from a partially hepatectomized donor [4]. Later work demonstrated a "wave" of mitoses in the injured liver, progressing from periportal to pericentral regions in a synchronous manner that exhibited a cell-autonomous function [5]. In fact, early xenotransplantation studies using mouse hepatocytes implanted into rat liver were noted to follow the same time course of regeneration as if they were still intrinsically in the mouse liver, and were not significantly impacted by the surrounding cellular milieu [6].

These findings and others led to search for a "master" mitogen that promotes the initiation of synchronized liver regeneration and maintains that process but only until the appropriate liver mass was attained. Ultimately, this expedition has demonstrated an ever-expanding catalog of contributors to the process of hepatic regeneration rather than a single factor. Our hope is to delineate the basis for the modern

understanding of hepatic regeneration—first through classical pathways, and then through the modern era of microRNAs and stem cells.

## Classical Pathways of Liver Regeneration

The classical description of liver regeneration focuses on signaling cascades, both intra- and extra-hepatic. These cascades occur with rapid precision, affecting the hepatocytes and the surrounding cellular matrix. This process has traditionally been termed "priming and progression," as hepatic regeneration is first preceded by a signal to hepatocytes "priming" them for mitosis and division, then prompting progression from $G_0$ [7]. This early signal is insufficient to push hepatocytes through the cell cycle and a second signal, a mitogen of extra-hepatic origin, is necessary for cellular progression through $G_1$ and mitosis. These mechanisms are further described later in the chapter.

## Intracellular Signaling Pathways

The study of the molecular mechanisms of liver regeneration requires identifying signaling pathways that stimulate a rapid response to hepatocyte injury. Transcription factors, such as STAT3, NF-κB, and β-catenin and their post-translational impact have been studied, and support an expedient mechanism of cell cycle regulation and gene expression. The hedgehog signaling pathway goes beyond liver development, but is upregulated in regeneration after PHx [8]. Further regulators of these processes will be discussed here [9, 10].

### *Role of Tumor-Necrosis Factor Alpha (TNF-α)*

TNF-α is a signaling protein and inflammatory cytokine primarily produced by macrophages/monocytes during acute inflammation and has a diverse range of signaling events within cells. It plays a significant role in liver regeneration both after PHx as well as $CCl_4$ induced injuries [11]. In the priming phase, TNF-α acts on hepatocytes to enter the cell cycle for regeneration [12]. It exerts many of its effects by binding to two types of receptors, namely TNFR-1 and TNFR-2. In $CCL_4$ induced liver injury, TNFR-1 knockout mice had impairment in cellular replication and delay in liver weight recovery of which both processes were reversed with IL-6 treatment. In PHx models, TNFR-1 knockout mice had severely impaired DNA synthesis of transcription factors, which recovered after injection of IL-6 [13]. In wild-type mice, treatment with anti-TNF prior to PHx increased the IL-6 levels whereas untreated mice had no effect [14]. These series of experiments showed that

TNF-α initiates a cascade of intracellular signaling via TNFR-1 receptor, eventually leading cells to enter the proliferation phase.

Intracellular signaling pathways initiated by TNF-α have been well studied. In the context of liver regeneration, NF-κB and STAT3 are transcription factors with key roles in the intracellular cascade of signals for proliferation of hepatocytes. NF-κB is essential to maintaining hepatocyte homeostasis, including cell survival and apoptosis [15]; and plays a crucial role during development [16]. It has been well established that NF-κB activation in Kupffer cells is crucial for liver regeneration after PHx [17]; and inactivation of NF-κB in both Kupffer cells and hepatocyte have been shown to impair cellular proliferation after PHx [18].

## *Role of Interleukin 6 (IL-6)*

Interleukin 6 has broad biological functions including pro-inflammatory, mediation of acute phase reactions, regeneration, and carcinogenesis. It is involved in two distinct pathways for signal transduction, both of which are important in liver regeneration—classical and trans-signaling [19]. In the classical pathway, IL-6 binds to membrane protein receptor IL-6-R (also known as glycoprotein GP-80) of effector cells. After binding, IL-6—gp80 complex interacts with gp-130, leading to homodimerization of the complex, autophosphorylation of gp-130 and activation of cytoplasmic tyrosine kinase JAK1. This subsequently activates STAT3, STAT1 and also leads to RAS/Map signal pathway activation [20]. Of note, IL-6 receptors that are expressed at the surface membrane are restricted to only certain types of cells, including hepatocytes, some epithelial cells and leukocytes. However, in the second pathway for signal transduction, known as trans-signaling, soluble IL-6R is cleaved from the cell membrane by metalloproteinase ADAM17 and shed into serum and cytoplasm [21]. The complex, IL-6-sIL-6R can then activate gp130 in a similar fashion to homodimerization in other types of cells and induce the cellular signaling cascade. The signaling cascade will have variable effects depending on the cell type, concentration of gp-130 and serum levels of sIL-6R, making IL-6 a somewhat pleiotropic cytokine.

In liver regeneration, Kupffer cells are the likely source of IL-6, demonstrated in bone marrow transplant and macrophage-specific IL-6 knockout experiments [22]. In rats, after hepatectomy, serum levels of TNF-α and then IL-6 were elevated within a few hours and subsequently associated with significant activation of transcription factors STAT3 and C/EBPβ/nuclear factor-IL-6 resulting in enhanced transcription of these genes. The results were suggestive that these may trigger G0/G1 phase transition in hepatocytes after partial hepatectomy [20]. The integral role of IL-6 for liver regeneration was demonstrated in IL-6 knockout mice, which after PHx had ALF due to lack of DNA synthesis and a G1 phase response [23]. This was also associated with reduced STAT3 activation and decreased expression of various factors involved in cell cycle regulation. Moreover, when these mice were injected

with IL-6, hepatocyte proliferation was restored, and liver failure was averted, indicating the fundamental importance of this cytokine in liver regeneration.

In acute-on-chronic liver injury models, it has been noted that there is a shift from the IL-6/STAT3 pathway. Chronic liver injury attenuates liver generation because the Kupffer cells in these liver models produce reduced levels of IL-6. In cases of acute injury against a backdrop of chronic liver disease, there is a robust innate response with IFN-γ, which then activates the STAT1 pathway [24]. Unlike that of STAT3, the STAT1 pathway is inhibitory and blocks liver regeneration. In liver injury models, there is a balance between the IL-6/STAT3 and IFN-γ/STAT1 pathways that controls liver regeneration [25]. Studies have shown that an imbalance of the two pathways can lead to impairment of liver regeneration. In acute-on-chronic liver injury models, it was shown that IL-22 recombinant dimer enhanced STAT3 pathway over the STAT1 pathway, which then enhanced liver regeneration [26]. IL-22 is a cytokine produced by multiple immune cells, and its key targets include nonhematopoietic epithelial and stromal cells, where it can promote proliferation and play a role in tissue regeneration. This novel approach has been shown experimentally and has therapeutic potential for liver injuries and ACLF.

## Immune Regulation in the Regenerating Liver

The liver serves as the initial sensor of all intestinal venous blood draining the gut, with the gut-liver axis being a complex and highly regulated system of immune tolerance in the setting of constant bombardment with toxins and a plethora of microbial antigens [27]. The gut-liver axis also serves as a reservoir for immune regulatory cells, most notably Kupffer cells—the resident macrophages of the liver. These Kupffer cells represent the majority of all tissue macrophages, including cells present in hepatic sinusoids [28]. The interactions between the Kupffer cells and intestinal venous blood promote their cell signaling and makes them an fundamental aspect of hepatic regeneration.

In the setting of hepatocyte injury, macrophage number and division is upregulated, while concurrently promoting recruitment of other inflammatory cells to liver tissue [29]. The decisive role of Kupffer cells and other recruited macrophages in the process of liver regeneration remains in question, as studies assessing both activation and depletion show varying outcomes. Hepatocyte-protective effects with macrophage inactivation are offset by results showing that macrophage depletion delays regeneration and loss of NF-κB activation, as well as recruitment of infiltrating macrophages [29–32]. Perhaps in part due to macrophage polarization and the M1/M2 phenotype, it is clear that Kupffer cells likely shift between phenotypes through the hepatocyte repair process as well as hepatic fibrosis [33].

Many of the mediators of regeneration discussed in this review are signaling molecules or cytokines that are essential to the normal function of the immune system. Their role in the immune response to regeneration has been elucidated with the

importance of each molecule changing over time. Early studies in rodent models bred to be athymic, germ free, and lipopolysaccharide (LPS) resistant implicated the innate immune response in liver regeneration [34]. The Toll like receptor 4 (TLR4) is an essential binding protein for routine immunity; and TLR4 knockout models have demonstrated intact hepatocyte regeneration. Knockouts, however, lacking signaling protein MyD88 (a common adaptor molecule required for signaling mediated by TLR) showed a significant decrease in regeneration [35, 36]. Complement pathways have also been implicated in hepatocyte regeneration, as C3 and C5 knockout models again demonstrated impaired hepatic regeneration [37].

After PHx, macrophage colony stimulating factor (CSF-1) serum levels increased proportionately to the amount of tissue resected and shown to accelerate the regenerative proecess [38, 39]. ALF in humans appears to provide a clinically representative model in which the immune response is altered. As example, toxic overdoses of acetaminophen decrease levels of circulating monocytes, and increase hepatic populations of circulation-derived macrophages as well as Kupffer cells compared to normal controls. These immune changes were seen as a result of elevated serum levels of chemokine ligands 2 and 3, interleukins 6 and 10, and transforming growth factor ß1 [29]. The acetaminophen ALF model has also demonstrated that serum levels of macrophage CSF-1 may predict mortality in this population, as lower levels were associated with a worse prognosis [40].

These translational studies and others support the concept of utilizing immune-modulating therapies in persons with ALF and ACLF to promote hepatocyte regeneration by targeting specific pathways [41]. To this end, numerous studies have evaluated the role of estrogens and androgens, corticosteroids, and exogenous stimulating factors in patients with ALF and ACLF [42–47].

## Growth Factors

Subsequent to liver injury, and after the G0 to G1 phase transition in hepatocytes, growth factors play an important role as the cell progresses through G1. Two growth factors and their respective receptors that are particularly relevant and critical to liver regeneration are epidermal growth factor (EGF) and hepatocyte growth factor (HGF).

### *Epidermal Growth Factor and Its Receptor (EGFR)*

During liver regeneration, the EGFR on hepatocyte is activated by one of many ligands, which leads to proliferation and survival of the cell. Several ligands are found to be upregulated during liver injury and PHx, including EGF, transforming growth factor (TGF)-α, heparin-binding EGF (HB-EGF), and amphiregulin [48]. These ligands are synthesized from various sources, adding to the redundancy in

upregulation during liver regeneration. EGFR knockout mice have multiple developmental defects mostly in the endothelium and neural tissue, and usually they are not viable for longer than 8 days. PHx in mice with a conditional knockout of EGFR has significant liver regeneration delay and death, mostly driven by lack of regeneration from cell cycle arrest and reduced levels and activity of cyclin D1, among other cellular factors [49].

HB-EGF is produced by Kupffer cells and sinusoidal endothelial cells to act in a paracrine manner [48]. In HB-EGF knockout models, the delay in hepatocyte proliferation was only transient, possibly because of upregulation of TGF-α as a compensatory mechanism. In PHx models, HB-EGF levels was directly correlated to the degree of hepatectomy in that 1/3 PHx had undetectable serum levels whereas 2/3 PH had increased levels, which subsequently correlated with DNA replication. Moreover, HB-EGF administered to 1/3 PHx mice resulted in >15-fold increase in DNA replication [50]. TGF-α and amphiregulin are produced by hepatocytes to act in an autocrine manner. PHx in mice lacking TGF-α surprisingly did not show any abnormality in liver regeneration, perhaps in part because of multiple redundant pathways. In contrast, defects in amphiregulin expression showed impaired cellular proliferation [51, 52]. EGF is secreted by salivary gland and Brunner's gland in the gut to act in endocrine manner. Early studies reported impaired regeneration in its absence, and upregulation when recombinant EGF was administered to PHx mice [53].

## *Hepatocyte Growth Factor*

Hepatocyte growth factor (HGF), also known as scatter factor (SF) is a paracrine growth factor primarily secreted by mesenchymal cells of the liver (primarily Kupffer cells and endothelial cells). HGF expression is upregulated in these cells as well as several other organs in response to liver injury. HGF production is also augmented by distant organs, in response to cytokines produced during liver injury (as discussed above, IL-6 and TNF-α play key roles here), highlighting some "endocrine-like" nature of this growth factor [54]. HGF stimulates epithelial cell proliferation, motility, morphogenesis and angiogenesis. In acute liver injury models, using $CCl_4$ induced hepatitis, rats that were given anti-HGF IgG showed reduced numbers of proliferating hepatocytes [55]. Specifically, HGF acts via tyrosine phosphorylation of c-Met receptor, a transmembrane protein that is activated by binding of HGF, and induces intracellular cascade promoting the wide array of cellular functions. In knockout models for c-Met, the organisms fail embryonic development and have significant liver abnormalities [56]. Also, in mice with the knockout c-Met gene in liver, regeneration after PHx was delayed due to disruption of the cell cycle [57]. Another study showed that deletion of c-Met in liver cells in a non-inducible manner showed severe liver necrosis and jaundice after PHx [58]. Additional studies have shown that c-Met is not only important in cell survival but has a crucial function in liver regeneration and cannot be compensated by other growth factors [59]. It is not surprising that a cellular and functional loss of liver endothelial cells, together with

their regenerative angiocrine functions, are associated with decreased hepatocyte proliferation and regeneration in ACLF compared to ALF patients [60].

## The Role of Metabolism in Liver Regeneration

It is now well recognized that bile acids play a major role in liver regeneration. PHx models with external biliary drainage demonstrated reduced regenerative capacity and those with carbon tetrachloride induced injury showed increased hepatocyte restoration with supplementation of bile acids. This later effect was shown to be related to increased FOXM1 signaling, which is a key transcription factor in cell cycle progression [62, 63]. This finding was confirmed in a human clinical study of patients undergoing PHx, where reduced liver volumes were observed at day 7 with external drainage of bile [64].

Nuclear receptor farsenoid X receptor (FXR) is a key receptor in the mechanisms of bile acid signaling, and is expressed in numerous tissues, including the liver and small bowel. It acts via multiple pathways in regulating bile acid, lipid homeostasis, including other key metabolic pathways in the body [65]. PHx and carbon tetrachloride toxicity in FXR knockout murine models demonstrated reduced early liver regeneration; and supplementation of bile acids did not ameliorate those effects. These studies also demonstrated that FXR binds to a fibroblast growth factor, which interacts with cytochrome P450 as a key pathway in bile acid synthesis. More specifically, decreased FOXM1 expression was associated with impaired bile acid production and liver regeneration [66]. To further delineate the role of FXR in liver regeneration, a study of hepatic and intestine-specific FXR knockout mice showed that hepatic FXR was necessary for induction of FOXM1, while this finding was also observed in intestine-specific FXR knockouts [67].

The role of gut microbiota and bile acid homeostasis is a popular topic with enormously important clinical implications. In the setting of liver injury, or PHx, there is increased bacterial translocation across gut mucosa and exposure to byproducts of the microbiome [68]. The composition of the microbiome is implicated in altering bile acid homeostasis via changes in primary and secondary bile acid synthesis. Reduced microbiome diversity in cirrhotic humans leads to decreased conversion of primary to secondary bile acids in this population. This could, in part, explain one at least one mechanism for the hepatic dysfunction and risk for liver failure in persons with acute on chronic liver failure [69].

### *Platelets and Platelet-Derived Factors*

Evidence suggests an essential role for platelets and platelet-derived factors in liver regeneration after PHx. Platelets accumulate in the liver remnant following PHx in human and murine models. While an elevated platelet count stimulates liver regeneration after PHx, regeneration is significantly delayed when platelets are depleted

or functionally impaired [70]. Several clinical studies have shown worse outcomes with regard to mortality, liver dysfunction, and reduced volumes of regeneration; and related to the finding that activated platelets secrete growth factors. Fibrinogen is one such factor that has been shown to deposit in the liver after PHx. and inhibition of fibrinogen deposition leads to decreased hepatocyte proliferation [71]. Studies in murine and human models after PHx suggest a unique mechanism in which intrahepatic fibrin(ogen) deposition drives platelet accumulation and ultimately promotes hepatic regeneration after PHx [72].

## Paracrine Mediators

### *Wnt/β-catenin Pathway in Liver Regeneration*

The Wnt/β-catenin pathway plays a critical role in liver regeneration, development, and normal physiology. In the absence of Wnt signaling, β-catenin is marked for degradation by a complex involving the tumor suppressor protein APC. When activated, free β-catenin will translocate to the nucleus and mediates target gene transcription via T-cell factor proteins [73]. β-catenin levels are tightly regulated, with a significant proportion typically bound to either the APC complex or E-cadherin at the cell membrane [74]. Following PHx, cytosolic β-catenin levels increase with subsequent translocation to the nucleus. The significance of β-catenin in liver regeneration after injury has been studied in β-catenin knockout models, where there is a delay in hepatocyte proliferation and decreased liver mass during early regeneration [75]. Acetaminophen-induced liver injury also serves as a clinically relevant model for the role of β-catenin in hepatic regeneration (Fig. 4.1). Murine models of acetaminophen overdose demonstrated activation of β-catenin with a subsequent increased expression of glutamine synthase (a β-catenin target), and ultimately increased cyclin-D1, thereby, promoting cellular proliferation [76]. Similarly, liver tissues from biopsies of persons with acetaminophen-induced liver injury have demonstrated correlation between nuclear β-catenin localization and spontaneous liver regeneration.

The Wnt/β-catenin pathway is also involved in the "metabolic zonation" of the liver during organogenesis and regeneration, via APC regulation. Based on varying signaling patterns, hepatocytes express a gradient between respective periportal and pericentral phenotypes and their associated metabolic activities [77, 78]. This pathway also drives architectural development during regeneration in PHx models by increasing levels of β-catenin and E-cadherin, for coordination of cell–cell adhesion [79, 80].

### *Transforming Growth Factor β*

Transforming growth factor beta (TGF-β) is a key factor in termination of liver regeneration. Early studies showed TGF-β to be a strong inhibitor of DNA synthesis in mitogen-stimulated hepatocytes, and this effect decreased in a time-dependent

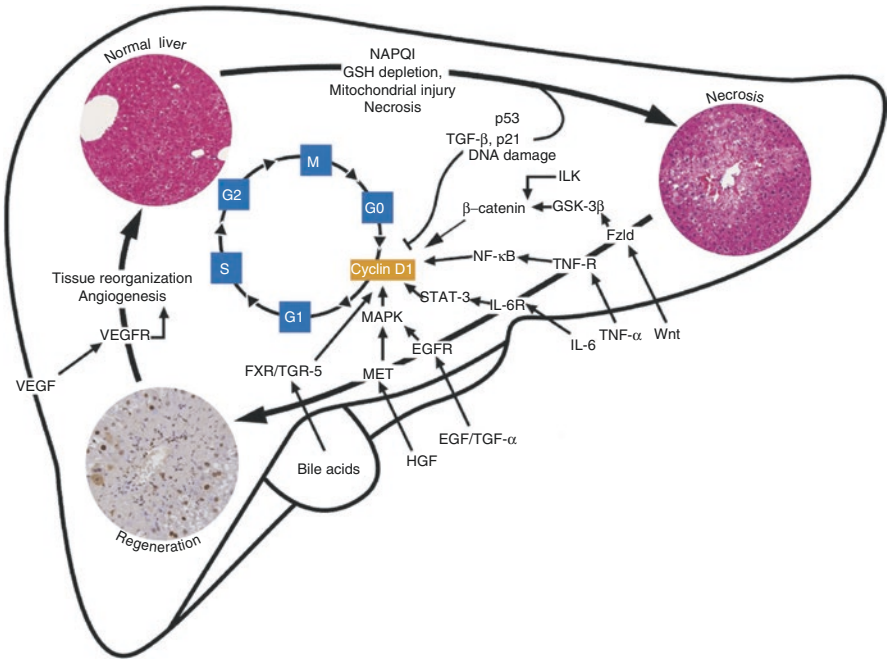


**Fig. 4.1** Molecular mechanisms of regeneration after acetaminophen (*N*-acetyl-para-aminophenol; APAP)-induced liver injury. Liver regeneration after APAP overdose involves a complex time- and dose-dependent interplay of several signaling mediators. Several proliferative signaling pathways that control cell cycle machinery, including growth factor signaling via epidermal growth factor receptor (EGFR) and c-MET [receptor for hepatocyte growth factor (HGF)], cytokine signaling [tumor necrosis factor (TNF)-α/NF-κB and IL-6/STAT-3], Wnt/β-catenin, and bile acid signaling are activated after APAP overdose, potentially contributing to liver regeneration. Some of these proliferative signaling pathways including Wnt/β-catenin and TNF-α/NF-κB signaling are inhibited after severe APAP overdose (others such as EGFR/c-MET and IL-6/STAT-3 signaling remain activated), which is accompanied by unchecked *DNA* damage and activation of antiproliferative pathways [transforming growth factor (TGF)–β and p53/p21] leading to cell cycle arrest and impaired liver regeneration. Angiogenesis and the restoration of microvasculature during normal liver regeneration involve the activation of vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) signaling, which also indirectly contributes to hepatocyte proliferation via the stimulation of HGF release from endothelial cells. Top, hematoxylin and eosin–stained liver sections that are normal (left) and necrotic (right). Bottom, regenerating liver, shown as proliferating cell nuclear antigen (PCNA)-positive hepatocytes (brown nuclear staining). *FXR* farnesoid X receptor, *Fzld* frizzled protein, *G0* gap 0 phase, *G1* gap 1 phase, *G2* gap 2 phase, *GSH* glutathione, *GSK* glycogen synthase kinase, *ILK* integrin-linked protein kinase, *M* mitosis phase, *MAPK* mitogen-activated protein kinase, *NAPQI N*-acetyl-p-benzoquinone imine, *S* synthesis phase, *TNFR* TNF receptor. (Figure and Caption source: Bhushan, Bharat et al., Liver Regeneration after Acetaminophen Hepatotoxicity, The American Journal of Pathology, Volume 189, Issue 4, 719–729) [61]

manner in hepatocytes that were isolated from the regenerating liver [81]. A corroborating study showed that TGF-β mRNA expression increased after PHx and peaked after the first round of hepatocyte cellular division has occurred. This increase in levels of TGF-β was countered by a reduction in TGF-β receptor

expression after the liver injury [82]. The importance of receptor expression in regeneration was shown in TGF-β receptor knockout models demonstrating an increase in hepatocyte proliferation with corresponding increase in liver mass. This inverse relationship was likely mediated by inhibition of cyclin D1 and arrest in the G1 phase of the cell cycle [83].

Beta-2 spectrin (β2SP) has been shown to be another key receptor in TGF-β signaling. Murine knockout models of β2SP resulted in dysfunctional hepatocyte cell cycle progression and delayed liver regeneration after PHx, in a p53-independent fashion [84]. These data suggested that TGF-β plays a coordinating role in regeneration, rather than simply acting as a terminal signal.

## Hippo/YAP *Regeneration Pathway*

Another pathway critical to regulation of liver mass and progenitor cell determination is the Yap/Hippo pathway. The transcription coactivator Yes-associated protein (YAP1) is the main effector of the pathway, with nuclear localization negatively controlled by Hippo upstream signaling. Hippo activation leads to phosphorylation and activation of mammalian Sterile20-like (MST) 1 and 2, which in turn phosphorylate and activate large tumor suppressor kinases (LATS) 1 and 2. When Hippo is turned off, YAP can translocate to the nucleus and bind to transcription factors, leading to transcription of genes involved in cell survival, growth, and proliferation. LATS phosphorylation of YAP1 prevents its translocation to the nucleus and therefore interactions with transcription factors and the Hippo/Yap pathway [85]. Induction of YAP1 in transgenic models with resultant overexpression created a 4-fold increase in liver size via an increase in cell number, and this effect was reversible with interruption of YAP1 expression [86]. Hepatocyte overexpression of YAP led to rapid growth of progenitor-like populations of hepatocytes, and increased nuclear localization of YAP1 has been associated with hepatocellular carcinoma [87]. Interestingly, while YAP protein levels increased significantly, mRNA levels did not reflect this large increase suggesting post-translational modification or inhibition of degradation during regeneration [88]. With greater understanding of the molecular mechanisms involved in this pathway, the list of regulators has grown significantly, and the pathway is seen as an integral part of the "hepatostat."

## *Idea of Hepatostat*

The recently coined term "hepatostat" defines the homeostatic mechanisms ensuring appropriate liver size and architecture following injury or stress [89]. Species-specific regenerative follows a typical time course, with final restoration of liver mass in 5–7 days in rodents and 3–4 months in humans after partial hepatectomy. However, this process of proliferation does not only involve mitosis and cellular

division, but rather a still incompletely understood concept of cell fate and replication. It has long been appreciated that hepatocytes divide at differing rates depending on location, with periportal and zone 2 hepatocytes accounting for as much as 80% of all cell division; and that nuclear ploidy affects this geographic difference [90]. While the size of an organ was determined, primarily by the number and size of its cells, this was not confirmed in the liver until relatively recently. Liver regeneration after a 30% hepatectomy was achieved solely through hypertrophy, without cellular division. Meanwhile, cellular hypertrophy preceded proliferation in the 70% hepatectomy model and both hypertrophy and proliferation contributed equally to hepatocyte cell mass [91, 92].

## The Role of microRNAs in Liver Regeneration

MicroRNAs (miRNA) are evolutionarily conserved, short non-coding RNAs, which play an integral role in virtually all biological pathways. MiRNAs are transcribed as primary transcripts (pri-miRNA) by RNA polymerase II. They then undergo cleavage by an RNAse III enzyme to release pre-miRNA hairpins that are exported to the cytoplasm where the nascent miRNA undergoes further processing by protein complexes (Dicer, RNAse III enzymes, TRBP) to produce mature miRNAs. These mature non-coding sequences can then bind to complementary sites on target messenger RNA transcripts to induce either translational pause or transcriptional degradation for regulation of these genes [93]. In the past decade, extensive studies have shown critical roles of miRNA in almost all aspects of liver development, including hepatic and biliary specification and differentiation, hepatocyte and HSC development, metabolic functions, liver zonation, as well as liver regeneration [94]. Most recently, it has been reported that specific regeneration-associated miRNAs, are predictive of outcome and patient selection for liver transplantation in both acute and chronic liver disease [95].

### *MicroRNA-122*

MicroRNA-122 (miR-122) is the most abundantly found in liver tissue constituting 70% of the total miRNA pool in the liver; and its concentration is almost undetectable in other tissues. Its role has been described as one of the key factors in normal liver functions as well as pathogenesis of liver diseases [96]. It has been associated with improved prognosis clinically in patients suffering from acute liver failure, which has also been demonstrated in the mouse model [97]. In acetaminophen-induced murine liver injury, there was a dose- and duration-dependent increase in circulating miR-122 levels [98]. It has been shown to promote levels of FoxA1 genes (responsible for liver specific transcripts such as albumin and transthyretin)

and HNF4a (Hepatic nuclear factor 4 alpha, responsible for the development of various organs including liver). This miRNA also has been known to alter the balance of the mesenchymal-to-epithelial transition (MET) and vice-versa; suggesting links to carcinogenesis [99].

### *MicroRNA-21*

Another miRNA, miR-21, has been well studied in its function in cell proliferation after cellular injury. miRNA upregulates liver regeneration acting via multiple pathways, including those associated with PTEN (Phosphatase and tensin homolog), a well-documented tumor-suppressor gene that inhibits cell growth and tumor development [100]. This gene is downregulated by increased levels of miR-21 after PHx and the downregulation/loss of PTEN leads to increased activity of AKT and mTOR kinase signaling, cell cycle progression and cellular proliferation [101–103]. *In vivo* studies showing correlation between miR-21 and PTEN requires further investigation. Another pathway which is activated by increased miR-21 pathway is Pellino-1, a mediator of IL-1R/TLR signaling, and inhibition of NF-κB signaling pathway; and together, it is postulated that they form negative feedback loop to regulate NF-κB pathway [104]. Dysregulation of miRNA-21 has been implicated in the pathogenesis of multiple chronic liver diseases including hepatocellular carcinoma, NAFLD, viral liver diseases, and liver fibrosis [105].

Antiapoptotic miRNA, miR-221, has been implicated in acceleration of hepatocyte proliferation which has been demonstrated in experiments with AAV-mediated overexpression of this miRNA in PHx *in vivo* mouse models [106]. The proposed mechanism is that the overexpression of miR-221 leads to rapid S-phase entry of hepatocytes by targeting p27, p57 and Arnt mRNA, contributing to rapid proliferation. miR-221 has also been shown to protect from Fas induced acute liver failure by p53 upregulated modulation of apoptosis [107].

## The Role of Stem Cells

Stem cells, by definition, have the ability to self-renew and differentiate into multiple cell line lineages. During embryonic development, the liver is generated from primarily endodermal-derived cells called hepatoblasts, which then differentiate into either hepatocytes or cholangiocytes, the two types of epithelial cells in the liver. However, the role of stem cells in liver regeneration after hepatectomy or injury is still debated. In PHx models, the remnant liver cells are not widely injured, and regeneration occurs primarily by hypertrophy and proliferation of mature hepatocytes. In rat model bile duct ligation studies, labeled hepatocytes were injected into their livers prior to bile duct ligation, and these rats were treated with

diaminodiphenylmethane (DAMP), a biliary toxin, or sham. In both experiments, regenerated cholangiocytes were labeled, indicating a trans-differentiation from hepatocytes, with higher contribution in DAPM treatment group [108]. The trans-differentiation was driven primarily via the NOTCH pathway, and experiments with Cre-induced transgenic models led the induced hepatocytes to express biliary epithelial cell markers. Blockage of this cascade significantly impaired the trans-differentiation as well as repressed YAP levels, suggesting cross talk between the NOTCH pathway and Hippo/YAP [109].

The PHx model, however, does not completely replicate the pathology of most liver diseases, which often are associated with hepatocyte damage/death from inflammatory and fibrogenic responses. In acute liver diseases as well as acute-on-chronic liver failure due to various toxin-induced (e.g. alcohol or drug related), metabolic (fatty liver diseases) and infectious (viral hepatitis), regeneration often requires the activation of a unique cell population called liver progenitor cells (LPC) [110]. While their site of origin is still unclear, but most studies have focused on canal of Hering as the potential source. In literature, they have been given various names, including "ductular hepatocytes", "atypical ductal cells", "intermediate hepatobiliary cells" or "hepatic/liver progenitor cells". The term "oval cells" is primarily used in rat models, which are only present in damaged liver [111]. The most established protocol used to induce oval cells is 2-acetylaminofluorene (2-AAF)/PHx systems, where hepatocyte proliferation is blocked by 2-AAF prior to PHx. Using this method, it was shown that oval cells have the biopotential to differentiate into both hepatocytes and cholangiocytes [112]. 2-AAF/PHx system does not work in mice, so other methods have been used (such as 3,5-diethyoxycarbonyl-1,4-dihidro-collidine (DDC)-containing diet or Choline-deficient ethionine-supplemented diet (CDE)), to induce hepatic injury [113, 114]. These methods serve as models for varying type of liver injury and their potential therapeutic targets. For example, DDC-induced liver injury acts as model for biliary fibrosis, and CDE induces fatty liver, which is used as model for NASH. The resultant oval cells from these various models are not truly the same, and therefore, the use of the term "oval cells" is becoming less common and "LPC" is broadly used.

Liver transplantation is the only realistic option when regeneration does not compensate for the loss of metabolic function. While the yearly trend has been in the positive direction for the number of transplants throughout the United States, a significant number of patients die every year while on the liver transplant waitlist. For this reason, regeneration medicine, especially with the use of stem cells has been widely investigated worldwide. In the last decade, several hepatic differentiation protocols for mesenchymal stem cells (MSCs) have been described (Fig. 4.2) [115]. In vitro, co-culture of MSCs with primary liver cells induces differentiation of MSCs into hepatocyte-like cells (HLCs) [116]. In $CCl_4$-induced murine models of liver failure, transplantation of MSC-derived hepatocytes have been shown to restore liver function, and a similar finding has been reported in drug-induced ALF [117, 118]. There are multiple ongoing trials for use of mesenchymal stem cell transfusions in patients with liver diseases. Most recently, it has been reported that

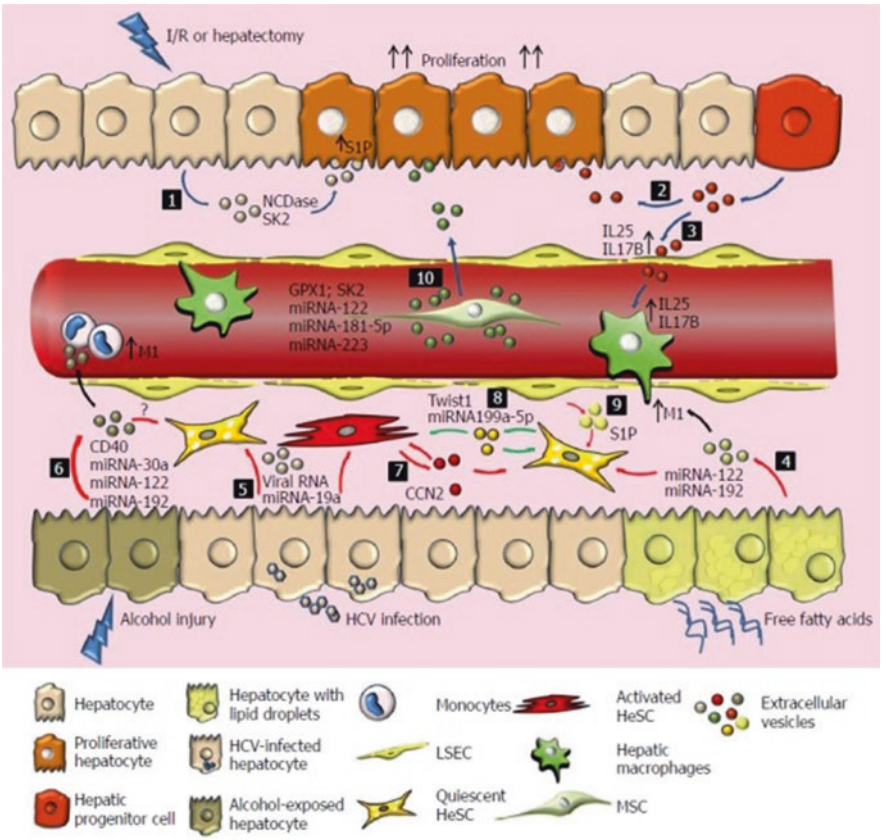


**Fig. 4.2** Extracellular vesicles as paracrine mediators in liver disease and therapeutic potential of mesenchymal stem/stromal cells. After ischemia reperfusion injury (I/R) or hepatectomy, hepatocytes (1) HPCs (2) release EVs with the ability to induce hepatocyte proliferation. (3) HPC-derived EVs stimulate LSEC and macrophage production of proliferative cytokines such as IL25 and IL17B. (4) On the other hand, free fatty acids induce the production of hepatocyte-derived EVs that result in the activation of quiescent HeSCs and pro-inflammatory macrophages (M1). (5) During chronic hepatitis C virus infection, EVs secreted by HCV-infected hepatocytes induce activation of HeSCs. (6) EVs secreted by hepatocytes after alcohol injury (containing CD40L and miRNAs) induce activation of monocytes and HeSCs. It seems to be a balance between EVs derived from active or quiescent HeSCs that promotes or inhibits fibrogenesis. Activated HeSC-derived EVs induce activation of quiescent HeSCs through CCN2 (7), and quiescent HeSCs inhibit activated HeSCs transferring Twist1 or miRNA199a-5p (8). LSEC-derived EVs could also regulate HeSC activation (9). MSC-EVs induce hepatocyte proliferation, reduce oxidative stress and apoptosis, and modulate inflammatory response by carrying GPX1 or SK2 (10). Engineered MSC-EVs transfer miRNA-122, miRNA 181-5p and miRNA-223 as potentially key modulators. The effects of MSC-EVs on HeSCs, hepatic macrophages, LSEC and infiltrated cells populations remain poorly explored. Green arrows: Inactivation of HeSCs; Red arrows: Activation of HeSCs; Blue arrow: Proliferative effect; Color spots represent EVs from different cell origin; *NCDase* Neutral ceramidase, *SK2* Sphingosine kinase 2, *S1P* Sphingosine-1-phosphate, *IL* Interleukin, *SK1* Sphingosine kinase 1, *CCN2* Connective tissue growth factor, Twist1: Basic helix-loop-helix transcription factor; *GPX1* Glutathione peroxidase 1, *HCV* Hepatitis C virus, *EVs* Extracellular vesicles. (Figure and Caption Source: Fiore EJ, Domínguez LM, Bayo J, García MG, Mazzolini GD. Taking advantage of the potential of mesenchymal stromal cells in liver regeneration: Cells and extracellular vesicles as therapeutic strategies. *World J Gastroenterol* 2018; 24(23): 2427–2440) [120]

mesenchymal stromal cells promote liver regeneration by inhibiting the activation of innate immune cells and activating those of the adaptive immune system including T (Tregs) and B (Bregs) regulatory cells [119].

## Acute-on-Chronic Liver Failure

Previous discussions in this chapter have focused on regeneration of a previously healthy liver after an acute insult. Once cirrhosis is present the natural progression to decompensated disease is a direct consequence of impaired liver function which ensues from a decrease in functional hepatocyte mass and disruption of hepatic architecture. This results clinically in an increased risk of bleeding, susceptibility to infection, and multisystem organ dysfunction—all of which are associated with a higher incidence of short-term mortality [121]. Rather than the natural progression of those with cirrhosis to develop decompensated disease, acute-on-chronic liver failure (ACLF) is an acute insult in patients with cirrhosis, which leads to rapid clinical deterioration in those individuals with previously compensated cirrhosis [122]. Typical clinical events that can precipitate ACLF include infections, gastrointestinal bleeding, viral hepatitis, drug toxicity or ischemic injury. It is noteworthy that persons with ACLF demonstrate upwards of 5-times the risk of mortality at both 28 days and 90 days [123, 124]. While infection can trigger ACLF, it is well recognized that the innate immune system can initiate an inflammatory response in the absence of infection, termed sterile inflammation. The process occurs via the release of host-derived products, called damage-associated molecular patterns (DAMPs) [125]. These DAMPs, which include interleukins, mitochondrial DNA, and bile acids, interact with immune cells and initiate an inflammatory signal through chemokine and cytokine release, which sustains and amplifies the inflammatory response [126, 127]. Therefore, in ACLF with reduced hepatic reserve and chronic circulatory dysfunction, hepatocyte death causes release of DAMPs and incites inflammation with resultant further liver failure.

In addition to diminished functional capacity, the ACLF population also demonstrates a significantly altered immune milieu, with significant alterations in pro- and anti-inflammatory cytokines such as TNF-α, interleukins, and interferons [128]. Levels of inflammatory markers such as IL-6 are lower in ACLF than in those patients with sepsis. However, the induction of TNF-α production and HLA-DR expression is significantly diminished with resultant dysfunction of regulatory monocytes and macrophages [129]. Kupffer cell populations are depleted in the setting of both ALF and ACLF, and it is hypothesized that the loss of these phagocytes leads to increased levels of circulating microbial antigens and exposure to DAMPs [126].

This alteration of immune function and cytokine milieu in ACLF therefore has a significant effect on hepatic regenerative capacity and serves as the basis behind emerging therapies to enhance recovery and regeneration. Macrophages, as a key

driving force of injury in ACLF, as well as upstream cytokines, which stimulate macrophage activity are attractive targets for potential therapies [129]. Although clinical trials involving molecular targeting in ACLF are limited, studies using endogenous stem cells to enhance tissue repair and therapies targeting inflammatory pathways and programmed cell death pathways have shown promise. As mentioned previously, g-CSF therapy mobilizes bone marrow derived stem cells in an effort to enhance hepatic tissue repair [45, 130].

**Conclusion**

We are hopeful that this review gives the reader a solid introduction and overview to the science and multi-faceted complex nature of liver regeneration. From growth factors, immune modulation, and metabolic changes to microRNA and stem cells, the breadth of influences on hepatic repair in part explains why this continues to be a nascent field of study. Given the significant heterogeneity in both the etiology of liver injury and associated repair mechanisms, the study of hepatocyte regeneration in ALF and ACLF will no doubt continue to evolve. Based on studies to date, it would be realistic to imagine therapeutic interventions after acute liver injury that could include infusion of NF-κB to stimulate Kupffer cells, macrophage colony stimulating factor to promote macrophage infiltrations into injured tissue, or heparin-binding epidermal growth factor to stimulate hepatic DNA replication. Most recently, it was demonstrated that administering a transfusion of readily-available platelets or fibrinogen can independently promote hepatic regeneration [72]. Mechanistically, we are capable of *in vivo* manipulation of miR-122 or miR-21 to stimulate or inhibit hepatocyte regeneration, depending on the unique clinical scenario. It is highly probably that near future therapeutic approaches to regenerate liver would include delivery of potent and durable hepatic mesenchymal stem cells into patients with ALF or ACLF as a means of promoting hepatocyte (and other liver cell) regeneration, preservation and a return to normal liver function.

We have attempted to highlight known pathways of cellular repair. Most notably, however, we recognize that elucidation of the interplay of these elements with host and microbiome factors is necessary for a more complete understanding of the mechanisms involved in hepatic regeneration.

**Questions**

1. All of the following mediators promote liver regeneration, except:

   (a) Wnt/β-catenin pathway
   (b) Transforming Growth Factor β pathway
   (c) IL-6/STAT3 pathway
   (d) TNF-α/TNFR pathway
   (e) HGF

2. Which of the following pathways drives the architectural development?

   (a) Wnt/β-catenin pathway
   (b) Transforming Growth Factor β pathway
   (c) IL-6/STAT3 pathway
   (d) TNF-α/TNFR pathway
   (e) HGF

3. What is the key difference in IL-6/STAT3 pathway in liver regeneration during hepatectomy compared to acute-on-chronic liver failure?

   (a) There is no difference in these two liver regeneration models
   (b) IL-6//STAT3 is upregulated in ACLF and downregulated in PHx
   (c) IL-6 levels are upregulated in PHx models, however, due to dysfunction of Kupffer cells, IL-6 production is not robust in ACLF
   (d) IFN-γ/STAT1 pathway acts in synergistic fashion with IL-6/STAT3 in both models of liver injury to promote liver regeneration

4. Which of the following is true regarding microRNA-122 (miR-122)?

   (a) This microRNA is almost never seen in hepatocytes
   (b) In mouse models, it's presence has been shown to have poor outcomes in liver failure
   (c) This microRNA suppresses the level of FoxA1 gene to reduce the liver specific transcripts such as albumin
   (d) This microRNA promotes HNF4a gene, which is responsible for the development of various organs including liver

5. In acute-on-chronic liver failure, which of the following mechanisms drive further liver failure?

   (a) Patients with ACLF have reduced hepatic reserve and chronic circulatory dysfunction
   (b) Hepatocyte death causes release of DAMPs (damage-associated molecular patterns) and incites inflammation with resultant further liver failure
   (c) ACLF population have a significantly altered immune milieu, with significant alterations in pro- and anti-inflammatory cytokines which can hinder liver regeneration
   (d) Kupffer cell populations are depleted in the setting ACLF, and loss of these phagocytes leads to increased levels of circulating microbial antigens and exposure to DAMPs
   (e) All of the above are true

**Answers**

Question 1: **Answer: b.** Transforming Growth Factor β pathway

**Explanation:**

Transforming growth factor beta (TGF-β) is a key factor in termination of liver regeneration. TGF-β is a strong inhibitor of DNA synthesis in mitogen-stimulated hepatocytes. TGF-β mRNA expression increases after partial hepatectomy (PHx) and peaks after the first round of hepatocyte cellular division has occurred. This increase in levels of TGF-β is countered by a reduction in TGF-β receptor expression after the liver injury. In TGF-β-receptor knockout models, there is an increase in hepatocyte proliferation with corresponding increase in liver mass. This inverse relationship is likely mediated by inhibition of cyclin D1 and arrest in the G1 phase of the cell cycle.

The other factors (a, c, d, e) all promote hepatocyte regeneration via various mechanisms.

Question 2: **Answer: a.** Wnt/β-catenin pathway

**Explanation:**

This pathway promotes architectural development during regeneration in PHx models by increasing levels of β-catenin and E-cadherin, for coordination of cell-cell adhesion. This pathway is also involved in the "metabolic zonation" of the liver during organogenesis and regeneration.

Question 3: **Answer: c.** IL-6 levels are upregulated in PHx models…

**Explanation:**

Due to the dysfunction of Kupffer cells, IL-6 production is not robust in ACLF. This, in part, underscores the importance of non-parenchymal cells in liver regeneration from whatever cause…be it surgical removal of a portion of the liver, or toxin-induced injury.

Question 4: **Answer: d.** This microRNA promotes HNF4a gene, which is responsible for the development of various organs including liver.

**Explanation:**

The other answers are incorrect because miR-122 is almost exclusively seen in hepatocytes, and its presence has been shown to be associated with improved prognosis in liver failure. Also, miR-122 promotes the level of FoxA1 gene expression, which increases liver specific transcripts.

Question 5: **Answer: e.** All of the above are true.

**Explanation:**

These are all salient points about patients with ACLF which puts them at a higher risk of further liver injury.

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# Chapter 5
# Prognostic Models in Acute and Acute on Chronic Liver Failure

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**Key Points**
1. Define and review acute liver failure
2. Discuss development of prognostic models and their utility
3. Define acute on chronic liver failure and the use prognostic models in these patients
4. Limitations of prognostic models

## Introduction

Acute liver failure (ALF), also known as fulminant hepatic failure [1] or acute hepatic necrosis [2], is the rapid deterioration of liver function resulting in altered mentation and coagulopathy in a patient without any preexisting cirrhosis [3]. More specifically, it is defined by an INR $\geq$ 1.5, severe hepatic dysfunction of less than 26 weeks duration, and encephalopathy [1, 3, 4]. Although patients with a diagnosis of Wilson's disease, perinatal acquired hepatitis B virus (HBV) or autoimmune hepatitis may have the presence of underlying cirrhosis, they may be included in the classification of ALF if the disease has been recognized for less than 26 weeks [1, 3, 4]. It should be noted that ALF is distinct from acute on chronic liver disease. For example, acute severe alcoholic hepatitis is characterized as acute on chronic liver given the assumption that the patient has a long history of alcohol abuse [4].

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ALF can be subcategorized based on the timing of jaundice to encephalopathy. This includes hyperacute (<1 week), acute (1–4 weeks), and subacute (4–12 weeks) [4, 5]. This classification is essential because it helps identify the etiology and provides some prognostic value. In hyperacute, causes include acetaminophen toxicity, acute hepatitis A (HAV), or acute hepatitis E [4, 5]. The clinical presentation includes severe coagulopathy, moderate intracranial hypertension, and cerebral edema while the prognosis for hyperacute is fair with a survival rate of 36% without a liver transplant [4, 5]. For acute cases, the most common etiology is HBV with findings of moderate coagulopathy and mild to moderate intracranial hypertension. The prognosis is poor as approximately only 14% survive without a liver transplant. As for subacute, it is associated with nonacetaminophen drug toxicity with mild coagulopathy, severe jaundice, ascites and renal failure. It carries the worst prognosis with a survival rate of 7% without a liver transplant [4, 5]. However, these classifications are limited as encephalopathy may precede jaundice [4]. Additionally, the clinical outcome is more reliant on the underlying etiology rather the timing of jaundice to encephalopathy which limits the utility of subcategorizing ALF for prognostication [6].

The incidence of ALF has been reported as fewer than 10 cases per million people per year in developed countries [7] with varying etiologies dependent on the location in the world. In Eastern developing countries viruses account for 95% of ALF cases whereas in Western developed countries it is more varied [8] with acetaminophen overdose as the leading cause in the United Kingdom and United States [6]. Although ALF has a high mortality rate, hospital survival has increased from 17% in 1973 to 1978 to 62% in 2004 to 2008 in a single center from the United Kingdom [9]. In a prospective observational cohort study at 31 centers in the United States, outcomes at 21 days were compared between 1998–2005 versus 2006–2013. It was found that overall survival increased from 67.1% to 75.3%. Transplant free survival increased from 45.1% to 56.2%. In cases where transplantation occurred, the survival rate increased from 88.3% to 96.3% [10]. Overall survival rates have increased from 15% in the pretransplant era to 40% spontaneously and ≥60% with auxiliary transplant [3]. The increased rate of survival has been attributed to earlier recognition of ALF, better management in the intensive care unit and the developments in emergent liver transplant [9].

Although the earlier detection and better management in the intensive care unit is instrumental in the increased rate of survival, liver transplantation is the only definitive therapy with proven survival benefit. However, it is not always an option given the variable course and rapid progression of ALF [11, 12]. Additionally, it may not always be necessary as transplant-free survival rates can be as high as 70% [6]. Conversely, nearly 30% of ALF patients that do receive a transplant die [9, 13, 14]. With ALF accounting for 8% of indications for liver transplantation in Europe [15] and 7% in the United States [16], it is essential to have prognostic models to accurately determine the need for liver transplant and who would most benefit.

## Etiology

There are many different etiologies resulting in ALF that vary greatly by country. It is essential to know the underlying diagnosis to better treat and determine the prognosis for each patient. The leading cause of ALF in the United States and Europe is acetaminophen toxicity [3] accounting for approximately 40–46% of adult cases and 25% of pediatric cases in the United States [7, 17–19]. A more prominent cause in Asian Pacific countries is viral hepatitis [8, 20] which only accounts for approximately 10–12% of ALF in the United States [3, 7, 18, 19]. Hepatitis C does not cause acute liver failure [3] while hepatitis E is significant where epidemic, such as Pakistan [8]. Other causes include idiosyncratic drug reactions, autoimmune hepatitis, Wilson's disease, ischemic hepatopathy, Budd-Chiari, veno-occlusive disease, acute fatty liver of pregnancy, partial hepatectomy, sepsis, heart stroke, and a significant number of drugs and toxins (Table 5.1) [3, 4, 7, 12, 18, 19, 21].

## Pathophysiology of Liver Failure

In ALF there is extensive death of hepatocytes. This causes the liver to lose its metabolic function resulting in decreased gluconeogenesis, lactate clearance, ammonia clearance, and its synthetic capacity. This ultimately results in findings such as hypoglycemia, lactic acidosis, hyperammonemia, and coagulopathy [7]. ALF also has systemic implications that affect multiple organs. With the death of hepatocytes,

**Table 5.1** Etiologies of ALF in the United States

| Etiologies of ALF in The United States | |
|---|---|
| Acetaminophen | 46% |
| Unknown | 14% |
| Drug induced | 11% |
| HBV | 7% |
| Other | 7% |
| Malignant infiltration | |
| Acute fatty liver of pregnancy | |
| Sepsis | |
| Heat stroke | |
| Autoimmune | 5% |
| Ischemia | 4% |
| HAV | 3% |
| Wilson | 2% |

The etiologies of acute liver failure in patients in the United States with their approximate percentiles [7, 18, 19]. HBV—hepatitis B virus, HAV—hepatitis A virus

there is activation of the innate immune system, which causes a large production of inflammatory mediators. This is associated with the failure of several other organ systems secondary to systemic inflammatory response syndrome (SIRS) [22, 23]. In the setting of inflammatory mediators there is a compensatory anti-inflammatory response. The anti-inflammatory response is meant to dampen pro-inflammatory responses, limit tissue injury, and promote liver regeneration [22, 24]. With the release of these anti-inflammatory mediators, there is an increased predisposition to infection as circulating leukocytes may have impaired function [7, 22, 25]. Due to this, sepsis and multi-organ failure are common causes of death in ALF.

ALF has the potential to impact virtually every organ. For instance, patients can develop hypovolemic shock secondary to circulatory dysfunction and hypotension. This is attributed to poor oral intake, fluid losses and vasodilation secondary to inflammatory mediators. This ultimately places the heart in a high output state and may result in myocardial injury [7]. Additionally, patients commonly present with encephalopathy and other neurological complications such as cerebral edema and intracranial hypertension. The pathogenesis is poorly understood but it is attributed to both systemic and local inflammation and circulating neurotoxins such as ammonia [7, 26, 27]. Inflammatory mediators may trigger or worsen encephalopathy by increasing the cerebral endothelial permeability to neurotoxins [28]. Additionally, without the liver functionality to convert ammonia to urea, there are increased levels of ammonia. This ammonia undergoes cerebral metabolism to glutamine, which increases the osmolarity of the brain, induces changes in neurotransmitter synthesis, and alters mitochondrial function. These changes result in altered cerebral function and swelling [7, 26, 27]. Other manifestations of ALF include renal dysfunction, acute respiratory distress syndrome, bone marrow suppression, portal hypertension, pancreatitis, and inability of the adrenal gland to produce adequate glucocorticoids [7].

## Prognostic Models

ALF has a high mortality rate and in many cases liver transplant is essential for survival. There are different prognostic models to help clinicians determine the eligibility for liver transplant. However, several of these models have differing sensitivities and specificities that result in significant controversy regarding their utility and efficacy. Currently, the most important prognostic factor is the etiology of ALF. In cases of ALF caused by acetaminophen toxicity, hepatitis A, ischemia, or pregnancy, the survival rate without liver transplant is greater than 50%, whereas other causes have a survival rate of less than 25% [6, 8, 29]. In the prospective cohort study completed by Ostapowicz et al., it was determined the degree of encephalopathy on presentation was also essential as it predicted transplant free survival. When comparing transplant free survival rates in grade I or II versus grade III or IV encephalopathy, it was found that the survival rate was 87–50% respectively for acetaminophen overdose [6]. Additionally, it was 35–12% for drug

reactions and 38–27% for other causes of ALF [6]. Overall, the spontaneous recovery of patients with grade 1–2 encephalopathy is 65–70%, for grade 3 is 40–50%, and for grade 4 it is <20% [30]. Although etioloy and degree of encephalopathy are essential, there are many other variables that demonstrate the degree of liver failure and have been incorporated into prognostic models.

## Child-Pugh Score

The first formal attempt at developing a prognostic model for acute liver failure was done by Child and Turcotte in 1964. Their objective was to determine operative risk classification for cirrhotic patients recovering from variceal bleeding and undergoing portosystemic shunt surgery. Their criteria graded ascites, encephalopathy, serum bilirubin, serum albumin, and nutritional status from 1 to 3 [31]. Pugh et al. modified this scoring system by replacing nutritional status with prothrombin time [32]. Patients with a combined score of 5 or 6 are considered Child-Pugh Class A which signifies well-compensated cirrhosis. A score of 7–9 is Class B which is significant functional compromise. Finally, a score of 10–15 is Class C which designates decompensated cirrhosis. Although the Child-Pugh score is still used for broad classification it is limited in multiple regards. To start, all of the variables were weighted the same regardless of their impact. Two of the variables, hepatic encephalopathy and degree of ascites, are subjective in their evaluation. These factors may also be affected by the use of diuretics and lactulose [33]. Prothrombin does not sufficiently reflect coagulopathy [34] while there is also variability between laboratories [35]. Finally, this scoring system does not take into account other vital information such as renal dysfunction, a known marker of liver failure [36, 37]. Although limited, the Child-Pugh classification is useful when comparing mortality and complications between classes. The 1 year survival rates for Class A, B, and C are approximately 100%, 80%, and 45% respectively [38, 39] and it has been found that those in Class C are much more likely to develop variceal hemorrhage [40].

## King's College Criteria

O'Grady et al. set out to determine factors that indicate a poor prognosis and ultimately a need for liver transplant as they developed the King's College Criteria (KCC). Univariate and multivariate analysis was performed on 588 patients with acute liver failure between 1973–1985 to identify these factors. In cases of acetaminophen-induced ALF, it was recommended to strongly consider listing for transplant if the arterial lactate was >3.5 mmol/L after volume resuscitation. In the same patients it was recommended to list for transplant if the patient had either an arterial lactate >3 mmol/L after volume resuscitation, pH < 7.3, or INR >6.5, creatinine >3.4 mg/dL (31 mg/dL), and presence of grade 3 or 4 hepatic encephalopathy

all within 24-h period (Table 5.2). For cases of nonacetaminophen induced ALF, it was recommended to list for transplant if either INR ≥ 6.5 with encephalopathy of any grade or any 3 of age <10 years or >40 years, INR ≥ 3.5, serum bilirubin >291 mcmol/L, jaundice for >7 days before development of encephalopathy, or an unfavorable etiology such as Wilson disease, drug reaction, or seronegative hepatitis (Table 5.2) [30].

KCC is the most widely applied prognostic system [3] with positive predictive values ranging from 70% to nearly 100% and negative predictive values ranging from 25% to 94% [41–43]. For patients with acetaminophen induced ALF, KCC appears to have high specificity and low sensitivity for predicting death in cases without liver transplantation [44]. In a systemic review of 14 studies with 1960 patients looking at this population, the pooled sensitivity was 58.2% and specificity was 94.6% [44]. As for nonacetaminophen-induced ALF and high grade encephalopathy, KCC may have good specificity for determining poor outcome in patients [45]. In a systemic review with heterogeneity analyzing 18 studies with a total of 1105 patients, it was found that the pooled sensitivity was 68%, pooled specificity was 82%, with a pooled positive likelihood ratio of 3.5 (95% CI 2.3–5.2) and pooled negative likelihood ratio of 0.3 (95% CI 0.2–35). In this review it was found that specificity was the highest in the 3 studies with high grade encephalopathy while the sensitivity was lowest in the 9 studies published after 2005 [45]. This was attributed to the improvement in medical management of hepatic encephalopathy which may ultimately modify the performance of KCC.

A weakness of KCC is its poor negative predictive value. In a study completed by Yantorno et al., it was found that a proportion of patients with negative criteria (23–70%) ultimately died or needed transplantation [46]. This stems from the fact that KCC allocates patients into one of two categories, survival or death [46]. Additionally, transplantation is preferable before the patient becomes

**Table 5.2** King's College criteria

| King's College criteria | |
|---|---|
| Acetaminophen induced ALF | Non acetaminophen induced ALF |
| 1. Arterial pH < 7.3 | 1. INR > 6.5 |
| Or presence of all the following 3 | Or presence of 3 of the following |
| 1. INR > 6.5 | 1. Age < 10 or >40 years |
| 2. Creatinine >3.4 mg/dL | 2. INR ≥ 3.5 |
| 3. Presence of grade 3 or 4 encephalopathy | 3. Serum bilirubin >18 mg/dL |
| | 4. Jaundice >7 days before encephalopathy |
| | 5. Etiology other than HAV, HBV, idiosyncratic drug reaction |

The King's College Criteria is one of the most widely used prognostic models to determine when to list patients with ALF for liver transplantation. Adapted from Mishra et al. [12, 30]

encephalopathic. However, in acetaminophen-induced ALF this is one of the necessary criteria that also happens to be subjective [47]. Therefore, although KCC continues to be the most widely used prognostic model for liver transplantation, it has its limitations.

## Clichy Criteria

The Clichy Criteria was developed by Bernuau et al. in 1986 by using multivariate analysis on 115 patients with hepatitis B (HBV). It was found that factor V level, the patient's age, absence of HbsAg in serum, and serum alpha fetoprotein concentration were independent predictors of survival [48]. These factors were applied to patients with ALF by Bismuth et al. in Paris between 1986 and 1991. The criteria for liver transplant was the presence of hepatic encephalopathy and factor V level of <20% if a patient's age was less than 30 years or <30% if the patients age was greater than or equal to 30 years. There were 139 patients that met these criteria and it was found that of the 116 that received transplants, the 1-year survival was 81% in those receiving an ABO compatible whole liver graft without steatosis [49]. Although still widely used in Europe, there are not many validation studies. However, two large criticisms involve the expense and limited availability of factor V level measurement and the lack of generalizability given that the subjects were suffering solely from HBV induced liver failure [50].

## Model for End-Stage Liver Disease

The Model for End-Stage Liver Disease (MELD) was originally developed to predict mortality within 3 months following elective transjugular intrahepatic portosystemic shunts (TIPS) procedure for either variceal rebleeding or for treatment of refractory ascites. Using cox proportional-hazards regression, Malinchoc et al. found that serum concentrations of bilirubin, creatinine, international normalized ratio for prothrombin time (INR), and the cause of the underlying liver disease were predictors of survival in patients undergoing elective TIPS [51]. Kamath et al. later expanded the use of the MELD score to determine the prognosis of liver disease and ultimately prioritize the allocation of liver transplants [52]. Kamath et al. tested MELD score in four populations: patients hospitalized for hepatic decompensation, ambulatory patients with noncholestatic cirrhosis, patients with primary biliary cirrhosis, and a set of historical patients from the 1980s with cirrhosis [52]. The MELD score was able to predict death within 3 months with a concordance (c)-statistic of

0.87, 0.80, 0.87, and 0.78 for each of the groups, respectively. A c-statistic of 0.87 implies that 87% of the time the model correctly predicted between a pair of cirrhotic patients that the one with the higher score had the higher short-term mortality and would more likely benefit from transplantation. Although the model proved to be successful, it was adjusted to not include the etiology of ALF as one of the variables. This was due to the fact that its absence in the score did not alter 3-month mortality while also posing difficulties given that patients typically had multiple causes of liver disease [52]. It was also found that the inclusion of the complications of portal hypertension did not provide further prognostic information [53]. Additionally, there were several changes made to the model when it was used for organ allocation to avoid negative scores and make it more objective. This included using lower bounds for serum creatinine and bilirubin, an INR fixed at 1, and an upper limit for creatinine of 4 mg/dL [54].

The MELD score was used for organ allocation by the United Network for Organ Sharing (UNOS) starting in February of 2002. It was found that there was a 12% reduction in waiting list registration, 3.5% reduction in death while on the waiting list, a decrease from 656 days to 416 days waiting for a transplant and ultimately an increase in number of transplanted patients within 30 days of listing without affecting overall post-transplant survival [55]. When prospectively applying the MELD score to 3437 adult liver transplant candidates it was found that patients with a MELD <9 had a 1.9% mortality rate, while those with a score ≥ 40 had a mortality rate of 71.3%. Using the c-statistic with 3 month mortality as the endpoint, the receiver operating characteristic curve was 0.83 compared to 0.76 for the Child-Turcotte-Pugh score [56]. When applying the MELD score to 312 ALF without acetaminophen toxicity it was found that these patients had the lowest survival probability that correlated with severity of their MELD score. These patients had an increase in survival from 58% to 91% after transplantation [57]. For cases of ALF secondary to acetaminophen toxicity, it was found that a MELD score >33 predicted death with a sensitivity of 60%, specificity of 69%, positive predictive value of 65%, and a negative predictive value of 63%. This did not prove to be superior to either INR alone or the KCC [42].

The MELD score has shown to be an objective metric that aids in the allocation of liver transplants; however there are several weaknesses associated with it. One example is the use of creatinine as one of the variables. Creatinine may be lower in cirrhotic patients that are malnourished or have decreased muscle mass ultimately underestimating the severity of liver disease. On the other hand, the MELD score does not take into account kidney disease independent of liver dysfunction which may overestimate the severity. Finally, creatinine measurement may be skewed by the assay used due to the elevated bilirubin concentration [58]. The MELD score is constantly evolving with modifications being made to the variables. Some examples of new applications of the MELD include: MELD Na [59]; ReFit MELD [60]; UKELD [61]; RE-weighted MELD [62].

## Acute Liver Failure Early Dynamic Model

In 2012, Kumar et al. wanted to determine if dynamic changes in laboratory values had more prognostic value than prior models. Their model, the Acute Liver Failure Early Dynamic (ALFED) model, was based on persistent or progressively increasing elevation in hepatic encephalopathy, INR, arterial ammonia, and serum bilirubin over the first 3 days of hospitalization. Two points were given for hepatic encephalopathy > grade II and arterial ammonia ≥123 mcmol/L, while one point was given for an INR ≥ 5 and serum bilirubin ≥15 mg/dL. It was initially studied in 244 patients and then validated with another 136. It was found this model predicted death with a sensitivity of 90%, specificity of 80%, positive predictive value of 85%, and negative predictive value of 87% in patients with a score ≥4. Additionally, it was found that this model was superior to the KCC and MELD even when their 3-day serial values were used [63]. Although this model has not been widely tested, it was validated by a study completed in India in 2018. Shalimar et al. compared ALFED, MELD, MELD-Na, Chronic Liver Failure-consortium ACLF score, and KCC in viral hepatitis related ALF. It was found that ALFED outperformed the other models with an area under the receiver operator characteristic curve of 0.95 with the best sensitivity (87.1%), specificity (89.5%), positive predictive value (93.8%), and negative predictive value (79.1%) [64].

## Other Prognostic Factors

In the process of developing prognostic models, several serological markers have been proposed as isolated prognostic entities [12]. There are limited data but these markers include serum lactate [65], arterial ammonia [66], galactose elimination capacity [67], serial prothrombin times [68], arterial ketone body ratio [69], factor V and VIII ratios [70], plasma Gc protein levels [71], and serum phosphate [71]. To give further information, it was found that an arterial lactate >3 mmol/L after fluid resuscitation predicted mortality with a positive predicative value of 89% and negative predictive value of 94% [65], while an arterial ammonia level ≥124 mcmol/L had a 78.6% positive predictive value and 76.3% negative predictive value for mortality [66]. Although useful, it does not take into account the other variables and etiologies of ALF. Therefore, none of these markers are considered adequate when compared to the previously mentioned models [12].

**Summary**
Each of the prognostic models previously discussed have been essential in the determination if a liver transplant is necessary in the setting of ALF. However, even though they have been invaluable, each has its own weaknesses. Please see Table 5.3 for a summary of the prognostic models.

**Table 5.3** Summary of the prognostic models used for ALF

| Summary of prognostic models used for ALF | | |
|---|---|---|
| | Pros | Cons |
| Child-Pugh score | First formal attempt | Does not account for other signs of liver failure (i.e. renal dysfunction) |
| | Good for broad classification | Variables are weighted the same |
| | Simple to use | Encephalopathy and ascites are subjective and can be affected by medical management |
| | Variables easy to obtain | Values are subject to variability between laboratories |
| King's College criteria | Most widely used | Poor negative predicative value |
| | High specificity and positive predictive value | Places patients into only two categories |
| | | Requirement of encephalopathy for prognostication that can be delayed and/or subjective |
| Clichy criteria | Widely used in Europe | Limited validation studies |
| | Able to accurately determine requirement for liver transplantation | Lack of generalizability-studied in HBV patients |
| | | Expense and limited availability of factor V measurement |
| Model for end-stage liver disease | Able to predict 3 month mortality well | Use of creatinine as a marker- highly variable in cirrhotic patients |
| | The variables have defined limits to avoid excessive scores | Does not account for kidney disease independent of liver disease |
| | Elevated scores correlate with lower survival probability | Not superior to KCC or INR alone when evaluating acetaminophen induced ALF |
| | Constantly evolving with modifications | |
| Acute liver failure early dynamic model | Uses dynamic information | Not widely studied, relatively new |

## Acute on Chronic Liver Disease

These prognostic models that were already discussed were intended specifically for ALF. However, a clinical purpose that was also investigated was their use in acute on chronic liver failure. There are multiple definitions for acute on chronic liver failure (ACLF) that differ greatly from each other. The concept was widely used in critical care hepatology for patients that underwent support therapies as a bridge to liver transplantation [72]. It was not until 2009 that the first consensus was provided by the Asian Pacific Association for the Study of the Liver, defining ACLF as "an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy [73]." This was further expanded in 2014 to include a high 28-day mortality [74]. In an attempt to identify and characterize

acute hepatic decompensation and determine diagnostic criteria for ACLF there were two large, prospective, observational studies of patients. This included one in Europe, the Chronic Liver Failure (CLIF) Consortium Acute on Chronic Liver Failure in Cirrhosis (CANONIC) [75], and one in Canada and the USA, the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) [76]. Their basic definitions of ACLF are shown in Table 5.4.

**Table 5.4** Definitions of acute on chronic liver failure as defined by different associations

| Various definitions of acute on chronic liver failure | |
|---|---|
| Asian Pacific Association for the Study of the Liver (2009, updated in 2014) | Direct hepatic insult that causes liver failure evidenced by jaundice, serum bilirubin ≥5 mg/dL, and coagulopathy with an INR ≥ 1.5 or prothrombin activity <40% that is complicated by ascites and/or encephalopathy within 4 weeks |
| Chronic Liver Failure (CLIF) Consortium Acute on Chronic Liver Failure in Cirrhosis (CANONIC) (2013) | There are three grades of ACLF (grades I–III) based on acute hepatic decompensation, organ failure assessed by the CLIF-SOFA score (see Table 5.5), and a high 28-day mortality rate |
| North American Consortium for the Study of End-Stage Liver Disease (NACSELD) (2014) | Patients with decompensated cirrhosis that developed two or more extrahepatic organ failures assessed by presence of shock, hepatic encephalopathy grade III or IV, need for dialysis, or requirement for mechanical ventilation |

**Table 5.5** The chronic liver failure-sequential organ failure assessment score

| Chronic liver failure-sequential organ failure assessment (CLIF–SOFA) score | | | | | |
|---|---|---|---|---|---|
| | 0 point | 1 point | 2 point | 3 point | 4 point |
| Bilirubin (mg/dL) | <1.2 | ≥1.2 to <2.0 | ≥2.0 to <6.0 | ≥6.0 to <12 | ≥12.0 |
| Creatinine (mg/dL) | <1.2 | ≥1.2 to <2.0 | ≥2.0 to <3.5 | ≥3.5 to <5.0 or use of renal replacement therapy | ≥5.0 |
| Hepatic encephalopathy grade | None | I | II | III | IV |
| INR | <1.1 | ≥1.1 to <1.25 | ≥1.25 to <1.5 | ≥1.5 to <2.5 | ≥2.5 or platelet count ≤20 × $10^9$ L |
| Mean arterial pressure (mm Hg) | ≥70 | <70 | Dopamine ≤5 or dobutamine or terlipressin | Dopamine <5 or epinephrine ≤0.1 or norepinephrine ≤0.1 | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 |
| Lung $PaO_2/FiO_2$ or $SpO_2/FiO_2$ | >400 > 512 | >300 to ≤ 400 > 357 to ≤512 | >200 to ≤ 300 > 214 to ≤357 | >100 to ≤200 > 89 to ≤214 | ≤100 ≤ 89 |

The CLIF-SOFA score is based on six components that are affected by liver failure with subscores ranging from 0 to 4. $PaO_2$—partial pressure of arterial oxygen, $FiO_2$—fraction of inspired oxygen, $SpO_2$—pulse oximetric saturation [75, 78]

The CANONIC study was a prospective, observational study with 1343 patients with cirrhosis admitted to 29 liver units in 8 European countries. In an attempt to develop diagnostic criteria Moreau et al. adapted the Sequential Organ Failure Assessment (SOFA) [77] score used for critically ill patients, to develop the CLIF-SOFA score [75]. CLIF-SOFA score includes sub-scores ranging from 0 to 4 for six components that are affected by liver failure (Table 5.4). This includes the liver, kidneys, brain, coagulation, circulation, and lungs. Higher scores indicate more severe organ impairment and the aggregated scores range from 0 to 24 to provide information on overall severity. The study defined ACLF using acute hepatic decompensation, organ failure based on CLIF-SOFA score, and a high 28-day mortality rate. With this definition, it was found that patients with ACLF were younger, more frequently alcoholic, had more associated bacterial infections, higher leukocytosis, and higher levels of c-reactive protein than those without ACLF. Additionally, it was discovered that higher CLIF-SOFA and leukocyte counts were independent predictors of morality. This study showed that ACLF is a separate entity from acute decompensation based on the presence of organ failure, high morality, age, precipitating events, and systemic inflammation [75].

Prognostic models in ACLF have limited utility given that they do not account for extrahepatic organ failure, an essential component of ACLF. Jalan et al. developed the CLIF Consortium ACLF (CLIF-C ACLF) score to improve the CLIF-SOFA, while also comparing it to the CLIF-SOFA score, MELD, MELD-Na, and Child Pugh scoring systems as a prognostic model [79]. Using the population data from CANONIC, the CLIF Consortium Organ Failure score (CLIF-C OFs) was developed to diagnose ACLF. The CLIF-C OFs was then combined with age and leukocyte count to develop CLIF-C ACLF. The CLIF-C ACLF performed similarly to the CLIF-SOFA, but showed a significantly higher predictive accuracy than MELD, MELD-Na, and the Child-Pugh score as it had a 19–28% reduction in prediction error rates at all main time points after an ACLF diagnosis. Additionally, it was found that CLIF-C ACLFs computed at 48 h, 3–7 days, and 8–15 days after ACLF diagnosis predicted the 28-day mortality significantly better than at diagnosis [79].

Another model used for the prognostication of ACLF is the APASL ACLF research consortium (AARC). A total of 1402 ACLF patients were enrolled with 480 in the derivation cohort and 922 were validated. Five variables were found to be independent predictors of mortality: total bilirubin, creatinine, serum lactate, INR, and hepatic encephalopathy. Each parameter was scored 1 to 3, with a total minimum score of 5 to a maximum of 15. Grade I designates a score of 5–7, Grade II 8–10, and Grade III for 11–15 with a 28-day mortality rate of 12.7%, 44.5%, and 85.9%, respectively. It was found to be superior to the MELD and CLIF-SOFA scores, but was not specifically compared to CLIF-C ACLF [80].

## The Overall Utility of Prognostic Models

The reliance on prognostic scoring systems is not currently recommended as they do not adequately predict outcome or determine candidacy for liver transplant [3]. This is based on the rationale that there are a wide variety of etiologies resulting in ALF, variability in patient survival, and subsequent complications that are unpredictable to ultimately determine who is a good candidate for transplantation. Even when considering KCC and MELD, two of the most commonly used models, their accuracy is largely dependent on the etiology. A meta-analysis of 23 studies including 2153 patients compared KCC and MELD as a predictor of morality. The study used the diagnostic odds ratio (DOR), defined as the ratio of positive to negative likelihood ratios, to determine the effectiveness of these tests. For all cases of ALF, it was 5.3 for KCC and 7.0 for MELD, indicating that MELD was more accurate. However, when accounting for etiology, it was found that the DOR for acetaminophen induced ALF for KCC was 10.4 while 6.6 for MELD. Conversely, for non-acetaminophen induced ALF, the DOC for KCC was 4.6 and 8.4 for MELD [45].

The meta-analysis comparing KCC and MELD demonstrates that the prognostic models developed for ALF are fundamentally flawed due to a myriad of factors. To begin, prognostic models for ALF do not use the full information. This may include using the variables incorrectly or missing variables entirely. This can translate to the model being too simple due to quantitative variables being reduced to binary scoring values. This results in loss of prognostic information [81–83]. Second, our incomplete knowledge of ALF limits our prognostic models. Many of the models previously discussed use variables such as INR, bilirubin, creatinine, hepatic encephalopathy, and the like. However, this does not account for precise information that can be elucidated by the etiology at hand. For example, the use of molecular biology has shown to be promising as it has been found that genotypes are particularly influential in certain disease states, such as hepatocellular carcinoma [84] or hepatitis C [85]. This mindset dictates that prognostic models need to be more individualized. This is especially true when considering that these prognostic models were developed when analyzing large cohorts of patients with different clinical courses. This results in crude, imprecise estimates when applying a model to an individual. Finally, prognostic models in ALF need to be dynamic. Data are collected from one particular point in time that does not account for the fluctuations in the clinical course of ALF. Simply put, prognostic models are merely a snapshot of a very dynamic process [86].

**Conclusion**

Prognostic models are a tool that aid in the evaluation of patients with ALF and ACLF. However, they cannot replace clinical assessment of the individual patients. Further work is needed to build on the groundwork that has been laid by Child-Pugh, KCC, Clichy Criterion, MELD, Acute Liver Failure Early

Dynamic Model, and the other prognostic models. Specifically, future models need to account for variables that reflect the underlying liver dysfunction, rather than generic laboratory findings. Additionally, they must have more advanced statistics to account for the dynamic nature of ALF and ACLF, and ultimately be applicable to the individual patient.

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

**Daniel M. Glass and Ali Al-Khafaji**

**Key Concepts**

ALF is a rare, heterogenous 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

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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 $\geq$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 proceed 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

**Table 6.1** Comparison of the definitions for ACLF by different hepatology societies

| 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<br>Superimposed hepatitis E<br>Alcoholic hepatitis | Alcoholic hepatitis<br>Bacterial infections<br>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]

**Table 6.2** Manifestations of hepatic encephalopathy by grade

| 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 |

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 ≥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 suck 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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# Chapter 7
# Non-Intensive Care Unit Management of Acute and Acute on Chronic Liver Failure


**Stephen M. Riordan**

**Key Concepts**

1. Given that aetiology of acute liver failure (ALF) is an important factor influencing both its natural history and prognosis, establishing the causative process where possible is crucial in formulating an appropriate management approach, including applicability or otherwise of urgent liver transplantation.
2. Close monitoring of organ function and early management of organ dysfunction are vital if outcomes of patients with ALF are to be optimised. Recognition of any progression of hepatic encephalopathy beyond grade 1 is of paramount importance and should prompt transfer to a specialised intensive care setting; any change in cognition in patients with ALF should be taken to reflect a change in hepatic encephalopathy status until proven otherwise, whilst remaining mindful of and effectively managing alternative explanations such as alcohol withdrawal, hypoglycaemia or hyponatraemia.
3. The approach to management of acute on chronic liver failure (ACLF) is currently less well-evolved than that for ALF. Currently accepted non-ICU management is to treat any identifiable precipitating factor, such as with antibiotic therapy for bacterial infection, corticosteroids for severe alcoholic hepatitis and nucleos(t)ide analogues for reactivation of chronic HBV infection.

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4. Whilst the early elucidation and treatment of any identifiable precipitating factor for ACLF is important, it is well recognised that the correction of the precipitating event may not necessarily be an essential arbiter of prognosis and that the ACLF may nonetheless progress despite reversal of the triggering process.
5. Furthermore, a substantial proportion of patients with ACLF will continue to deteriorate despite full supportive measures, as in ALF, and may require urgent liver transplantation.

**Summary**
Acute liver failure (ALF) is defined by the occurrence of hepatic encephalopathy as the consequence of severe liver injury in a patient without pre-existing chronic liver disease, an exception being a fulminant presentation with hepatic encephalopathy of a patient with previously asymptomatic Wilson's disease. ALF must be distinguished from acute on chronic liver failure (ACLF), a relatively recently described clinical entity in which an acute decompensation of chronic liver disease is accompanied by multi-organ failure and an high short-term mortality rate, mimicking that of ALF. An excessive systemic inflammatory response plays a crucial role in poor outcomes related to both of these liver failure syndromes. Close monitoring of organ function and support of failing organs, along with the identification and correction of the aetiology of the underlying liver insult and reversal of harmful systemic inflammation, are crucial if patient outcomes are to be optimised. This chapter focuses on the non-intensive care unit (ICU) management of these separate clinical entities of ALF and ACLF, including both aetiology-related and general supportive medical measures of proven value.

Acute liver failure (ALF) is a specific, potentially catastrophic but uncommon clinical syndrome, defined by the occurrence of hepatic encephalopathy as the consequence of severe liver injury in a patient without pre-existing chronic liver disease, an exception being a fulminant presentation with hepatic encephalopathy of a patient with previously asymptomatic Wilson's disease [1, 2]. Key components of the ALF syndrome include cerebral oedema, haemodynamic instability, renal failure, coagulopathy, profound metabolic disturbances, a particular susceptibility to bacterial and fungal infection and an often-marked systemic inflammatory response syndrome (SIRS), reflected by the occurrence of at least two of the following components: a body temperature >38 °C or <36 °C; heart rate >90 beats/min; tachypnoea greater than 20 breaths/min or $PaCO_2$ less than 4.3 kPa; white cell count $>12 \times 10^9$/L or $<4 \times 10^9$/L or the presence of >10% immature neutrophils [3].

The specific cause of the liver insult responsible for the development of ALF is an important factor influencing the rate of progression of the clinical syndrome, with the latter, in turn, impacting upon the likelihood of spontaneous recovery.

Indeed, the term ALF may be considered as an umbrella term, with "hyperacute", "acute" and "subacute" variants [2, 4]. In this schema, jaundice-to-encephalopathy times range from seven days or less (hyperacute liver failure), between 8 and 28 days (acute liver failure) and between 29 and 84 days (subacute liver failure). Once hepatic encephalopathy develops in the subacute form of ALF, the likelihood of spontaneous recovery is only low, in contrast to those with an hyperacute presentation, in whom the chance of spontaneous recovery is typically higher, even in the presence of complicating multiorgan dysfunction [5]. While advances in supportive medical care have led to improved survival, ALF, in its most severe form, continues to carry a high mortality rate unless emergency liver transplantation is performed. Nonetheless, the rapidity with which the clinical syndrome often progresses results in many patients dying or developing contraindications to liver transplantation before a donor liver becomes available, even with priority listing, highlighting the need for more effective support measures as a bridge to liver transplantation or to actively promote hepatocellular regeneration, upon which spontaneous recovery ultimately depends.

ALF should not be confused with the separate and relatively recently described clinical entity of acute on chronic liver failure (ACLF), in which an acute decompensation of chronic liver disease is accompanied by multi-organ failure and an high short-term mortality rate, mimicking that of ALF [6]. An excessive systemic inflammatory response, either to the initiating event or consequent to the resultant severe liver injury or both, as in ALF, seems to play a crucial role in the pathogenesis of ACLF [7, 8]. In Western countries, the most frequently identified precipitating factors are bacterial infection (33%), active alcohol excess leading to severe alcoholic hepatitis (25%) and gastrointestinal bleeding (13%), while no identifiable precipitating event is apparent in over 40% of cases [9]. Intestinal dysbiosis and increased translocation of gut flora from the intestinal lumen have been postulated to at least contribute to the systemic inflammation in this latter group [6]. The most frequent precipitating event in Asia is reactivation of hepatitis B virus (HBV) infection [10].

This chapter focuses on the non-intensive care unit (ICU) management of these separate clinical entities of ALF and ACLF, including both aetiology-related and general supportive medical measures of proven value.

## Initial Management Considerations

The key initial assessment task in a patient presenting with hepatic encephalopathy in the context of a severe liver injury is to discriminate between ALF and ACLF, given the need in ALF to consider emergency liver transplantation according to both prognostic criteria and the presence or absence of contraindications, aiming at an early stage to identify those who would most benefit, since urgent liver transplantation has transformed the chance of survival related to ALF in its most severe form [11, 12]. Early referral to a dedicated liver transplant centre, such as when hepatic encephalopathy is of only low grade and even before specific transplant criteria are

met, is recommended for all ALF patients, whether or not transplant candidates, in order that they benefit from focused expertise and stand the greatest chance of survival, either spontaneous or with eventual liver transplantation [13].

Access to a patient's medical history, including whether or not there is a known history of liver disease or hepatotoxin exposure, including potentially hepatoxic alcohol use, is crucial in helping to discriminate ALF from ACLF. Liver imaging appearances of a reduced liver volume, an irregular liver border and the appearances of liver nodules may point to underlying cirrhosis, but it must be emphasised that both clinical and imaging features of a subacute presentation of ALF can mimic those of cirrhosis. Indications for liver biopsy are limited in the ALF setting, especially in the setting of often profound coagulopathy, but may be considered, preferably via a transjugular route at a specialised centre with established expertise in this technique, especially if looking to establish a particular cause for which specific treatment is available, such as autoimmune hepatitis that may respond to a trial of immunosuppressive therapy, or to exclude an aetiology for which emergency liver transplantation is contraindicated, such as malignant infiltration of the liver, in which case significant hepatomegaly with or without focal abnormalities may be apparent on imaging.

## Aetiology-Related Non-ICU Management Considerations in ALF

Given that aetiology of ALF is an important factor influencing both its natural history and prognosis, establishing the causative process where possible is crucial in formulating an appropriate management approach, including applicability or otherwise of urgent liver transplantation. Key aetiological issues include assessing for causes for which specific therapies may be applicable and those for which emergency liver transplantation is not indicated. In addition to malignant infiltration of the liver, these latter aetiologies include haemophagocytic syndromes and acute ischaemic liver injury, the latter of which is often reversible following improvement in haemodynamic status.

The relative prevalences of the various aetiologies of ALF vary according to geographical location. Rate of progression of the clinical syndrome varies according to aetiology and, somewhat paradoxically, spontaneous survival with medical management alone is inversely related to rapidity of onset of encephalopathy [14–16]. In a non-transplant series, survival was 36% when encephalopathy was hyperacute in onset, occurring within one week of the development of jaundice, but no more than 14% with longer jaundice to encephalopathy times. ALF due to acetaminophen hepatotoxicity is nearly always hyperacute in onset, as is the case in the majority of cases related to infection with hepatitis A virus (HAV) and HBV but in a lower proportion of patients with other aetiologies [2, 4]. Due to the rapidity of progression of encephalopathy in the hyperacute category, patients may become comatose before clinical jaundice is even apparent. Within the acetaminophen

hepatotoxicity group, survival with medical management is inversely correlated with the admission grade of encephalopathy, at least in non-acidotic patients, highlighting the potential benefit of early referral to a specialised center [4, 15, 17].

## *Acetaminophen*

Most instances of acetaminophen-induced ALF are the consequence of an overdose of the drug taken at a single time point with suicidal or parasuicidal intent [18, 19]. Cases of severe hepatotoxicity after repeated ingestion of recommended (or near-recommended) doses of acetaminophen, mostly over several days to weeks, have also been reported, including in patients with chronic exposure to alcohol or use of other enzyme-inducing drugs, such as anti-tuberculous chemotherapy (rifampicin and isoniazid) and anti-convulsants (phenytoin, carbamazepine and phenobarbital) [20–23] and in the setting of reduced glutathione reserve related to prior starvation or malnutrition [18, 24, 25].

Assessment of a blood acetaminophen level should be viewed as an essential component of the diagnostic work-up of every patient with ALF at presentation [13]. Nonetheless, acetaminophen may be undetectable in peripheral blood by this time, in which setting ascribing aetiology becomes dependent upon the clinical history and typical laboratory features. Acetaminophen-related hepatotoxicity is characterised by very marked elevations in peripheral blood aminotransferase values, often in excess of 10,000 international units per litre and grossly out of proportion to serum bilirubin values that can be normal or near normal in the early stages of the clinical syndrome, along with metabolic acidosis and acute renal impairment. The development of ALF due to acetaminophen may be prevented if the antidote, N-acetylcysteine, is given within 15 hours of exposure. Furthermore, the later use of this agent, after signs of liver necrosis have developed, has been shown to ameliorate associated multi-organ failure and to improve survival [26]. Indeed, spontaneous survival with modern supportive care is in the order of 20–40% in patients with acetaminophen-related ALF, despite fulfilling emergency liver transplant selection criteria [13].

## *Non-Acetaminophen Drug-Related*

Non-acetaminophen drug reactions, mostly idiosyncratic, account for only approximately 10–15% of cases of ALF in Western countries [27]. By contrast, up to 80% of this group will die or require emergency liver transplantation [28]. Many drugs have been implicated, most commonly including isoniazid, nitrofurantoin, ketoconazole, phenytoin, valproate, non-steroidal anti-inflammatory agents, propylthiouracil and disulfiram [29–31]. Non-acetaminophen-related drug-induced ALF mostly follows an acute or subacute course. “Ecstasy” (3,4-methylene-dioxymethamphetamine)

and other illicit drugs are increasingly recognised causes of ALF [32], with "ecstasy"-induced ALF typically following an hyperacute course with early multi-organ failure, in keeping with other aetiologies of heatstroke-related liver injury [13]. Instances of severe liver damage with use of anti-retroviral agents in patients with human immunodeficiency virus infection are also recognised, either as a direct drug effect or in relation to immune reconstitution in the setting of associated chronic HBV or hepatitis C virus (HCV) infections [33]. Hepatotoxicity due to Chinese herbs and other "over the counter" supplements is also increasingly seen in as a cause of ALF in Western patients [34].

A non-acetaminophen-related drug cause for ALF is often a diagnosis of exclusion, such that other aetiologies, most particularly viral infection alone or in combination, must be considered.

## *Viral Infection*

Any virus which can cause an acute hepatitis may potentially result in ALF and laboratory screening for a possible viral aetiology forms an important part of the initial diagnostic assessment at presentation, irrespective of travel history. Such viruses can be broadly categorised as those which primarily affect the liver, such as the hepatitis viruses A to E, and those in which liver involvement may occur as part of disseminated infection, as with Epstein-Barr virus, cytomegalovirus (CMV), varicella-zoster virus, enteroviruses, parvovirus B19, adenovirus, herpes simplex virus (HSV), Toga virus-like particles, papilloma virus, paramyxoviruses and haemorrhagic fever viruses [34]. ALF due to HSV may respond to high dose acyclovir, while treatment with ganciclovir is instituted in cases of ALF related to CMV infection [34, 35].

Fewer than 1% of patients with acute hepatitis A virus (HAV) infection develop ALF, with risk increasing markedly in those older than 40 years, in whom prognosis is worse [36–38]. HAV superinfection in patients with chronic HCV infection resulting in ALF in one series from Italy was attributed to the HAV, in view of a reduced rate of HCV replication observed during acute HAV infection [39]. The implication of this finding is that those with chronic HCV infection should be vaccinated pre-emptively against HAV.

HBV infection is highly endemic in the South East Asian and Western Pacific regions, along with parts of the Mediterranean, the Middle East and sub-Saharan Africa and, accordingly, is the major cause of ALF in such areas. Fewer that 4% of patients with acute HBV infection develop ALF, although the resultant mortality rate associated with ALF due to acute HBV infection that is higher than that associated with ALF due to other hepatitis viruses [40–43]. Reactivation occurring in the context of chronic HBV carriage, arising either spontaneously or in the setting of pharmacological immunosuppression for solid organ or haematological malignancies, is more common than de novo HBV infection as a cause of ALF in these areas [34]. A nucleos(t)ide analogue such as entecavir or tenofovir is usually given in

patients with HBV-related ALF and detectable circulating HBV DNA levels, although viral replication is characteristically already low or absent by the time that ALF has developed [34].

Hepatitis E virus (HEV) is the most common cause of epidemic hepatitis and ALF in tropical countries such as India and other developing countries of South East Asia [44–46]. A particularly high prevalence of infection with HEV, along with a high mortality rate, has been documented in pregnant women, especially during the second and third trimesters [47–49]. HEV infection has also occasionally been implicated in a relatively small number of sporadic cases of ALF in the West [34].

There is also a striking geographical difference in the prevalence of ALF due to HCV infection. In Japan and Taiwan, HCV positivity has been found in nearly 60% of patients with ALF of presumed viral origin and in whom markers for HAV and HBV were negative [50–52]. Conversely, infection with HCV alone is an uncommon cause of ALF in Western countries [34].

Bone marrow suppression and aplastic anaemia are uncommon but well-recognised complications of ALF due to viral hepatitis, especially in children. Recognised associations are with parvovirus B19 and hepatitis viruses A, B and C. However, the presumed viral infection remains undiagnosed in the majority of cases [53–56]. Treatment options include antithymocyte globulin (ATG) and anti-lymphocyte globulin (ALG). Improvement in bone marrow function has also been reported following successful liver transplantation.

### *Other Causes*

Other uncommon aetiologies of ALF include autoimmune hepatitis, pregnancy-related disorders such as acute fatty liver and the HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome, *Amanita phalloides* poisoning, veno-occlusive disease, acute Budd-Chiari syndrome, hepatic ischaemia related to heart failure or septic shock, heatstroke, Wilson's disease and infiltrative disorders, including lymphoma, disseminated carcinoma and haemophagocytic syndromes.

An history of other autoimmune disorders in a patient presenting with ALF should raise the prospect of autoimmune hepatitis as the possible cause. A raised serum globulin level and strongly positive autoantibody titres, such as smooth muscle or liver kidney microsomal antibodies, are suggestive but liver biopsy may be required to definitively make the diagnosis in this setting. A trial of corticosteroids can be effective if instituted early in the clinical course but is not without risk, given the propensity of such treatment to promote septic complications [57]. It is recommended that lack of response within seven days should constitute treatment failure and lead to listing for urgent liver transplantation [13].

Acute fatty liver of pregnancy typically presents in the third trimester of pregnancy with non-specific symptoms including malaise and abdominal discomfort, accompanied on occasion by polydipsia and polyuria. Hypoglycaemia is often evident and occurs out of proportion to only modestly elevated peripheral blood

aminotransferase levels. ALF due to acute fatty liver of pregnancy carries a maternal mortality rate in the order of 20%, although emergency delivery of the baby offers a good outcome and emergency liver transplantation is rarely required. Emergency delivery of the baby also generally results in a favourable outcome for the HELPP syndrome, another pregnancy-specific aetiology of ALF that similarly typically presents in the third trimester. The sudden onset of right upper quadrant abdominal pain in a patient with known pre-eclampsia complicating pregnancy suggests liver rupture. Laparotomy may be necessary to control excessive bleeding consequent to a liver capsular tear, while an extensive subcapsular haematoma may result in compression of hepatic veins, leading to a Budd-Chiari-type syndrome [13, 58].

Budd-Chiari syndrome and veno-occlusive disease (also known as sinusoidal obstruction syndrome) present with abdominal pain, hepatomegaly and ascites. Imaging characteristics are important in establishing these diagnoses. Decompressive vascular shunting (surgical or radiologically-achieved) can be effective in selected patients. Investigation for an underlying pro-coagulant disorder and malignancy is mandatory in Budd-Chiari syndrome. Interventional radiology including not only placement of a transjugular intrahepatic portosystemic shunt (TIPSS) but also hepatic venous angioplasty and stenting of the inferior vena cava may also have roles in selected patients with hepatic venous outflow block, depending on the exact clinical context [34]. Therapeutic paracentesis, following appropriate measures to reduce bleeding risk, may improve venous return, renal function and cardiac index in those patients with Budd-Chiari syndrome or veno-occlusive disease who develop tense ascites [13]. Treatment of precipitating cardiac dysfunction is necessary in ischaemic ALF due to left ventricular failure, along with appropriate antibiotics and vasopressor agents in septic shock. Circulatory collapse with resultant ischaemic liver injury also contributes to the pathogenesis of ALF associated with heatstroke [34].

Recognition of the rare fulminant presentation of Wilson's disease, suggested clinically by the presence of Coombes-negative haemolysis and splenomegaly in a young patient, is crucial as mortality in those presenting with severe hepatic encephalopathy is virtually 100% without urgent liver transplantation. By contrast, survival without transplantation can be achieved with early D-penicillamine treatment in most non-advanced encephalopathic Wilson's disease patients who present acutely with other manifestations of severe hepatic insufficiency, highlighting the importance of early recognition of this disorder [59, 60]. Notably, Kayser-Fleischer rings are apparent in only 50% of cases [13]. Lymphomatous infiltration of the liver is another rare but potentially treatable cause of ALF [34].

*Amanita phalloides* poisoning follows the ingestion of toxic mushrooms, with profuse vomiting and diarrhoea typically preceding the onset of liver injury [61, 62]. ALF related to *Amanita phalloides* toxicity tends to follow an hyperacute course. Penicillin and silibinin have been proposed as antidotes [34]. Similarly, documentation of cases of ALF due to ingestion of food contaminated with the *Bacillus cereus* emetic toxin, which inhibits hepatic mitochondrial fatty-acid oxidation [63], raises the possibility that other hitherto poorly categorised

mitochondrial toxins may be responsible for many cases of ALF currently considered cryptogenic or indeterminant in aetiology.

## General Supportive Non-ICU Management Considerations in ALF

Close monitoring of organ function and early management of organ dysfunction are vital if outcomes of patients with ALF are to be optimised. Recognition of any progression of hepatic encephalopathy beyond grade 1 is of paramount importance and should prompt transfer to a specialised intensive care setting [34]. Any change in cognition should be taken to reflect a change in hepatic encephalopathy status until proven otherwise, whilst remaining mindful of and effectively managing alternative explanations such as alcohol withdrawal, hypoglycaemia or hyponatraemia. The latter require judicious correction. Over-correction of hypoglycaemia resulting in hyperglycaemia should be avoided so as to avoid exacerbating raised intracranial pressure, while rapid correction of hyponatraemia by more than 10 mmol/L per 24 h should be avoided so as to avoid the possibility of central pontine myelinolysis. Anti-hepatic encephalopathy treatments of value in the chronic liver disease setting, such as lactulose and rifaximin, have no role in the ALF setting. Hypovolaemia must be corrected, preferably via crystalloid volume resuscitation, whilst maintaining the serum sodium level in the normal range and avoiding fluid overload [13]. As with progressive hepatic encephalopathy, persistent hypotension despite adequate cardiac filling pressures requires specialist intensive care-setting transfer for commencement of vasopressor support. Stress ulcer prophylaxis is usually recommended [64, 65], although the use of proton pump inhibitor therapy for this purpose must be balanced against the risk of inducing both *Clostridium difficile* overgrowth and gastric bacterial overgrowth with consequent risk of pneumonia, especially in those that subsequently require mechanical ventilation [13, 66]. In any case, consideration should be given to the early suspension of proton pump inhibitor therapy once adequate enteral nutrition is established, as risk of stress ulceration is reduced in this circumstance [13].

### *Nutritional and Metabolic Management*

Energy requirements in ALF are increased by up to 30% and are further elevated by complicating infection, such that enteral or parenteral nutritional support strategies are warranted. Mean energy expenditure has been estimated at 4.05 kJ/kg/hr. Despite the reduction in functioning liver mass, the metabolic rate is substantially increased [67], in keeping with the marked SIRS which typically accompanies this syndrome. Rapid deterioration in nutritional status with depletion of muscle and fat

stores is often seen. Impairment of glycogen storage and reduced capacity for gluconeogenesis result in increased breakdown of adipose tissue and muscle consequent upon the use of fat and protein as alternative fuel sources [68]. However, the predominant factor responsible for the exaggerated whole body protein degradation is likely reduced hepatic synthesis of insulin-like growth factor-1 [69]. Hypophosphataemia, which can reflect increased utilisation consequent to hepatocellular regeneration in response to the severe underlying liver injury and be a good prognostic marker [70], hypokalaemia and hypomagnesaemia are common, the latter two deficiencies especially in patients who maintain an adequate urine output, and require appropriate replacement.

Caloric requirements in the order of 35–50 kcal/kg daily are required to meet resting metabolic demand. Protein intakes in excess of 1 g/kg/day are necessary to maintain nitrogen balance. Up to 50% of non-protein calories should be delivered as lipid [71]. Enteral nutrition is preferable to the parenteral route if possible, in view of reports of maintained integrity of gut mucosa and reduced rates of bacterial translocation and sepsis in experimental animals [72]. Early introduction of enteral feeding has been shown to reduce the risk of upper gastrointestinal bleeding from stress ulceration [13], although nasogastric feeding may be better avoided in those with gastric stasis and progressive hepatic encephalopathy in view of risk of microaspiration. Any decision to implement total parenteral nutrition should be based on baseline nutritional status, the likely duration of ongoing low caloric intake and whether or not nutritional support via the preferred enteral route is feasible [13]. Recent data derived from the critical care setting indicate that there is no benefit to be gained in commencing total parenteral nutrition prior to day 5 or day 7 post-presentation [73–75].

## *Management of Renal Failure*

Up to 80% of ALF patients referred to tertiary liver units with ALF have acute kidney injury, an entity associated with adverse survival but which is reversible following recovery from ALF, either spontaneous or following liver transplantation, in the majority of cases [76]. Risk factors for the development of acute kidney injury complicating ALF include older age, a documented episode of systemic hypotension, an acetaminophen aetiology of ALF, an episode of complicating infection and the presence of the SIRS [76, 77]. Preventative strategies include attention to ensuring adequate intravascular volume status, prompt correction of any systemic hypotension and effective treatment of infection, while avoiding exposure to potentially nephrotoxic antibiotics and radiological contrast agents as far as is practical [13]. Where required (uncontrolled acidosis, hyperkalaemia, fluid overload and oliguria associated with either a serum creatinine >300 micromol/L or cerebral oedema requiring treatment with mannitol) [34], continuous modalities of renal replacement therapy

are preferred to intermittent haemodialysis in order to provide greater haemodynamic stability, since complicating hypotension with intermittent haemodialysis results in a fall in cerebral perfusion pressure which may exacerbate or precipitate cerebral oedema in the ALF setting [11, 78]. The preferred strategy for anticoagulation of renal replacement circuits remains the subject of much conjecture, with little current data to support which is the safest approach. If citrate is used in the setting of ALF, it is recommended that close monitoring of total calcium levels compared with ionised calcium levels be undertaken [79].

### *Haematological Management*

Contrary to previously held assumptions, most patients with ALF have a normal coagulation state, despite prolongation of measured prothrombin times, with a significant proportion actually hypercoagulable when assessed by thromboelastography [80–82]. The latter group should be considered for venous thrombosis prophylaxis. Prophylactic correction of coagulation factor or platelet levels is not only generally unnecessary but may be counter-productive in patients with ALF by increasing risk of thrombosis and transfusion-related acute lung injury [13]. Of course, coagulation factor and platelet support, as appropriate, may be warranted in the setting of active bleeding. Haemoglobin levels in excess of 7 g/dL are generally accepted to be appropriate in patients with ALF, although this cut-off can be modified in those with comorbid cardiovascular disease [83].

### *Management of Sepsis and Inflammation*

Patients with ALF are at increased risk of complicating infection, consequent to various immunological disturbances and the frequent requirement for invasive procedures for organ support and/or monitoring [34]. Severe, unresolved infection may preclude liver transplantation. Bacterial infection, most commonly pneumonia, urinary tract sepsis, intravenous cannula-related bacteraemia and spontaneous bacteraemia, has been documented to complicate the clinical course in up to 80% of ALF patients [84, 85]. Fungal infection occurs in approximately one third of cases, typically later in the clinical course [13]. A high level of clinical suspicion is required for early diagnosis, while interval routine microbiological surveillance also has a role [84]. Deterioration in hepatic encephalopathy grade and in renal function, along with the development of the SIRS, are clinical clues to the possible development of otherwise occult bacterial or fungal infection [86]. Proven bacterial infection should be treated according to in vitro sensitivities, while invasive fungal infection requires parenteral treatment with an appropriate anti-fungal agent. In the absence of a

positive isolate, the possibility of fungal infection should be considered in the settings of a fever unresponsive to broad-spectrum antibiotics, leukocytosis or deterioration in neurological status after initial improvement, especially in the presence of renal failure [34].

While prophylactic use of broad-spectrum antibacterial or antifungal antibiotics has not been shown to improve survival in ALF [87], antibiotic therapy should be instituted whilst awaiting microbial culture results if hepatic encephalopathy is progressive, otherwise unexplained deterioration in renal function should ensue or elements of the SIRS develop, since significant associations have been demonstrated between infection, severity of the SIRS and progressive hepatic encephalopathy, reducing the chance of emergency liver transplantation and conferring a poor prognosis [88]. SIRS, whether related to complicating infection or to the underlying severe liver injury per se, reflects a state of initial immune activation that over time tilts towards an anti-inflammatory response associated with immune suppression, predisposition to recurrent infection and increased mortality [89].

### *Use of N-Acetylcysteine*

In addition to its proven role in acetaminophen-related ALF when given up to 48 hours after overdose, N-acetylcysteine has been shown to improve outcome in adults with ALF and low grade HE related to non-acetaminophen aetiologies [90]. Proposed beneficial mechanisms include anti-oxidant effects promoting hepatocyte survival, anti-inflammatory effects consequent to inhibition of the transcription factor, nuclear factor kappa B, and vasodilatory effects resulting in improved microcirculatory function [26, 91, 92]. Nonetheless, it has been proposed that the duration of N-acetylcysteine therapy be limited to five days, beyond the duration of the initial ALF-associated pro-inflammatory cytokine storm, in order to counter the possibility of functional immunosuppression, which might further increase the risk of complicating nosocomial sepsis [93, 94].

## Non-ICU Management Considerations in ACLF

The approach to management of ACLF is currently less well-evolved than that for ALF. Currently accepted non-ICU management is to treat any identifiable precipitating factor, such as with antibiotic therapy for bacterial infection, corticosteroids for severe alcoholic hepatitis, although efficacy of corticosteroid therapy is substantially reduced in those with alcoholic hepatitis and ACFL (38%) compared to those

with alcoholic hepatitis without ACLF (77%) [95], and nucleos(t)ide analogues for reactivation of chronic HBV infection [96]. The management of the ACLF per se is supportive, based on close monitoring of organ function and support of failing organs [97]. In one large study, the incidences of extrahepatic organ/system failure associated with ACLF were kidneys (56%), coagulation (27%), the brain (24%), the circulation (17%) and the lungs (9%) [9]. Terlipressin given in combination with intravenous albumin is the preferred treatment for hepatorenal syndrome associated with ACLF [98], although the response rate is substantially reduced in more advanced stages of the ACLF syndrome compared to those with less severe manifestations (29% versus 60%, respectively) [99]. A prospective observational study has raised the possibility that non-selective beta blocker therapy may have a role in reducing the systemic inflammation that has been identified as a key factor associated with worse outcomes in ACLF [100].

Whilst the early elucidation and treatment of any identifiable precipitating factor for ACLF is important, it is well recognised that the correction of the precipitating event may not necessarily be an essential arbiter of prognosis and that the ACLF may nonetheless progress despite reversal of the triggering process. Furthermore, a substantial proportion of patients will continue to deteriorate despite full supportive measures, as in ALF, and may require urgent liver transplantation, although outcome data specifically related to liver transplantation for ACLF are still relatively scarce. For these reasons, patients with ACLF should preferably be managed in a specialist centre with focussed expertise in the management of liver failure syndromes and with access to urgent liver transplantation if necessary [6].

Various experimental therapies, including treatment with granulocyte colony-stimulating factor (G-CSF), infusion of mesenchymal stromal cells and faecal microbiota transplantation, have been trialled as possible supportive measures in ACLF. In two small, randomised controlled trials, G-CSF was shown to improve liver function and organ failure scores in ACLF, while preventing the occurrences of hepatic encephalopathy, hepatorenal syndrome and complicating sepsis [101, 102]. More recently, the peripheral infusion of allogeneic bone marrow-derived mesenchymal stromal cells was shown in a randomised controlled trial in patients with HBV-related ACLF to improve 24 week survival by both improving hepatic function and reducing the incidence of severe infections [103]. Finally, a small pilot study of healthy donor faecal microbiota transplantation in eight patients with ACLF due to alcoholic hepatitis ineligible for corticosteroid therapy, based on the premise that intestinal dysbiosis and increased bacterial translocation from the intestinal lumen may contribute to the systemic inflammation associated with ACLF, found an improved 12 month survival rate compared to that in historical controls [104]. Findings of these various analyses require confirmation in additional studies but raise the prospect of more effective non-ICU-based therapies for ACLF, based on a better understanding of the pathogenesis of this relatively recently described clinical entity.

**Questions**

1. With regard to the aetiology of acute liver failure (ALF):
   (a) The specific aetiology has an important impact on the subsequent natural history.
   (b) Acetaminophen overdose leading to ALF typically follows a subacute course.
   (c) Liver biopsy should be performed routinely for diagnosis.
2. Regarding a possible therapeutic role for N-acetlycysteine in acute liver failure (ALF):
   (a) This may be of value only in cases of acetaminophen overdose.
   (b) The mechanism of action is limited to a possibly beneficial nutritional effect.
   (c) It has been suggested that treatment duration be limited to a maximum 5 days.
3. The systemic inflammatory response syndrome (SIRS):
   (a) May occur in ALF but is not a feature of acute on chronic liver failure (ACLF).
   (b) Is always the consequence of unresolved microbial infection.
   (c) Is significantly associated with likelihood of progressive hepatic encephalopathy in ALF.
4. With regards to therapies for acute on chronic liver failure (ACLF):
   (a) Corticosteroid therapy for alcoholic hepatitis is as efficacious in patients with and without acute on chronic liver failure.
   (b) Terlipressin plus intravenous albumin is as efficacious for hepatorenal syndrome complicating advanced and earlier stages of acute on chronic liver failure.
   (c) Reversal of the specific trigger, such as bacterial infection, may not necessarily prevent progression of the clinical syndrome.

**Answers**

Question 1 answers:

(a) This is true. The specific cause of the liver insult responsible for the development of ALF is an important factor influencing the rate of progression of the clinical syndrome, with the latter, in turn, impacting upon the likelihood of spontaneous recovery. Indeed, the term ALF may be considered as an umbrella term, with “hyperacute”, “acute” and “subacute” variants. In this schema, jaundice-to-encephalopathy times range from seven days or less (hyperacute liver failure), between

8 and 28 days (acute liver failure) and between 29 and 84 days (subacute liver failure). Once hepatic encephalopathy develops in the subacute form of ALF, the likelihood of spontaneous recovery is only low, in contrast to those with an hyperacute presentation, in whom the chance of spontaneous recovery is typically higher, even in the presence of complicating multiorgan dysfunction.

(b) This is false. ALF due to acetaminophen hepatotoxicity is nearly always hyperacute in onset.

(c) This is false. Indications for liver biopsy are limited in the ALF setting, especially in the setting of often profound coagulopathy, but may be considered, preferably via a transjugular route at a specialised centre with established expertise in this technique, especially if looking to establish a particular cause for which specific treatment is available, such as autoimmune hepatitis that may respond to a trial of immunosuppressive therapy, or to exclude an aetiology for which emergency liver transplantation is contraindicated, such as malignant infiltration of the liver, in which case significant hepatomegaly with or without focal abnormalities may be apparent on imaging.

Question 2 answers

(a) This is false. In addition to its proven role in acetaminophen-related ALF when given up to 48 h after overdose, N-acetylcysteine has been shown to improve outcome in adults with ALF and low grade hepatic encephalopathy related to non-acetaminophen aetiologies.

(b) This is false. Proposed beneficial mechanisms include anti-oxidant effects promoting hepatocyte survival, anti-inflammatory effects consequent to inhibition of the transcription factor, nuclear factor kappa B, and vasodilatory effects resulting in improved microcirculatory function.

(c) This is true. It has been proposed that the duration of N-acetylcysteine therapy be limited to five days, beyond the duration of the initial ALF-associated pro-inflammatory cytokine storm, in order to counter the possibility of functional immunosuppression, which might further increase the risk of complicating nosocomial sepsis.

Question 3 answers

(a) This is false. The SIRS is a common feature of both acute and acute on chronic liver failure syndromes.

(b) This is false. The SIRS may occur as the consequence of microbial sepsis or liver damage per se.

(c) This is true. A significant association has been demonstrated between severity of the SIRS and progressive hepatic encephalopathy in ALF, reducing the chance of emergency liver transplantation and conferring a poor prognosis.

Question 4 answers

(a) This is false. Efficacy of corticosteroid therapy is substantially reduced in those with alcoholic hepatitis and ACFL (38%) compared to those with alcoholic hepatitis without ACLF (77%).
(b) This is false. Terlipressin given in combination with intravenous albumin is the preferred treatment for hepatorenal syndrome associated with ACLF, although the response rate is substantially reduced in more advanced stages of the ACLF syndrome compared to those with less severe manifestations (29% versus 60%, respectively).
(c) This is true. Whilst the early elucidation and treatment of any identifiable precipitating factor for ACLF is important, it is well recognised that the correction of the precipitating event may not necessarily be an essential arbiter of prognosis and that the ACLF may nonetheless progress despite reversal of the triggering process. Furthermore, a substantial proportion of patients will continue to deteriorate despite full supportive measures, as in ALF, and may require urgent liver transplantation.

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# Chapter 8
# Management of Acute and Acute on Chronic Liver Failure in the Intensive Care Unit Setting


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**Key Concepts**

- Acute Liver Failure (ALF) and Acute on Chronic Liver Failure (ACLF) are disease states that can affect all organ systems, and call for comprehensive critical care.
- Hepatic Encephalopathy (HE) occurs in both ALF and ACLF, however, the cerebral edema that can occur with HE in ALF is more likely to be life-threatening, and needs to be treated in an expeditious manner.
- Hemodynamics and fluid management in ALF and ACLF can be quite difficult. Volume status needs to be assessed frequently at the bedside to avoid both under and over-volume resuscitation.
- Patients with ALF and ACLF are prone to infections, and may not display typical signs and symptoms; particularly concern is for occult fungal infections.
- The care of patients with ALF and ACLF in the ICU requires excellent communication with many disciplines, attention to the complex hemodynamic and metabolic needs, as well as supportive emotional care for their families.

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## Introduction

The care of the patient with serious liver disease in the intensive care unit is challenging. There are two broad categories of patients with liver disease that physicians in the ICU may be called upon to care for—Acute Liver Failure (ALF) and Acute on Chronic Liver Failure (ACLF). While the etiology and ultimate management of these patients are different, much of the basic ICU care is similar, and relies upon the foundation of high-quality critical care.

Acute liver failure (ALF), formerly known as fulminant hepatic failure, is a syndrome of severe, rapid-onset hepatic dysfunction without evidence of prior liver disease that is associated with high morbidity and mortality. The criteria for Acute Liver Injury (ALI) are (1) INR > 1.5, (2) no evidence of prior liver disease and (3) illness duration of <26 weeks. If patients go on to develop Hepatic Encephalopathy (HE) they are characterized as having ALF. In those with severe HE, progression to cerebral edema (CE) and intracranial hypertension (ICH) is a feared outcome, often with fatal consequences. ALF is often rapidly progressive and is associated with multi-organ dysfunction. Thankfully, ALF is rare, with an incidence in the developed world of probably fewer than five cases per million per year [1]. Throughout the last few decades, ALF outcomes have improved due to earlier recognition, the improvement of the intensive care management, and developments in emergent liver transplantation.

Acute on Chronic Liver Failure (ACLF) is a clinical syndrome that was first characterized in the CANONIC Study [2]. ACLF is characterized by acute liver decompensation (defined as the development of ascites, encephalopathy, gastrointestinal (GI) hemorrhage and/or bacterial infections) and organ failure in hospitalized patients who have pre-existing liver disease. The CANONIC study delineated a group of patients with advanced liver disease with a rapid decline in organs outside of the liver, to distinguish patients with ACLF from patients with an acute decompensation of liver disease. In order to diagnose organ failure, the CANONIC investigators chose to combine the Sequential Organ Failure Assessment (SOFA) with markers of hepatic failure to devise the CLIF-C ACLF score, which determines the severity of illness and the likelihood of mortality in patients with ACLF. Cirrhotic patients admitted to the hospital without organ failure (no ACLF) have a very low 28-day mortality rate (5%), while patients with 2 organ failures (ACLF Grade 2) or those with 3 organ failures or more (ACLF Grade 3) have high mortality rates (32% and 79%, respectively, as seen in Table 8.1). Most patients with ACLF require intensive care and organ support.

The use of this scoring system can help with determining prognosis, and utility of continued treatment. In a recent retrospective study of 202 patients admitted to a single ICU, a CLIF-C ACLF score of greater than 70 after 48 h of intensive care was associated with a 100% 28 day mortality [4]. This information can be helpful when discussing prognosis and addressing palliative care options with surrogate decision makers, as the patients themselves are typically too ill to participate in these discussions. A similar study looked at the ACLF grade and score at the end of 7 days of intensive care, and suggested that a ACLF-Grade of 3 after 7 days of ICU care, with

**Table 8.1** ACLF grades based on results at enrollment in the CANONIC study

| Definitions | 28-day transplant-free mortality rate |
|---|---|
| ACLF grade 1<br>Kidney failure<br>Single-organ failure (liver, coagulation, circulation, lungs) with serum creat. 1.5–1.9 mg/dl<br>Hepatic encephalopathy with serum creat. 1.5–1.9 mg/dl | 22.1% |
| ACLF grade 2<br>Two organ failures | 32.0% |
| ACLF grade 3<br>Three organ failures or more | 78.6% |

Adapted from [3]

4 or more organ failures or a CLIF-C ACLF-score >64 is strongly associated with mortality if the patient cannot be offered a liver transplant [5].

In some centers, liver transplant can improve the poor prognosis of the most severely ill patients with cirrhosis and ACLF Grade 3, enabling them to achieve survival rates similar to transplanted patients with a lower ACLF grade. These good survival results are associated with an increased post-liver transplant hospital stay and high rate of complications. However, to obtain these good results a rapid decision-making process is needed because of the short transplantation window; patients with ACLF-3 should be rapidly referred to a liver transplant center in order to determine eligibility for liver transplant [6].

## Initial Assessment of ALF and ACLF

Patients with ALF or ACLF can be admitted to the ICU for a variety of reasons. Patients with ALF, have a clinical course that can deteriorate rapidly, requiring mechanical ventilation for airway support, careful fluid and cardiovascular management, and possible aggressive management of elevated Intracranial Pressure (ICP). Patients with ALF require testing to determine the etiology of the liver failure, which should include hepatitis serologies, an autoimmune work-up, acetaminophen levels, HIV testing, and a careful social history, paying close attention to potential toxic exposures, and recent drug and alcohol use.

Patients with ACLF frequently need admission to the ICU for management of multiple organ failures. The precipitants for ACLF are both extrahepatic (i.e., infection and bleeding) and intrahepatic (i.e., alcohol and viral hepatitis). Infection is the most frequent cause, precipitating up to 40% of cases of ACLF [7]. The most common reason for admission to the ICU are hepatic encephalopathy requiring intubation, acute GI bleeding, septic shock, or volume overload coupled with acute kidney injury (AKI) and respiratory failure. Upon arrival to the ICU, the patient needs to be assessed for the need for mechanical ventilation and renal replacement therapy, and aggressively treated for all reversible causes of the acute decompensation.

Communication with Gastroenterology and the Hepatology Service is important to facilitate the evaluation for potential liver transplant. All patients should be pan cultured, including ascites if present, to evaluate for spontaneous bacterial peritonitis.

In addition to the rapid initiation of acute medical management, ICU teams must be aware of who the main social supports and potential surrogate decision makers are for the patient. Patients with both ALF and ACLF can deteriorate rapidly, and difficult decisions may need to be made. Additionally, it is prudent to find out if the patient has any advance directives or a living will at the time of admission, which can be used to help guide treatment that is in accordance with known patient preferences, especially if the patient does not improve with ICU care.

## Neurological Dysfunction

As noted, Hepatic Encephalopathy (HE) is one of the defining elements of ALF. HE is a neuropsychiatric syndrome and is staged using the West Haven Criteria for encephalopathy (Table 8.2). The scale ranges from minimal changes which are very subtle, and then progressing from Stage I to Stage IV, going from a shortened attention span and anxiety in Stage I, to coma in Stage IV, where the patient is unresponsive to verbal or noxious stimuli [8–10].

### *Hepatic Encephalopathy in ALF*

Hepatic encephalopathy (HE) is the clinical manifestation of cerebral edema which often leads to Intracranial Hypertension (ICH) in patients with ALF. The development of diffuse cerebral edema in patients with ALF is thought to result from an elevated serum level of ammonia, which crosses the blood-brain barrier to react

**Table 8.2** Hepatic encephalopathy grades

| Stages of hepatic encephalopathy | Signs and symptoms |
|---|---|
| Stage I | Trivial lack of awareness<br>Euphoria or anxiety<br>Shortened attention span<br>Impaired performance of addition |
| Stage II | Lethargy or apathy<br>Minimal disorientation for time or place<br>Subtle personality change<br>Inappropriate behavior<br>Impaired performance of subtraction |
| Stage III | Somnolence to semi-stupor, but responsive to verbal stimuli<br>Confusion<br>Gross disorientation |
| Stage IV | Coma, unresponsive to verbal or noxious stimuli |

with glutamate to form glutamine within astrocytes. The large quantity of intracellular glutamine is then thought to result in an osmotic shift of fluid into astrocytes, and this astrocyte swelling leads to cerebral edema [11]. Loss of cerebral vascular autoregulation, systemic inflammation and metabolic disturbances also play a role [12]. In patients with severe HE (stage 3–4), progression of cerebral edema and intracranial hypertension can lead to transtentorial herniation and brain death. While a specific ammonia level cannot accurately predict the degree of HE, a plasma ammonia level of more than 150–200 μmol/L in ALF is considered a risk factor for ICH. Historically, the progression from HE to transtentorial herniation accounted for up to 75–80% of deaths in ALF, however with improved ICU care focusing on neuroprotective interventions, the mortality attributable to ICH is in the range of 10–20% [1].

Treatment in the ICU for ICH is targeted on lowering the Intracerebral Pressure (ICP) and metabolic demands on the brain. Once HE has reached Grade 3, the patient should be intubated and sedated. Patients with ALF routinely hyperventilate on their own due to the increased respiratory drive present during liver failure. This is important for intensivist to note, so that abrupt drops in minute ventilation are avoided after intubation. It is prudent to set the respiratory rate to achieve a $pCO_2$ of 35, which can usually be monitored with end-tidal $CO_2$.

Aggressive lowering of ammonia is warranted at levels greater than 150 μmol/L, with continuous renal replacement therapy (CRRT), even in the absence of acute kidney injury and other indications for renal replacement therapy [1]. Although ammonia reducing strategies may be beneficial, the evidence that conventional treatments for HE (lactulose and rifaximin) improve outcomes in patients with ALF is lacking [13].

A recent retrospective study of early CRRT started in the intensive care unit for patients with grade 3–4 encephalopathy, showed that the therapy can reduce the levels of ammonia to safe levels within 5 days of initiation. The median time to initiation of CRRT from admission to the unit was 4 h [14].

Ammonia should be checked upon admission to the ICU in all patients with ALF. Hyperosmotic therapy with hypertonic saline can be considered for any patient with grade 3–4 encephalopathy to achieve a goal Na of 145–155. Mannitol can also be given emergently to raise the blood osmolality, and try to prevent brain swelling [13]. By increasing serum tonicity, the administration of concentrated saline induces the movement of water from brain tissue into the bloodstream, decreasing cerebral edema [15]. In a prospective randomized controlled trial of patients with ALF and Grade 3–4 HE, hypertonic saline was shown to decrease the incidence of ICH [16]. If the patients go on to develop refractory elevations in ICP, despite all of the above measures, some centers will then go on to induce hypothermia to 32–34 °C along with a pentobarbital coma.

The use of invasive intracerebral pressure monitoring in patients with ALF and HE of grade 3–4 is controversial. While it is appealing to have real-time monitoring of the ICP in order to rapidly respond to changes in the ICP, the use of these devices have been declining in recent years. Many centers feel that the risks of bleeding and infection outweigh the utility of placing these invasive devices [17]. However, in a

single center study, the use of Invasive ICP monitoring with a protocolized approach to reducing the risks of insertion was shown to be safe with only 1 complication, and no deaths attributable to the monitoring [18]. The best approach is to have a multidisciplinary discussion with the intensivist, hepatologist and neurosurgeon to individualize decision-making for patients where it is believed that ICP monitoring may allow for optimization of a patient that would not otherwise be eligible for liver transplantation.

### *Hepatic Encephalopathy and ACLF*

In patients with ACLF, even with mild, low-grade HE, cerebral edema occurs. The presence of HE even without ACLF is associated with a significantly worse outcome compared with non-HE patients. HE, independent of other organ failures, adds significantly to the risk of death [19]. Treatment focuses on removal of bacterial-derived toxins and manipulating gut floral levels, as well as treating complicating diagnoses, such as GI bleeding, infections, electrolyte disturbances and acute kidney injury [20].

Current therapies for HE are based on the hypothesis that the colon is the primary organ that generates ammonia. Non-absorbable disaccharides such as lactulose acidify the colon and create a hostile environment for the survival of intestinal bacteria involved in the production of ammonia. Non-absorbable disaccharides also cause a four-fold increase in fecal nitrogen excretion due to their cathartic effect. Doses are generally titrated to achieve two to four semi-soft stools daily. Whole gut decontamination with Polyethylene Glycol 3350-Electrolyte Solution was found to be superior to lactulose in a small single-center study [21], though more studies are needed. Antimicrobial agents can also be used to inhibit ammonia production by intestinal bacterial. The main agent used in this manner is rifaximin, which is a poorly absorbed synthetic antimicrobial with a broad spectrum of antibacterial activity. Being virtually non-absorbed, its bioavailability within the GI tract is high, and due to its low rate of systemic absorption, rifaximin appears to be relatively safe [22].

In the ICU we give oral lactulose and rifaximin for all patients admitted with ACLF and AMS. If the patient needs to be NPO, usually secondary to an acute GI bleed, we will give lactulose via rectal enemas. While we will check the ammonia level when patients are admitted, we titrate the lactulose to effect in ACLF, not to the absolute number, given that there is only a loose correlation with ammonia level and grade of encephalopathy in patients with chronic liver disease [23].

## Analgesia and Sedation

The first approach to patients with liver failure in the ICU who are agitated is to determine the cause. Frequently however, patients with ACLF and ALF require sedation in order to facilitate mechanical ventilation and/or to treat the ICP

associated with HE. It is crucial to try to avoid medications that cause prolonged sedation, as the examination of mental status is important when determining if the patient is a liver transplant candidate. In our unit, we first treat patients with fentanyl given in low doses, as needed, escalating to an infusion when the nurse needs to give 3 or more boluses in a 4-h period. We find that most of the time this allows us to keep the patient comfortable, without adding longer-lasting medications that may make intermittent assessment of mental status difficult. If sedation is required, we use a short acting sedative such as propofol or dexmedetomidine. Benzodiazepines should only be used as a last resort, and only those agents that are short-acting [24]. Treatment is guided by The Richmond Agitation Sedation Scale with a target goal of −1.

## Cardiovascular Dysfunction

In patients with ALF and ACLF, hemodynamic instability can play a large role in their ICU course. Most patients with ALF are young, and thus rarely have underlying chronic cardiovascular disease. Rather, hemodynamic instability in ALF is usually a late manifestation of the disease, attributable to the hemodynamic effects of elevated ICP, concomitant sepsis, or the sepsis like-picture that comes with hepatic necrosis. In contrast, there are many hemodynamic alterations that are part of the pathogenesis of patients with chronic liver disease. It is incumbent upon the intensivist caring for patients with ACLF to assess cardiovascular function and monitor hemodynamic changes that can occur in these patients.

Hemodynamic instability in critically ill patients with ACLF can have many causes. Patients with advanced cirrhosis and portal hypertension have a hyperdynamic circulation characterized by low arterial pressure, high cardiac output, and low systemic vascular resistance [25]. In addition, patients with ACLF can have cardiomyopathy and alcoholic related cardiomyopathy, sepsis-related cardiovascular dysfunction, volume overload associated with acute kidney injury (AKI) and hepatorenal syndrome, or simply underlying cardiovascular disease that is evident in the general population.

Early in liver disease, total blood volume increases but is largely sequestered in the splanchnic vascular bed, leading to “splanchnic steal” and systemic hypovolemia. The hyperdynamic circulation associated with cirrhosis is characterized by increased heart rate, increased cardiac output, and systemic hypotension. Portal hypertension-mediated engorgement of collateral veins (as occurs in esophageal varices, hemorrhoids, and caput medusae) also increases the circulatory surface area [26].

The dysregulation of the splanchnic vasculature in patients with ACLF plays a large role in the hypotension and organ dysfunction that is frequently seen in patients with ACLF in the ICU. Splanchnic vasodilation reduces the effective arterial blood volume and causes renal vasoconstriction, sympathetic stimulation, stimulation of the renin-angiotensin-aldosterone system and vasopressin secretion [27]. These pathophysiological responses are key to the development of progressive ascites and

subsequent renal vasoconstriction and dysfunction as portal hypertension evolves, most marked in ACLF [28].

Cirrhotic cardiomyopathy is a specific form of cardiac dysfunction characterized by blunted contractile responsiveness to stress stimuli, altered diastolic relaxation and prolongation of the QTc in the absence of more traditional cardiac disease or alcohol related cardiomyopathy [29]. Cirrhotic cardiomyopathy may be present in up 50% of patients with cirrhosis and can occur independently of other complications of cirrhosis such as the portopulmonary syndrome and the hepatopulmonary syndrome. It may be implicated in complications such as development of hepatorenal syndrome as part of a cardio-renal syndrome.

## *Cardiovascular Assessment and Support*

The use of Point of Care Ultrasound (POCUS) by intensivists to aid in narrowing the differential diagnosis of shock and to help guide fluid replacement is becoming standard of care while management critically ill patients in the ICU [30]. One of the challenges to using this modality in the critically ill patient with end stage liver disease is being able to image the IVC through what can be a significant amount of ascites. Also, given that there are dynamic changes to the splanchnic and hepatic vasculature, it is not clear how reliable standard measurements of the IVC may be in patients with end-stage liver disease. However, POCUS remains a useful tool to look for cardiac dysfunction, structural kidney abnormalities, and to aid in performing invasive procedures in critically ill patients with liver disease.

Critically ill liver patients may need volume and vasopressor support to achieve a targeted mean arterial pressure of 60 mm Hg. Given the propensity of patients with end stage liver disease to develop volume overload, the use of POCUS to guide the judicious use of fluids is prudent [31].

Crystalloids are our fluid of choice though excess volume can easily result in worsening extravascular fluid overload and pulmonary edema. Albumin has a role in volume expansion in patients with advanced liver disease. The use of albumin for volume expansion for patients with spontaneous bacterial peritonitis (SBP) in order to prevent hepatorenal syndrome (HRS) is well established. In patients with SBP, giving albumin at 1.5 g/kg of body weight within 6 h of the diagnosis of SBP, and then 1 g/kg of body weight on day 3 after diagnosis, decreases mortality and the incidence of HRS [32]. The strength of this evidence has yet to be repeated in patients with ACLF, but there is some data suggesting that a similar protocol of volume expansion with albumin may hasten the resolution of ACLF, however more studies are needed to determine if there is a mortality benefit [33].

Norepinephrine is the first-line vasopressor of choice in all patients with distributive shock who do not respond to fluid resuscitation, including patients with liver

disease [34]. Vasopressin is a reasonable second pressor to add. In a prospective observational study, it was shown that patients with liver disease undergoing liver transplantation demonstrated low baseline vasopressin levels and a greater likelihood to respond with an increase of mean arterial pressure to exogenous vasopressin than control patients with normal liver function [35]. Vasopressin causes vasoconstriction and improves preload by mobilization of the splanchnic blood volume, and can be norepinephrine sparing. However, the use of vasopressin in cirrhotic patients has been challenged. The potential adverse effects of vasopressin may theoretically be amplified in patients with cirrhosis with the worsening of liver function tests, thrombocytopenia, and hyponatremia. However, in a single center retrospective cohort study, the use of vasopressin as a second line agent for vasodilator shock was not associated with these adverse effects nor was there any increase in mortality [36].

## Endocrine Abnormalities in ACLF and ALF

### *Glucose Control and Nutrition*

Hypoglycemia occurs in both patients with ACLF and ALF and is due to hepatic necrosis, with depletion of glycogen stores and impaired gluconeogenesis. ICU patients should have their fingerstick glucose checked at least every 2–4 h, and replacement should be started when levels are less than 60 mg/dl. Hyperglycemia should also be avoided as glucose crosses the blood-brain barrier, and hyperglycemia contributes to elevated ICP. Nutrition should be initiated as soon as possible, as liver failure is a catabolic state. We will typically initiate at least trophic feeding in patients with both ALF and ACLF within 24 h of ICU admission, of at least 20 ml/h [37].

### *Adrenal Insufficiency*

Liver cirrhosis is considered to be among the major groups of high-risk diseases with a predisposition to adrenal insufficiency (AI), with some studies finding a prevalence of up to 50% of critically ill cirrhotic patients meeting the criteria for diagnosis of relative adrenal insufficiency [38]. The term hepato-adrenal syndrome is used to define AI in patients with advanced liver disease with sepsis. As in other patient populations, diagnosis is made on clinical grounds, with hypotension unresponsive to fluids and vasoactive agents. Serum free cortisol and salivary cortisol are the most accurate methods for the diagnosis of AI in cirrhotic patients but are not used in routine clinical practice. As in patients without liver disease, it remains

controversial as to whether physiological steroids improve outcomes [39]. In our practice, we will typically start physiological steroids (50 mg of hydrocortisone IV every 6 h), on patients on high doses of 2 pressors.

## Renal Function in Liver Failure

Many patients with liver disease who are admitted to the ICU also have kidney disease, either long standing disease that worsens with critical illness, or new onset acute kidney injury (AKI). In both ALF and ACLF, the presence of kidney injury worsens the prognosis and complicates the management of patients with liver disease. When kidney disease is present, intensivists have to pay close attention to volume and acid-base status, dosing of drugs, and decide when the risk of placing large bore catheters for Renal Replacement Therapy (RRT) is warranted, given the risks due to coagulopathy present in patients with liver disease.

### *ALF and AKI*

The current definition of AKI in most of the critical care and hepatology literature is based on a modification of the Risk, Injury, Failure, Loss and End stage kidney disease (RIFLE) criteria proposed by the Acute Kidney Injury Network and is referred to as the AKIN criteria. AKI is defined as any one of the following: an increase in serum creatinine by ≥0.3 mg/dl within 48 h, increase in serum creatinine by ≥1.5 times baseline, or urine volume <0.5 mg/kg/h for 6 h [40].

AKI complicates the clinical course of many patients with ALF. In a study of 1600 patient with ALF in the US, AKI was found in 70% of patients with ALF, with up to 34% of these patients requiring renal replacement therapy. AKI is associated with worse survival with patients with ALF [41]. The etiology of AKI in ALF can be multifactorial. Volume depletion and hemodynamic instability likely play a role in kidney injury [42]. If the patient developed ALF secondary to an acetaminophen overdose, the drug has direct nephrotoxic properties as well as the known effects on the liver.

The standard criteria to initiate RRT are applicable to patients with ALF and AKI, namely severe acidemia, refractory hyperkalemia, and volume overload causing hypoxia. We prefer that when patients with ALF require RRT, Continuous Renal Replacement Therapy (CRRT) be initiated. CRRT allows for better hemodynamic stability, and further, only CRRT has been shown to reduce ammonia levels, which is a major cause of mortality due to brain swelling in patients with ALF. There is also gathering evidence that initiating CRRT during the first day of admission to the ICU for patients with ALF, AKI and elevated ammonia, leads to improved outcomes [14, 43].

## *ACLF and Kidney Injury*

Patients with ACLF and an elevated creatinine with reduced renal function could be at risk of having a life-threatening complication of cirrhosis—hepatorenal syndrome (HRS). Similar to patients without cirrhosis, in patients with cirrhosis, AKI can be due to prerenal (volume depletion, gastrointestinal bleeding), intrarenal or intrinsic (bile acid nephropathy, acute tubular necrosis, acute interstitial nephritis, acute glomerular and vasculitic renal diseases) and/or post-renal (acute obstructive nephropathy) causes. Additionally, hepatorenal syndrome (HRS) should be included in the differential diagnosis.

Hepatorenal syndrome is renal dysfunction in cirrhotic patients in the setting of abnormalities in the arterial circulation and overactivity of the endogenous vasoactive systems [44]. HRS can be diagnosed based on the International Club of Ascites criteria with an increase in creatinine >0.3 mg/dl over baseline over 48 h, or an increase of creatinine ≥50% from baseline. It is then staged from 1 to 3 based on severity. In addition to meeting the criteria for the increase in creatinine, patients must have cirrhosis and ascites, no response to plasma volume expansion with albumin 1 g per kg of body weight over 48 h, no signs of structural kidney disease, and an absence of shock [44]. The addition of decreased urine output of ≤0.5 ml/kg of BW or ≥6 h was recently proposed to be added, as well as changing the nomenclature of HRS-1 to HRS-AKI, and HRS-2 to HRS-NAKI [45].

The use of biomarkers of kidney injury such as interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver type fatty acid-binding protein (L-FABP) and neutrophil gelatinase-associated lipocalin (NGAL) can be used to help differentiate between HRS-AKI and ATN-AKI [46], though they are not routinely used in clinical practice.

Patients with HRS-AKI who do not have indications for RRT, should be supported with vasopressors and albumin. If patients have tense ascites, a therapeutic paracentesis should be performed in order to relieve the pressure in the abdomen, and to increase renal blood flow. This needs to be undertaken cautiously, avoiding the removal of too much volume, which can worsen the hemodynamics of the patient [47]. There is some data that terlipressin and albumin may be superior to albumin alone for the treatment of HRS-AKI [48], though terlipressin is currently not available in the US. If the patient is in the ICU, we typically will use albumin and levophed to try to treat HRS [49].

The decision to initiate RRT in patients with ACLF should not be taken lightly, especially when the patients are not liver transplant candidates. The Acute Dialysis Quality Initiative group recommends renal support for patients with HRS-AKI only if there is an acute potentially reversible event, or if liver transplantation is planned. This is based on the lack of evidence for a major survival benefit for RRT in HRS-AKI, and that without a reversible precipitant or potential liver transplant, 3-month survival is marginal at best [50]. When initiating RRT in patients with ACLF it is important to talk with families about the expected outcomes and goals for the therapy.

## Infection and Immune Dysfunction

Infection in patients with ALF and ACLF is very common. The liver is a frontline immune organ designed to detect and clear potential pathogens from the blood. Liver failure is thus an immunocompromised state. The balance between immunotolerance and effective immune responses is mediated by the interactions occurring between the numerous populations of immune cells that reside within, and are recruited to, the liver [51]. When this balance is disturbed either acutely in ALF or over time in ACLF, severe infection can set in, and lead to morbidity and mortality.

### *ALF and Infection*

Patients with ALF have an increased susceptibility for infections as a result of excessive systemic inflammation, mainly from cytokine storm, multiple organ dysfunction, and functional immunoparesis. Risks of infection are further amplified by the presence of indwelling lines, catheters, and tubes. Microbial infections have been documented in up to 80% of ALF cases [12]. Gram positive and gram negative bacteria are most frequently isolated, though fungal infections have been reported to occur in about 30% of patients [52].

Many patients with ALF who are admitted to ICUs receive prophylactic or empiric antibiotics and antifungals [53]. This makes sense as the hemodynamic profiles of patients with ALF and septic shock are very similar, and it can be difficult to differentiate the two. A recent retrospective cohort study of 1551 patients with ALF showed that 34% experienced at least 1 culture-documented infection, with 14.6% with a blood stream infection (BSI), 14.4% with at least 1 positive sputum culture/tracheal aspirate, and 16.6% had at least 1 positive urine culture. Of the patients with a BSI, 9% had fungemia. The study then went on to look at the effect of prophylactic antibiotics in this cohort, and found that the use of antibiotics did not decrease the incidence of BSI and positive tracheal aspirate or improve the 21-day survival of patients [54]. When managing patients with ALF and hypotension requiring pressors, broad spectrum antibiotics should be started. If cultures remain negative for 48–72 h, and the patient starts to improve, the decision to hold antibiotics can be considered.

### *ACLF and Infection*

Predisposition for sepsis in cirrhosis is multifactorial. A complex pattern of compromised cellular and humoral immune defenses and immunodeficiency coexist, which worsens with increasing severity of liver disease [37]. The immunodeficient state is most apparent in the setting of ACLF, which resembles the immunopathology of

sepsis, with an initial systemic inflammatory response (cytokine storm) leading to a compensatory anti-inflammatory response that impairs resistance to infection. The dynamic spectrum of immunological disturbances that develop in patients with cirrhosis is referred to as cirrhosis associated immune dysfunction. The majority of infections in patients with cirrhosis are caused by Gram-negative bacteria of intestinal origin, although Gram-positive infections have been associated with severe sepsis in cirrhotic patients in intensive care units. Pathological translocation of intestinal bacteria into the portal blood circulation or ascites is implicated as a major pathogenic mechanism in the development of these infections, especially SBP and bacteremia [55].

A recent prospective cohort study of cirrhotic patients at tertiary liver care centers characterized the types of infections found in patients with advanced liver disease. The most common primary infections were UTI, SBP, spontaneous bacteremia, then skin and lower respiratory tract infections. Nosocomial infections were more likely to be UTIs or *C. difficile* [56]. Any nosocomial infection in patients with advanced liver disease is associated with worse 30-day mortality, independent of other factors, including MELD, age, AKI episodes and ACLF development [57].

Patients with ACLF and fungal infections have worse outcomes. The diagnosis of fungal infections can be difficult, as fungal culture can take a while to grow, delaying prompt therapy. Risk factors that are associated with fungal infections in patients with cirrhosis are diabetes, AKI, ICU admission, and bacterial infection upon admission [58].

Similar to a general population with septic shock, delays in appropriate, broad spectrum antimicrobials is associated with a higher risk of death, starting with 3 h after the onset of hypotension. Fungal infections are associated with the longest delay to appropriate therapy [59]. Thus when patients are initially admitted to the ICU with signs of shock, broad spectrum antibiotics should be initiated, with strong consideration being given to adding fungal coverage if the risk factors mentioned above are present. Even if cultures remain negative, a short course of empiric antibiotics for at least 5 days should be considered. Procalcitonin is a biomarker that has been used in the general population for aid in de-escalating antibiotics. There is insufficient evidence to support using procalcitonin in patients with liver disease, both ALF and ACLF, in this manner [60].

## Respiratory Failure in ALF and ACLF

Patients with both ALF and ACLF frequently develop respiratory failure. Both of these patient groups are at increased risk for aspiration pneumonitis/pneumonia due to altered mental status. Lower respiratory tract infections are common due to immune deficiency as discussed earlier, and may lead to respiratory failure with the need for mechanical ventilation, necessitating admission to the ICU.

### *ALF*

The incidence of ARDS in patients ALF is felt to be relatively low, especially in the setting of systemic inflammatory response. In a review of 200 acute liver failure patients receiving mechanical ventilation, 21% had acute respiratory distress syndrome within the first 72 h after admission; most were mild and there was limited impact on outcome [61].

### *ACLF*

There are three main complications of advanced liver disease that can impact the lungs: hepatopulmonary syndrome, portopulmonary hypertension (part of WHO group 1 pulmonary hypertension), and hepatohydrothorax. Further, significant ascites can reduce diaphragmatic excursion, leading to impaired compliance of the respiratory system. While none of these diagnoses necessitate admission to the ICU, they may cause hypercapnia or hypoxemia, and in the setting of sepsis or volume overload, may lead to the need for non-invasive or mechanical ventilation.

### *Support of Acute Respiratory Failure in ALF and ACLF*

Patients with altered mental status may require intubation and mechanical ventilation in order to decrease the risk of aspiration. We do not recommend the use of non-invasive positive pressure ventilation (Bi-Level) in these patients given the altered mental status and high risk for aspiration. For those patients with pure hypoxemic respiratory failure due to a potentially quickly reversible cause, it is reasonable to initiate treatment with High-Flow Nasal Oxygen (HFNO). Scenarios where this may be considered include volume overload with the plan for RRT, or hypoxemia from a hepatohydrothorax with a thoracentesis planned.

Intubation in patients with both ALF and ACLF can be a high-risk period, and should be performed by providers that are experienced with emergency airways. Patients with ACLF and large ascites who require intubation, can have profound hypoxemia when lying flat due to the loss of vital capacity when the abdominal contents move upwards. Patients with altered sensorium and acute variceal bleeding are at risk for aspiration of gastric contents if intubation is delayed. Rapid intubation, usually with the aid of paralytics can be warranted in these patients to reduce the risk of aspiration.

## Acute GI Bleeding in Patients with ACLF

One of the most common causes for admission to the ICU for patients with liver disease is an acute GI bleed. The role of the ICU in patients with liver disease and acute GI bleeding is to support the blood pressure, and to address coagulopathies until a procedure to stop the bleeding can be undertaken. The mainstay of this treatment is transfusion of blood products, initiation of vasoactive agents (to decrease splanchnic blood flow), and starting antibiotics. Intubation to protect the patient from aspiration of gastric contents into the lungs is often required, and allows for sedation while procedures are being performed.

In patients with severe, acute upper GI bleeding without massive, exsanguinating blood losses, a restrictive blood transfusion strategy to a hemoglobin goal of 7 g/dl leads to improved outcomes when compared with a liberal blood transfusion goal of 9 g/dl [62]. Clotting factors, platelets and cryofibrinogen are commonly transfused as well. In our unit, we use Thromboelastography (TEG)-directed therapeutic algorithms to guide blood product replacement (discussed further, later on in this chapter) [63].

Two classes of vasoactive agents that have been studied for treatment during an acute variceal bleed—vasopressin and its analogues, and somatostatin and its analogues. Vasopressin is a potent splanchnic vasoconstrictor, and terlipressin is an analogue of vasopressin that has a longer biological activity. Somatostatin, and its analogues octreotide and vapreotide, cause splanchnic vasoconstriction due to inhibition of the release of vasodilatory peptides such as glucagon. Evidence for a local vasoconstrictive effect also exists. The use of vasoactive agents is associated with a lower risk of 7-day mortality, lower transfusion requirements, and decreased length of stay in the hospital. There has been no difference found when comparing the use of different agents [64].

Short-term antibiotics should be started on all patients with liver disease and an acute upper GI bleed to decrease the incidence of bacterial infection, re-bleeding and mortality.

Endoscopic examination of the patient with an acute upper GI bleed should take place as soon as the patient is stable, and no later than 12 h after the initial bleeding episode as per GI guidelines [65]. This identifies the source of bleeding—whether it be esophageal or gastric varices, portal gastropathy, or a bleeding ulcer, and helps guide targeted therapy and subsequent treatments.

Endoscopic variceal ligation (EVL) is considered to be the first line of endoscopic treatment for the management of bleeding esophageal varices. EVL has better hemostasis, a lower rate of side effects (i.e., ulcer, stricture), a reduced rate of early re-bleeding, and a lower rate of early mortality compared to sclerotherapy [66]. The bleeding risk for small varices and large varices is around 5 and 15% per year respectively. However, despite applying this therapy, 10–15% of patients with acute variceal bleeding experience treatment failure, 21% rebleed, and 24% die during the first 6 weeks [67].

If the endoscopist is unable to control the bleeding with EVL, temporary therapy with a Sengstaken-Blakemore tube or a covered metal stent should be used as a bridge to a more definitive therapy such as Transjugular Intrahepatic Portosystemic Shunt (TIPS).

### *Gastric Varices*

Gastric varices are less frequent compared to esophageal varices and are reported to be seen in 20% of the patients with portal hypertension. The main stay of treatment for gastric variceal bleeding is initially similar to that of esophageal variceal bleeding with transfusion, correction of coagulopathies, early pharmacological treatments with antibiotics and vasoactive medications and early endoscopic intervention. The early use of interventional radiological procedures is likely to play a greater role in the management of gastric variceal bleeding, given that the ligation of gastic varices is associated with a high risk of rebleeding. Interventional radiology can be involved early to evaluate for TIPS or balloon-occluded retrograde transvenous obliteration (BRTO). A BRTO involves retrograde cannulation of the outflow channels that drain the gastric varices through the femoral or jugular vein, and obliteration of the varices and collaterals assisted by balloon occlusion and followed by coil and sclerosant. Various studies have evaluated the efficacy of BRTO in treating gastric varices, with a recent meta-analysis showing a success rate for obliteration of 97.3%, and a recurrence rate of 33.3%. BRTO therefore can be considered as an alternative to TIPS in managing gastric varices [68].

## Commonly Performed Procedures in Patients

Patients in the ICU often require invasive procedures such as central lines for hemodynamic support and renal replacement therapy, arterial lines for invasive monitoring, as well various diagnostic procedures such as thoracentesis and paracentesis. Patients with advanced liver disease commonly have abnormal coagulation profiles such as low platelet count, and elevated prothrombin time and partial thromboplastin time. These abnormalities lead to a fear of bleeding during invasive procedures. The use of blood products to prevent potential bleeding however is of unclear benefit, and exposes patients to the risks of transfusion. Patients with liver disease may, on balance, be more prone to a hypercoagulable state [69, 70]. We have found that there is no increase in bleeding risk in stable patients with cirrhosis undergoing thoracentesis for hepatohydrothorax (unpublished personal data). An alternative approach is to use Viscoelastic testing prior to procedures, such as TEG and

rotational elastometry (ROTEM). Both TEG and ROTEM are whole blood assays used to measure the evolution of clot structural development and the ability of the clot to perform its basic role in promoting hemostasis. These techniques have been used for years to guide rational blood product resuscitation in trauma patients, liver transplant patients and patients undergoing cardiac surgery. This test is beginning to be incorporated in the routine care of cirrhotic patients who need to undergo invasive procedures. Use of TEG has been shown to decrease the use of pre-procedure blood products, with no increase in post-procedure bleeding [63].

The use of ultrasound also increases the safety of procedures. In our unit, we routinely use ultrasound for all of our invasive procedures, including central venous cannulation, thoracentesis and paracentesis. This allows us to not only find the optimal place for insertion of the needle, but scanning with the linear probe at a depth of 2–3 cm also allows us to identify dilated surface vessels that should be avoided when puncturing the skin to perform these procedures.

## The Value of Palliative Care Consultation in Patients with ALF and ACLF

Patients who are critically ill in the ICU from ALF or ACLF have a large symptom burden, and a high likelihood of dying. This places an enormous emotional toll on the family and caregivers that are experiencing the ICU along with the patient. Palliative care consultation in the ICU is associated with greater patient and caregiver satisfaction, and improved communication with the primary team. Many critical care societies support family-centered guidelines that advocate for the inclusion of family meetings and palliative care in the care of patients with complex critical care needs [71]. In a recent NIS database study of patients dying in the hospital with decompensated liver disease from 2009 to 2013, 30.3% received a palliative care consultation during the hospitalization. Palliative care consultation for patients with advanced liver disease increased annually from 18.0% in 2009 to 36.6% in 2013 [72]. Palliative care consultation is not at odds with the goal of transplantation and cure. Palliative care providers can serve as a liaison between the care team, which is usually comprised of many different services, the patient and their family members. Some centers are looking at protocols for integrating palliative care into the routine work-up for patients undergoing evaluation for liver transplant [73]. There is some gathering evidence that the integration of palliative care into the management of patients with end stage liver disease may result in more patient days out of hospital, compared to patients who did not receive the consultation [74]. We routinely include our palliative care consultants in our meetings with families of patients with ACLF and ALF. This improves communication and allows for an additional avenue of support to be available to families during a very stressful time.

In conclusion, the care of patients with ALF and ACLF in the ICU is a complicated endeavor. It requires excellent communication with many disciplines, attention to the complex hemodynamic and metabolic needs of these dynamic patients, plus supportive care for their families.

**Review Questions**

1. Based on the available literature, when treating a patient with ALF and Grade 3–4 Hepatic Encephalopathy, which of the following is the most optimal strategy?

   (a) Lactulose and rifaxamin alone
   (b) Continuous Renal Replacement Therapy and consideration of Hyperosmotic therapy
   (c) Invasive ICP monitoring should be used for all patients
   (d) Avoidance of intubation.

2. When considering the etiology and management of acute kidney injury (AKI) in patient with ACLF, which of the following statements is the most correct?

   (a) All AKI in patients with ACLF is caused by Hepatorenal syndrome
   (b) Hepatorenal syndrome can be definitively diagnosed in the setting of septic shock
   (c) Patients with Hepatorenal syndrome should be treated with vasopressors and albumin
   (d) All patients with acute kidney injury in ACLF should be started on Renal Replacement Therapy, regardless of liver transplant potential.

3. When thinking about patients with ALF and infection, it is important to remember that

   (a) Patients with ALF almost never have concurrent infections
   (b) Patients can be infected with Gram Positive and Gram negative bacterial as well as fungus
   (c) Broad spectrum antibiotics should be continued for as long as the patient remains critically ill
   (d) Patients with ALF are only hypotensive if they are infected.

4. When patients are critically ill with ALF or ACLF the involvement of Palliative Care in the treatment of these patients has been found to

   (a) Interfere with the critical care of these patients, and Palliative care should only be consulted when the patient is actively dying
   (b) Decrease patient and caregiver satisfaction.
   (c) Potentially increase the number of patient days out of the hospital
   (d) Be decreasing in the number of consultations

**Answers**

- Question 1 Answer: B.

The progression from HE to transtentorial herniation can account for up to 75–80% of deaths in ALF, however with improved ICU care focusing on neuroprotective interventions, the mortality attributable to ICH is in the range of 10–20%. Once HE has reached Grade 3, the patient should be intubated and sedated. Aggressive lowering of ammonia is warranted at levels greater than 150 μmol/L, with continuous renal replacement therapy (CRRT), even in the absence of acute kidney injury and other indications for renal replacement therapy. Although ammonia reducing strategies may be beneficial, the evidence that conventional treatments for HE (lactulose and rifaximin) improve outcomes in patients with ALF is lacking. Hyperosmotic therapy with hypertonic saline can be considered for any patient with grade 3–4 encephalopathy to achieve a goal Na of 145–155. Mannitol can also be given emergently to raise the blood osmolality, and try to prevent brain swelling.

The use of invasive intracerebral pressure monitoring in patients with ALF and HE of grade 3–4 is controversial. While it is appealing to have real-time monitoring of the ICP in order to rapidly respond to changes in the ICP, the use of these devices have been declining in recent years. Many centers feel that the risks of bleeding and infection outweigh the utility of placing these invasive devices.

- Question 2 Answer: C.

In patients with cirrhosis, AKI can be due to prerenal (e.g., volume depletion, gastrointestinal bleeding), intrarenal or intrinsic (e.g., bile acid nephropathy, acute tubular necrosis, acute interstitial nephritis, acute glomerular and vasculitic renal diseases) and/or post-renal (e.g., acute obstructive nephropathy) causes. Additionally, hepatorenal syndrome (HRS) should be included in the differential diagnosis. HRS can be diagnosed based on the International Club of Ascites criteria with an increase in creatinine >0.3 mg/dl over baseline over 48 h, or an increase of creatinine ≥50% from baseline. In addition to meeting the criteria for the increase in creatinine, patients must have cirrhosis and ascites, no response to plasma volume expansion with albumin 1 g per kg of body weight over 48 h, no signs of structural kidney disease, and an absence of shock. Patients with HRS-AKI who do not have indications for RRT, should be supported with vasopressors and albumin. The decision to initiate RRT in patients with ACLF should not be taken lightly, especially when the patients are not liver transplant candidates. The Acute Dialysis Quality Initiative group recommends renal support for patients with HRS-AKI only if there is an acute potentially reversible event, or if liver transplantation is planned. This is based on the lack of evidence for a major survival benefit for RRT in HRS-AKI, and that without a reversible precipitant or potential liver transplant, 3-month survival is marginal at best.

- Question 3 Answer: B.

Patients with ALF have an increased susceptibility for infections as a result of excessive systemic inflammation, mainly from cytokine storm, multiple organ dysfunction, and functional immunoparesis. Risks of infection are further amplified by the presence of indwelling lines, catheters, and tubes. Microbial infections have been documented in up to 80% of ALF cases [12]. Gram positive and gram negative bacteria are most frequently isolated, though fungal infections have been reported to occur in about 30% of patients. Hemodynamic instability in ALF is usually a late manifestation of the disease, attributable to the hemodynamic effects of elevated ICP, concomitant sepsis, or the sepsis like-picture that comes with hepatic necrosis.

- Question 4 Answer: C.

Palliative care consultation in the ICU is associated with greater patient and caregiver satisfaction, and improved communication with the primary team. Many critical care societies support family-centered guidelines that advocate for the inclusion of family meetings and palliative care in the care of patients with complex critical care needs. A recent NIS database study of patients dying in the hospital with decompensated liver disease from 2009 to 2013, showed 30.3% received a palliative care consultation during the hospitalization. Palliative care consultation for patients with advanced liver disease increased annually from 18.0% in 2009 to 36.6% in 2013. Palliative care consultation is not at odds with the goal of transplantation and cure. Palliative care providers can serve as a liaison between the care team, which is usually comprised of many different services, the patient and their family members. There is some gathering evidence that the integration of palliative care into the management of patients with end stage liver disease may result in more patient days out of hospital, compared to patients who did not receive the consultation.

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# Chapter 9
# Viral Hepatitis B, C and D in ALF and ALF/CLD


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## Viral Hepatitis B

**Key Concepts**
- Prevalence of hepatitis B varies from high to low endemic regions
- Hepatitis B was once the most common cause of acute liver failure in United States
- Acute on chronic liver disease (ACLD) can be due to an acute hepatitis B infection
- ACLD can also be secondary to spontaneous reactivation of a chronic infection or after immunosuppression or chemotherapy
- There are seven drugs approved for treatment of active viral hepatitis B replication
- These medications can also be used for anti-hepatitis B prophylaxis in patients receiving immunosuppression or chemotherapy

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## *History and Epidemiology of Hepatitis B*

Hepatitis appears to have plagued mankind throughout its history. The oldest known reference to jaundice was inscribed on a Sumerian clay tablet in the 3rd millennium BCE. Since then, reports of jaundice have appeared throughout recorded history and in all cultures [1].

The discovery of the hepatitis B virus (HBV) in 1965 by Nobel Prize winner Dr. Baruch Blumberg, a geneticist working at the National Institutes of Health, changed the history of viral hepatitis. The virus was originally called the "Australian Antigen" and later recognized to be the HBV surface antigen (HbsAg); it was the first infection marker to be assayed with a highly sensitive radioimmunoassay [2].

The virus belongs to the Hepadnaviridae family. It is a small (3.2-kilobase [kb]) virus with a DNA genome that has a relaxed, circular, partially double-stranded configuration. There are four known genes encoded by the genome, called C, X, P, and S. The gene C gives rise to the hepatitis B e antigen (HBeAg) and core protein, the S gene encodes the viral surface envelope protein (hepatitis B surface antigen, HBsAg), and the DNA polymerase is encoded by gene P. The X gene is not well understood and may be associated with the development of hepatocellular carcinoma.

Infection with hepatitis B virus is transmitted through contact with blood or other bodily fluids of an infected person and may lead to acute or chronic hepatitis. The World Health Organization estimates that in 2015, 257 million people were living with chronic hepatitis B infection, defined as positivity of the hepatitis B surface antigen. In that year, hepatitis B had resulted in an estimated 887,000 deaths, largely due to complications from cirrhosis and hepatocellular carcinoma. As of 2016, 27 million people were aware of their infection, and 4.5 million (16.7%) were receiving treatment [3]. The prevalence of chronic HBV infection worldwide is categorized as high, intermediate and low endemicity. Highly endemic areas are defined as areas where at least 8% of the population are chronic hepatitis B carriers, such as in Southeast Asia, South and Western Pacific Islands, Africa (all countries except Algeria, Egypt, Libya, Morocco and Tunisia in the north), Central and Eastern Europe (including the independent states of the former Soviet Union), and the Middle East (all countries except Cyprus and Israel), Central and South America (interior Amazon basin and parts of the Caribbean), Alaska Native populations and indigenous populations in Northern Canada [4]. Intermediate endemicity, where 2-7% of the population are chronic carriers, is seen in parts of Eastern Europe (all countries except Hungary), Southern Europe, Japan, and parts of South America; and low endemicity is seen in North America, Northern and Western Europe and Australia, New Zealand, where <2% of the population are chronic carriers [5].

## *Hepatitis B Causing Acute Liver Failure*

Acute HBV infection and acute exacerbations of chronic HBV infection can cause acute liver injury or fulminant liver failure. In a study from 1998 to 2001, hepatitis

B accounted for 7% of all cases of acute liver failure (ALF) caused by viral hepatitis in United States as compared to 20–30% in Europe, South America and Asia.

Hepatitis B infection was once considered the most common cause of acute liver failure in the United States, however, over the past decades, we have seen decreasing trend of ALF due to viral hepatitis B from 34% in the 1970s, 18–19% in the 1980s, to 10% in the 1990s. A recent study using NHANES showed that from 1988 to 2016 the overall prevalence of chronic hepatitis B in the United States remained stable between 0.3 and 0.4%. This is likely due to intensive vaccination campaigns, screening of blood products and initiation of anti-hepatitis B prophylaxis for patients receiving immunosuppressants [6–10].

Acute liver failure caused by hepatitis B virus can occur in patients who have had no previous contact with the virus (primary infection) and in cases of chronic HBV infection. The mechanisms by which HBV induces ALF are not well known as the virus itself is generally not a cytopathic virus. However, during acute HBV infection, the severity of HBV-associated liver disease may be related to the host's aggressive immune response against the virus, causing both hepatocellular damage and viral clearance.

The incubation period of acute hepatitis B infection varies from a few weeks to 6 months, with an average of 2–3 months. Patients may initially experience loss of appetite, nausea, vomiting, and serum sickness-like symptoms such as body aches, mild fever and rash, which can be maculopapular or urticarial. In 30% of patients, it may progress to development of dark urine and jaundice. Serum aminotransferase levels of 1000–2000 U/L are not unusual during acute hepatitis B infection, with the alanine aminotransferase higher than aspartate aminotransferase level and the rise in serum bilirubin lagging behind. Acute liver failure may develop within 4 weeks of the onset of symptoms and is associated with multi-organ failure, coagulopathy, encephalopathy, and high mortality rate if not treated promptly. The rate of spontaneous survival in acute liver failure caused by HBV is only approximately 20%. Liver transplantation has increased survival rates to 50–60%.

## *Hepatitis B Virus Related Acute-on-Chronic Liver Failure*

The term acute-on-chronic liver failure (ACLF) was first used in the 1990s to describe liver failure that was triggered by an acute insult causing acute liver failure in a patient with preexisting liver disease. This is a syndrome distinct from acute or chronic liver failure, which has recently gained considerable worldwide attention. Despite the acceptance of syndrome, there is no consensus regarding specific diagnostic criteria for ACLF, in part because of the great diversity in its underlying etiology, precipitating factors, and clinical presentation.

The Asian Pacific Association for the Study of the Liver (APASL) defines ACLF as an acute hepatic insult manifesting as jaundice with serum bilirubin ≥5 mg/dL and coagulopathy with international normalized ratio [INR] of ≥1.5 or prothrombin activity of less than 40%, complicated by clinical ascites and/or encephalopathy

within 4 weeks, in a patient with previously diagnosed or undiagnosed chronic liver disease; this is associated with a high 28-day mortality rate [11]. The European Association for the Study of the Liver (EASL) definition of ACLF through its CANONIC study in 2013 requires an acute decompensation either as hepatic encephalopathy, gastrointestinal bleeding, ascites, or bacterial infection followed by the development of organ failures using a modified Sequential Organ Failure Assessment (SOFA) score, called the CLIF SOFA scoring system which assigns severity grades of ACLF [12].

The pathogenesis of ACLF is not well understood. One hypothesis is that ACLF is associated with systemic inflammation from endogenous or exogenous inducers, and organ failures as a consequence of an excessive immune response to the patient's inflammation [13].

ACLF can be induced by any precipitating factor like those leading to severe liver injury, and ALF in patients with chronic hepatitis B infection. Viral hepatitis A, C, D and E and other viral infections such as CMV, EBV and herpes virus, drugs, alcohol, autoimmune diseases, Wilson's disease, portal vein thrombosis, and ischemic hepatitis can induce acute liver failure in chronic hepatitis B. Acute infection with hepatitis B can also precipitate acute liver failure in a patient with known chronic liver disease secondary to alcoholic, metabolic, viral or autoimmune causes. Viral hepatitis, especially HBV, is the major cause for ACLF in eastern countries such as Asia, as compared to western countries, where alcoholic liver disease (ALD) is the most common cause for ACLF.

HBV-associated ACLF is estimated to be 30% of all HBV-related cirrhosis patients with acute decompensation [14, 15]. Spontaneous flares have been observed in patients with HBeAg-positive chronic hepatitis B. At least one study has shown that patients with hepatitis B genotype B and the G1896A mutation have a higher risk of developing acute-on-chronic liver failure [16]. In a CANONIC study, other, non-hepatic etiologies leading to ACLF in patients who have known chronic hepatitis B infection include bacterial infection, such as spontaneous bacterial peritonitis, pneumonia, urinary tract infection and bacteremia, gastrointestinal bleeding, dehydration, TIPS, and surgery [12]. The concomitant use of paracetamol, methamphetamine or alcohol may also be risk factors for developing fulminant hepatitis B [17].

Acute liver failure in those who are already affected by chronic HBV infection can be induced by various causes of immunosuppression, such as chemotherapy, immunosuppressive agents, CD20 antibody therapy, and immune reconstitution caused by anti-human immunodeficiency virus (HIV) treatment. This is usually due to reactivation or flare-up of chronic HBV infection. A reactivation of HBV is defined by AASLD by a rise in HBV DNA compared to baseline (or an absolute level of HBV DNA when a baseline is unavailable) and reverse seroconversion from a previous HBsAg negative to HBsAg positive for HBsAg-negative and anti-HBc–positive patients. Following HBV reactivation, a hepatitis flare demonstrated by ALT elevation can occur and may progress to fulminant hepatic failure [18].

Reactivation of chronic hepatitis B infection has occurred in 41–53% of cases undergoing anticancer therapies [19], and 12.3% in cases of anti-rheumatic

medications [20]. The AASLD recommends that patients found to be positive for HBsAg who are to begin such therapies should be treated prophylactically with a nucleos(t)ide analog with a high resistance barrier such as entecavir or tenofovir and that it should be continued for 6 months after completion of immunosuppressive therapy. For patients receiving anti-CD 20 antibody, the anti-HBV therapy should be continued for 12 months after completion of immunosuppressive treatment with continued further monitoring of the hepatitis B status as there have been reports of reactivation beyond 12 months [18]. Lamivudine is least favored since it is associated with a high rate of drug resistance. In patients that are isolated HBc antibody positive, there is a lower risk of reactivation compared to patients with HBs antigen positivity, and therefore the AASLD suggests initiating either anti-HBV prophylaxis or monitoring with the intent of on-demand anti-HBV therapy initiation at the first sign of HBV reactivation, depending on the feasibility of monitoring and clinical condition. However, the American Gastroenterological Association guidelines recommend offering HBsAg-negative but anti-HBc-positive patients a prophylactic therapy if treated with B-cell-depleting agents (eg. rituximab or ofatumumab), TNF inhibitors (etanercept, adalimumab, certolizumab and infliximab), integrin inhibitors (abatacept, ustekinumab, natalizumab and vedolizumab) and tyrosine kinase inhibitors (imatinib and nilotinib) with the same duration of therapy as recommended in the AASLD guidelines [18, 21].

## *Therapy for Acute Liver Failure and Acute-on-Chronic Liver Failure Due to Hepatitis B*

In general, there is no proven therapy for ALF and ACLF. Management consists of intensive supportive care to prevent the onset of multi-organ failure. Careful attention to fluid management, hemodynamics and metabolic parameters, as well as surveillance and treatment of infection. Antiviral therapy should be initiated rapidly in a specialized center with access to transplantation. This therapy should never delay the timing of transplantation.

Currently, there are seven drugs approved for the treatment of chronic hepatitis B and these are divided into two main treatment options either treatment with a nucleos(t)ide analogs (NA) which suppresses HBV replication through an inhibitory effect on the viral DNA polymerase or with pegylated (PegIFNα). In United States, the FDA approved NAs include lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir. Emtricitabine is a structurally similar to lamivudine and also inhibits HBV DNA polymerase and HIV reverse transcriptase, but is not FDA approved for use in hepatitis B. Entecavir, and tenofovir are known to have high barrier to HBV resistance and are frequently the first line therapy for acute infection, reactivation and hepatic failure caused by hepatitis B virus due to their safety profiles. In a meta-analysis comparing lamivudine and entecavir in treating chronic hepatitis B virus flare and hepatitis B related acute-on-chronic liver failure, entecavir shows beneficial long-term outcome in patients with ACLF as compared to

lamivudine, as well as more favorable virological and biochemical responses. However, entecavir did not improve short-term mortality in HBV-related flare with or without ACLF [22].

In a recent study comparing tenofovir and entecavir in treatment of acute-on-chronic liver failure due to reactivation of chronic hepatitis B infection, tenofovir led to higher reduction of HBV-DNA levels at 2 weeks, higher proportion of patients with undetectable HBV-DNA levels at 2 weeks, and higher frequency of HBeAg loss at 3 months as compared to entecavir. The study however is limited by small sample size and not randomized [23]. At this time, entecavir and tenofovir are both used as treatment options for hepatitis B-induced acute and acute-on-chronic liver failure.

The survival rates in ALF have improved dramatically with advancements in technology and treatment strategies. Despite these advancements, and even with initiation of anti-viral therapy, a majority of patients are unable to achieve regeneration of sufficient hepatocyte mass to sustain life and require orthotopic liver transplantation. Transplant-free survival rates of ALF due to hepatitis B range from 26 to 53% [24]

## *Prevention*

Screening should be initiated for individuals who are at high risk for HBV infection and receive hepatitis B vaccine if seronegative (Table 9.1) [18, 25]. Immunoprophylaxis against HBV is of 2 types: passive immunization using HBIG and active immunization using inactive HBsAg. Active immunization confers long-term immunity, whereas passive immunization provides only immediate and short-lived protection. HBIG is recommended post-exposure prophylaxis in sexual partners of patients with hepatitis B, and newborn infants of HBsAg-positive mothers within 12 h of birth along with simultaneous vaccination.

In the United States, there are currently three approved single-antigen vaccines (Engerix-B, Recombivax HB, Heplisav-B) and three combination vaccines (Pediarix, Twinrix). The active immunization is typically scheduled at 0, 1, and 6 months. A new formulation, Heplisav-B (HepB-CpG), is approved for two doses one month apart. In immunocompetent adults and children with low or undetectable antibody titers, a booster vaccine is not recommended due to strong immune memory caused by active vaccination. However, in patients undergoing hemodialysis, a booster dose should be given if the titer is lower than 10 mIU/mL.

Patients who are chronic hepatitis B carriers requiring immunosuppressive therapy, the recommendation is to start anti-HBV prophylaxis using a high resistance barrier agent such as entecavir or tenofovir and this should be initiated as soon as possible before or, at the latest, simultaneously with the onset of immunosuppressive therapy. Once started, anti-HBV prophylaxis should continue during immunosuppressive therapy and for at least 6 months (or for at least 12 months for patients receiving antiCD20 therapies) after completion of immunosuppressive therapy.

**Table 9.1** High risk groups for HBV infection who should be screened and vaccinated if seronegative

| |
|---|
| Persons born in regions of high or intermediate HBV endemicity |
| Travelling to countries with intermediate to high levels of endemicity with chronic hepatitis B* |
| U.S.-born persons not vaccinated as an infant whose parents were born in regions with high HBV endemicity |
| All pregnant women |
| Infants born to HBsAg-positive mothers* |
| Chronic liver disease patients including, but not limited to, persons with cirrhosis, HCV, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase or aspartate aminotransferase level greater than twice the upper limit of normal* |
| Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatological or gastroenterologic disorders. |
| Blood and tissue donors |
| People with HIV* |
| People who are incarcerated* |
| People at risk for infection by sexual exposure* |
| • Sex partners of hepatitis B surface antigen (HBsAg)–positive persons |
| • Sexually active people who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months) |
| • People seeking evaluation or treatment for a sexually transmitted infection |
| • Men who have sex with men |
| People at risk for infection by percutaneous or mucosal exposure to blood* |
| • Current or recent injection-drug users |
| • Household contacts of people who are HBsAg-positive |
| • Residents and staff of facilities for developmentally disabled people |
| • Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids |
| • Hemodialysis patients and predialysis, peritoneal dialysis, and home dialysis patients |
| • People with diabetes aged 19–59 years; persons with diabetes aged ≥60 years at the discretion of the treating clinician |

* The population per Advisory Committee on Immunization Practices (ACIP) who should receive vaccination against hepatitis B

## Hepatitis C

**Key Concepts**

- Most cases of acute hepatitis C are asymptomatic
- Acute or acute on chronic liver failure appears to occur most often secondary to reactivation of a chronic infection C after immunosuppression or chemotherapy
- There are many drugs approved for treatment of active viral hepatitis C replication
- These medications can also be used for anti-hepatitis C prophylaxis in patients receiving immunosuppression or chemotherapy
- There are no vaccines available for hepatitis C as yet

## *History and Epidemiology*

The Hepatitis C virus (HCV) was unknown before 1989. Reports from WWII have suggested that soldiers may have contracted hepatitis C during that period, but it was not until 1987 that a group of scientists at Chiron Corporation, collaborating with Dr. Daniel W. Bradley, an American virologist at the Centers for Disease Control and Prevention, were able to isolate and clone a virus called at the time non-A, non-B hepatitis (NANBH). In 1989, hepatitis C was identified, leading to significant improvements in diagnosis and improved antiviral treatment [26–28].

HCV is a small, enveloped, single-stranded, positive-sense RNA virus belonging to the genus Hepacivirus in the family Flaviviridae, and has six known major genotypes. Genotype 1 is the most prevalent worldwide, accounting for about half (49.1%) of all cases. It is commonly seen in the United States, (74.5% of cases), Asia (46.6%), Australasia (55%) and Europe (64.4%). Genotype 4 is prevalent in Central and South African countries (28.1%) and commonly seen in Northern Africa and the Middle East (65.3%) [29].

The virus is spread primarily by blood-to-blood contact associated with intravenous drug use, needle stick injuries in health care and transfusions. Nosocomial patient to patient transmission may occur via a contaminated colonoscope, dialysis or surgery. HCV can be transmitted sexually, however, studies of heterosexual couples with discordant serostatus have shown that such transmission is extremely inefficient. A higher rate of transmission is seen in men who have sex with men, particularly with unprotected anal intercourse and HIV infection. Although maternal-fetal HCV transmission may occur at a rate of 4–5%, breast feeding is not associated with transmission. The WHO estimates that globally, there are approximately 71 million people with chronic hepatitis C virus infection. In 2016, approximately 400,000 people died from hepatitis C, largely due to complications of cirrhosis and hepatocellular carcinoma [30]. The countries with highest HCV prevalence are in Northern Africa and the Middle East regions, where Egypt, Cameroon, Saudi Arabia, Iraq and Syria account for the majority of cases [31]. In the United States, the prevalence of chronic hepatitis C decreased nearly twofold: 1.6% in 1988–1994 to 0.9% in 2013–2016 [10]. It is expected to either further decrease or remain stable due to heightened screening practices for baby boomers, proper sterilization of medical instruments and introduction of effective therapy for hepatitis C.

## *Hepatitis C Causing Acute Liver Failure*

In clinical practice, acute hepatitis C infection is rarely recognized initially as nearly all cases are asymptomatic. Within 7–21 days after viral transmission, HCV RNA becomes detectable in serum. Some patients may develop clinical symptoms 2–12

weeks after viral transmission and most of the clinical symptoms are nonspecific, including fatigue, nausea, and abdominal pain, loss of appetite, mild fever, itching, and myalgia. Jaundice develops in 50–84% of patients with acute HCV infection.

Acute hepatitis C leading to acute liver failure is controversial. There are reports of acute liver failure in hepatitis C infected patients following immunosuppression or chemotherapy [32, 33] and spontaneously without known cause [34]. The detection of serum HCV RNA by PCR is the earliest and most valuable marker for the diagnosis of fulminant hepatitis C. In a study in Japan from 2004 to 2009, there were only two cases of hepatitis C leading to acute liver failure in 212 patients with viral infection [35].

## *Hepatitis C Virus Related Acute-on-Chronic Liver Failure*

The rate of viral persistence after acute infection ranges from 45% greater than 90%. The presence of detectable viral replication for at least 6 months progresses to chronic infection. Most patients are asymptomatic, perhaps complaining only of fatigue and depression. Chronic infection after several years can lead to cirrhosis and increased risk for hepatocellular carcinoma. Multiple factors are associated with progression of fibrosis in patients with chronic HCV infection (Table 9.2) [36]. Of these, alcohol, hepatitis B co-infection, HIV co-infection and an immunosuppressed state may cause acute on chronic liver failure. As mentioned earlier, HBV infection is the major cause for ACLF in eastern countries such as Asia, while in western countries, alcoholic liver disease (ALD) predominates.

**Table 9.2** Factors that affects progression to cirrhosis in HCV infection

| Host Factors | Viral Factors | Environmental Factors |
|---|---|---|
| Age at the time of infection<br>Adult > childhood<br>Age > 40 years old | HBV coinfection | Alcohol consumption |
| Gender<br>Female > male | HIV coinfection | Smoking |
| Race<br>Hispanic > African Americans | HCV viral load | Marijuana use |
| Obesity | HCV genotype<br>Genotype 3 > other genotypes | Caffeine |
| Serum ALT level | | Schistosomiasis |
| Genetics | | |
| Immunosuppressed state | | |
| Insulin resistance<br>Diabetes mellitus | | |

### *Therapy for Acute Liver Failure and Acute-on-Chronic Liver Failure Due to Hepatitis C*

Significant advances have been made in the treatment of hepatitis C infection from initial injection with interferon to co-therapy with ribavirin, and then advancing to treatment with multiple tablets per day, to currently, a single daily pill that covers all the genotypes with and without ribavirin.

Reports of acute liver failure associated with hepatitis C treatment with the several direct-acting antiviral agents have been published. Drugs such as sofosbuvir–simeprevir (Sovaldi) [37], sofosbuvir–ledipasvir (Harvoni) [38], have been shown to induce drug-induced liver injury in patients with decompensated liver disease. Recently, the FDA has issued warnings for glecaprevir–pibrentasvir (Mavyret), elbasvir–grazoprevir (Zepatier), sofosbuvir–velpatasvir–voxilaprevir (Vosevi) of serious liver injury associated with the use of these hepatitis C medicines. These medications contain a protease inhibitor and are not indicated in moderate to severe liver impairment [39].

### *Prevention*

Hepatitis C infection continues to be a global concern despite available effective treatments. Unfortunately, a vaccine has yet to be developed as the main challenge is the genetic diversity of the virus, with six major genotypes. Several HCV vaccine candidates are currently in preclinical or early phases of clinical trials [40].

Due to the risk of viral co-infections leading to acute on chronic liver failure, tests for concurrent hepatitis B and HIV infections should be completed prior to starting treatment with HCV direct-acting antiviral agents.

## Hepatitis D

**Key Concepts**

- Hepatitis D requires the presence of hepatitis B for replication
- The hepatitis D viruses is highly pathogenic and often causes fulminant hepatic failure or rapidly progressing disease leading to cirrhosis
- Co-infection is the simultaneous acute infection of both hepatitis B and hepatitis D
- Superinfection is where a patient with chronic hepatitis B requires a superimposed acute hepatitis D infection
- Treatment of the hepatitis B with a nucleoside or nucleotide antiviral is ineffective

## *History and Epidemiology*

In 1977, while studying liver biopsies of patients who were seropositive for the hepatitis B surface antigen (HBsAg), Rizzetto and his colleagues noted the presence of a new antigen-antibody system associated with HBsAg positivity. This was detected by direct immunofluorescence in the liver cell nuclei. The new antigen was proposed as delta antigen [41].

Hepatitis D virus (HDV) is a small, spherical, single RNA strand and believed to be the smallest infectious agent known to man. It is considered a defective subviral satellite as it is dependent on the coexistence of the hepatitis B virus for replication and transmission in the hepatocytes. The damage to the liver is thought to be Immune-mediated, although there have been studies showing that it may be cytopathic to the hepatocytes as well [42]. Despite its co-existence with hepatitis B virus, HDV has been frequently shown to suppress HBV replication and can even suppress the replication of both HBV and HCV in cases of triple infection with HBV, HDV and HCV [43].

While the transmission of HDV is similar to the hepatitis B virus, vertical transmission from mother to offspring, men who have sex with men or nosocomial exposure appears to be a low in comparison to hepatitis B infection [44]. The virus is a highly pathogenic virus that causes acute, often fulminant hepatitis, as well as a rapidly progressive form of chronic viral hepatitis, leading to cirrhosis in 70–80% of the cases.

The World Health Organization estimates that at least 5% of people with chronic HBV infection are co-infected with HDV, resulting in a total of 15–20 million persons infected with HDV worldwide [45], but in a recent meta-analysis done by Chen et al, the prevalence of HBs antigen carrier who were infected with HDV was calculated at 10.58%, two fold higher than the previously reported, thus increasing the global burden of HDV infection to approximately 62–72 million individuals infected [46]. High-prevalence areas include Africa (Central and West Africa), Asia (Central and Northern Asia, Viet Nam, Mongolia, Pakistan, Japan, and Chinese Taipei), Pacific Islands (Kiribati, Nauru), Middle East (all countries), Eastern Europe (Eastern Mediterranean regions, Turkey), South America (Amazonian basin), and Greenland. The overall number of HDV infection has decreased since 1980s in industrialized countries and this is mainly due to a successful HBV vaccination program, however, HDV infection is still a medical problem in poor countries where HBV remains endemic [44, 45].

## *Hepatitis D Virus Related Acute and Acute-on-Chronic Liver Failure*

Since hepatitis D infection relies on the coexistence of the hepatitis B virus for its replication in the hepatocytes, there are two clinical patterns of infection with HDV: as a co-infection with HBV or a superinfection with HBV.

Co-infection is the simultaneous acute infection of HBV and HDV. This infection begins only after HBV has infected hepatocytes, and is similar to acute hepatitis B. Acute infection can present either with a single peak of serum transaminase (monophasic) or with two distinct peaks of serum transaminase (biphasic) depending on the relative titers of HBV and HDV. As with acute HBV infection, the diagnosis of HDV infection is made by serologic tests. In patients with acute co-infection, tests for IgM antibodies to both HDV and HBV core antigen are positive.

In super-infection, a person with established chronic HBV infection acquired an acute HDV. Clinically, it may present with an exacerbation of the preexisting chronic hepatitis B leading to liver decompensation, or as a new hepatitis in a previously asymptomatic HBsAg carrier and this is suggested by a negative (or very low tittered) IgM anti-HBc and confirmed by the detection of HDV markers.

Co-infection evolves to chronicity in only 2% of cases since both of the organisms are usually eradicated, often resulting in complete recovery, while super-infection results in chronic infection in at least 90% of cases. The chronic HDV/HBV infection causes more severe liver disease compared to HBV monoinfection. This chronic viral infections runs a rapidly progressive course, leading to early cirrhosis, decompensation and hepatocellular carcinoma, with a shorter 5 year survival.

Liver failure in the form of acute-on-chronic is seen in HBV/HDV super-infection leading rapid hepatic decompensation such as ascites and hepatic encephalopathy. However, there are also data to suggest that HBV/HDV co-infection enhances the risk of acute liver failure [47–49].

In cases of triple infection with hepatitis B, hepatitis D and hepatitis C, HDV infection often tends to be dominant virus as it can inhibit replication of both the hepatitis B and C virus [43]. The clinical and virologic profile of triple infection is expectedly more often described in the setting of chronic rather than acute hepatitis. In a study by Wu et al, triple infection with HBV, HDV and HCV increases the risk of fulminant hepatic failure, especially in patients super-infected with HDV [50].

Regardless of clinical patterns of infection, whether in the form of a co-infection, super-infection, or triple infection with hepatitis C, HDV infection is a significant cause of fulminant liver failure with a very poor prognosis.

## *Therapy for Acute Liver Failure and Acute-on-Chronic Liver Failure Due to Hepatitis D*

The management of acute hepatitis D generally relies on supportive measures or referral for liver transplantation if acute liver failure develops. Antiviral treatment has not proven useful. Despite the developments in the treatment of HBV mono infection, results of therapy for HDV-HBV infection is still disappointing. Nucleotide and nucleoside therapies for HBV infection are not effective in HDV infection. The currently approved HDV treatment is limited to a prolonged course of IFN-alpha and only in compensated HDV-associated liver disease, though most

studies have used pegylated IFN-alpha due to its prolonged plasma half-life that allows a once-a-week administration, with better efficiency and compliance than the standard IFN-alpha. For these reasons, pegylated IFN-alpha has been the drug of choice and is now the recommended treatment for HDV infection for 12 months duration in patients with elevated HDV-RNA levels and ALT elevation [18].

Studies looking at adding a second agent with interferon alpha such as ribavirin [51, 52] or nucleot(s)ide analogue in the treatment of HDV infection have shown no benefit [53], however, current international guidelines recommend treatment with low resistance barrier NA drugs such as entecavir or tenofovir) if the HBV DNA is elevated or above 2000 IU/ml [18, 54, 55]

Several therapies are currently under investigation that include an interferon with broad spectrum antiviral activities and immunomodulatory properties targeting the interferon-stimulated gene induction pathway (peginterferon Lambda-1a). Other therapies target the key steps in the HDV life cycle such as the hepatitis B virus and hepatitis D virus entry inhibitor (bulevirtide), HBs antigen secretion inhibitors (REP 2139-Ca) and virus assembly inhibitors (lonafarnib) [53].

## *Prevention*

HDV infection is a dynamic disease. The virus is highly pathogenic, causing severe acute hepatitis, which may run a fulminant course, or progress to an advanced form of chronic viral hepatitis. The virus's ability to infect a host depends mainly on the existence of the hepatitis B antigen, thus eliminating hepatitis B virus by vaccination is protective against HDV.

Testing for hepatitis D virus in patients with chronic hepatitis B infection is recommended: The American Association for the Study of Liver Disease currently recommends anti-HDV testing for HBsAg carriers who are at high risk of HDV infection (HIV positive persons, persons who inject drugs, men who have sex with men, those at risk for sexually, transmitted diseases, and immigrants from areas of high HDV endemicity) [18]. Note that the European and Asian Associations for the Study of the Liver both recommend routine screening anti-HDV testing among all HBsAg carriers [54, 55].

**Questions**

**Question 1**. A 48-year-old Chinese woman is diagnosed with advanced stage non-Hodgkin's lymphoma and is being considered for chemotherapy. She currently has normal liver enzymes and complete blood count. HBV serology including HBV DNA PCR is pending. An ultrasound of the abdomen shows a normal appearing liver.

Which of the following pre-treatment serologic profiles, if any, is associated with worsening viral disease on treatment of the lymphoma?

| | HBs Ag | Anti-HBc | Anti-HBs |
|---|---|---|---|
| a. | – | – | – |
| b. | – | + | – |
| c. | + | + | – |
| d. | – | – | + |
| e. | – | + | + |

**Question 2**. A 40-year-old male with history of unprotected sex with men is hospitalized with acute hepatitis and jaundice. Laboratory studies demonstrate AST: 1500 U/L, ALT: 1950 U/L, bilirubin: 11 mg/dl, INR: 1.5, normal alkaline phosphatase, albumin and platelet count. An acute hepatitis panel demonstrates the following:

- Anti-HAV IgM: non-reactive
- HBs antigen: reactive
- Anti-HB core IgM: reactive
- Anti-HCV: non-reactive

Over the next 2 days, the serum ALT declines to 150 U/L and INR normalizes. Patient was discharged but returns 2 days later with confusion. AST and ALT is now 1850 and 2500 U/L respectively and INR is 5.4 with bilirubin of 22 g/dl. Which of the following is true of this patient's condition?

(a) He likely has acute liver failure secondary to acute HCV superimposed on chronic HBV infection
(b) He likely has acute liver failure secondary to acute HBV infection
(c) He likely has acute liver failure secondary to hepatitis A infection
(d) He likely has acute liver failure secondary to superinfection with HDV on top of chronic HBV.
(e) He likely has acute liver failure secondary to co-infection with HBV and HDV

**Question 3**. A 45-year-old intravenous drug user comes to your clinic for a liver consult. She was diagnosed with chronic hepatitis C and is asking to initiate therapy.

- Laboratory:
- Bilirubin: 1.0 mg/dl
- AST: 58 U/L
- ALT: 79 U/L
- ALP: 90 U/L
- HCV genotype: 1 a

- HCV RNA: 4 million IU
- Urine toxicology: + opiates and benzodiazepine
- Fibroscan: stage 3 fibrosis
- US showed normal liver

What would be the best next step?

(a) No further work up needed. Initiate therapy at this time
(b) Order liver biopsy prior to treatment
(c) Check for hepatitis B status prior to treatment
(d) No therapy until negative urine toxicology
(e) Repeat HCV RNA in 3 months to monitor spontaneous resolution

**Question 4.** Which of the following HBs Ag positive/HBc antibody positive individuals is at greatest risk of hepatitis B reactivation?

(a) A 40-year-old man with ulcerative colitis starting vedolizumab
(b) A 30-year-old woman with autoimmune hepatitis starting daily prednisone 20 mg and azathioprine
(c) A 65-year-old male with rheumatoid arthritis starting adalimumab
(d) A 69-year-old woman with chronic lymphocytic leukemia starting ofatumumab
(e) A 50-year-old woman with systemic lupus erythematosus starting hydroxychloroquine

**Question 5.** A 32-year-old man with ulcerative colitis presents to follow-up. The disease involves the entire colon. Routine pre-treatment testing before starting infliximab is notable for HBs antigen negative, anti-HBc positive, HBV DNA undetectable and negative QuantiFeron-TB testing.

What is the best next step?

(a) Re-check HBV DNA in 3 months
(b) Start tenofovir
(c) Start lamivudine
(d) Observation
(e) Hepatitis B vaccination

**Answers**

1. **Answer: C**

Answer A indicates susceptible for hepatitis B infection. Answer D indicates immune to hepatitis B due to vaccination while answer E is immune to hepatitis B due to natural infection. Although answer B would indicate prophylaxis for hepatitis B prior to chemotherapy to prevent reactivation of

hepatitis B, answer C is the more appropriate answer as this indicates active infection and would cause worsening of hepatitis B with chemotherapy.

**Reference**

- https://www.cdc.gov/hepatitis/hbv/pdfs/SerologicChartv8.pdf

2. **Answer: E**

HDV is a defective RNA virus that needs hepatitis B virus to replicate. The incubation period for HDV is 5-64 days. There are 2 types of HDV infection: a co-infection in which the HBV and HDV infections occur simultaneously, or superinfection in which HDV infection is superimposed on preexisting HBV infection. Therefore, patients with HDV co-infection have serologic evidence of acute hepatitis B infection as shown by positive IgM anti-HBc; whereas IgM anti-HBc is negative in patients with superinfection. Co-infection also presents with bi-phasic rise in ALT, which occasionally results in acute liver failure. The serology indicates acute infection with HBV rather than a chronic HBV infection. Thus, the correct answer is E. He does not have acute liver failure from acute HBV infection since his ALT had declined and normalization of INR prior to discharge making answer B wrong. He does not have acute HAV (C) or HCV infection (A).

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3. **Answer: C**

According to 2019 AASLD/IDSA guidelines, treatment is recommended for all patients with chronic HCV infection except those with a short life expectancy who cannot be remediated by HCV therapy, liver transplantation, or another directed therapy. Most studies now show PWID's (persons who inject drugs) will respond quite well with the same SVR as non-drug users. Even if they continue to use drugs, the SVR rate is equivalent to non-drug users. However, prior to initiating treatment, it is important to check for the status of hepatitis B as HBsAg-positive patients are at risk of HBVDNA and ALT flares with HCV DAA therapy. Thus, monitoring of HBV DNA levels every 4–8 weeks during treatment and 3 months post treatment is recommended as compared to HBsAg-negative, anti-HBc–positive patients with HCV who are at very low risk of reactivation with HCV-DAA therapy. ALT levels should be monitored at baseline, and at the end of treatment.

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4. **Answer: D**

The risk for hepatitis B reactivation is based on patient's hepatitis B serologic status and the immune suppressive agent used. An anti-CD20, B-cell depleting therapy such as rituximab and ofatumumab are considered high risk by AASLD for HBV reactivation in HBs Ag positive/HBc antibody positive and HBs Ag negative/HBc antibody positive patients. Thus, they would require prophylaxis with Anti-HBV drugs with a high resistance barrier such as entecavir, TDF, or TAF prior to treatment with anti-CD20 therapies.

**Reference**


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5. **Answer: B**

American Gastroenterology Association guidelines state that patients who have HBs Antigen +/ anti-HBc positive or HBs antigen negative/anti-HBc positive serologic profiles who are being treated with TNF alpha inhibitors such as etanercept, adalimumab, certolizumab and infliximab are at moderate risk of hepatitis B reactivation (1–10% of cases) and require hepatitis B prophylaxis during treatment and for at least 6 months after stopping immunosuppression. Patients who are HBs antigen negative/anti-HBc positive are likely to have a lower reactivation rate with anti-TNF therapy as compared to patients with HBs antigen positive/anti-HBc positive serostatus, but given the paucity of data in this patient population, prophylaxis is recommended. Multiple meta-analyses have demonstrated reduced reactivation and development of virological resistance after the use of third generation nucleos(t)ide drugs such as tenofovir and entecavir over lamivudine.

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# Chapter 10
# Viral Hepatitis Non: B, C, D and Acute and Acute on Chronic Liver Failure


**Ben L. Da, Andrew Nguyen, Ali Khan, and Douglas T. Dieterich**

**Key Concepts**

1. Non-B, C, and D viruses that can cause hepatitis can also cause acute liver failure and acute on chronic liver failure.
2. Diagnosis of ALF and ACLF due non-B, C, and D viral hepatidities relies on proper physician awareness, knowledge of each virus's clinical presentation, and diagnostic capabilities in at-risk populations.
3. HAV and HEV related ALF and ACLF are commonly found in endemic populations while EBV, CMV, and VZV related ALF and ACLF usually only occurs in those who are immunocompromised.
4. Prevention of certain viruses such as HAV and HEV can be effectively done with proper hygiene or vaccination.
5. Management of ALF or ACLF related to non-B, C, and D viral hepatidities includes supportive care for failing organ systems, viral directed medical therapy, and liver transplantation.

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## Introduction

Acute liver failure (ALF) and acute on chronic liver failure (ACLF) are two distinct clinical syndromes that both carry a substantial mortality risk [1]. ALF is defined as a coagulation abnormality (International Normalized Ratio (INR) ≥1.5), any degree of altered mental status (encephalopathy) in a patient without preexisting cirrhosis with illness lasting less than 26 weeks [2]. On the other hand, acute on chronic liver failure (ACLF) is syndrome of acute clinical worsening of a patient with pre-existing chronic liver disease (CLD). ACLF is present in approximately 30% of patients with cirrhosis admitted to the hospital and is a systemic syndrome that is marked by multi-organ failure and high short-term mortality [3]. Compared to "decompensated cirrhosis", ACLF carries a significantly worse prognosis with a mortality rate similar to ALF [1]. However, ACLF is a relatively newer term and there is no consensus definition of ACLF but the most commonly used definitions include the American Association for the Study of Liver Diseases (AASLD) /European Association for the Study of Liver (EASL) [4], EASL-chronic liver failure (CLIF) [5], North American Consortium for the Study of the Liver Disease (NACSELD) [6], and Asian Pacific Association for the Study of the Liver (APASL) [7] (See Table 10.1).

The major etiologies of CLD in patients with ACLF include viral hepatitis, alcohol, and non-alcoholic steatohepatitis (NASH) [8]. Meanwhile, the major triggers of decompensation in ACLF include bacterial infections, acute viral hepatitis, and ongoing alcohol use. Among these, viral hepatitis related ACLF is of particular interest because of the availability of effective treatments and prevention strategies for several of the most common hepatotrophic viruses such as hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection. Viral hepatitis related ACLF can happen in two manners, the first through the virus itself causing CLD which may decompensate in similar manner to other CLDs, or the second through acute viral hepatitis (AVH) acting as an insult in a patient with pre-existing CLD. In the latter case, the typical causes of AVH that trigger viral related ACLF can be

**Table 10.1** The different definitions of acute-on-chronic liver failure (ACLF)

| EASL-AASLD [4] | APASL [7] | EASL-CLIF [5] | NACSELD [6] |
|---|---|---|---|
| Acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure. | Acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or underdiagnosed chronic liver disease. | Acute decompensation (i.e. ascites, encephalopathy, gastrointestinal hemorrhage, bacterial infection) followed by the development of one or more organ failures. | Two or more extrahepatic organ failures (brain failure, renal failure, respiratory failure, and/or shock) in a patient with pre-existing cirrhosis. |

*EASL* European Association for the Study of Liver, *AASLD* American Association for the Study of Liver Diseases, *APASL* Asian Pacific Association for the Study of the Liver, *CLIF* chronic liver failure, *NACSELD* North American Consortium for the Study of End-stage Liver Disease

comparable to the typical causes of ALF in the same geographical region. For example, in countries where hepatitis A virus (HAV) and hepatitis E virus (HEV) are endemic such as India, HAV and HEV are responsible for a significant number of ALF and ACLF cases. Meanwhile, in non-endemic countries such as the United States, they are considered rare causes of ALF and ACLF [4].

The aim of this review is to discuss in depth how ALF and ACLF relate to non-HBV, hepatitis D virus (HDV), and HCV viral hepatitis. The specific hepatotrophic viruses that will primarily be reviewed will include HAV and HEV, as well as non-hepatotrophic viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV). For each respective virus, we will proceed to delineate epidemiology, pathophysiology, risk factors, clinical presentation, prognosis and prognostic assessment, and management as it applies to the two syndromes.

## Hepatitis A Virus

Hepatitis A is a communicable disease targeting the liver caused by the HAV. HAV belongs to the family *Picornaviridae* and genus *Hepatovirus*. HAV is a small, non-enveloped, single-stranded RNA virus [9]. Four of its seven reported genotypes have been associated with human disease and infection with one genotype usually results in lifelong immunity against all strains [9, 10]. HAV is a major cause of AVH throughout the world and although infection in children is often asymptomatic and leads to lifelong immunity, adults and elderly populations are at a higher risk of severe infections that can lead to ALF and ACLF [11–13].

### *Epidemiology*

Prevalence of hepatitis A varies with geographic location and socioeconomic conditions; standards of hygiene and sanitation are strongly associated with its incidence. For example, in areas of high endemicity such as parts of Asia and Africa, most infections occur in children before the age of 10 years leading to high rates of population immunity and low risk of outbreaks [10, 11, 14]. In areas of low or intermediate prevalence areas, childhood transmission is less frequent and more adolescents and adults are infected with certain groups such as international travelers, elderly populations and intravenous drug users, who are at particularly high risk of infection [10, 11, 14, 15].

Globally, an estimated 1.4 million cases of hepatitis A occur each year. Since the introduction of the hepatitis A vaccine in 1995, rates of hepatitis A infection have declined from 6.0 cases/100,000 population in 1999 to 0.4 cases/100,000 in 2011 in the United States [16]. Although the incidence rate of HAV infections have decreased, a large population of susceptible, unvaccinated adults in low to intermediate endemic areas remain vulnerable to infection [17]. In 2017, 649 people in San

Diego, California were infected with hepatitis A leading to 417 hospitalizations and 21 deaths, making it the largest outbreak in the United States over the last 20 years [18]. Overall, from 2016 to 2018 reports of hepatitis A cases in the United States have increased by 294% as compared to 2013–2015 [17].

HAV related ALF is an uncommon manifestation and occurs in less than 1% of cases [13, 19–21]. Certain groups such as those above the age of 50 or those with underlying CLD are at the most risk of ALF and ACLF [19, 22]. Vento et al. prospectively followed 595 patients with chronic HBV and HCV and found 27 cases of superimposed HAV infection. Of the 17 patients that had underlying HCV infection, 7 developed ACLF leading to 6 deaths. A similar study in Thailand compared HAV infections in patients who were asymptomatic HBV carriers or had underlying CLD from HBV and HCV to isolated HAV infections and found high rates of ACLF in HBV carriers (55% of cases) and HBV/HCV CLD (33% of cases) [13]. Patients with CLD were significantly older (age >43 years of age, $p < 0.02$) compared to patients with isolated HAV. Interestingly, there were no differences in mortality rates between asymptomatic HBV carriers and CLD patients.

The vast majority of studies studying HAV related ACLF comes from South Asia where HAV related AVH is prevalent [23]. Gupta et al. studied cases of AVH related ACLF as defined by the APASL criteria and found HAV to be the cause of ACLF in 7.8% of cases [12]. Krishna et al. reported that out of 121 cases of ACLF in their series, HAV was the a trigger in 33 (27.2%) cases [24].

## *Transmission and Pathophysiology*

Early in the 1900s, physicians recognized that HAV was spread by person to person contact. Although there have been rare reports of vertical transmission or parenteral transmission through contaminated blood product, HAV is mainly spread through the fecal-oral route [9]. Given it's thermostable and acid resistant properties, HAV is able to survive for extended periods of time in the environment and can be a source of sporadic or epidemic infections [11, 15]. Contaminated foods such as frozen strawberries, ice slush beverages and salad food items have all been reported as sources of outbreaks and in the largest known global epidemic that took place in Shanghai in 1988, 292,301 cases of acute hepatitis A were attributed to eating contaminated seafood [9, 25]. Other sources of infection include waterborne transmission from contaminated sewage, international travelers returning from highly endemic areas and intravenous drug users. However, in nearly 40–47% of cases, no identifiable source can be found [9, 26, 27].

The incubation period is estimated to be between 15 and 50 days with a mean of 30 days. HAV is excreted in the feces for about 1–2 weeks before the onset of illness and up to at least 1 week afterwards [26]. HAV replicates primarily in hepatocytes and although not directly cytopathic, it sparks an immune response that causes liver inflammation [15, 20]. Cell mediated responses from cytotoxic T lymphocytes and

natural killer cells have been implicated and in vitro studies have proposed that interferon gamma production from HAV specific T cells play a central role in the clearance of HAV infected hepatocytes [20, 28]. In an interesting study by Rezende et al., cases of HAV related ALF were reviewed and a lower HAV viral load was found to be significantly associated with ALF; suggesting an excessive host response to the virus [20]. Similarly, although mechanisms are still unclear, ACLF is also associated with marked systemic inflammation, circulatory dysfunction, and pro-inflammatory molecules such as IL-6 or IL-8 [1, 29].

## *Clinical Manifestations*

Clinical manifestations of HAV can vary, but usually present as a mild illness with full recovery or can even be asymptomatic. Ford et al. observed that the rate of clinically apparent disease was much lower in children under 5 years of age [15, 30]. If symptoms do occur, they usually present as a non-specific prodromal illness of fever, malaise, nausea, vomiting, anorexia and abdominal pain [15]. Flu-like symptoms may be present in children [26]. These symptoms typically persist for an average of 5–7 days and tend to decrease with the onset of jaundice which lasts for several weeks followed by a convalescent period [9, 15]. Infected individuals remain contagious during the incubation period for up to about a week after the jaundice appears and full clinical and biochemical recovery is observed within 2–3 months in 85% of patients [31].

Atypical presentations of HAV have been observed and include a prolonged cholestatic pattern, relapsing HAV infection, and extrahepatic manifestations. A study in Korea by Jung et al. followed 595 patients prospectively that were admitted for acute hepatitis A and found 4.7% to have prolonged cholestasis defined as hyperbilirubinemia lasting more than 4 weeks. Patients with prolonged cholestasis were found to be comparatively older and were more likely to be HBV carriers [32]. A biphasic or relapsing form of viral hepatitis A has also been reported in about 6–10% of cases of hepatitis A where after apparent initial clinical and biochemical recovery there is a relapse mimicking the initial episode which can vary in severity from mild to severe [33]. Typically, there is a persistence of anti-HAV IgM antibodies during the entire course and HAV has been recovered in stool during relapses [33, 34]. Cases of leukocytoclastic vasculitis, arthritis and cryoglobulinemia have also been reported with HAV and have been associated with the relapsing form of the infection [35]. Majority cases of either atypical presentation (cholestasis vs relapsing) spontaneously recover without any chronic manifestations [33].

HAV related ALF or ACLF are the two most severe forms of HAV related liver disease. ALF typically presents as hepatic encephalopathy and coagulopathy [13, 21, 22]. In cases of HAV related ACLF, extra-hepatic manifestations such as renal failure, sepsis, ARDS or circulatory disturbances can occur akin to other types of ACLF [1, 23, 24]. Hyponatremia, grade III or IV hepatic encephalopathy and renal failure may be important predictors of mortality in these cases [24]. Shi et al.

compared clinical characteristics of ACLF triggered by hepatic insults such as alcohol, HAV/HEV superimposed infections or HBV flare to extrahepatic insults such as bacterial infections and upper gastrointestinal bleeds and found liver and coagulation failures to be more prevalent in those with hepatic insults as compared to those with extra-hepatic triggers [36]. ACLF has also been reported to be caused by dual insults such as infections of HAV with HEV or HBV or mixed presentations of HAV with extra-hepatic insults. There appears to be a higher rate of mortality with co-infections [23]. Common causes of underlying CLD that have been reported include HBV, alcohol, and cryptogenic causes [24, 37].

## *Diagnosis*

Since AVH due to HAV infection is clinically indistinguishable from infection by other hepatotropic viruses, testing for HAV should be pursued in patients at high risk for transmission or those with recent exposure. The diagnosis is established primarily by the presence of anti-HAV IgM antibodies that can detected from the time of symptom onset to approximately 3–6 months [9, 38] (See Table 10.2). Occasionally, the test is negative at the time of clinical presentation, but repeat testing 1–2 weeks

**Table 10.2** Diagnostic tests for non-HBV/HCV/HDV viral hepatitis related ACLF

| | Screening test | Comment | Confirmation test | Comment |
|---|---|---|---|---|
| HAV | Anti-HAV IgM | Can be detected for up to 6 months | HAV RNA PCR | Can be used to detect infection sooner than IgM test |
| HEV | Anti-HEV IgM | Can be detected for up to 8 weeks | HEV RNA PCR | Excellent specificity but may be negative if past the acute hepatitis phase |
| CMV | Anti-CMV IgM | Can be detected for up to 4 weeks | CMV DNA PCR | More sensitivity than IgM test in early infection |
| | | | Liver biopsy | Intranuclear inclusions called "Owl's eye"<br>Immunohistochemical staining for CMV protein |
| EBV | Anti-EBV VCA IgM | Can be detected for up to 4 weeks | EBV DNA PCR | More sensitive than IgM test in early infection |
| | | | Liver biopsy | Microscopy or EBV staining |
| VZV | Anti-VZV IgM | Can be detected for up to 12 months | VZV DNA PCR | More sensitive than IgM test in early infection |
| | | | Liver biopsy | Eosinophilic Cowdry type A intranuclear inclusions<br>VZV DNA PCR<br>Immunofluorescence for VZV antigen |

*HAV* hepatitis A virus, *HEV* hepatitis E virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *VZV* varicella zoster virus, *VCA* viral capsid antigen

later usually demonstrates positivity [9, 32]. Jung et al. reported that 6.7% of symptomatic hepatitis A patients have a delayed IgM conversion. These patients also had more severe symptoms requiring earlier hospital admission, suggesting repeat serologic testing needs be considered for those patients with a high clinical suspicion of hepatitis A who have an undetectable anti-HAV IgM at presentation [32].

Viremia is present 3–4 weeks before the onset of jaundice and high blood viral concentrations are present prior to the onset of liver test abnormalities. Viremia is thought to persist through the clinical and biochemical disease phase with a gradual decline in the convalescent phase [38, 39]. In a study on the outbreaks of HAV in Rio De Janeiro, Brazil, out of 195 patients who tested negative for anti-HAV antibodies, about 12–13% tested positive for HAV RNA, suggesting that RNA testing could be used for earlier detection [40]. Serum anti-HAV IgG antibodies appear early in the convalescent phase and persists for years to decades after the infection conferring immunity to HAV [26]. Individuals with detectable anti-HAV IgG in the absence of anti-HAV IgM reflect either past infection or vaccination.

## *Prognosis*

Mortality from HAV usually occurs after the development of ALF or ACLF however direct literature that enables true characterization of prognosis are lacking. A study by Gupta et al. showed that mortality in with HAV related ACLF is significantly higher than those presenting with simple AVH (28% vs 1.94%) [12]. 3-month mortality with HAV related ACLF have been reported to be as high as 51.5% [24]. In addition, other studies on HAV related ACLF have reported high rates of mortality of up to and exceeding 50% listing clinical factors such as old age, high white blood cell count, elevated international normalized ratio and creatinine, hyponatremia and the presence of hepatic encephalopathy as independent predictors of worse outcomes [23, 24, 36, 41]. The number of organ systems failing is expected to positively correlate with mortality rates as in typical ACLF with mortality rates ranging from 26% in patients with only one organ failure to > 90% in patients with four or more organ systems affected [37, 41]. However, further studies are needed to elucidate the optimal prognostic models for HAV related ALF and ACLF.

## *Management*

Uncomplicated HAV AVH is typically conservatively managed [9]. Most patients can be treated at home unless persistent vomiting or severe anorexia is present. Prohibition of alcohol and medications that might cause liver damage is recommended [26]. Post-exposure prophylaxis with immunoglobulin is advised for those <12 months or >40 years of age and for those who are immunocompromised or have CLD [42]. Use of oral corticosteroids in cases of severe cholestatic hepatitis A have

**Table 10.3** Groups for hepatitis A vaccination is recommended

| Persons at Increased Risk for Infection |
|---|
| • Travelers to countries with high endemicity for hepatitis A virus infection;<br>• Men who have sex with men;<br>• Users of injection and non-injection illegal drugs;<br>• Persons who receive blood product replacement therapy for clotting factors;<br>• Children and adolescents living in states with historically elevated rates of hepatitis A.[a] |
| Persons at Increased Risk for Adverse Consequences of Hepatitis A |
| • Persons with chronic liver disease of any etiology. |

Source: CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practice (ACIP). MMWR 1999;48(RR-12):1–37
[a]Routine vaccination recommended: Alaska, Arizona, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Utah and Washington; routine vaccination should be considered: Arkansas, Colorado, Missouri, Montana, Texas and Wyoming

been reported with favorable results but the majority will show full clinical and biochemical recovery with conservative management within 3–6 months [9, 43].

When HAV is complicated by ALF or ACLF, management is determined by the complications that develop and the availability of transplantation. Extra-hepatic manifestations such as renal failure, circulatory disturbances or sepsis require supportive care including intensive care services [1]. Patients with ALF or ACLF from HAV should be evaluated for liver transplantation however HAV related ALF resolves more frequently than other causes of ALF making the decision for transplant particularly difficult [20]. Data on liver transplant and outcomes in patients with HAV related ACLF are lacking but expectations can be extrapolated from studies that have shown acceptable one year post-transplant survival rates ranging from 75 to 84% in all-cause ACLF [44, 45].

The most effective strategy for HAV related ALF or ACLF is prevention. Basic approaches such as handwashing, avoiding tap water in endemic areas, and heating foods appropriately can help limit disease transmission [9]. Although the development of the HAV vaccine has led to a substantial decrease in hepatitis A outbreaks, many developing countries are experiencing an epidemiological shift of HAV exposure leading to more adults being at risk [16, 46]. Targeting high risk groups for vaccination such as those with CLD or those who are immunocompromised would be beneficial in reducing chances of developing ALF or ACLF and is safe and cost-effective strategy [47]. Groups for whom HAV vaccine is recommended from the Advisory Committee on Immunization Practices of the United States Centers for Disease Control and Prevention are shown in Table 10.3.

## Hepatitis E Virus

HEV is a non-enveloped virus measuring approximately 24–37 nm in size and is the sole member of the *Hepevirus* genus belonging to the *Hepeviridae* family [48]. HEV was first identified in 1983 by the Russian virologist Mikhail Balayan and thus

far, eight genotypes have been identified with four genotypes predominately affecting humans [49, 50]. HEV may be the most common cause of AVH in the world and is an important cause of ALF and ACLF in endemic areas [51].

## *Epidemiology*

HEV is endemic to Asia, Africa, and Central America and is an especially common cause of AVH, ALF, and viral hepatitis related ACLF in those countries but rarely found elsewhere [12, 52]. Studies regarding HEV related ALF and ACLF have been published primarily from developing countries in Asia and Africa with the vast majority of studies coming from India [24, 53–56]. HEV in these regions is caused primarily by genotypes 1 and 2 [51].

HEV related ACLF is responsible for nearly 50% of ACLF cases in endemic countries [23]. Gupta et al. reported in a study from India that 60 of 89 cases of viral hepatitis related ACLF was solely due to acute hepatitis E [12]. Jha et al. found in a prospective study of consecutive cases of ACLF from any etiology that 13.5% of cases were HEV related [23]. A collective review reported a median of 21% (range 4–72%) of ACLF cases in endemic countries were from HEV. Although HEV and HAV related ACLF are both endemic to India, the prevalence of HEV related ACLF occurs more often. Krishna et al. found that HEV related ACLF occurred about twice as often as HAV related ACLF although 6.1% of their cases had evidence of acute HEV and HAV [24]. Meanwhile, Shalimar et al. showed 67 of 368 (18.2%) of ACLF cases were HEV related compared to only 2 of 368 (0.5%) that were HAV related [57].

Interestingly, despite a high seroprevalence of HEV IgG in non-endemic countries, sporadic outbreaks of HEV ALF and ACLF outside of endemic regions including developed countries of Asia, Europe, and the United States is thought to be rare but conflicting data exists [58, 59]. Genotypes 3 and 4 are the predominant HEV pathologic genotypes in these regions [51]. Fontana et al. reported that only 3 of a cohort of 681 ALF patients were positive for HEV IgM [58]. In addition, 294 patients or 43.4% of the cohort were positive for anti-HEV IgG. In contrary, Manka et al. reported from Germany that 8 of 80 patients or 10% with ALF had detectable HEV viremia [60].

## *Transmission, Pathophysiology, and Risk Factors*

HEV is transmitted predominately via the fecal oral route akin to HAV. Transmission of HEV is different in endemic compared to non-endemic areas [61]. In endemic areas, transmission usually occurs through contaminated water. In non-endemic countries, transmission is primarily through animal vectors such as swine from unclean food consumption. HEV induced liver injury results from the patient's

immune response rather than direct viral injury to the hepatocytes [62]. Chandra et al. showed HEV viremia can be present despite normalization of liver chemistries further suggesting that liver injury is independent of viral replication [63]. This immune-mediated inflammatory response is excessive, systemic, and subsequently leads to decompensation in a patient with already pre-existing CLD resulting in multi organ failure and ACLF. Interestingly, although HEV results in significantly mortality in pregnant patients, pathogenesis remains unknown [64].

Pregnancy appears to be the biggest risk factor of HEV ALF which is likely related to a dramatic increase in viral replication [65]. Kar et al. reported that 38/50 or 76% of pregnant ALF patients were infected with HEV compared to only 17/50 or 34% of non-pregnant ALF patients [65]. Jilani et al. showed that 38/50 or 76% of pregnant ALF patients had HEV compared to only 15/50 or 30% of non-pregnant ALF patients [66]. These findings are hypothesized to be due to diminished cellular immunity and alteration in sex steroid hormones that can influence viral replication [67]. Risk factors for HEV related ACLF includes males, age less than 45 years, and albumin level < 3.5 g/dl [12, 24, 54]. HEV genotype 3 is the only genotype that has been reported to cause CLD [68].

## *Clinical Presentation*

HEV usually causes a mild, self-limiting infection that lasts a few weeks in most patients or can even be even asymptomatic [51]. Symptoms may include malaise, abdominal discomfort, jaundice, nausea, vomiting, and fevers after a viral incubation period of approximately 4–10 weeks [61]. However, HEV can also cause two other types of life-threatening syndrome. First, in certain patients, particularly pregnant women, HEV can result in an AVH that may progress to ALF. Second, a syndrome of HEV related ACLF can occur from either acute HEV occurring in a patient with pre-existing CLD leading ACLF or rarely from HEV infecting a patient (usually post-transplant) leading to CLD that may become ACLF with viral or non-viral associated ACLF insults. Kamar et al. showed that 66% of post solid organ transplant patients who were found to have AVH from HEV developed chronic hepatitis and 9.4% developed cirrhosis [69]. These insults can include bacterial sepsis such as spontaneous bacterial peritonitis, hepatic and portal vein thrombosis, hepatocellular carcinoma, and gastrointestinal bleed [70]. HEV resulting in CLD is primarily an issue in patients in the post-transplant setting, those receiving chemotherapy, and those with HIV.

Presenting symptoms of HEV ALF or ACLF can include jaundice, hepatic encephalopathy, and ascites [24, 52]. Most patients with HEV related ACLF will present with all three findings however a small subset may present with only encephalopathy and jaundice [41]. It is important to note that patients with acute hepatitis E may present with a variety of extrahepatic manifestations including neurologic syndromes, pancreatitis, thrombocytopenia, and aplastic anemia [51]. On laboratory, leukocytosis, elevated alanine aminotransferase (ALT) levels around

1000–3000 IU/L, and hyperbilirubinemia are common [51]. The underlying chronic disease in HEV related ACLF can significantly vary and will depend on the patient population and geographical region. Based on available data regarding where HEV related ACLF is the most common, HBV and cryptogenic cirrhosis appears to be the two most common underlying chronic liver diseases [24]. In addition, patient's with Wilson's disease may be at increased risk of HEV related ACLF for unclear reasons [70].

It is important to keep in mind that patients with HEV related ACLF may rarely be co-infected with another acute or chronic viral hepatitis such as HAV or HBV. Gupta et al. reported that 2 of their 89 cases of viral hepatitis related ACLF were co-infected with acute HEV plus HBV [12]. HEV super-infection may be especially common in patients with HBeAg (+) patients from endemic countries accounting for 36.2% of acute exacerbations in one study [71]. Jha et al. found that 2 of their 52 cases of all cause ACLF were co-infected with acute HEV plus HAV [23]. It is also important to note that patients may also present with dual acute insults such as HEV/HAV, HEV/sepsis, or HEV/drug toxicity triggered ACLF. Thus, in patients with HEV related ACLF, a healthy amount of awareness needs to be paid to other etiologies of ACLF especially in patients with systemic inflammatory response syndrome (SIRS). HEV with *P. falciparum* have also been reported to be a cause of ACLF [23].

## *Diagnosis*

The diagnosis of HEV related ACLF requires special awareness especially in patients from high endemic areas and those who are immunocompromised (i.e. post-transplant). Initial testing in a patient suspected to have HEV ALF or ACLF include testing for anti-HEV IgM via ELISA or immunochromatographic assays that are based on ORF2/ORF3 peptides or recombinant HEV antigens [72]. Anti-HEV IgM is a marker of acute infection and may remain significantly elevated for up to 8 weeks [51] (See Table 10.2). However, false positive and negative anti-HEV IgM can occur depending on the timing of the testing in respect to the infection. Thus, if the suspicion is high then a serum HEV RNA PCR should be sent [60]. The anti-HEV IgM ELISA reads out within days but the performance of available anti-HEV IgM ELISA assays ranges significantly. One study comparing five different assays showed that the sensitivities ranged from 42 to 96%, respectively [73]. Lower performance of these assays typical occurs due to a lesser ability to detect a particular genotype. Immunochromatographic assays have been shown to have higher sensitivity and specificity compared to the ELISA and can read out results within minutes [74]. Both types of assay will detect antibodies induced by any of the major genotypes of HEV such that there is no genotype specific assay [75].

After a patient is found to be anti-HEV IgM positive, confirmation should be done via the serum HEV RNA PCR test. HEV RNA PCR has high specificity and accuracy for anti-HEV IgM [54]. Zaki et al. showed that all HEV related ACLF

patients in their cohort that had a positive anti-HEV IgM had a positive HEV RNA PCR. HEV viremia only lasts a few weeks in AVH so if a HEV RNA PCR is checked too late, negative results does not rule out HEV related ALF or ACLF. Fontana et al. reported three possible HEV ALF cases with positive anti-HEV IgM but negative HEV RNA PCR [58]. Davern et al. showed that only 4 of 9 patients with severe liver injury and positive anti-HEV IgM had a positive HEV RNA PCR [76]. However, commercial HEV RNA PCR assays have recently been shown to have excellent performance and are now available for order [77]. Interestingly, stool shedding of the virus can last for weeks after a patient stops being viremic [52].

After the initial anti-HEV IgM response during HEV AVH, patients will usually develop anti-HEV IgG antibodies. However, a positive anti-HEV IgG is not helpful in diagnosing HEV ALF or ACLF. Positive anti-HEV IgG can suggest either past HEV exposure in which the protective role of anti-HEV IgG from past exposure is not fully understood or it can suggest chronic HEV infection. Either way, it does not guarantee protection against HEV ALF or ACLF. Positivity to anti-HEV IgG may be linked to patient qualities such as being a farmer, drinking water from wells, and handling pig and eating pork [55]. In fact, one study showed that anti-HEV IgG had only 13% sensitivity and 63% accuracy for detecting HEV related ACLF patients who were HEV viremic by PCR [54].

Since HEV can be a cause of ALF and ACLF regardless of geographical region, it is important for the diagnosing physician to be aware of that possibility [78]. This is especially true in cases that are suspected to be drug-induced liver injury (DILI) related ALF or ACLF since they can mimic HEV ALF or ACLF [60, 76, 78]. Davern et al. reported that 3% of 318 patients with DILI were positive for anti-HEV IgM [76]. Thus, anti-HEV IgM should be checked in patients with DILI who are at high risk of HEV.

## *Prognosis and Prognostic Assessment*

When HEV outbreaks occur, mortality rates of 0.5–4% are seen in hospitalized patients [79]. Mortality typically occurs either from HEV ALF or ACLF. When HEV ALF is associated with pregnancy, particularly high mortality rates (20–65.8%) to the mother and fetus are encountered [65, 80].

HEV ACLF appears to have a worse prognosis compared to HEV ALF when it does not occur in pregnant woman. This mortality risk is comparable to that of other causes of ACLF [81]. However, this risk may be somewhat less than that of alcohol-related ACLF [82]. The mortality risk in HEV related ACLF is significantly higher than that of HAV related ACLF [83]. In a cohort of primarily HEV related ACLF, a mortality rate of 28% has been reported [12]. Acharya et al. reported in a large cohort of cirrhotic patients that HEV infection was independently associated with rapid decompensation and death. The mortality rate of HEV related ACLF was

nearly double that of non-HEV infected patients with cirrhosis (43% vs. 22%, $p = 0.001$) [84]. Similarly, Krishna et al. described a 3-month mortality rate of 44.6% in a cohort made up of 61% HEV related ACLF. A collective review published by Kumar et al. summarized the findings of 12 studies totaling 464 subjects with HEV related ACLF and found a 34% median short-term mortality [56]. Interestingly, mortality may be increased when patient is co-infected with HEV and another viral hepatitis [23].

Prognostic models such as the MELD score that have been validated in ACLF can be applied to HEV related ACLF [85]. In a study by Krishna et al., MELD was found to have an area under the receiver operating characteristic (ROC) curve of 0.941 in predicting mortality [24]. A MELD score of 27 was 91% sensitive and 85% specific. Meanwhile, Child-Turcotte-Pugh score is not an adequate prognostic model with an area under the ROC (AUROC) curve of 0.631. Such as the case as other causes of ACLF, hyponatremia can also be an important prognostic marker in HEV related ACLF. Krishna et al. found that a hyponatremia carried an adjusted odds ratio of 9.2 in predicting mortality within 3 months [24].

## *Management*

The most critical step in the management of HEV related ACLF is to prevent the initial infection. Healthy practices that can prevent HEV infection includes drinking clean water, practicing hygienic sanitation practices, and avoiding undercooked meats especially pork [51]. HEV vaccination is on the horizon and would be an ideal way to prevent HEV related ACLF in those who are anti-HEV IgG negative and perhaps even in patients with low anti-HEV IgG titers. A significant percentage of CLD patients in endemic areas (44–82%) are negative for anti-HEV IgG and thus would benefit. This rate is similar to, if not higher than the general population creating a large need for vaccination [70, 86]. A recombinant hepatitis E vaccine given as a 3-shot series has shown 100% efficacy in preventing HEV infection within a year in a randomized, double-blinded placebo-controlled, phase 3 trial conducted in China [87]. However, data on the efficacy of this vaccine elsewhere in the world is lacking and availability of this vaccine is limited.

Once HEV related ACLF develops, the primary goals are supportive such as preventing further decompensation of liver function, treating other insults such as sepsis and gastrointestinal bleed, and support failing organs. Medical care to support failing organs may include blood pressure support with vasopressors, hepatorenal syndrome treatment with medications such as albumin, terlipressin, and norepinephrine, intubation for a Glasgow coma score <8, and lactulose/rifaximin for hepatic encephalopathy [56].

Ribavirin is the treatment of choice in chronic HEV with sustained viral clearance rates of approximately 78% after a 3-month course of therapy [88]. In vitro and

in vivo studies have shown that ribavirin inhibits HEV replication through the depletion of cellular guanosine triphosphate (GTP) pools [89, 90]. Studies in HEV related ACLF are lacking however. A pilot study exploring the use of ribavirin in 4 patients with HEV related ACLF suggested that the medication is safe and effective [91]. Treated with a dose ranging from 200 to 600 mg/day for a median of 12 (range 3–14) weeks, HEV RNA became undetectable in all four patients and survival was 100%. There were no serious adverse events reported.

Literature regarding alternative HEV therapies is lacking. Interferon alpha has been shown to have synergism with ribavirin in in vitro studies and may be a potential alternative method of treatment [89]. Kamar et al. showed that a 3-month course of pegylated interferon-alpha-2a can clear chronic HEV [92]. Additionally, sofosbuvir has demonstrated anti-viral effect in chronic HEV and can be used in conjunction with ribavirin. However, results have been mixed with some patients achieving sustained virologic response but others only having temporary viral suppression [93, 94]. Finally, immunosuppression via steroids ± azathioprine has also been reported to be of possible benefit in the setting of autoimmunity associated with HEV AVH [95]. Liver transplantation for the treatment of HEV related ACLF has not been well studied. Moreover, expertise and organ availability are often limited in regions where HEV is endemic.

## Epstein-Barr Virus

### *Epidemiology*

EBV is a double-stranded DNA γ human herpes virus that has a seroprevalence of over 95% worldwide. It infects the B lymphoid system typically during childhood, affecting 345–671/100,000 people aged 15–19 years per year [96, 97]. In contrast, the incidence decreases to 2–4/100,000 per year in patients over the age of 34 years [97]. Once infected, EBV cannot be eradicated as it remains latent in B cells throughout the lifespan of the host. As such, EBV has been associated with both acute primary and acute reactivation, as well as chronic active EBV infection [98].

EBV infection is commonly self-limited, however, in rare cases, it has been associated with ALF and ACLF. EBV ALF has been reported to occur in up to 0.21% of patients with ALF [99]. Of these cases, the median age was 30 and it occurred primarily in males [99]. However, there have also been cases reported in patients over the age of 60 resulting in increased mortality risk. EBV ALF can occur in both immunocompromised and immunocompetent patients with primary infection and reactivation [100]. Unfortunately, data regarding EBV related ACLF is limited. In one study, EBV viremia was present in 8.24% of patients and the presence of EBV was associated with a higher rate of ACLF in comparison to those patients without EBV [101].

## *Transmission, Pathophysiology, and Risk Factors*

EBV is commonly transmitted via saliva, however, it can also spread through blood and semen. EBV can present as either a primary infection or as reactivation of latent infection. During the primary EBV infection, B cells are infected with EBV and polyclonal B cell expansion is followed by a oligoclonal or monoclonal proliferation of CD8-positive cytotoxic T cells [102]. After primary infection, EBV develop a lifelong latency in B cells [96]. EBV can be reactivated from these latent B cells by chemicals, antibodies, or immunoglobulins which stimulate the expression of the EBV BZLF1 gene product, triggering viral replication [103].

Age, especially those who are 60 years or older, are at a significantly increased risk of EBV AVH [104]. Unfortunately, there is a paucity of data assessing risk factors for EBV related ALF and ACLF. Malignancy, CMV, HIV, and use of immunosuppressant drugs has been implicated in EBV ALF. However, cases of EBV ALF have been described in immunocompetent patients as well [100].

## *Clinical Presentation*

Acute EBV infection typically presents in childhood and can be subclinical in 80–90% of cases [105]. However, patients may develop symptoms of mononucleosis including fever, tonsillitis, and lymphadenopathy. Interestingly, only 50% of patients with EBV AVH will have all three symptoms at presentation [106]. Approximately 80–90% of infectious mononucleosis cases will have a moderate and transient elevation in liver enzymes, however, clinical symptoms are rare. Serum aminotransferases are commonly elevated in a hepatocellular pattern and are typically less than five-fold normal [105]. Transaminase abnormalities occur within the first week after onset of illness, peak during the second, and return to normal during the third week [107]. Hyperbilirubinemia is present in 45% of patients, however, clinical jaundice occurs in less than 5% of patients [108]. Cholestatic liver disease is uncommon, however, but jaundice can occur during EBV infection due to autoimmune hemolytic anemia, cholestasis due to acalculous cholecystitis or biliary obstruction, or rarely cholestatic hepatitis [109–112]. Jaundice occurs more frequently in people aged 35 years or older [113]. In a case series of those with ALF due to EBV. The median AST was 654 Iu/L (range 192–2690) and median serum ALT was 504 (range 156–4920). The median total bilirubin was 17.5 mg/dL (range 11.1–27) with a median INR of 2.3 (range 1.6–3.6). The pattern of liver injury was variable, including both hepatocellular injury and cholestatic injury [99].

While there is little data on EBV related ACLF and its clinical presentation, there is one case report of an elderly male who presented with fever and general malaise for 2 months and developed shock, multi-organ failure, and death. Post-mortem, he was found to have severe chronic active EBV with the presence of EBV DNA in the

liver and lymphatic tissue [114]. In addition, there is one study that showed that patients with ACLF associated with presence of EBV had no difference in the rate of complications such as ascites, hepatic encephalopathy, gastrointestinal bleeding, hepatorenal syndrome, infections, and hepatocellular carcinoma compared to those without EBV [101].

## *Diagnosis*

EBV infection can be diagnosed via serology, PCR, and/or by evidence of EBV infection in liver tissue by light microscopy or EBV-encoded RNA positive staining. Typically, the heterophile antibody will be negative. If serology is performed, an acute EBV infection is defined by positive anti-EBV viral capsid antigen (VCA) IgM with or without positive anti-EBV VCA IgG titers [99]. Anti-EBV VCA IgG are produced concurrently during early infection and in an immunocompetent person lasts a lifetime, thus it is not a good marker for acute infection [115]. During early EBV infection, EBV DNA PCR is more sensitive [116].

Although there is not a set diagnostic criteria of EBV ALF pathologically, one study of patients who underwent liver transplant found that in the explanted liver there was more than 90% hepatocellular necrosis with extensive lymphohistiocytic infiltrate in both the portal and lobular distributions, presence of ductular reaction, cholestasis and central venulitis, and numerous parenchymal macrophages. Hepatic lymphocytes stained positive for cytoplasmic CD3, CD8, granzyme B, perforin, and EBERS, but they were negative for CD4, CD20, and CD56. EBER-positive lymphocytes were positive for CD45RO but negative for CD20 [117].

## *Prognosis and Prognostic Assessment*

The data on prognosis of EBV ALF and ACLF Is limited to case reports and case reviews. From the limited data, the mortality rate of EBV associated ALF is approximately 68–87% [117, 118]. While the MELD, Child-Pugh score and King's College Criteria can be applied as a prognostic score, there is little data to suggest benefit of one over the other. Kumar et al. used the Acute Liver Failure Early Dynamic (ALFED) model which is based on arterial ammonia, serum bilirubin, INR, and hepatic encephalopathy and whether these variables remain high or increases over 3 days. The ALFED model has been shown to accurately predict outcomes in patients with ALF [119]. Serial assessment of the severity of ALF based on the ALFED model during the first 5 days after initiation of artificial liver support assisted in determining the need for LT in patients with EBV ALF [117].

### *Management*

The overall benefit of anti-viral treatment in EBV is unclear as controlled trials have shown that anti-virals neither reduce the severity or duration of clinical symptoms. However, in severe EBV AVH, the use of anti-viral drugs such as ganciclovir, valganciclovir, acyclovir, and steroids are supported. Still, there are no specific guidelines or randomized controlled trials that support a specific treatment or recommended dose, or duration of therapy [120]. Definitive treatment for EBV ALF is liver transplantation [117]. Although there is a paucity of information, successful liver transplantation for EBV ALF have been reported [99, 100, 121]. Five-year survival rate post liver transplantation is excellent at approximately 80% [122]. In the post-transplant setting, consideration of treatment with acyclovir is important as it can assist preventing infection of the graft liver as immunosuppression may increase the replication of EBV [100].

## Cytomegalovirus

### *Epidemiology*

CMV is a double-stranded DNA β human herpes virus with a seroprevalence of 30–100% [123–125]. It can cause infection either via primary infection or reactivation in both immunocompetent and immunocompromised hosts. Immunocompetent individuals usually develop primary CMV infection, in contrast to immunocompromised individuals who typically develop infection via reactivation. CMV can cause clinically apparent liver disease ranging from mild elevation in transaminases, to CMV hepatitis, and rarely ALF or ACLF. The incidence of CMV AVH ranges from 2 to 34% [126]. The cases of CMV related ALF and ACLF are only limited to case reports and case reviews [127, 128].

### *Transmission, Pathophysiology, and Risk Factors*

CMV is transmitted via secretions such as tears, saliva, urine, genital secretions, breast milk or blood. Incubation of the virus is for 4–6 weeks and often may be asymptomatic. However, CMV can present with mononucleosis like symptoms with fever, cough, and fatigue.

The key to CMV infection is viremia as CMV requires a high viral load to cause end-organ disease. Thus, an intact immune system with humoral immunity and innate immunity involving a complex role of natural killer cells and T-cell mediated response is important in controlling viral replication [129]. After primary infection, CMV causes a lifelong latent infection.

CMV reactivation occurs via three main pathways which require TNF-α, inflammatory prostaglandins, and catecholamines. Release of TNF-α binds to TNF-α receptors on latently infected cells and activates nuclear factor κB and allows for initiation of viral replication. In addition, inflammatory prostaglandins and catecholamines assist in activation and production of cAMP, respectively.

As a result of the physiology of CMV infection, those who are immunosuppressed are at the highest risk; this includes immunosuppression or high dose corticosteroid use, T-cell depletion, acute and chronic GVHD, rejection, and viral co-infection [130–133]. In addition, patients who have received bone marrow and solid organ transplant are frequently at risk post-transplantation. However, this risk is dependent on the serostatus of the donor and the recipient with the greatest risk in a positive donor/negative recipient (D+/R-) [134]. Recipients who are CMV seropositive can also develop a CMV infection via reactivation of latent CMV infection or by de novo infection with a different strain. CMV replication is increased after transplantation with peak viremia occurring at 35–40 days post-transplantation, thus providing an opportune time to develop an acute or reactivation infection [135].

In regard to ACLF, patients who have chronic alcohol consumption and cirrhosis may be at risk of latent CMV reactivation as control of viral replication is dependent on CD4+ and CD8+ T cell function, which is impaired in this population [136, 137]. Furthermore, HBV infection has also been found to be a risk factor for CMV related ACLF, especially if the HBV DNA is <1000 IU/mL, increasing risk to 34-fold [138]. Studies have shown that 5–10% of patients with HBV infection may be co-infected with CMV [138, 139]. This may be due to inhibition of HBV replication and gene expression or increase in HBV viral clearance [140, 141].

## *Clinical Presentation*

In the immunocompetent population, most infections with CMV are asymptomatic, however, 10% of affected individuals may have clinical symptoms [142]. Symptoms on presentation can include a mononucleosis-like syndrome such as fever, pharyngitis, lymphadenopathy, arthralgia, lymphocytosis, and splenomegaly [143]. During clinically evident primary CMV infection, liver test abnormalities can occur in up to 90% of cases, with a mild to moderate transaminitis, but rarely exceeds five-fold above normal [144]. ALT tends to be higher than AST level, while alkaline phosphatase and bilirubin levels are within normal ranges. These laboratory abnormalities generally normalize within a few weeks [145]. In patients with CMV hepatitis, the most common symptoms include fever, tonsillitis, abdominal pain, vomiting, and anorexia [106]. Peripheral adenopathy, neutropenia, and monocytosis may also be seen. On histology, there may be findings of focal lobular hepatocyte necrosis with the presence of macrophages or CMV nuclear inclusions.

Data on the clinical presentation of CMV related ALF and ACLF is limited to case reports. Shusterman et al. reported the first case of CMV ALF in 1978 in a 33-year-old with general malaise, fever, and night sweats for 2 weeks [146]. Since then, there have been numerous other case reports in which patients presented with

a range of symptoms including fever, general malaise, jaundice, headache, plantar rash, and associated Q fever [128, 145, 147].

## *Diagnosis*

Diagnosis of CMV infection is achieved through serology or detection of CMV DNA. CMV induces the production of IgM and IgG. Anti-CMV IgM is the first to appear in serum and can last up to 4 weeks. Determination of the IgG avidity index allows the confirmation of recent infection if both IgG and IgM are positive; avidity is weaker in a recent infection [148]. Thus, diagnosis of CMV infection can be confirmed with the presence of anti-CMV IgM antibodies. In addition, a four-fold increase over the upper limit of normal of anti-CMV IgG titers is also diagnostic of infection [149]. In contrast to serology, during early infection, quantitative PCR is the standard method for diagnosis. CMV DNA viral load of 1000–100,000 copies/mL suggests active infection, reactivated infection, or latent infection without disease [126]. In the post-transplant period, the pp65 antigenemia assay can be used to differentiate CMV reactivation from acute CMV infection [150].

Histologic features on biopsy of CMV hepatitis include sinusoidal infiltration by mononuclear cells and mild hepatocellular necrosis along with granuloma formation. Intranuclear inclusions also known as "Owl's eye" may be present but are not specific. In immunocompetent individuals with CMV hepatitis, intranuclear inclusions and immunohistochemical staining may not be seen because a strong immune response may destroy the infected cells [151]. CMV ALF on explant can show massive hepatic necrosis with positive immunohistochemical staining for CMV protein [145].

## *Prognosis and Prognostic Assessment*

Unfortunately, the data for CMV related ALF and ACLF is limited. However, case reports have shown good outcomes with early detection and treatment with antivirals or liver transplantation.

## *Management*

CMV infection is typically self-limited and does not require treatment. This is especially true in the immunocompetent patient. Treatment is recommended in severe CMV infection in immunocompromised individuals [152]. However, as there is no data to support for or against anti-viral treatment of immunocompetent patients with ALF, we would suggest the use of anti-virals in these patients as they are at high risk of morbidity and use of anti-virals have shown success [128].

The end point of treatment is clearance of the virus from the blood. Valganciclovir can be used 2–3 months after completion of treatment to avoid CMV recurrence in high risk individuals [153]. However, the treatment of CMV with valganciclovir and ganciclovir is not a benign treatment. Potential side effects include myelosuppression, central nervous system disorders, hepatotoxicity, irreversible infertility, and teratogenesis [154].

In addition, when discussing the management of CMV, it is also important to discuss prophylaxis, especially in the post-transplant period. Prophylaxis with ganciclovir or valganciclovir is commonly used in the post-transplant period. The risk of CMV infection post liver transplant ranges between 25 and 80%, however, the mortality rate is only 0.9%, thus one study suggests that CMV prophylaxis may not be mandatory [155].

## Varicella Zoster Virus

### *Epidemiology*

VZV is a double-stranded DNA α herpes virus that only naturally infects humans [156]. The incidence of VZV ranges from 13 to 16 cases per 1000 persons per year, with the greatest incidence of disease during childhood and adolescence [156]. Primary infection of VZV, which is also known as chickenpox, infects 1–2% of adults, among whom complications and mortality are 10–20 times more frequent [157].

After primary infection, VZV remains latent in ganglionic neurons and can develop as a secondary reactivation infection later in life. This is also known as zoster. As age increases, the severity and incidence of zoster also increases [156]. The incidence of zoster goes from ~1 per 1000 patients per year in children <10 years to >10 per 1000 patients per year in adults ≥60 years [158].

In addition to its characteristic cutaneous manifestations, VZV is also associated with neurologic disorders, ocular disorders, and gastrointestinal disorders including hepatitis, pancreatitis, and ulcers. VZV-associated hepatitis is rare, and cases of VZV ALF are only limited to case reports [159–168]. There have been no reported cases of VZV related ACLF.

### *Transmission, Pathophysiology, and Risk Factors*

VZV is transmitted via the respiratory route and by direct contact. The incubation period averages 14 days with a range of 10–23 days. During primary infection, VZV infects T cells and the virus disseminates to the skin and potentially other organs. At first, viral replication in the skin is delayed by innate immunity, however, after time, this cutaneous innate immune response is overcome by virus and there is substantial viral replication resulting in a characteristic rash [156]. Latency then develops in the ganglionic neurons, however, its transference to neurons is unclear. As cellular

immunity declines with advancing age or an immunocompromised state, VZV reactivates causing a secondary infection, although the direct mechanism is also unclear.

Rarely does VZV cause ALF, but when it occurs, it is usually due to primary VZV infection [160, 169]. Immunosuppressed patients including those with either iatrogenic or acquired immunosuppression (i.e. status post organ transplantation or splenectomy, patients on steroids or other immunosuppressive agents, and patients with AIDS) are at the greatest risk [167]. However, there have been 2 reported cases of VZV ALF in immunocompetent patients [162, 170].

### *Clinical Presentation*

VZV can cause primary infection, chickenpox, and secondary infection, herpes zoster. Primary infection typically presents in childhood with a generalized rash. The virus then remains latent in the dorsal root ganglia and can later reactivate as shingles or herpes zoster with a localized dermatomal vesicular eruption. This rash is characterized by a pruritic, vesicular lesion in successive crops, with various stages of development noted simultaneously including papules, vesicles, pustules, and crusts. Patients with VZV hepatitis are often asymptomatic with mild and limited elevation in transaminases. However, if symptomatic, they may initially present with severe abdominal or back pain, fever, chills, malaise, or fatigue. During early presentation, there may be few or no cutaneous lesions [171, 172]. However, the rash can precede, occur concurrently, or develop after the onset of abdominal pain [167]. Patients are moderately ill for a few days with only mild elevations of liver enzymes, however, a small subset can develop ALF with coagulopathy and encephalopathy, followed by multi-organ failure [167]. In these patients, liver tests can reach levels in the thousands secondary to hepatic necrosis from VZV [169, 173].

### *Diagnosis*

Diagnosis is confirmed with additional presence of VZV DNA, VZV antigens in infected tissue, or positive viral culture in the appropriate clinical setting. VZV DNA can be detected by PCR in the serum or in tissue samples of the liver [174, 175]. Skin biopsy is diagnostic for varicella infection when immunofluorescent staining identifies VZV antigen [166]. VZV cultures can also be done on skin lesions, blood, or other infected tissue. Liver biopsy is rarely done for diagnostic purposes because of severe coagulopathy. However, biopsy generally reveals hemorrhagic necrosis and eosinophilic Cowdry type A intranuclear inclusions [165, 174]. Occasionally intracellular virions and multinucleated giant cells can be identified. Immunofluorescence for VZV antigen and PCR of VZV DNA on liver tissue are also diagnostic [166, 174]. In addition, pANCA may be positive in some cases.

Tzanck smear of skin lesions can also be helpful but a positive smear does not differentiate HSV from VZV. Serology can support the diagnosis with positive IgG

antibodies in reactivation and positive IgM antibodies in primary infection. However, there is one reported case of VZV ALF that did not develop VZV antibodies and diagnosis was confirmed with detection of VZV DNA by PCR in the serum and liver [174].

### *Prognosis and Prognostic Assessment*

Unfortunately, the data on prognostic measurements of VZV ALF are limited. However, VZV ALF has a poor prognosis with a fatal outcome in the majority of cases (~75%) within 3–13 days of initial presentation despite early therapy with acyclovir [168].

### *Management*

Early diagnosis and IV acyclovir is critical in the management of VZV ALF. Treatment with IV acyclovir at a dosage of 10 mg/kg every 8 h should be initiated if the diagnosis is considered and the patient should be evaluated for emergent liver transplantation as there have been a few cases of successful transplantation for VZV ALF [160, 176, 177].

Furthermore, in immunocompromised patients who have been exposed to an individual with chickenpox, despite the patients' previous exposure, consideration should be given to the administration of VZIG within 72–96 h [178, 179]. As a result of varicella's high mortality rate when associated with ALF, attention should also be focused on prevention with vaccination.

**Conclusion**

ALF and ACLF are two unique clinical syndromes associated with a high risk of mortality. Non-HBV/HCV/HDV viruses including the hepatotrophic viruses (HAV and HEV) and non-hepatotrophic viruses (EBV/CMV/VZV) are important causes of ALF and ACLF. HAV and HEV infection are especially common in endemic countries and needs to be on the differential for a patient presenting with ALF or ACLF. In those who are immunosuppressed, EBV, CMV, and VZV needs to be considered. However, early diagnosis based on awareness is critical and relies primarily on the detection of IgM antibodies and/or viremia in the correct clinical context. Studies on the presentation, prognosis, and management of ALF and ACLF associated with these viruses are lacking. Correct management includes supportive care for failing organ systems, virus directed treatment such as ribavirin for HEV, and liver transplantation.

**Questions**

1. What is the typical serologic pattern of HAV related ALF and ACLF?

   (a) HAV IgM negative, HAV IgG negative
   (b) HAV IgM positive, HAV IgG negative
   (c) HAV IgM negative, HAV IgG positive

2. Which of the following appears to be the biggest risk factor for HEV related ALF?

   (a) Smoking
   (b) Alcohol use
   (c) Pregnancy
   (d) Tylenol

3. What are some of the risk for HEV related ALF?

   (a) Being from a HEV endemic country
   (b) Pregnancy
   (c) Post-transplant
   (d) All of the above

4. How can EBV related ALF or ACLF be diagnosed?

   (a) Anti-EBV viral capsid IgM
   (b) EBV DNA PCR
   (c) Liver biopsy
   (d) All of the above

5. The risk of CMV hepatitis is highest in which post-transplantation donor-recipient combination?

   (a) Donor CMV negative/Recipient CMV negative
   (b) Donor CMV positive/Recipient CMV negative
   (c) Donor CMV positive/Recipient CMV positive
   (d) Donor CMV negative/Recipient CMV positive

**Answers and Explanations**

1. Answer—B. HAV IgM will usually become positive at time of symptom onset. If HAV IgM is negative but high clinical suspicion remains, repeat testing can be performed in 1–2 weeks. Conversion to HAV IgG positivity occurs later and confers immunity to HAV.
2. Answer—C. Pregnancy appears to be the biggest risk factor for ALF from HEV due a dramatic increase in viral replication due to diminished cellular immunity and alterations in sex steroid hormones.

3. Answer—D. Risk factors for HEV ALF includes being from a HEV endemic country, being immunocompromised (i.e. post-transplant state), and pregnancy.
4. Answer—D. The diagnosis of EBV ALF can be made via positive anti-EBV viral capsid antigen IgM with or without anti-EBV viral capsid antigen IgG, detectable serum EBV PCR, and/or evidence of EBV infection in liver tissue by light microscopy or EBV-encoded RNA positive staining.
5. Answer—B. The risk of CMV hepatitis in highest when the donor is CMV seropositive and the recipient is CMV seronegative. These patients commonly receive prophylaxis for at least 3–6 months post-transplantation.

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# Chapter 11
# Drug-Induced Acute and Acute on Chronic Liver Failure


**Rajan Vijayaraghavan and Shiv Kumar Sarin**

## Abbreviations

| | |
|---|---|
| ACLF | Acute-on-chronic liver failure |
| ALF | Acute Liver Failure |
| AARC | APASL ACLF research consortium |
| APASL | Asian Pacific Association for the Study of the Liver |
| CANONIC | CLIF Acute-oN-ChrONic LIver Failure in Cirrhosis |
| DILI | Drug-Induced Liver Injury |
| DAMPS | Damage associated molecular patterns |
| EASL CLIF | European Association for the Study of the Liver Chronic Liver Failure consortium |

Drug induced liver injury (DILI) has varied presentation and a small subset of these patients presents as acute liver failure (ALF) or acute-on-chronic liver failure (ACLF) in clinical setting. In the current era, where medication and dietary supplements are easily available, herbal and dietary supplement (HDS) are leading causes inciting liver injury. DILI is still a diagnosis of exclusion. Absence of defined biomarkers adds to under diagnosis or misdiagnosis of this important disease entity. DILI-ALF or DILI-ACLF usually presents as idiosyncratic DILI (iDILI). iDILI carries a high risk of mortality in the setting of development of liver failure. DILI is a disease manifestation of an interaction of drugs pharmacodynamics and patients genetic behaviour. iDILI is a complex interplay between host, drug and environmental factors. Host factors like older age, female preponderance and co-morbid conditions are associated with development of DILI [1]. Liver injury may be dose dependent, which is more predictable, or

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it may be idiosyncratic, which is immunologically mediated and is thus unpredictable and more severe (Fig. 11.1). Drugs with higher dose per day and lipophilicity have increased risk of developing DILI [2].

**Definition**

In a systematic review [3], ALF is defined by more than 40 definitions but the most widely used is given by O'Grady [4] which defines development of jaundice followed by encephalopathy from 7 days to 28 days in the absence of pre-existing liver disease. AASLD defines acute liver failure (ALF) as an acute insult resulting in jaundice along with encephalopathy and coagulopathy over a duration of 26 weeks in a patient without previous history of cirrhosis [5]. ACLF is defined as clinical syndrome characterised by severe and acute hepatic dysfunction from varying insults and carries high short-term mortality. The APASL ACLF Research Consortium proposed the first consensus definition [6] in 2009 based on a prospective study of 200 patients, i.e. "ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin≥5 mg/dL (85 micromol/L) and coagulopathy (INR≥1.5 or prothrombin activity <40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, " which was improved by addition of a statement "…associated with a high 28-day mortality" in 2014 [7]. Moreau et al. [8] defined the ACLF on basis of the CANONIC study as an acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure. Subsequently the duration of mortality for ACLF has been reduced to 4 weeks even in the Western definitions.

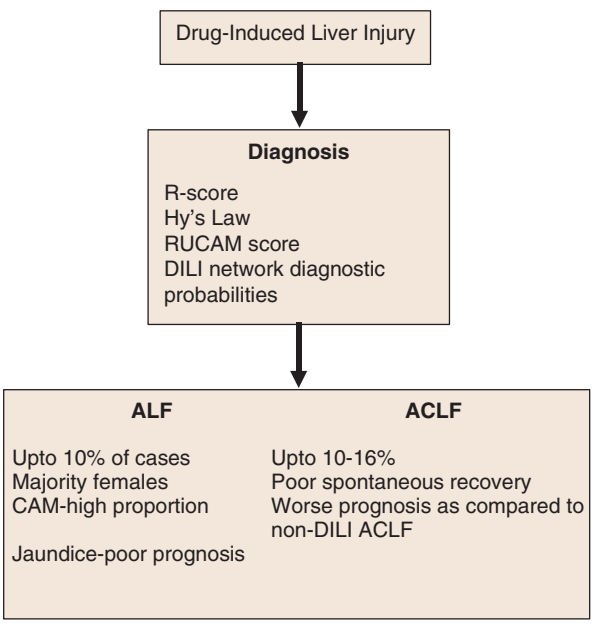


**Fig. 11.1** Drug-induced liver injury presenting as acute liver failure or acute-on chronic liver failure—salient features

Some of the cases of DILI-ALF have subacute presentation with jaundice to encephalopathy duration of less than 26 weeks, having a worse prognosis [9].

## Drug Induced Liver Injury Presenting as Acute Liver Failure

In acute liver failure study group (ALFSG) registry over period from 1998 to 2007, out of 1198 patients enrolled, 11.1% ($n = 133$) patients were DILI-ALF with majority being women (70.7%), and anti-microbials (46%) were most common causative drugs [10]. More recent published data from the ALFSG (from 1998 to 2015, 2646 hospitalised patients) shows upto 16% of patients developing ALF or acute liver injury (ALI) due to complementary and alternative medications (CAM) [11]. Overall, transplant free survival was poor in DILI-ALF but patients undergoing transplant fared well with overall survival of 66.2% [10]. Ten percent of patients with definitive or probable DILI among 899 patients of drug induced liver injury network (DILIN) registry underwent liver transplantation or had developed chronic liver injury [12]. A follow-up study of 2 years duration showed a total fatality rate of 9.8% among 1089 patients registered and DILI was the primary cause in 64% of patients [13]. The Swedish registry also shows similar proportion of patients with DILI-ALF with 9.2% of patients dying of liver failure or undergoing transplant over period of around 35 years (1970–2004) [14]. They also found that old age, high AST level, high bilirubin and cholestatic or mixed pattern of injury are responsible for non-recovery with transplant or death. The Spanish registry reported around 4% of patients developing ALF among 771 patients with DILI episodes [15], with predominantly hepatocellular pattern of injury and the new ratio (nR) model (Ratio of ALT or AST whichever is high/ULN of ALT or AST and ALP/ULN of ALP) identified patients during presentation, who develop ALF with 90% sensitivity.

Patients in DILIN registry who underwent liver transplant or died, azithromycin was the most common anti-microbial agent responsible for liver injury [12]. Prognosis is considered worse in patients who had jaundice at the time of presentation. Overall prognosis was worse in patients with underlying chronic liver injury (16% vs. 5.2%). Progression to DILI-ALF was more commonly seen in female sex and with hepatocellular damage [16]. Patients with advanced age, female sex, alcohol consumption, underlying chronic liver disease and genetic association are at increased risk of developing iDILI [17].

## Drug Induced Liver Injury Presenting as Acute-on-Chronic Liver Failure

Recently published data from the DILIN registry, divided the clinical presentation of patients with DILI as acute, chronic, acute on chronic and acute cholestatic liver failure. Acute presentation was seen in 64% and acute on chronic presentation seen

in 7% patients [13]. In a data based on 3132 ACLF patients from APASL-ACLF research consortium (AARC) prospectively enrolled, Deverabhavi and coworkers [18] reported 10.5% of patients having drugs as etiology for acute worsening. These patients had higher MELD and a significantly higher 90-day mortality as compared to non-drug ACLF. Among 1089 patients, 107 (9.8%) fatalities were seen over 2 years with primary cause of DILI in 64% of mortalities. DILI was more common in patients with NAFLD as compared to those with no NAFLD (0.8% vs. 0.2%), however the frequency of patients undergoing liver transplant or death was higher but not significant among NAFLD [19]. Similar finding of severe injury was seen in a large cohort of 195,334 azole users in population based study where presence of chronic liver disease resulted in a higher level of transaminases (hazard ratio-4.68, 95% CI, 3.68–5.94) and greater chance of severe liver injury [20].

## Population Based Study

Population based studies are reported from France, Iceland and the US. The annual incidence of DILI in population-based study from France estimated to be around 13.9 per 100,000 persons [21]. In a prospective study from Iceland, data were collected over a 2-year period and the crude annual incidence of DILI was estimated to be around 19.1 per 100,000 persons [22]. Prospective data from the DILIN registry reports annual incidence 2.7 cases per 100,000 population [23]. A population-based study retrospective cohort study of 15,353 diagnosed DILI patients conducted in Northern California [24], Lo Re et al. proposed a ALF predictive model on patients who were suspected to have DILI based on platelet count and total bilirubin level with an overall sensitivity of 91% and specificity of 76%, a good negative predictive value (99%) but a very low positive predictive value of 1% limiting its clinical utility (Table 11.1).

## Diagnostic Criteria

Clear cut diagnostic criteria are lacking in diagnosing DILI and the biochemical parameters taken into consideration for the diagnosis include elevation of serum bilirubin, transaminases or alkaline phosphatases, which are neither specific nor sensitive for particular liver injury. Both the Hy's law or the modified Hy's law and R score take into consideration these biochemical parameters. RUCAM scoring is elaborative, difficult to use in clinical practice and has many pitfalls. The DILIN structured expert opinion process correlated with the RUCAM score but had high interobserver variability [25]. The commonly used criteria are listed in Table 11.2.

**Table 11.1** Profile of patients of drug-induced liver injury and ALF or ACLF presentation in various registries

| | India (*N* = 313) Devarbhavi et al. [26] | Iceland (*N* = 96) Bjornsson et al. [22] | Spain (*N* = 446) Andrade et al. [16] | DILIN (*N* = 899) Chalasani et al. [12] |
|---|---|---|---|---|
| Sex | Males—58% | Females—56% | Males—51% | |
| Individual drugs (%) | Anti TB drugs—58%<br>AED—11%<br>Olanzapine—5.4% | Amox-Clav—22%<br>Diclofenac—6%<br>Azathioprine—4% | Amox-clav—12.8%<br>INH+ anti TB drugs—6.9% | Amox-clav—10%<br>INH—5.5% |
| Clinical presentation | FHF—higher in females (23% vs. 17%) | Jaundice—27% | FHF—4.03%<br>Jaundice—71% | 10% patients had DILI in pre-existing liver disease |

Anti TB drugs—Anti tubercular drugs, AED—anti epileptic drugs, Amox-clav—amoxycillin clavulanic acid, INH—Isoniazid, FHF—Fulminant Hepatic Failure

**Table 11.2** Definitions and diagnostic criteria's for drug-induced liver injury

| Criteria | Definition | |
|---|---|---|
| Hy's Law | ALT/AST > 3 X S. bilirubin > 2 X ULN in the absence of cholestatic features | Observation made by Hyman Zimmerman, with mortality upto 10% in cases of DILI |
| R-score | Ratio of ALT/ULN of ALT and ALP/ ULN of ALP | R>5= hepatocellular injury<br>R<2= Cholestatic injury<br>2<R<5= mixed injury |
| RUCAM score | Appropriate temporal relationship (time to onset, latency) +1 to +2<br>Clinical course after drug withdrawal (dechallenge). −2 to +3<br>Presence of DILI risk factor (age>55 years, alcohol, 0 to +3 Pregnancy)<br>Presence or absence of concomitant hepatotoxic drugs. 0 to −3<br>Search for and exclusion of nondrug causes −3 to +2<br>Prior reports/ information confirming the 0 to +2 Suspected drugs hepatotoxicity<br>Response to re-administration (rechallenge) −2 to +3 | |
| DILI network diagnostic probabilities | *Unlikely* = < 25% chance of drug responsible | Evidence of etiology other than drug is likely |
| | *Possible* = 25–49% chance that drug is responsible | Evidence for drug as cause is equivocal but likely |
| | *Probable* = 50–74% chance that drug is responsible | Preponderance of evidence links drug to the injury |
| | *Highly* = likely 75–95% chance that drug is responsible | Evidence of drug causing injury is clear and convincing but not definite |
| | *Definite* = >95% chance that drug is responsible | Evidence of drug as the reasonable cause if beyond doubt |

## Role of Liver Biopsy

Liver biopsy is not routinely required in the diagnosis of DILI. In patients with suspected auto-immune hepatitis, drug-induced auto-immune hepatitis, atypical presentation of acute or chronic hepatitis, acute-on-chronic liver failure, liver biopsy may be helpful in establishing the diagnosis or planning specific therapies, such as steroids [27]. Although, liver biopsy helps in making diagnosis it also helps in identifying mechanistic features of acute liver insult due to drugs. Studies based on liver biopsy samples have shown increased CD8+ cells in patients with idiosyncratic DILI, possibly due to intrahepatic production of antigens released from the drugs. Also, as compared to other causes of liver injury, these patients will have less population of natural killer cells, CD4+$T_H$ cells and B-cells [28]. DILI has varied histological presentation and the degree of injury correlates with outcome. Broadly, histological patterns are classified into acute and chronic hepatitis, acute and chronic cholestasis and cholestatic hepatitis. Also, degree of necrosis, fibrosis stage, macrovescicular and panacinar steatosis, cholangiolar cholestasis, ductular reaction, presence of neutrophils and portal venopathy too are associated with more severe disease while presence of eosinophils or granuloma is associated with mild to moderate liver injury [29]. In prospectively followed patients in DILIN registry, 363 patients of suspected DILI underwent liver biopsy and 7% of these patients had reported bile duct loss with likely immunologically mediated idiosyncratic pattern of liver injury. The area of bile duct loss in these patients was associated with poorer outcome with more severe cholestatic pattern of liver injury and chronic injury [30] (Fig. 11.2).

## Biomarkers

Idiosyncratic DILI is difficult to predict and has worse presentation and prognosis. The conventional laboratory markers for DILI include the alanine and aspartate transaminases (ALT and AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidases (GGT) and total bilirubin level (TBIL) with history of culprit medication intake. These markers lack sensitivity and specificity for early detection of DILI and also to detect DILI-ALF or DILI-ACLF. Various biomarkers are detected which detect DILI in much early phase of disease progression in animal model and few are in clinical phase. Broadly, biomarkers are divided into, liver injury markers, mechanistic markers and prognostic markers. MicroRNA-122 (miR-122) and glutamate dehydrogenase (GLDH) are specific newer biomarkers for liver injury and is based on the fact that the type of injury, either apoptotic or necrosis, will influence the percentage loss of hepatocytes and thereby ALT elevation (Table 11.3).

## Keratin 18

K18 is an intermediate filament providing structural support to the epithelial membrane. Apoptotic index (AI) is the ratio of capsase cleaved keratin 18 to total keratin 18 (ccK18: K18). During apoptosis, this filament is cleaved by capsases and ccK18 is released into the circulation. During necrosis, the whole of K18 is released and little of filament is cleaved [31]. The level of elevation of K18 and ccK18 is detected in the setting of liver failure and it is found that patients with acetaminophen overdose ($n$ = 78) meeting King's College Criteria (KCC) had a lower AI (less ccK18, more necrosis), increased FL-K18 (Full length K18) and had more severe liver injury and higher mortality or requirement for transplantation as compared to patients showing spontaneous recovery [32]. An important drawback is the presence

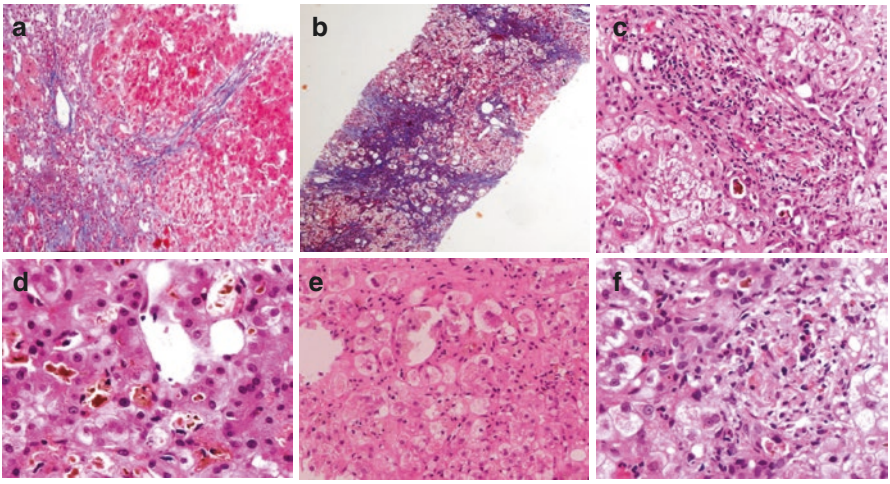


**Fig. 11.2** Biopsy features of drug-induced liver injury presenting as acute-on chronic liver failure and acute liver failure (**c** and **f**). (**a**) Biopsy showing fibrosis and large areas of necrosis (Masson's Trichrome, MT, ×100). (**b**) Biopsy showing increased portal, periportal fibrosis with bridges (arrow), liver parenchyma showing steatohepatitis (MT, ×100), (**c**) Portal area infiltrated by mixed inflammatory cells including fair number of neutrophils, at the periphery of expanded portal tract (arrow), ductular bile plugs noted (arrowhead). Hepatocytes are showing mosaic pattern of staining (star). Suggestive of acute injury. (Hematoxylin and eosin, H & E, ×400). (**d**) Hepatocytes showing cellular (arrowhead) and canalicular cholestasis (arrow) (H & E, ×400). (**e**) Hepatocytes showing mosaic pattern of staining (arrow) with enlargement and feathery changes. Scattered inflammatory cells also seen (H & E, ×400). (**f**) Area of confluent necrosis infiltrated by eosinophils and mononuclear cells (H & E, ×400). (Picture Courtesy- Dr Chhagan Bihari, Department of Pathology, Institute of Liver and Biliary Sciences, New Delhi, India)

**Table 11.3** Different biomarkers for drug induced liver injury with their significance in clinical setting

| Biomarker | Marker | Disease | Clinical significance |
|---|---|---|---|
| Micro RNA [36]<br>– miRNA- 122<br>– mi-RNA 192 | Liver damage and inflammation | APAP- acute liver injury, anti TB drugs | Correlated with peak ALT level<br>High level in patients meeting KCC<br>Elevated earlier than ALT |
| HMGB [32]<br>Full length keratin 18<br>Hyperacetylated HMGB<br>Caspase cleaved keratin 18 | Necrosis<br>Necrosis<br>Apoptosis<br>Necrosis/apoptosis | APAP overdose | Correlated with ALT level, Prothrombin time<br>High level has worse prognosis<br>Identified development of liver injury |
| GLDH, mitochondrial DNA, nuclear DNA [41] | Mitochondrial dysfunction, DAMP's | APAP overdose | Significantly higher in non-survivors |

*APAP* Acetaminophen, *GLDH* Glutamate dehydrogenase

of K18 not limited to the hepatic epithelial cells, concomitant muscle injury may cause a higher level of K18 levels.

## Glutamate Dehydrogenase

Glutamate dehydrogenase (GLDH) is a mitochondrial enzyme and is responsible for amino acid oxidation and is predominantly located in the pericentral region [33]. A clinical study on APAP-DILI showed that GLDH was better than ALT in predicting liver injury and release of GLDH into the serum suggest mitochondrial toxicity as the cause of liver injury [34]. The half-life of GLDH is less than that of ALT and thus predicted an ongoing better than ALT.

## MicroRNA

MicroRNA's are small, non-coding structural RNA's that help in the post transcriptional changes. Among the MicroRNA's, miR-122 constitute around 70% of the total hepatocyte released and is considered an ideal biomarker for liver injury. In cases of acetaminophen induced liver injury (AILI), miR-122 was elevated before the elevation of ALT, as detected in serum [35]. In another study, in patients with APAP-DILI, the elevation of miR-122 correlated with ALT elevation and also with patients who meet Kings Collecge Criteria (KCC) and had a worse clinical outcome as compared to those who showed a spontaneous resolution [36]. Urinary miRNA's has been identified to increase in rat models for DILI, however lack of specificity limits its clinical utility [37].

## High Mobility Group Box 1(HMGB1)

High mobility group box 1 (HMGB1), a chromatin binding nuclear protein and produced in the setting of DILI, is a product of necrotic cellular injury. It binds to Toll-like receptors (TLR), thereby acting as damage associated molecular pattern for liver injury. In a prospective cohort-based study, a panel of miRNA, HMGB and k18 was found to have prognostic value and helps in early risk stratification in patients with paracetamol poisoning [38]. miRNA isoforms are estimated using next-generation sequencing, with increase in particular isoform specific to a particular etiology, hence often termed as "liquid biopsies" [39].

## Ideal Biomarker

The mechanistic basis of DILI-ALF and DILI-ACLF is more related to idiosyncratic DILI pathway rather than intrinsic pathway. The activation of innate immune response against the liver's own cell result in the rapid development of clinical worsening along with production of damage associated molecular pattern or DAMP's [40]. Studies have shown a significant higher levels of mitochondrial degradation markers and DAMP's, especially GLDH, mitochondrial DNA and nuclear DNA levels in APAP-ALF non-survivors, significantly higher than survivors [41]. Estimation and correlation of DAMP's is required for early identification of DILI [42].

## HLA Genotypes Association

Genome-wide association studies (GWAS) have shown the exact dominant alleles which are associated with complex genetic diseases and is being tested for association of drugs with DILI [43]. Various HLA alleles are identified which are associated with increased risk of development of DILI with different class of drugs. Association of HLA-B*5701 and Flucloxacillin induced DILI is well established but around 13,500 persons need to be tested to prevent one case of DILI, limiting its clinical utility [43]. Abacavir, a nucleoside reverse transcriptase inhibitor, is associated severe hypersensitivity reactions and avoidance of this drug in patients with HLA-B*5701 positive allele, has markedly reduced prevalence of hypersensitivity [44]. Susceptibility of DILI related to co-amoxyclav is established with reports from nation-wide study based on HLA analysis, with data from UK showing increased HLA-DRB1*15 in 53 % of patients compared to treated patients (33%) and control population (30%), and a reduced HLA-DRB1*07 in only 9.8% of susceptible patients as compared to treated (35%) and population control (29%) [45]. Nitrofurantoin related hepatic injury study in 52 patients showed higher association

of HLA DR2 (56%) and HLA DRw6 (56%) in these patients as compared to controls [46]. Significant association is seen in patients with minocycline related liver injury and presence of HLA-B 35:02 [47].

## Etiological Presentation

### *Antitubercular Medication*

Isoniazid related hepatic failure was reported in 1975, when 114 patients on treatment for tuberculosis had hepatocellular liver injury and mortality rate upto 12.3%, with histology showing features of massive or sub-massive necrosis in these patients [48]. Data from India of consecutively followed 1223 patients, suggest that antitubercular medication is responsible for around 5.7% of all causes ALF. These patients had a younger age of presentation (32.9 ± 15.8 years), majority were women (70%) and had an hyperacute presentation (median icterus- encephalopathy interval was 4.5 (0–30) days). These patients had a higher mortality (67%) with poorer spontaneous recovery (33%). On multivariate analysis, patients with high bilirubin (>10.8 mg%), prolonged prothrombin time (>26 s) and grade 3 and more of encephalopathy (West Haven classification), had a poorer overall outcome [49]. Higher incidence of DILI due to anti-tubercular medications was seen in patients with chronic hepatitis B and C patients [50].

### *Antibiotics*

Antibiotics are an important non-acetaminophan cause of drug induced liver failure with higher proportion seen with nitrofurantoin, amoxycillin-clavulanic acid, trimethoprim-sulphamethaxole, minocycline among many different classes of antibiotics. The Spanish registry published a higher DILI-ALF with amoxycillin-clavulanic acid (12.8%) with hepatocellular injury as the predominant cause of liver injury [16]. Similar reports from UNOS database shows a 6% cause of DILI-ALF due to antibiotics with better overall transplant free recovery (upto 79%). Nitrofurantoin showed acute presentation (upto 80%) with hepatocellular injury as the predominant pattern of live injury [46].

In another case series of 25 cases due to minocycline related liver injury, females were predominantly affected with a prolonged latency of development of DILI (median duration—319 days). Hepatocellular injury seen in 76% of cases and 90% of these patients had ANA positivity. All the patients had favourable outcome and none required liver transplantation or died during follow-up [47].

### *NSAIDs*

Data from the Spanish and Latin American registry has shown NSAIDs causing idiosyncratic DILI in around 3–10% patients with ibuprofen as the most common NSAID agent seen in 29% of cases in Spanish registry and accounts for 17% of cases in Latin-American registry [51]. These patients have a worse outcome as compared to those with other NSAID agent.

### *Herbal and Dietary Supplements (HDS)*

HDS are currently recognised as leading cause of liver injury due to their wide availability and over the counter prescription. A single-center experience reports high proportion of CAM usage seen among 1666 cirrhotic patients with 68% of patients using CAM at some point of treatment, carrying a high risk for developing acute decompensation or ACLF [52]. AARC database registry recently reported CAM as implicating agent of DILI-ACLF in upto 71% of patients [18]. HDS was seen as cause of 15.5% of total DILI cases in prospectively enrolled cases in DILIN registry from 2004 to 2013. Out of 130 cases, 45 cases were due to bodybuilding HDS seen predominantly in young men and with prolonged median duration of jaundice and had favourable outcome as compared to non-bodybuilding HDS [53]. High proportion of patients in China and Japan develop DILI due to traditional medicines as well.

**Conclusions**

Non-viral or drugs and complimentary and alternative medicines can lead to acute or ACLF. In fact, idiosyncratic DILI induced ALF and ACLF, carry high mortality rates with limited chances of spontaneous recovery, requiring early liver transplantation. Progressive liver failure with or without features of acute portal hypertension in the form of ascites and development of renal dysfunction, and liver biopsy suggestive of significant loss of bile ducts are bad prognostic signs. There are no reliable biomarkers for early detection and prognostication of DILI. Efforts should be made in atypical cases to exclude underlying chronic liver diseases, such as non-alcoholic fatty liver disease, undisclosed alcohol associated liver disease or metabolic disorders. One needs to exclude at initial assessment, underlying advanced chronic liver disease as severe DILI may lead to ACLF with overall worse prognosis and poor transplant free survival. Newer therapeutic options such as plasma exchange and liver dialysis hold some promise, but early assessment for liver transplantation is advisable.

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# Chapter 12
# Acetaminophen syn. Paracetamol: Acute Liver Injury and Acute on Chronic Liver Failure with Case Analysis and Causality Assessment Using RUCAM


**Rolf Teschke**

**Key Concepts**
- The use of acetaminophen may affect the liver in various ways ranging from asymptomatic liver adaptation to the more severe acute liver injury including acute liver failure
- Acute liver injury is attributable to the rare idiosyncratic toxicity or to the more common intrinsic toxicity
- Overdosed acetaminophen causes intrinsic liver injury and acute liver failure confined by definition to cases without preexisting liver disease
- On theoretical grounds, an acute on chronic liver failure may exist but this question has not yet sufficiently been studied
- For all injury stages, the use of RUCAM helps assessing causality for acetaminophen and comedicated drugs or herbs

## Introduction

The cases of acute drug induced liver injury (DILI) and acute liver failure (ALF) due to overdosed acetaminophen (paracetamol) are still diagnostic challenges when confounding variables including risk factors prevail and causality assessment was

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insufficient. Experimental studies have helped clarify risk factors and mechanistic steps leading to the various types of injury [1–4]. These studies elucidated risk factors such as prolonged alcohol consumption [5, 6] that upregulates isoforms of the hepatic microsomal cytochrome P450 (CYP) mainly CYP 2E1, a major component of the microsomal ethanol-oxidizing system (MEOS) [7–10]. In addition, sufficient evidence exists that the enzymatic transformation of acetaminophen at high doses also proceeds mostly via CYP 2E1 [1–4]. Through this reaction, hepatotoxic metabolites are formed like *N*-acetyl-p-benzoquinone imine (NAPQI) that normally binds to hepatic glutathione if available in sufficient amounts but otherwise may initiate the liver injury [1, 2].

The involvement of CYP 2E1 in the toxic activation of acetaminophen led to the recent proposal of a specific pharmacotherapy option [2], in addition to the well established therapeutic measures using *N*-acetylcysteine (NAC) to increase the amounts of hepatic glutathione [11, 12], one of the most important liver antioxidant with a high potency of scavenging reactive oxidative species (ROS) [1–3]. The newly proposed pharmacotherapy option focuses on the use the proton inhibitor cimetidine in order to inhibit CYP 2E1, given intravenously by the physician first in contact with the intoxicated patient [2]. This regimen is commonly applied in patients with acute intoxication by carbon tetrachloride, which is also metabolized by CYP 2E1 [13–15]. Cimetidine reduces lethality and ameliorates liver injury in animals intoxicated by carbon tetrachloride [16] and acetaminophen [17]. Experimentally, cimetidine and NAC work synergistically in liver injury caused by acetaminophen, likely due to differences in molecular targets, cimetidine for CYP 2E1 and NAC for glutathione [2, 17]. In addition, intravenous administration of glucose in high amounts downregulates CYP and could be another therapeutic option in acute acetaminophen intoxication [2]. Overall, using cimetidine and glucose as additional therapeutic options in patients with acute acetaminophen intoxication is worth to being considered in future cases. A recent Cochrane analysis mentioned that there were no clinical trials of agents that inhibit CYP to decrease NAPQI production [18]. It also highlighted the paucity of the low quality level of the evidence due to the paucity of randomized clinical trials comparing different interventions for paracetamol overdose and their routes of administration, although it is worth mentioning that a single trial found activated charcoal as the best choice to reduce acetaminophen absorption from the gut [18].

Patients with non intentional acute acetaminophen intoxication often have a history of alcohol abuse associated with various stages of alcoholic liver disease (ALD) and might be more susceptible to acute DILI [19–22]. However, uncertainty still remains on the use of acetaminophen in patients with chronic liver disease (CLD) and what daily dose should be recommended for uneventful treatment [23]. To address some of these issues, a careful analysis of hepatic involvement at recommended doses or overdose is needed, and criteria of liver injury stages caused by acetaminophen should be helpful.

The focus of the current analysis is to compare patients with and without signs of a preexisting liver disease, who experienced acute DILI caused by acetaminophen that required a robust evaluation of causality for acetaminophen using RUCAM (Roussel Uclaf Causality Assessment Method).

**Definitions Liver Adaptation, Acute Liver Injury, and Acute Liver Failure**

Whenever synthetic drugs or phytochemicals as constituents of herbal drugs or herbal products enter the hepatocytes following intestinal absorption, interactions between these chemicals and the liver are unavoidable because the liver commonly takes care of their degradation or conjugation [2, 24]. The enzymatic processes are usually carried out without damaging the liver cells or their subcellular organelles and thus do not lead to abnormal liver tests (LTs) in the serum.

## *Liver Adaptation*

In some individuals under a drug therapy, small increases in aminotransferases and/or alkaline phosphatase (ALP) may be observed and disappears while on treatment, viewed as liver adaptation (Table 12.1). This is best explained by low graded metabolic actions of the drug within the liver cell and its organelles [2, 25]. By definition, thresholds of drug related liver adaptation are low for serum ALT (alanine aminotransferase) with <5 × ULN and for serum ALP (alkaline phosphatase) with <2 × ULN,

**Table 12.1** Criteria of liver adaptation and liver inury types

| Mechanistic background | Thresholds of liver tests | Criteria and characteristic features | Recommended description |
|---|---|---|---|
| Adaptive | ALT <5 × ULN<br>ALP <2 × ULN | • Develops by most drugs at recommended daily doses and by few drugs at overdose<br>• Presumably the majority of drugs have the potency of causing rare but clinically not apparent liver adaptation<br>• Normalization of liver tests is commonly observed whether drug use is discontinued or continued<br>• With continuation of drug use, there is a rare risk of transition to idiosyncratic DILI | Liver adaptation |
| Idiosyncratic | ALT ≥5 × ULN<br>ALP ≥2 × ULN | • Caused at recommended daily doses, cessation of drug use is obligatory<br>• Most drugs cause rare idiosyncratic DILI, often called DILI in short if not specified<br>• Risk of acute liver failure | Acute idiosyncratic DILI |
| Intrinsic | ALT ≥5 × ULN<br>ALP ≥2 × ULN | • Emerges soon after acute drug overdose<br>• Only a few drugs are known for causing intrinsic DILI, antidotes may be available<br>• Risk of acute liver failure | Acute intrinsic DILI |

*ALP* alkaline phosphatase; *ALT* alanine aminotransferase; *DILI* drug induced liver injury; *ULN* upper limit of normal

where ULN is the upper limit of normal [25]. These thresholds are below the corresponding values of acute DILI (Table 12.1), allowing for a clear differentiation between liver adaptation and acute liver injury [26, 27]. In the clinical context, patients with drug associated liver adaptation commonly have no symptoms or signs such as jaundice. Clinical course is uneventful with good prognosis and regression of the increased LTs even under continued use of the suspected drug [25].

## *Acute Liver Injury*

Whatever the mechanism of liver injury, idiosyncratic or intrinsic, an acute liver injury (ALI) is defined by serum activities of ALT of ≥5 × ULN and ALP ≥2 × ULN (Table 12.1) [25–27]. Among 46,266 patients with RUCAM based DILI and ALI, some were asymptomatic but most described a broad spectrum of clinical signs [25]. Variably reported symptoms were fatigue, loss of appetite, weight loss, vomiting, abdominal discomfort or pains in the right upper quadrant, dark urine, light colored stool, pruritus, or even jaundice. These symptoms are not specific to DILI, found in many other liver diseases, and have therefore to be differentiated from alternative causes in order to prevent incorrect diagnoses.

## *Acute Liver Failure*

In rare instances, ALI by drugs evolves to acute liver failure (ALF), characterized by laboratory results of serum ALT activities of 10–100 × ULN and INR ≥2, with clinical features of hepatic encephalopathy, jaundice and bleeding, with less than 26 weeks of illness without preexisting chronic liver disease (Table 12.2) [28–30]. This high-mortality condition may require early liver transplantation to prevent death [28, 29]. Many other causes of ALF are known, among which drugs must be identified, problems that are not sufficiently considered in large ALF case series.

## *Acute on Chronic Liver Failure*

Acute on chronic liver failure (ACLF) is a specific syndrome requiring also LT thresholds (Table 12.2) and is otherwise variably defined as an acute decompensation of a chronic liver disease, which may include or exclude a compensated cirrhosis as preexisting liver disease [31–47]. A superimposed acute liver injury

**Table 12.2** Definition of acute liver failure and acute-on-chronic liver failure by drugs

| Mechanistic background | Thresholds of liver tests | Criteria and characteristic features | Recommended description |
|---|---|---|---|
| Severe, acute liver injury in a healthy individual | ALT >10 × ULN<br>ALP >2 × ULN | • Develops in a setting of severe, acute idiosyncratic liver injury or intrinsic liver injury of an individual with a normal healthy liver.<br>• The severity of the liver injury reflects clinical signs and laboratory parameter of an acute liver failure.<br>• Hepatic encephalopathy, jaundice, coagulopathy (INR ≥2.0), and serum ALT activities of 10 to 100 × ULN are among the most characteristic features of the acute liver failure. | Acute liver failure (ALF) |
| Severe, acute liver injury in a patient with known chronic liver disease | ALT >10 × ULN<br>ALP >2 × ULN | • Develops from a serious and acute idiosyncratic liver injury or intrinsic liver injury, superimposed on a chronic liver disease, and leads finally to acute liver failure through an exacerbation of a pre-existing chronic liver disease including compensated cirrhosis of the patient that is causally unrelated to the current drug use.<br>• Clinical and laboratory signs of liver failure are similar to those described above, but in addition clinical signs of the decompensated chronic liver disease including esophageal varices and ascites due due to portal hypertension are diagnostic hallmarks. | Acute on chronic liver failure (ACLF) |

*ALP* alkaline phosphatase; *ALT* alanine aminotransferase; *INR* international normalized ratio; *ULN* Upper limit of normal

causally unrelated to the chronic liver disease leads to chronic liver failure, mostly due to transition of the compensated cirrhosis to a decompensated stage. For sake of clarity, a chronic liver disease is commonly assumed if the disease lasts for 6 months or longer whatever the cause, may include alcoholic liver disease (ALD) and chronic infections by HBV (hepatitis B virus), HCV (hepatitis C virus), while multiple causes of the acute insult are known such as sepsis or blood loss due to esophageal bleeding. Of note and as correctly stated in a clinical setting and in some publications, ACLF may commonly be misdiagnosed as ALF and erroneously included in the ALF cohort, if strict criteria of ACLF were not followed [47]. This certainly impedes diagnostic accuracy and valid clinical conclusions.

## *RUCAM Based Causality Assessment*

Assessing causality for individual drugs in patients with suspected DILI requires a robust causality assessment method (CAM) such as RUCAM [48, 49], now best in its updated RUCAM version [26] that clearly outperforms other CAMs [26, 50–52]. Due to recognized specificities (Table 12.3) as discussed in various publications [25, 26, 50–53], RUCAM will confidently ensure that a suspected DILI case is a real DILI [53]. This is also in support of its use in 46,266 DILI cases assessed for causality by RUCAM and published from 2014 to early 2019 [25], in addition to many other cases assessed between 1993 and 2014 [26]. Even in suspected liver injury cases associated with the use of acetaminophen, it is recommended to use RUCAM to make sure that other concomitant agents are properly excluded, expanding approaches in previous cases published earlier [2].

Details how to apply the updated RUCAM have been published previously [26, 27]. Briefly, thresholds for ALT and ALP are essential (Tables 12.1 and 12.2) [26], as

**Table 12.3** Advantages and limitations of RUCAM

| |
|---|
| **Advantages of RUCAM** |
| • Worldwide experience and use in more than 46,266 DILI cases and many HILI cases, published in recognized scientific journals |
| • Worldwide application and appreciation: international registries, regulatory agencies and pharma companies |
| • Prospective use |
| • Clinical approach |
| • User-friendly and cost-saving method |
| • Effective use without the need of a subjective expert panel |
| • Timely use at the bedside of the patient |
| • Clearly defined key items of clinical features and course |
| • Full consideration of comedications and alternative causes |
| • Consideration of prior known hepatotoxicity |
| • Use of specifically defined criteria of unintentional reexposure |
| • Quantification of unintentional reexposure results |
| • Hepatotoxicity specific method |
| • Structured and quantitative liver related method |
| • Individual scoring system of all key items facilitating objective assessment |
| • Transparent documentation of case data and causality assessment details |
| • Works well even with incomplete data |
| • Prepared for reevaluation by peers |
| **Limitations of RUCAM** |
| • Poor results if users miss rules required for RUCAM |
| • RUCAM was not designed for suspected chronic DILI, which is mostly an unrecognized preexisting liver disease |

Adapted from previous reports [26, 50, 51]. Abbreviations: *DILI* drug induced liver injury; *HILI* herb induced liver injury; *RUCAM* Roussel Uclaf Causality Assessment Method

well as the classification of the liver injury [26] because RUCAM provides two different scales, one for the hepatocellular injury (Table 12.4) and one for the cholestatic or mixed liver injury (Table 12.5) [26]. The scores of each key element (Tables 12.4 and 12.5) are summed up providing a final score with five gradings for the relationship between the suspected drug and the liver injury: score ≤ 0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; ≥9, highly probable (Tables 12.4 and 12.5) [26].

**Table 12.4** RUCAM worksheet for hepatocellular injury

| Suspected product | Date | |
|---|---|---|
| Items for hepatocellular injury | Score | Result |
| **1. Time to onset from the beginning of the drug/herb** | | |
| • 5–90 days (rechallenge: 1–15 days) | +2 | ☐ |
| • <5 or >90 days (rechallenge: >15 days) | +1 | ☐ |
| Alternative: Time to onset from cessation of the drug/herb | | |
| • ≤15 days (except for slowly metabolized chemicals: >15 days) | +1 | ☐ |
| **2. Course of ALT after cessation of the drug/herb** | | |
| **Percentage difference between ALT peak and ULN** | | |
| • Decrease ≥50% within 8 days | +3 | ☐ |
| • Decrease ≥50% within 30 days | +2 | ☐ |
| • No information or continued drug use | 0 | ☐ |
| • Decrease ≥50% after the 30th day | 0 | ☐ |
| • Decrease <50% after the 30th day or recurrent increase | −2 | ☐ |
| **3. Risk factors** | | |
| • Alcohol use (current drinks/day: >2 for women, >3 for men) | +1 | ☐ |
| • Alcohol use (current drinks/day: ≤2 for women, ≤3 for men) | 0 | ☐ |
| • Age ≥55 years | +1 | ☐ |
| • Age <55 years | 0 | ☐ |
| **4. Concomitant drug(s)/herb(s)** | | |
| • None or no information | 0 | ☐ |
| • Concomitant drug/herb with incompatible time to onset | 0 | ☐ |
| •Concomitant drug/herb with time to onset 5–90 days | −1 | ☐ |
| • Concomitant drug/herb known as hepatotoxin and with time to onset 5–90 days | −2 | ☐ |
| • Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test) | −3 | ☐ |
| **5. Search for alternative causes** | Tick if negative | Tick if not done |
| **Group I (7 causes)** | | |
| • HAV: Anti-HAV-IgM | ☐ | ☐ |
| • HBV: HBsAg, anti-HBc-IgM, HBV-DNA | ☐ | ☐ |
| • HCV: Anti-HCV, HCV-RNA | ☐ | ☐ |
| • HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA | ☐ | ☐ |
| • Hepatobiliary sonography/Doppler/CT/MRC | ☐ | ☐ |
| • Alcoholism (AST/ALT ≥2) | ☐ | ☐ |
| • Acute recent hypotension history (particularly if underlying heart disease) | ☐ | ☐ |

(continued)

**Table 12.4** (continued)

| Suspected product | Date | |
|---|---|---|
| Items for hepatocellular injury | Score | Result |
| **Group II (5 causes)** | | |
| • Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases | ☐ | ☐ |
| • Infection suggested by PCR and titer change for | | |
| • CMV (anti-CMV-IgM, anti-CMV-IgG) | ☐ | ☐ |
| • EBV (anti-EBV-IgM, anti-EBV-IgG) | ☐ | ☐ |
| • HSV (anti-HSV-IgM, anti-HSV-IgG) | ☐ | ☐ |
| • VZV (anti-VZV-IgM, anti-VZV-IgG) | ☐ | ☐ |
| **Evaluation of groups I and II** | | |
| • All causes-groups I and II—reasonably ruled out | +2 | ☐ |
| • The 7 causes of group I ruled out | +1 | ☐ |
| • 6 or 5 causes of group I ruled out | 0 | ☐ |
| • Less than 5 causes of group I ruled out | −2 | ☐ |
| • Alternative cause highly probable | −3 | ☐ |
| **6. Previous hepatotoxicity of the drug/herb** | | |
| • Reaction labelled in the product characteristics | +2 | ☐ |
| • Reaction published but unlabeled | +1 | ☐ |
| • Reaction unknown | 0 | ☐ |
| **7. Response to unintentional reexposure** | | |
| • Doubling of ALT with the drug/herb alone, provided ALT below 5 × ULN before reexposure | +3 | ☐ |
| • Doubling of ALT with the drug(s)/herb(s) already given at the time of first reaction | +1 | ☐ |
| • Increase of ALT but less than ULN in the same conditions as for the first administration | −2 | ☐ |
| • Other situations | 0 | ☐ |
| Total score | | |

Adapted from a previous report on the updated RUCAM [26]. The above items specifically refer to the hepatocellular injury rather than to the cholestatic or mixed liver injury. Abbreviations: *ALT* alanine aminotransferase; *AST* Aspartate aminotransferase; *CMV* cytomegalovirus; *CT* computer tomography; *EBV* Epstein Barr virus; *HAV* hepatitis A virus; *HBc* hepatitis B core; *HBsAg* hepatitis B antigen; *HBV* hepatitis B virus; *HCV* hepatitis C virus; *HEV* hepatitis E virus; *HSV* Herpes simplex virus; *MRC* magnetic resonance cholangiography; *ULN* upper limit of normal; *RUCAM* Roussel Uclaf Causality Assessment Method; *VZV* Varicella zoster virus. Total score and resulting causality grading: ≤0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; ≥9, highly probable

## Variability of Acetaminophen Use and Liver Test Abnormalities

Annual acetaminophen (paracetamol) sales variably differ from one country to the other. For instance, in Europe it ranges from under 200 tons in Greece and Portugal to 6300 tons in the UK and 10,000 tons in France; on a per capita basis the range is

**Table 12.5** RUCAM worksheet for cholestatic or mixed liver injury

| Suspected product | Date | |
|---|---|---|
| Items for cholestatic or mixed liver injury | Score | Result |
| **1. Time to onset from the beginning of the drug/herb** | | |
| • 5–90 days (rechallenge: 1–90 days) | +2 | ☐ |
| • <5 or >90 days (rechallenge: >90 days) | +1 | ☐ |
| Alternative: Time to onset from cessation of the drug/herb | | |
| • ≤30 days (except for slowly metabolized chemicals: >30 days) | +1 | ☐ |
| **2. Course of ALP after cessation of the drug/herb** | | |
| Percentage difference between ALP peak and ULN | | |
| • Decrease ≥50% within 180 days | +2 | ☐ |
| • Decrease <50% within 180 days | +1 | ☐ |
| • No information, persistence, increase, or continued drug/herb use | 0 | ☐ |
| **3. Risk factors** | | |
| • Alcohol use current drinks/day: >2 for women, >3 for men) | +1 | ☐ |
| • Alcohol use (current drinks/day: ≤2 for women, ≤3 for men) | 0 | ☐ |
| • Pregnancy | +1 | ☐ |
| • Age ≥55 years | +1 | ☐ |
| • Age <55 years | 0 | ☐ |
| **4. Concomitant use of drug(s)/herb(s)** | | |
| • None or no information | 0 | ☐ |
| • Concomitant drug/herb with incompatible time to onset | 0 | ☐ |
| • Concomitant drug/herb with time to onset 5–90 days | −1 | ☐ |
| • Concomitant drug/herb known as hepatotoxin and with time to onset 5–90 days | −2 | ☐ |
| • Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test) | −3 | ☐ |
| **5. Search for alternative causes** | Tick if negative | Tick if not done |
| Group I (7 causes) | | |
| • HAV: Anti-HAV-IgM | ☐ | ☐ |
| • HBV: HBsAg, anti-HBc-IgM, HBV-DNA | ☐ | ☐ |
| • HCV: Anti-HCV, HCV-RNA | ☐ | ☐ |
| • HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA | ☐ | ☐ |
| • Hepatobiliary sonography/Doppler/CT/MRC | ☐ | ☐ |
| • Alcoholism (AST/ALT ≥2) | ☐ | ☐ |
| • Acute recent hypotension history (particularly if underlying heart disease) | ☐ | ☐ |
| Group II (5 causes) | | |
| • Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases | ☐ | ☐ |
| • Infection suggested by PCR and titer change for | | |
| • CMV (anti-CMV-IgM, anti-CMV-IgG) | ☐ | ☐ |
| • EBV (anti-EBV-IgM, anti-EBV-IgG) | ☐ | ☐ |

(continued)

**Table 12.5** (continued)

| Suspected product | Date | |
|---|---|---|
| Items for cholestatic or mixed liver injury | Score | Result |
| • HSV (anti-HSV-IgM, anti-HSV-IgG) | ☐ | ☐ |
| • VZV (anti-VZV-IgM, anti-VZV-IgG) | ☐ | ☐ |
| Evaluation of group I and II | | |
| • All causes—groups I and II—reasonably ruled out | +2 | ☐ |
| • The 7 causes of group I ruled out | +1 | ☐ |
| • 6 or 5 causes of group I ruled out | 0 | ☐ |
| • Less than 5 causes of group I ruled out | −2 | ☐ |
| • Alternative cause highly probable | −3 | ☐ |
| **6. Previous hepatotoxicity of the drug/herb** | | |
| • Reaction labelled in the product characteristics | +2 | ☐ |
| • Reaction published but unlabeled | +1 | ☐ |
| • Reaction unknown | 0 | ☐ |
| **7. Response to unintentional reexposure** | | |
| • Doubling of ALP with the drug/herb alone, provided ALP below 2 × ULN before reexposure | +3 | ☐ |
| • Doubling of ALP with the drugs(s)/herbs(s) already given at the time of first reaction | +1 | ☐ |
| • Increase of ALP but less than ULN in the same conditions as for the first administration | −2 | ☐ |
| • Other situations | 0 | ☐ |
| **Total score** | | |

Adapted from a previous report on the updated RUCAM [26]. The above items specifically refer to the cholestatic or mixed liver injury rather than to the hepatocellular injury. Abbreviations: *ALP* alkaline phosphatase; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *CMV* cytomegalovirus; *CT* computer tomography; *DILI* drug induced liver injury; *EBV* Epstein Barr virus; *HAV* hepatitis A virus; *HBc* hepatitis B core; *HBsAg* hepatitis B antigen; *HBV* hepatitis B virus; *HCV* hepatitis C virus; *HEV* hepatitis E virus; *HSV* Herpes simplex virus; *MRC* magnetic resonance cholangiography; *ULN* upper limit normal; *RUCAM* Roussel Uclaf Causality Assessment Method; *VZV* Varicella zoster virus. Total score and resulting causality grading: ≤0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; ≥9, highly probable

4–5 to 30–50 tons per million residents [54]. High amounts are likely consumed also in the US but lack of market transparency including over-the-counter (OTC) sales and large numbers of variable products containing acetaminophen and other compounds additionally impede presentation of valid data in tons in the US. However, high numbers of cases with liver failure in the US are evident [28, 29, 40] and in support of their high frequency of acetaminophen consumption.

Another concern of variability focuses on the heterogeneity of the study cohorts consisting of patients who used variable amounts of acetaminophen and experienced various stages of liver involvement, ranging from liver adaptation to acute on chronic liver failure, with preexisting liver disease such as cirrhosis (Tables 12.1 and 12.2) [2, 18–23]. The variable doses and associated uncertainties explain the large range of abnormal LTs observed following acetaminophen use.

Analyzing the effect of acetaminophen on the liver requires definition of the maximum recommended dose for safe use, limited to 4 g daily for the general population without an alcohol problem [2, 23, 55, 56]. It has also been shown that acetaminophen at a single dose of 325–500 mg will not cause DILI in patients with an alcohol problem or known ALD [1]. Using only ALT rather than ALP as primary parameter of liver involvement for the subsequent evaluation will add to transparency and clarity, although both parameters are essential for causality assessment by the updated RUCAM.

## *Liver Adaptation to Acetaminophen Use*

Criteria of liver adaptation in the sense of tolerance have been well established (Table 12.1) with details discussed in the literature [2, 25, 57]. The most important criterion is ALT <5 × ULN whatever the dose is taken by the patient.

### Cohort Studies

A randomized controlled trial in healthy adults receiving 4 g of acetaminophen daily for 14 days reported variable ALT elevations with small increases in a subgroup compatible with liver adaptation, because among 106 participants, 71 individuals had ALT values ≤5 × ULN (Table 12.6), corresponding to 67% [55]. These data were obtained in the absence of any confounding factors and are similar to previous reports with variable study designs showing minor or no ALT elevations [65–70]. Consensus exists that these minor transient increases are of little clinical relevance [2, 23, 55], also observed during treatment with other drugs [25, 55, 57].

Another large case series from Thailand included several patients with acetaminophen overdose who qualified for liver adaptation in addition to cases considered as intrinsic liver injury (Table 12.6) [58].

### Confounding Variables

The randomized controlled trial in healthy adults receiving 4 g of acetaminophen daily was designed to eliminate *a priori* all potential confounders [55]. For instance, participants were considered healthy by measures including clinical and laboratory tests, hepatitis B surface antigen results, and hepatitis C antibody tests, and probands on concomitant medications were excluded. To minimize extraneous sources of variability, all participants were confined to clinical pharmacology units during the study, received standardized catered meals, and had no access to food or beverages other than those provided, meaning also exclusion of beverages containing alcohol. Causes of ALT elevation other than acetaminophen were not evident. Finally, ALT values that increased during acetaminophen use dropped after

discontinuation, suggesting the drug as cause for the abnormal LT values. Overall, prospective trials or studies like the one on acetaminophen are highly appreciated and certainly considered as gold standard for future projects.

Cases of liver adaptation were also described in cohorts with overdosed acetaminophen (Table 12.6) [58]. However, these cases with low or even normal ALT values may not reflect the natural course of the intoxication but are possibly confounded by the appreciated rapid antidote treatment within a median of 2 h after initial presentation, which retards liver injury development and moves cases from the category of intrinsic liver injury down to liver adaptation.

**Table 12.6** Selected reports on liver involvement in connection with acetaminophen use considering ALT values and various causality assessment methods

| Liver involvement | Cases (n) | Strong causality assessment | Cohort details and comments | First author |
|---|---|---|---|---|
| Liver adaptation ALT <5 × ULN | 71 | None, not required due to perfect study design | Careful prospective study on cases with recommended doses of acetaminophen, without confounders | Watkins, 2006 [55] |
| | 27 | None, but for future cases the updated RUCAM was recommended | Large scale study on acetaminophen overdose including few cases with liver adaptation | Pholmoo, 2019 [58] |
| Acute idiosyncratic DILI ALT ≥5 × ULN | 35 | None, not required due to perfect study design | Trial with a priori exclusion of potential confounding variables and risk factors | Watkins, 2006 [55] |
| | 7 | Done, using the RUCAM in its original version [48] | High frequency of comedication of potentially hepatotoxic drugs | Sabaté, 2011 [56] |
| | 1 | Done, using the updated RUCAM [26] | Clear case data without confounding variables | Teschke, 2018 [2] |
| Acute intrinsic DILI ALT ≥5 × ULN | 7 | Done, using the RUCAM in its updated version [26] | The top RUCAM based causality grading was achieved in all cases | Vliegenthart, 2017 [59] |
| | 250 | None | Large retrospective study that included also 912 cases of aminophen ALF | Rubin, 2018 [60] |
| | 14 | None, but for future cases use of UCAM recommended in its updated version | Inclusion of cases with severe injury and ALT >10 × ULN rather than the commonly used threshold of ALT ≥5 × ULN | Pholmoo, 2019 [58] |
| | 1 | None | One case as example;online many references of other case reports | LiverTox, 2019 [61] |

**Table 12.6** (continued)

| Liver involvement | Cases (n) | Strong causality assessment | Cohort details and comments | First author |
|---|---|---|---|---|
| Acute liver failure (ALF) ALT >10 × ULN | 275 | None | Prospective study with interesting data despite lack of a robust formal causality assessment like RUCAM, alcohol use was found as confounder | Larson, 2005 [62] |
| | 113 | None | Prospective study with missing of a formal causality assessment, providing evidence that mortality does not increase above a certain threshold | Gregory, 2010 [63] |
| | 344 | None | Retrospective study without using a formal causality assessment method but alternative causes have reportedly been exlduded. Focus is on epidemiology aspects. overdose pattern, and outcome | Craig, 2011 [64] |
| | 912 | None | Cases as part of a large retrospective study that also included 250 cases of intrinsic liver injury | Rubin, 2018 [60] |
| | 1 | None | One case as example; online many references of other case reports | LiverTox, 2019 [61] |
| | 3 | None | Retrospective study with inclusion of various other subgroups | Pholmoo, 2019 [58] |
| Acute on chronic liver failure (ACLF) ALT >10 × ULN | Unknown | Not available | Not available from any prospective ALF study cohort because potential cases of ACLF had to be excluded a priori along meeting requiremments of a strict study protocol | Larson, 2005 [62] Gregory, 2010 [63] |
| | Unknown | Not available | Not available from any retrospective ALF study cohort because potential cases of ACLF had to be exluded due to missing criteria of ACLF | Craig, 2011 [64], Rubin, 2018 [60], Pholmoo, 2019 [58] |

Note: For the item of strong causality assessment, an objective formal method like the original RUCAM [48] or the updated RUCAM [26] is required that is liver specific and quantifies the final causality grading for aminophen by summing up individual scores of key elements, by definition this excludes any subjective method of global introspection, not based on individually scored key elemenets [26, 51, 52]. Abbreviations: *DILI* drug induced liver injury; *RUCAM* Roussel Uclaf Causality Assessment Method

## *Acute Idiosyncratic Acetaminophen Liver Injury*

Clearly defined with ALT ≥5 × ULN and use of acetaminophen as recommended, acute idiosyncratic acetaminophen liver injury can easily be diagnosed and differentiated from a liver adaptation and intrinsic liver injury (Table 12.1).

### Cohort Studies and Single Case Reports

Widely neglected is the topic of acute idiosyncratic liver injury causally related to acetaminophen used in recommended daily doses of 4 g [2, 55, 56], as opposed to the more frequent intrinsic liver injury due to acetaminophen overdose [11, 12, 18–23]. In the study quoted as gold standard above, idiosyncratic liver injury with ALT >5 × ULN was found in 35 out of 106 participants corresponding to 33% following daily use of 4 g acetaminophen (Table 12.6), with 8 of these 35 participants experiencing severe injury with ALT >8 × ULN [55]. Comparing these figures reveals that two thirds of the overall cohort consisting of 106 participants showed signs of liver adaptation and one third experienced idiosyncratic liver injury [55]. This leads to the conclusion that 4 g acetaminophen daily commonly considered as safe does not hold in consumers even without risk factors, because in a subgroup of healthy consumers 4 g of acetaminophen causes moderate idiosyncratic liver injury and in a minority even severe injury.

A prospective population based study from Spain reported on acetaminophen use in therapeutic dosages and acute liver injury with causality assessment by RUCAM. In a case series consisting of initially 32 patients without an alcohol problem [56]. Six out of these 32 cases were not included in the following evaluation step because of RUCAM based causality gradings for acetaminophen classified them as unlikely or unrelated. In the remaining 26 cases, all of them with comedication, 19 were excluded from further analysis because causality assessment by RUCAM scored the concomitant drugs equal to or higher than acetaminophen, leaving 7 cases with RUCAM gradings lower than that of acetaminophen [56]. Consequently, specific characteristic case details of the finally included 7 patients were described who experienced idiosyncratic liver injury due to the use of acetaminophen in therapeutic daily doses ranging from 0.5 to 3.25 g. The pattern of use was variable, ranging from once a week for years, daily from 1 day up to 22 days, and a latency period from last use until onset was reported as a narrow range from 11 to 13 days [56]. Neglecting such a long latency period in patients with unknown increased LTs and lacking details of their past medical history may impair identifying acetaminophen as causative chemical [2]. Findings of clinical importance in idiosyncratic liver injury by acetaminophen are immunological signs of rash, eosinophilia, arthralgia, fever, and thrombocytopenia [56]. The 7 cases had been assessed for acetaminophen causality using RUCAM and were graded as probable in four cases and in three cases only as possible that limits somewhat the strength of the conclusions of the study. Case data were derived from a prospective cohort study of the Spanish Group for the Study of Drug-induced Liver Disease [71].

Another case of a patient from China was reported [2]. She experienced idiosyncratic liver injury after use of acetaminophen in recommended doses, published with case details, a case narrative, and a causality assessment applying a RUCAM working sheet specifically for this patient by using the updated RUCAM. This case was assessed as probable based on a RUCAM sore 8 [2] and was originally published within a case cohort study [30].

#### Confounding Factors

In the prospective US study, as a randomized controlled trial in healthy volunteers known confounding variables were excluded [55]. In the Spanish study, patients with alcohol problem as possible confounding variable were not included in the study, and cases with comedication had been handled appropriately using RUCAM. However, some issues remained as a few patients used small amounts of alcohol and only 4 out of the finally included 7 cases were assessed as probable causality grading for acetaminophen [56]. In the patient from China no confounding variables were documented [2].

### *Acute Intrinsic Acetaminophen Liver Injury*

Due to paracetamol overdose, acute intrinsic liver injury with ALT ≥5 × ULN (Table 12.1) is well described in the literature but distinction from its idiosyncratic form or liver adaptation was sometimes missed.

#### Cohort Studies and Single Case Reports

A small study cohort consisting of 7 patients with intrinsic liver injury by acetaminophen and high ALT values ranging from 1103 to 10.453 U/L was reported in the UK [59]. Causality for acetaminophen was assessed using the updated RUCAM, with causality gradings that were reported as definite [59], although the highest grading of the updated RUCAM is highly probable and not definite [26]. The UK study is also one of the few reports that used the updated RUCAM for analysis of DILI as compared to diagnostic biomarkers such as microRNA-122, now even measurable in the capillary blood [59]. Although microRNA-122 is considered by many experts in the field as a good parameter for liver injury, it is not specific to DILI by acetaminophen because the parameter is also found in DILI caused by other hepatotoxins such as nitrofurantoin [59]. It is also clear that microRNA-122 and other biomarkers cannot replace RUCAM in establishing the diagnosis of DILI [25, 72].

A recent large retrospective study reported details of 184 adult patients from Bangkok who experienced intrinsic liver injury by overdosed acetaminophen [58]. Overdose was mostly intentional in 90.8% of the study cohort with reported median

doses of 10.5 g, ranging from 4.5 to 15 g. Overall, 15.6% developed mild liver injury with ALT >3 × ULN, 6.4% experienced severe liver injury with ALT >10 × ULN, and 3 patients developed ALF. These data provide a rough estimate of the percentage distribution of liver injury stages that clinicians may likely be confronted with when treating patients with acetaminophen overdose [58]. Interestingly, data have been interpreted being in accordance with data from Western countries, with minor differences in the prevalence of the female gender and the unintentional overdoses [58] in reference to a recent report [73].

A large study of the US Acute Liver Failure Study Group on acetaminophen-induced acute liver failure focused on case details of women and included cases of acute intrinsic liver jury that were not separately characterized as a subgroup from overall ALF cases (Table 12.6) [60]. This report expanded earlier studies but failed to use RUCAM to establish causality for acetaminophen.

A single case with typical features of acute intrinsic liver injury is described as an example (Table 12.6), and many references of other case reports are provided online by LiverTox [61]. Unfortunately, most cases were not assessed with RUCAM for acetaminophen, a problem known also for other DILI cases provided online by LiverTox, as analyzed and controversially discussed recently [25, 53, 74, 75].

### Confounding Variables

As in any retrospective study, confounding variables are also found in the study from Thailand [58]: alcohol use, preexisting cirrhosis, comedication, lacking distinction between liver adaptation and intrinsic liver injury by threshold based criteria, and lack of a formal causality assessment using for instance the updated RUCAM, most of these confounding items have critically been discussed as limitation of the study [58].

Major confounding variables were present in a retrospective study of patients during their hospital stay when they received more than 4 g of acetaminophen in one dose on at least 1 day [76]. Of 43,761 admissions involving acetaminophen administration, the recommended maximum cumulative doses exceeded in 1119 patients (2.6%). ALT levels were checked in this study cohort within 14 days following acetaminophen exposure in a minority of 3.1% of the patients. Therefore, the authors were unable to quantify the incidence of ALT level elevation in this small study population, let alone establish a causal relationship between acetaminophen use and the liver test abnormalities. The authors of this report [76] discussed previous prospective studies showing 25% to 40% of ALT level elevations to at least twice the ULN in healthy volunteers under acetaminophen of 4 g daily [55, 77]. Overall, the validity of the study results [76] are disputable due to major confounding variables: (1) paucity of ALT level monitoring; (2) incomplete information available in hospital charts; (3) retrospective study design; and (4) lack of a formal causality analysis to assess the association between acetaminophen exposure and elevations of ALT levels [76]. A study like this one is highly problematic due to major confounding variables that could have been prevented by a correct prospective study design.

## *Acute Liver Failure Caused by Acetaminophen*

Reports on ALF commonly follow the inclusion criteria of ALT 10–100 × ULN, INR ≥2, hepatic encephalopathy, jaundice, bleeding, and illness less than 26 weeks, not allowing the inclusion of patients with preexisting chronic liver disease, an essential exclusion criterion of ALF but prerequisite to diagnose acute on chronic liver failure (ACLF) (Table 12.2). More frequently described in Western countries as compared to the Asian region [58], the high number of publications on ALF related to overdosed acetaminophen is impressive, reflects clinical interest and concern, and requires careful analysis of uncertainties and ambiguities [28, 29, 58, 60, 61]. Uncertainties in a number of these reports include lack of a robust causality assessment for acetaminophen, heterogeneity of study cohorts by incorporating cases of intrinsic liver injury or acute on chronic liver failure, and inadequate handling of confounding variables; these include alcohol use, preexisting liver disease and comedication, with the risk of impeding correct case evaluation management.

### Cohort Studies and Single Case Reports

Abundant and otherwise highly appreciated are case series of overall ALF by various causes including acetaminophen [28, 78–82]. However, these cohorts lack homogeneity regarding acetaminophen and are thereby not suitable for the current analysis. The US and the UK are among the countries with a high incidence of ALF caused by overdosed acetaminophen [83] in support of various reports and databases [28, 29, 58, 60, 61, 73, 76]. However, exact comparative data are not available because definitions of ALF and criteria of patient cohorts are variable and differ from one country to the other, with the most striking issue focusing on the heterogeneity of the study cohorts and redundant reports including previous cases. Among the multiple reports, a few will be analyzed in detail and discussed.

An early report from the US Acute Liver Failure Study Group focused on 275 patients with acetaminophen induced ALF and provided useful details (Table 12.6) [84]. Although published and designed as a prospective study, a few cases were included having used acetaminophen >4 g daily (minimum 1.2 g) or presented an ALT of only 126 U/L, problematic was also an alcohol use in 55% and alcohol abuse in 35% and missing use of a robust CAM such as RUCAM. Nevertheless, this study is likely among the best ones addressing ALF by acetaminophen despite the CAM problem. Considering the limitations this study [85], ALF by overdosed acetaminophen is described by the following features: median dose ingested was 24 g, unintentional overdoses accounted for 48% of the patients and intentional use for 44%, whereas in 8% the intent was unknown. Clinical data revealed that 65% of the patients survived, 27% died without liver transplantation, and 8% of the patients received a liver transplant.

In another report of the US Acute Liver Failure Study group, cases of 113 patients with ALF by overdosed acetaminophen were included following a strict study

protocol but lacking a robust formal causality assessment method such as RUCAM (Table 12.6) [62]. The most interesting finding was that the acetaminophen dose does not predict outcome in acetaminophen induced ALF, likely by a plateau effect of acetaminophen toxicity as found after serial acetaminophen doses.

A large UK study with 344 patients experiencing ALF by acetaminophen (Table 12.6) confirmed that the risk of mortality is higher after unintentional acetaminophen overdose as compared with intentional use [63]. Reported was exclusion of alternative causes without applying a formal algorithm to verify causality for acetaminophen.

The most recent study of the US reported on patients with ALF in connection with the use of overdosed acetaminophen, the high number of 912 patients collected between 2000 and 2016 is impressive (Table 12.6) [60]. Apart from the high case number, no new information or highlights can be drawn from this study because cases were mixed with 250 patients experiencing acute intrinsic liver injury without clear separation of the two different cohorts that would allow an individual case characterization.

#### Confounding Variables

The high number of confounding variables in various reports is difficult to interpret if poorly or not considered for causality evaluation. Examples of confounders are among others (1) mix of study cohorts [84]; (2) lacking use of a robust causality assessment such as RUCAM [28, 58, 60–62, 84]; (3) issue of alcohol use [84]; (4) ALF cohorts with undetermined etiologies [64, 78, 79]; and (5) ALF cohorts with unrecognized acetaminophen cause [60, 85].

### *Acetaminophen in Acute on Chronic Liver Failure*

Limited clinical interest exists for acute idiosyncratic and intrinsic DILI in patients with preexisting liver disease, classified as ACLF, leading in publications to small case numbers [33, 40, 45, 46, 57, 86, 87] and discussions about the use of a global introspection causality assessment for DILI cases evaluating issues of mortality and liver transplantation [87]. By definition, the diagnosis of ACLF requires two steps (Table 12.2). First, the acute liver injury by the drug must be firmly established, and second, the chronic liver disease must be diagnosed. Diagnosing one of these two diseases is already a challenge.

#### Cohort Studies and Single Case Reports

Recognizing overdosed acetaminophen as potential trigger of the acute injury in patients with preexisting chronic liver disease that finally leads to ACLF is tricky (Table 12.6) [58, 60, 62, 63, 84] as partially already known from acetaminophen

induced ALF (Table 12.6) [58, 60–63, 84], now requiring for ACLF the verification of a preexisting chronic liver disease, the updated RUCAM [26], and diagnostic biomarkers [79]. However, an ACLF cohort meeting these requirements clearly does not exist (Table 12.6). A variety of reasons may account for this missing information, among these are the required exclusion of potential ACLF cases from any study of ALF that correctly included only cases without a preexisting chronic liver disease (Table 12.6), an essential criterion of ACLF, and the lack of scientific scrutiny and clinical interest to evaluate a separate cohort of ACLF with assumed difficulties achieving a correct diagnosis and a high case number for valid conclusions. In this context it is refreshing from the current analysis that all ALF studies followed strict inclusion and exclusion criteria regarding lack of chronic liver disease and provided cohort homogeneity regarding cases without preexisting liver diseases. The current evaluation confirms that published ALF cohorts are devoid of overt ACLF cases (Table 12.6), considering both, prospective studies [62, 84] and retrospective studies [58, 60, 63]. In future cases, ALD including cirrhosis as preexisting liver disease should be carefully be excluded because the ALF cohorts may contain patients with a high percentage of alcohol users or alcohol abusers. A clear differentiation of acetaminophen induced ALF from ACLF is needed for clinical purposes, because the clinical course of patients with ACLF may be more severe compared to ALF and requires early consideration of a liver transplantation.

### Confounding Variables

There is nothing to be discussed due to unavailability of cases meeting criteria of ALCF following use of overdosed acetaminophen.

**Conclusions**

Acetaminophen affects the liver in different ways. Used in recommended doses or in overdose it may cause a simple and clinically not relevant liver adaptation with ALT >5 × ULN. Normal dosed acetaminophen may also lead to acute idiosyncratic DILI and has to be differentiated from acute intrinsic DILI due to overdosed acetaminophen, both DILI types are found with ALT ≥5 × ULN that do not allow differentiation. Defined as a severe and potentially life-threatening stage, ALF with ALT 10–100 × ULN is caused in patients without preexisting chronic liver disease following intake of overdosed acetaminophen, to be differentiated from ALCF in patients with similar conditions but with preexisting chronic liver disease. For virtually all stages of liver disease, which are caused by acetaminophen, sufficient case numbers are available allowing clear disease characterization, with the exemption of the ALCF stage for which no cases are available. In fact, no studies have been

published as potential ALCF cases had to be excluded from cohorts of ALF strictly limited to patients without chronic liver disease. Presumably, the prognosis of ALCF by acetaminophen will be more critical as compared to ALF, a clinical issue that should be analyzed using a study protocol with case inclusion of only ALCF by acetaminophen. More specifically, members of the US Acute Liver Failure Study Group or similar groups from other countries should be encouraged to initiate a prospective study on acetaminophen induced ACLF.

**Questions**

- Question 1: What is the main initial mechanistic step leading to AFL by overdosed acetaminophen?

  1. Low oxygen content in the liver?
  2. High iron content in the liver?
  3. Metabolism through hepatic microsomal CYP 2E1?
  4. Reduced levels of hepatic glutathione?

- Question 2: Why is RUCAM an essential part of the diagnostic workup in patients with increased liver tests after use of acetaminophen?

  1. It clarifies prognosis?
  2. It suggests the best time when a liver transplantation should be performed?
  3. It replaces diagnostic liver biopsy?
  4. It establishes the diagnosis?

- Question 3: How is liver adaptation defined?

  1. Severe clinical course combined with pronounced jaundice?
  2. Serum liver tests?
  3. Poor clinical outcome?
  4. No clear definition exists?

- Question 4: Are 4 g acetaminophen daily safe for the liver?

  1. Yes?
     Answer: No, there is good evidence that in a few individuals idiosyncratic liver injury may develop.
  2. Only in well nourished patients?
  3. Only in patients with an alcohol problem or ALD?
  4. In patients aged >75 years?

**Answers**

- Question 1: Answer 3—Metabolism through hepatic microsomal CYP 2E1
- Through this enzymatic reaction, hepatotoxic metabolites are formed like N-acetyl-p-benzoquinone imine (NAPQI) that normally binds to hepatic glutathione if available in sufficient amounts but otherwise may initiate the liver injury.
- Question 2: Answer 4—It establishes the diagnosis
- RUCAM is in worldwide use as a validated tool to assess causality in drug induced liver injury and helps in cases of suspected acetaminophen liver injury, considering also alternative causes such a comedication by drugs or herbs.
- Question 3: Answer 2—Serum liver tests
- By defining thresholds of drug related liver adaptation that are low for serum ALT (alanine aminotransferase) with <5 × ULN and for serum ALP (alkaline phosphatase) with <2 × ULN, where ULN is the upper limit of normal.
- Question 4: Answer 1
- No, there is good evidence that in a few individuals idiosyncratic liver injury may develop

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# Chapter 13
# Non-viral or Drug-Induced Causes of Acute Liver Failure


**Nyan L. Latt and Sanjaya K. Satapathy**

**Key Concepts**

- Acute liver failure (ALF) is a rare but life-threatening medical condition in which rapid decline in liver synthetic function results in coagulation abnormality and hepatic encephalopathy in individuals with no known pre-existing liver disease.
- Drug-induced liver injury (DILI) and acute viral hepatitis are the predominant causes of ALF. However, several other conditions such as autoimmune hepatitis, PBC, PSC, overlap syndrome, Budd-Chiari syndrome, portal vein thrombosis, sinusoidal obstruction syndrome, NASH and Wilson disease, need to be considered in the differential diagnosis of ALF. ALF in pregnancy or ischemic hepatitis should be considered in specific circumstances.
- Early diagnosis is key to potential for reversibility of ALF.
- It is critical to refer patients early in their course for potential liver transplantation to avoid fatality.

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## Introduction

Acute liver failure (ALF) is a rare but life-threatening medical condition in which rapid decline in liver synthetic function results in coagulation abnormality and hepatic encephalopathy in individuals with no known pre-existing liver disease. It is defined as elevated International Normalized Ratio (INR) $\geq$ 1.5 and new onset altered mental status with an acute illness of <26 weeks duration. It is estimated that 2000 of ALF cases occur annually in the United States [1]. Based on the Scientific Registry of Transplant Recipients (SRTR), ALF constitutes approximately 8% of all liver transplantations in the United States. It is critical to evaluate patients with ALF for liver transplantation as soon as possible to avoid fatality. Post-liver transplant 1-year survival rates are 84% in the United States and 79% in Europe, respectively [2].

Although the most common etiology of ALF is drug-induced liver injury (DILI), there is an extensive list of various etiologies which can lead to severe liver injury and ALF. Early diagnosis of specific etiology can lead to disease-specific, life-saving therapies without the requirement of liver transplantation (LT). The goal of this chapter is to review non-viral and nondrug-induced metabolic and vascular causes of ALF, specifically autoimmune liver diseases, vascular disorders of the liver, non-alcoholic fatty liver disease, Wilson's disease and pregnancy-related causes of acute liver injury.

## Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a complex genetic and inflammatory disorder in which immune-mediated reactions trigger hepatocytes inflammation, injury and necrosis. AIH can affect both pediatric and adult population of various ethnic groups. The estimated incidence of AIH can vary widely from 0.67 (Israel) to 2 cases per 100,000 person-years (New Zealand) depending on specific region of the world. The estimated prevalence of AIH can range broadly from 4 (Singapore) to 43 (Alaskan natives) per 100,000 persons. AIH is more prevalent in females as about 70% of patients are females. Although AIH can affect all ages, the onset of AIH has traditionally been described as "bimodal" distribution where the peak onset is seen among ages 10–30 years and 40–60 years [3].

The exact cause of AIH is unknown, however, AIH is associated with genetic predispositions. Several human leukocyte antigen (HLA) associations clusters have been described in AIH. Non-HLA genetic associations have also been associated with AIH with lower risk of occurrences. Environmental triggers such as viral exposures activate genetic predispositions resulting in loss of self-tolerance to autoantigens. The proliferation of both cellular and humoral immune responses and cytokine productions cause hepatocyte inflammation and injury.

Patients with AIH can present with wide range of symptoms. Majority of AIH patients experience non-specific symptoms such as fatigue, joint pain and malaise.

About 25% of AIH patients are asymptomatic and diagnosed based on abnormal liver chemistry tests. The diagnosis of AIH is challenging and can be established by constellations of biochemical and histological findings after ruling out viral hepatitis, alcohol-induced hepatitis and drug-induced liver injury [3]. Elevation of serum aspartate (AST) and alanine (ALT) aminotransferases and serum immunoglobulin G (Ig GI) are seen in active AIH. Antinuclear antibodies (ANA), smooth muscle antibodies (SMA) and antibodies to liver-kidney microsome type-1 (LKM1) are the key autoantibodies detected in patients with AIH. ANA and SMA can be detected in 80% and 63% while LKM1 antibodies are detected in 3% of patients with AIH. AIH can be divided into type 1 (ANA/SMA predominant) and type 2 (LKM-1 predominant). SLA (soluble liver antigen) antibodies are present in 7–22% of patients with type 1 AIH. 20% of patients with AIH has no autoantibodies.

The diagnosis of AIH should not be established without liver biopsy. Histopathological features of AIH include interface hepatitis with lymphoplasmacytic infiltration, lobular hepatitis, emperipolesis and rosettes formation. Centrilobular zone injury is predominant in AIH patients with severe liver injury and ALF. Central perivenulitis, plasmacytic inflammatory infiltrates and massive hepatic necrosis are principal features of AIH patients with ALF. A diagnostic scoring system was created by International Autoimmune Hepatitis Group in 1993, it was revised in 1999 and then simplified in 2008 to help improve in diagnostic accuracy of AIH [4] (Table 13.1).

Treatment of AIH is primarily focused on immunosuppression. First line treatments include glucocorticoids and azathioprine. Budesonide has been found to be effective in achieving remission in active AIH patients without high grade fibrosis or ALF. Once biochemical remission is achieved, glucocorticoids should be tapered off and azathioprine (AZA) should be continued as maintenance therapy. AIH patients with treatment failure, drug intolerance or incomplete response to first-line treatments can be treated with second-line therapies such as mycophenolate mofetil (MMF) and calcineurin inhibitors such as tacrolimus or cyclosporine. MMF is a preferred choice in second-line treatment as drug trough levels do not need to be monitored. MMF is contraindicated in pregnant patients due to high risk of birth defects. Rituximab, anti-CD-20 monoclonal antibody, or anti-TNF-alpha agents such as infliximab can be considered in patients AIH who fail second-line therapies.

3–6% of AIH patients present with severe liver injury and ALF. About one-third of patients with AIH has cirrhosis at presentation. AIH must be ruled out in all patients presenting with ALF. Although glucocorticoid therapy is effective in patients with acute severe AIH, it does not improve overall survival in AIH patients with ALF. In contrast, overall survival has been lower in AIH patients with ALF who had model for end-stage liver disease (MELD) score > 40 and were treated with glucocorticoids [5]. We recommend short-term 1–2-week trial of glucocorticoid therapy for AIH patients with ALF and liver transplant evaluation if no improvement. It is vital to recognize rapid clinical deterioration and to promptly proceed with liver transplantation in order to improve overall survival [6].

**Table 13.1** Simplified scoring system for autoimmune hepatitis by International Autoimmune Hepatitis Group

| Features | Points |
|---|---|
| ANA or SMA titer | |
| ≥1:40 | +1 |
| ≥1:80 | +2 |
| LKM-1 titer | |
| ≥1:40 | +2 |
| SLA positive | +2 |
| Ig G | |
| Upper normal limit | +1 |
| >1.1 times upper normal limit | +2 |
| Liver histology | |
| Compatible with AIH[a] | +1 |
| Typical of AIH[b] | +2 |
| Absence of viral hepatitis | +2 |

*ANA* anti-nuclear antibody; *SMA* anti-smooth muscle antibody; *LKM-1* anti-liver/kidney microsomal antibody type 1; *SLA* anti-soluble liver antibodies; *IgG* immunoglobulin G; *AIH* autoimmune hepatitis

[a]Compatible histological features of AIH: chronic hepatitis with portal lymphocytic infiltrates without all the typical features

[b]Typical histological features of AIH: interface hepatitis, portal lymphoplasmacytic portal infiltrates, lobular hepatitis, emperipolesis and rosette formation

Total points are 8—1 to 5 points: possible AIH; 6 points: probable AIH; 8 points: likely AIH

Adapted from Balitzer D, Shafizadeh N, Peters MG, et al. Autoimmune hepatitis: review of histologic features included in the simplified criteria proposed by the international autoimmune hepatitis group and proposal for new histologic criteria. Mod Pathol. 2017;30(5):773–783; with permission

## Primary Biliary Cholangitis

Primary biliary cholangitis (PBC) is the most common autoimmune liver disease which is characterized by chronic inflammation of bile ducts and cholestasis. Females are predominantly affected by PBC with 9:1 female to male ratio. The median age at presentation is approximately in 50 years. The prevalence of PBC is estimated to be 19–402 cases per million. The hallmark of PBC is anti-mitochondrial antibody (AMA) which is positive in more than 95% of patients with PBC. PBC can be seen in patients with other autoimmune diseases and it is frequently associated with scleroderma. The clinical manifestations of PBC range include asymptomatic appearance with elevated alkaline phosphatase (ALP), fatigue, itching, sicca syndrome (dry eyes/dry mouth). The diagnosis of PBC is established when patient meet 2 out of 3 criteria: (1) Positive AMA >1:40 titer, (2) chronic cholestasis as

evidenced by unexplained elevation of ALP for more than 6 months and (3) histology showing non-suppurative destructive cholangitis and bile duct loss. Liver biopsy is only needed in AMA-seronegative patients and in those who are suspected for overlap syndrome with AIH.

The first line therapy of PBC is ursodeoxycholic acid (UDCA) 13–15 mg/kg/day in divided doses. UDCA has multiple therapeutic actions including choleretic, cytoprotective, anti-inflammatory and immunomodulatory properties. UDCA has been shown to improve transplant-free survival at 5, 10 and 15 years. Therapeutic response to UDCA should be monitor with biochemical evidence of reduction in ALP. Non-responders after 12 months of UDCA use should be considered the second line therapy with obeticholic acid (OCA). OCA is a farnesoid X receptor (FXR) agonist and it modulates bile acid metabolism: synthesis, absorption, transport and secretion as well as exerts anti-inflammatory and anti-fibrotic properties. The initial dose of OCA in well-compensated PBC is 5 mg/day and it can be increased to 10 mg/day after 3 months if biochemical liver tests remain elevated. The use of OCA in decompensated PBC patients is not recommended due to risk of worsening liver function and increased risk of mortality. Fibrates can be considered as an add-on therapy to UDCA when patients do not respond to UDCA adequately. Fibrates plus UDCA therapy has been shown to improve liver chemistries, pruritus and fibrotic markers. The first-line therapies for pruritus in PBC due to cholestasis are anion-exchange resins such as cholestyramine, colestipol and colesevalam in divided doses. Second-line agents for pruritus in PBC are rifampicin 150 to 300 mg twice daily, oral opiate antagonists such as naltrexone titrated to a dose of 50 mg daily and sertraline 75–100 mg daily. PBC does not present with acute liver failure [7].

## Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is an immune-mediated, chronic cholestatic liver disease characterized by progressive biliary inflammation leading to fibrosis. PSC is strongly associated with inflammatory bowel disease, predominantly ulcerative colitis. Emerging data suggests that alterations of circulating bile acids and the gut microbiota may play a great role in the pathophysiology of PSC. Approximately 80% of PSC patients also has concomitant IBD and it is a risk factor for colon cancer, cholangiocarcinoma and gall-bladder cancers. PSC is more common in men than women with male to female ration 2:1. The incidence of PSC is approximately 1.3 cases per 100,000 persons per year and the prevalence is estimated 0 to 16.2 cases per 100,000 persons.

Majority of patients with PSC do not have any symptoms. Some may suffer from abdominal pain, pruritus, jaundice and fatigue. The diagnosis of PSC can be

established in patients with persistently elevated ALP > 6 months and biliary strictures "bead on a string" appearance on magnetic resonance cholangiopancreaticography (MRCP) or endoscopic retrograde cholangiopancreaticography (ERCP). ERCP is not a necessity to establish the diagnosis of PSC. Small-duct PSC, which affects only microscopic bile ducts, can only be diagnosed based on histopathological findings such as classic onion-skinning around the bile ducts, ductal proliferation and ductopenia after liver biopsy is obtained. PSC can progress to fibrosis and cirrhosis. Patients with PSC are at high risk of cholangiocarcinoma formation.

There is no established medical therapy for PSC. Medium dose UDCA (13–15 mg/kg/day) has been shown no benefit for PSC. Higher dose UDCA > 20 mg/kg/day has been associated with worse outcomes in PSC. Medium dose UDCA can be used for pruritus treatment in PSC. PSC patients with dominant stricture need ERCP with balloon dilation and/or biliary stenting. Prior studies suggested biliary stenting was associated with increased risk of adverse events and cholangitis. There is no superiority of balloon dilation versus biliary stenting in a recent multi-center study in Europe. We recommend ERCP with balloon dilation for dominant strictures in PSC and biliary stenting should be reserved for refractory strictures. Oral vancomycin has therapeutic benefits in patients with PSC and ulcerative colitis as vancomycin alters gut microbiome. Antibiotic therapies targeting gut microbiome and fecal microbiota transplantation are emerging therapeutic options for PSC.

Approximately more than 40% of PSC patients die from cancer-related causes. It is vital to identify the risks of colorectal cancer, cholangiocarcinoma and gallbladder cancer in patients with PSC and to place them on appropriate cancer surveillance. t is recommended to obtain MRI/MRCP every 6–12 months along with cancer-antigen-19-9 to screen for cholangiocarcinoma. For colon cancer screening, PSC patients with no history of IBD require a screening colonoscopy at the time of PSC diagnosis. PSC with IBD patients need annual colonoscopy with random colonic mucosal biopsies to screen for dysplasia. PSC patients with any size of gallbladder polyps are recommended to have cholecystectomy due to high risk of gallbladder cancer.

PSC patients with end-stage liver disease can manifest with complications of portal hypertension. The definitive treatment for PSC with decompensated liver disease is liver transplantation. Post-LT 5-year survival is 80–85% in PSC patients and the recurrent rate at 5-year is approximately 20%. Younger patients and patients with ulcerative colitis have fourfold increase in PSC recurrence after LT. PSC does not present with ALF [8].

## Overlap Syndrome

Autoimmune liver diseases such as AIH, PBC and PSC can be overlapped with each other and manifest in some individuals as overlap syndrome. The most common overlap syndrome is AIH-PBC. AIH-PSC is the second common overlap syndrome

and PBC-PSC is very rare with only 2 cases reported in the literature. Patients with overlap syndromes present with elevated aminotransferases as well as cholestasis with elevated ALP. The key is to identify patients with overlap syndrome and obtain liver biopsy for histopathological diagnosis. The principal treatment of AIH overlap syndromes is to add immunosuppression such as corticosteroid +/− with azathioprine. The treatment regimen for AIH-PBC is UDCA plus corticosteroid or azathioprine. AIH-PSC patients can benefit from addition of immunosuppression. The management of overlap syndrome patients who present with ALF is no different than AIH-ALF [9].

## Immunoglobulin G4-Related Sclerosing Cholangitis

Immunoglobulin (Ig) G4-related sclerosing cholangitis (IgG4-SC) is an autoimmune condition characterized by progressive obliteration, fibrosis and stenosis of the bile ducts secondary to Ig G4-rich lymphoplasmacytic infiltration and inflammation. The clinical manifestations of IgG4-SC include elevated cholestatic liver enzymes, jaundice and cholangitis. The diagnosis of IgG4-SC is established with radiographic or histologic evidence of intra- and/or extra-hepatic biliary strictures, cholestasis and markedly elevated serum IgG4 levels [10]. It is vital to identify and diagnose IgG4-SC as it is responsive to corticosteroid therapy. There is no case of IgG4-SC presenting with ALF in the literature.

## Ischemic Hepatitis

Ischemic hepatitis is a common clinical syndrome in which systemic hypoperfusion and ischemia resulting in an elevation of liver chemistry tests. Ischemic hepatitis is usually seen in a setting of critical illness with cardiovascular dysfunction, circulatory shock or respiratory failure. However, ischemic hepatitis can be seen without clinically significant findings of circulatory compromise as hypotensive or hypoxemic episode can be transient and brief. 2.5% of patients who are admitted to intensive care unit can develop ischemic hepatitis. The most common underlying etiologies of ischemic hepatitis are cardiovascular dysfunction and sepsis. Experts believe that the pathophysiology of ischemic hepatitis comprises of “two-hit” phenomenon where an acute insult such as septic shock occurs in underlying hypoperfusional state such as reduced cardiac ejection fraction. The aspartate aminotransferase (AST) is a mitochondrial enzyme and AST is usually higher than alanine aminotransferase (ALT) is ischemic hepatitis. Bilirubin usually lags approximately 48 h behind aminotransferase elevation. The diagnosis of ischemic hepatitis is established by clinical suspicion and ruling out other etiologies. Liver biopsy is not recommended for patients with apparent risk factors of ischemic hepatitis. Liver

biopsy can be necessary when clinical suspicion for ischemic hepatitis is low. Histopathological finding of centrilobular (zone 3) necrosis is a hallmark of ischemic hepatitis.

The principal treatment of ischemic hepatitis is the correction of underlying cardiopulmonary dysfunction. Ischemic hepatitis can lead to ALF. Prognosis of ischemic hepatitis with ALF is poor [11].

## Budd Chiari Syndrome

Budd Chiari syndrome (BCS) is a rare medical condition characterized by hepatic venous outflow tract obstruction (HVOTO). BCS was first described by William Budd, a British physician, in 1845. Hans Chiari, an Austrian pathologist, later illustrated histopathological characteristics of BCS as obliterating endophlebitis of hepatic veins. The estimated incidence of BCS is one in 2.5 million person per year in the Western countries while it was reported as 0.13 per million per year in Japan. Gender and age distribution can also vary by geographical region. While males with median age of 45 years are more affected in Asia, BCS is more prevalent among younger females with median age of 35 years.

BCS is classified as primary (75%) or secondary (25%). Primary BCS involves intrahepatic vein obstruction due to thrombosis. Secondary BCS is regarded as the narrowing of the hepatic outflow tract due to external compression of a structure such as benign or malignant tumors, cysts or abscesses. Primary BCS can be further divided into three types depending on the anatomical location of the obstruction: intrahepatic small vessel obstruction, large vessel hepatic vein obstruction and obstruction extending into the inferior vena cava (IVC).

Primary BCS can be caused by numerous prothrombotic conditions. The most common causes of primary BCS are myeloproliferative disorders such as polycythemia vera, essential thrombocythemia and primary myelofibrosis. Janus kinas 2 (JAK2) V617F mutation is a hallmark of myeloproliferative disorders. 97% of patients with polycythemia vera carries JAK2 mutation. Other prothrombotic conditions include pregnancy, oral contraceptive use, protein C or S deficiencies, factor V Leiden mutation, anti-thrombin deficiency, antiphospholipid syndrome, hyperhomocysteiniemia, paroxysmal nocturnal hemoglobinuria (PNH) and Behcet's disease.

Patients with BCS usually present with abdominal pain, ascites, portosystemic encephalopathy and variceal bleeding. Initial presentation of some BCS patient is variceal bleeding. The initial work up for BCS is imaging study such as Doppler ultrasound of the liver, triple phase contrasted computed tomography (CT) or triple phase contrasted magnetic resonance imaging (MRI). Radiographic signs of BCS include hepatic vein or IVC occlusion or narrowing, reverse venous blood flow and indirect signs of HVOT such as hepatomegaly secondary to hepatic venous congestion, caudate lobe hypertrophy as the veins that drain caudate lobe tend to be not

affected by HVOTO and signs of portal hypertension such as ascites, splenomegaly and variceal formation. Cross-sectional imaging techniques such as CT or MRI can detect tumor or lesions which can cause secondary BCS by causing external compression of HV or IVC. If non-invasive imaging findings are atypical for BCS, transjugular hepatic venogram can be performed to evaluate HV and IVC. In some occasions, liver biopsy can be helpful to rule out small-vessel BCS and veno-occlusive disease (VOD). Typical histopathologic features of HVOTO comprise of centrilobular congestion and red blood cells in the space of Disse and perisinusoidal dilation/fibrosis. Once the diagnosis of BCS is established, patients should be screened for hypercoagulable prothrombotic conditions. JAK-2 mutation is the most common hypercoagulable state in patients with BCS and it should be performed. Referral to hematology is necessary for thorough hypercoagulable work up prior to starting anti-coagulation therapy.

BCS patients present with acute liver failure—hepatic encephalopathy and coagulopathy. According to Acute Liver Failure Study Group (ALFSG) registry, 0.9–1.5% of all ALF cases comprise of BCS patients [12]. Clinical prediction scoring system, namely Rotterdam score [13] (Table 13.2), was validated as the best discrimination index to predict the 3-month mortality of BCS patients. Rotterdam score can be utilized preferentially to determine treatment urgency. Parameters used to calculate Rotterdam score include presence of hepatic encephalopathy, ascites, severe coagulopathy (INR > 2.3) and serum total bilirubin level. Rotterdam class 3 predicts the highest mortality and poor prognosis [13].

The management of BCS entails multidisciplinary approach including hepatologist, hematologist, interventional radiologist and hepato-biliary/abdominal transplant surgeons. Initial management in stable patients is anti-coagulation. Warfarin, a vitamin-K antagonist, has been a preferred choice for anticoagulation in patients with BCS as its coagulation effect can simply be reverse with vitamin K and fresh frozen plasma (FFP). However, recent studies have shown that direct oral anticoagulants (DOACs) such as apixaban or rivaroxaban are safe and effective in patients with cirrhosis. The advantage of DOACs use is no requirement of frequent testing

**Table 13.2** Rotterdam score to predict prognosis of patients with Budd-Chiari Syndrome

| 1.27 × encephalopathy + 1.04 × ascites + 0.72 × pro-thrombin time + 0.004 × bilirubin | | |
|---|---|---|
| Encephalopathy—[1] present and [0] absent | | |
| Ascites—[1] present and [0] absent | | |
| Pro-thrombin time—[1] if INR > 2.3 and [0] if INR < 2.3 | | |
| | Scores | Prognosis |
| Class 1 | 0–1.1 | Good |
| Class 2 | 1.1–1.5 | Intermediate |
| Class 3 | 1.5–4 | Poor |

Source: Montano-Loza AJ, Tandon P, Kneteman N, Bailey R, Bain VG. Rotterdam score predicts early mortality in Budd-Chiari syndrome, and surgical shunting prolongs transplant-free survival. Aliment Pharmacol Ther. 2009;30(10):1060–1069. https://doi.org/10.1111/j.1365-2036.2009.04134.x

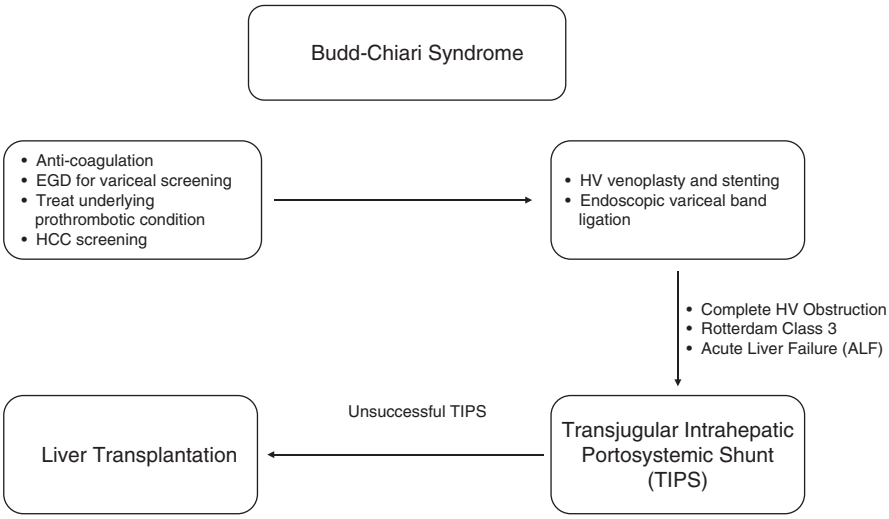


**Fig. 13.1** Budd-Chiari Syndrome—Stepwise Management Algorithm

for therapeutic monitoring. Patients with BCS are high risk of developing hepatocellular carcinoma (HCC) and warrant routine surveillance with ultrasound every 6 month.

Patients with BCS who have clinical and imaging evidence of portal hypertension need esophagogastroduodenoscopy (EGD) to screen for esophageal and gastric varices as portosystemic variceal bleeding can be life-threatening. Endoscopic variceal band ligation should be performed in patients with large (>5 mm) esophageal varices. The definitive treatment of HVOTO requires hepatic vein venoplasty with balloon dilation and stenting by interventional radiology. If unsuccessful, transjugular intrahepatic portosystemic shunt (TIPS) should be considered as a next step in management of BCS. If TIPS is technically not feasible, interventional radiologist can also perform direct intrahepatic portocaval shunt (DIPS). TIPS and DIPS should be considered "first line" therapies in patients who present with ALF or patients who have Rotterdam Class 3 score. Patients with BCS who fail TIPS or DIPS as well as patients who present with acute liver failure or Rotterdam class 3 (Fig. 13.1) should be considered for liver transplantation as a life-saving treatment option [12].

## Portal Vein Thrombosis

Portal vein thrombosis (PVT) is characterized by the development of a thrombus in the portal vein, sometimes extending into the superior mesenteric vein (SMV). PVT can be classified into acute, chronic and tumor-related malignant. Malignant PVT or tumor thrombus is secondary to hepatocellular carcinoma invading into the portal vein, illustrated by arterially enhanced expansion of thrombus on contrasted

cross-sectional imaging such as triple-phase magnetic resonance imaging (MRI) or CT. PVT can be further divided into its relationship with chronic liver disease: cirrhotic and non-cirrhotic.

PVT in individuals without cirrhosis is rare. A recent Italian study investigated 3535 patients found that the overall incidence of PVT was 3.8 per 100,000 in men and 1.7 per 100,000 in women. Non-cirrhotic PVT usually occurs in patients with hypercoagulable conditions. The common risk factors for non-cirrhotic PVT are similar to prothrombotic conditions aforementioned in BCS such as myeloproliferative disorders, JAK2 V617F mutation, prothrombin gene G20201A mutation, protein C and S deficiencies, antithrombin deficiency, antiphospholipid syndrome, PNH and vasculitis. Approximately 20–25% of non-cirrhotic PVT cases are secondary to anatomically localized etiologies such as intra-abdominal infection, pancreatitis, umbilical vein sepsis, diverticulitis, gastric-bypass surgery and Whipple surgery.

In contrast to non-cirrhotic PVT, it is not uncommon among patients with cirrhosis. Cirrhotic patients with more advanced liver disease have higher prevalence of PVT. The incidence rates of PVT were 5% at 1 year, 8% at 3 years and 11% at 5 years among patients with Child-Turcotte-Pugh A and B in a multicenter prospective study in France. The estimated incidence of PVT is approximately 10–15% and the estimated prevalence is 10% in patients with cirrhosis. The pathophysiology of cirrhotic PVT can be explained by Virchow's triad which describes the three categories of prothrombotic risk factors. Cirrhotic patients manifest with all three components of Virchow's triad—hypercoagulability (e.g., acquired protein C/protein S deficiencies), vascular stasis (e.g., diminished portal blood flow) and endothelial injury (e.g.; increased production of vasodilator molecules mainly nitric oxide can contribute to increased endothelium-dependent relaxation in hepatic microcirculation).

Patients with acute non-cirrhotic PVT usually manifest with abdominal pain and fever. Acute non-cirrhotic PVT which extends into SMV can present with life-threatening intestinal ischemia and infarction. The mainstay of treatment for acute non-cirrhotic PVT is anti-coagulation at the time of diagnosis. Initial anti-coagulation therapies are preferably low molecular-weight heparin (LMWH) or unfractionated heparin in acute setting. Vitamin-K antagonist, warfarin, can be used for long-term treatment and minimal 6-month anticoagulation is recommended. Despite anticoagulation therapy, if PVT progresses or signs of intestinal ischemia develop, thrombectomy and interventional recanalization may be needed. Interventional radiologist can perform transjugular PV thrombectomy. TIPS or DIPS or trans-splenic approach portal shunts can be placed for sustained recanalization.

Patients with chronic PVT usually presents with complications of portal hypertension such as variceal bleeding, ascites, splenomegaly or hepatic encephalopathy. Gastroesophageal variceal bleeding is the most common complication. Collateral veins secondary to chronic non-cirrhotic PVT can compress intrahepatic bile ducts and lead to portal bilopathy. Figure 13.2 demonstrates the recommended algorithm for PVT treatment. Chronic cirrhotic PVT patients who are on liver transplant waiting list should be treated to achieve the goal of recanalization. Chronic PVT which

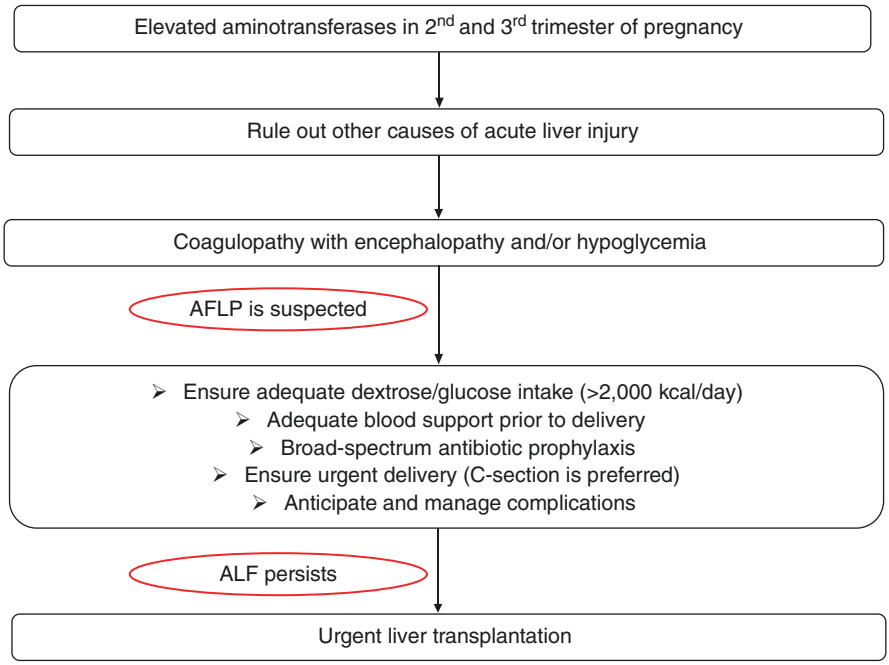


**Fig. 13.2** Management Algorithm for Suspected Acute Fatty Liver of Pregnancy (AFLP)

are progressive (i.e.; extending into SMV or splenic vein) should undergo anti-coagulation therapy. Prior to anti-coagulation, esophagogastroduodenoscopy (EGD) should be performed to assess portal hypertensive changes or mucosal lesions and subsequent prophylaxis, such as esophageal band ligation or non-selective beta-blocker, is recommended for high risk varices. The minimum recommended duration of anti-coagulation for PVT is 6 months. After 6-month anti-coagulation, PVT should be re-assessed with cross-sectional imaging +/− doppler sonography. If the resolution of PVT is observed, anti-coagulation can be discontinued, and the surveillance imaging should be performed every 6 months. Liver transplant waitlisted patients should continue anti-coagulation until liver transplant surgery takes place. Patients with underlying hypercoagulable conditions may need to continue anti-coagulation therapy indefinitely. TIPS or DIPS can be considered in patients who do not respond to 6-month of anti-coagulation [14].

## Sinusoidal Obstruction Syndrome

Sinusoidal obstruction syndrome (SOS), previously known as hepatic veno-occlusive disease, is characterized by non-thrombotic obstruction of the hepatic sinusoids and the central veins. The first case series of SOS was reported in South

Africa in 1920, after ingestion of food containing pyrrolizidine alkaloids which is a hepatotoxin. The pathophysiology of SOS is due to toxic agent damaging endothelial cells, likely via glutathione and NO. The endothelial denudation leads to embolic obstruction around the central veins of hepatic lobules.

SOS is a well-established complication of hematopoietic stem cell transplant (HSCT). The incidence of SOS after HSCT is about 5%. Other risk factors for SOS include chemotherapy drugs (oxaliplatin, cytosine arabinoside, cyclophosphamide, gemtuzumab, mitomycin), immunomodulators (azathioprine, 6-mercaptopurine) and toxins (pyrrolizidine alkaloids) which can cause SOS. Patients with SOS manifest with painful hepatomegaly, jaundice and signs of portal hypertension such as ascites, variceal bleeding. SOS can develop within 3 weeks after HSCT.

The diagnosis of SOS can be difficult as there is no definitive test available. European Society for Blood and Marrow Transplantation (EBMT) proposed a diagnostic criterion for SOS in HSCT patients (Table 13.3). Transjugular liver biopsy with hepatic venous pressure measurement is helpful in diagnosing SOS. Hepatic venous pressure gradient (HVPG) > 10 mmHg has a sensitivity of 52%, specificity of 91% and positive predictive value >85% for SOS. Histopathologic features of SOS comprise hemorrhage into dilated sinusoids with hepatocyte atrophy and sinusoidal denudation in early stage and obliteration of small central veins by subendothelial fibrosis in later stage. In chronic disease, sinusoidal fibrosis and nodular regeneration may occur.

**Table 13.3** New EBMT criteria for diagnosis of sinusoidal obstruction syndrome in adults

| Classical SOS in the first 21 days after HSCT | Late onset SO > 21 days after HSCT |
|---|---|
| Bilirubin ≥ 2 mg/dL AND two of the following criteria must be present: | Classical SOS beyond day 21<br>OR<br>Histologically proven SOS<br>OR<br>Two or more of the following criteria must be present |
| 1. Painful hepatomegaly<br>2. Weight gain >5%<br>3. Ascites | 1. Bilirubin ≥ 2 mg/dL<br>2. Painful hepatomegaly<br>3. Weight gain >5%<br>4. Ascites<br>5.<br>AND<br>Hemodynamic or/and ultrasound evidence of SOS |

*EBMT* European Society for Blood and Marrow Transplantation; *SOS* sinusoidal obstruction syndrome

Adapted from Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2016;51(7):906–912

Primary prophylaxis for patients who are at risk for SOS is UDCA. UDCA prophylaxis has been shown to decrease mortality unrelated to relapse and increase overall survival patients with HSCT. For patients with moderate to severe SOS, defibrotide can be used. Defibrotide has antithrombotic, fibrinolytic and angiogenic properties. Defibrotide (25 mg/kg/d in 4 divided doses) for 21 days was found to improve post-HSCT survival. If SOS symptoms resolve quickly after starting therapy, treatment duration of defibrotide can be shortened to 14 days.

Patients with SOS do not usually present with ALF [15].

## Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of common hepatic steatotic disorders ranging from non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatits (NASH) to advanced fibrosis and cirrhosis. NAFL is defined as the presence of more than 5% hepatic steatosis (HS) whereas NASH is defined as the presence of more than 5% HS with evidence of inflammation, hepatocellular injury and ballooning hepatocytes. Approximately 25% of patients with NASH can progress to advanced fibrosis and cirrhosis. The incidence rate of NAFLD is estimated as 29.7 per 1000 persons annually. It is estimated that the global prevalence of NAFLD is approximately 25%. The prevalence of NASH among NAFLD patients is estimated from 7% to 30%. The major risk factors for NAFLD are features of metabolic syndrome (MetS) such as obesity, type 2 diabetes mellitus (T2DM) and dyslipidemia. NAFLD patients are at increased mortality risk from cardiovascular diseases. Advanced fibrosis is the most important independent predictor of NAFLD-associated mortality.

Patients with NASH (elevated transaminases: classically ALT > AST) should be investigated to rule out other causes of liver diseases with serologies and biomarkers. Patients with only HS do not need an extensive work up. The useful non-invasive screening tools for patients with NAFLD include fibrosis-4 index (FIB-4), vibration-controlled transient elastography (VCTE) and MRE (magnetic resonance elastography). FIB-4 is based on a calculation of blood tests and it is particularly helpful in identifying NAFLD patients with high grade fibrosis (stage 3) or cirrhosis (stage 4). VCTE is an office-based, point-of-care test is useful in screening of HS and fibrosis, however its validity is limited in patients with BMI > 40, congestive heart failure, cholestasis and severe inflammation. Liver biopsy is the gold standard in the assessment of NASH and fibrosis with histopathological findings of steatosis, lobular and portal inflammation and hepatocellular ballooning. The severity of inflammation can be described as mild, moderate or severe by using NAFLD Activity (NAS) Score. Trichrome stain can quantify the severity of fibrosis.

The keystone of NAFLD management is counseling for life-style modifications to lose weight with modified hypocaloric diet (800 kcl/day) in conjunction with moderate to high intensity physical exercise, control T2DM and dyslipidemia. 3–5% of weight reduction has been shown to improve HS. However, 7–10% of

weight reduction is usually necessary to improve steatohepatitis and fibrosis. There is no current FDA-approved medication to treat NASH/NAFLD. PIVENS trial demonstrated that pioglitazone can improve steatohepatitis in patients with biopsy-proven NASH. The current literature does not recommend pioglitazone to treat NAFLD without biopsy-proven NASH. Glucagon-like peptide-1 (GLP-1) agonists such as liraglutide has been associated with weight loss, resolution of steatohepatitis and delayed progression of fibrosis. However, due to the lack of strong evidence, we do not recommend GLP-1 agonists to specifically treat NAFLD without T2DM. GLI-1 agonists or pioglitazone should be considered in NAFLD patients with T2DM. For non-diabetic patients with biopsy-proven NASH, 800 IU/day vitamin E is recommended as it has been associated with improvement in steatohepatitis. High dose vitamin E > 800 IU/day has been linked with higher all-cause mortality and thus should be avoided. Vitamin E has also been associated with a slight increase in prostate cancer risk in a large clinical trial in 2011. Therefore, we do not recommend vitamin E for all patients with NAFL without biopsy-proven NASH as its risk may outweigh the benefit. Studies have shown that statins can improve hepatic steatosis and statins can be used to treat dyslipidemia in patients with NAFLD. OCA, FDA-approved treatment for PBC, has shown positive outcomes in NASH patients. However, it is premature to prescribe off-label OCA to treat NAFLD until further safety and efficacy data becomes available. Several other agents have been studied to treat NAFLD. Clinical trials of selonsertib, a potent apoptosis signal-regulating kinase-1 (ASK-1) inhibitor, and emricasan, a caspase inhibitor, did not meet primary outcome for NASH treatment. Several other agents, such as cotadutie (GLP-1 agonist), licogliflozin (SLGT1-2 inhibitor), tropifexor (FXR agonist), saroglitazar (peroxisome proliferator-activated receptor agonist) are being investigated in clinical trials for NAFLD treatment.

NASH cirrhosis is the second common etiology of liver transplantation in the United States and it is en route to becoming the leading cause of LT due to rising incidence of NAFLD. It is very important to carefully risk stratify patients with NASH cirrhosis for occult cardiovascular diseases before LT listing due to their unique high risk. Calcineurin inhibitors and corticosteroids use in LT recipient can exacerbate diabetes and insulin resistance. Therefore, LT recipients due to NASH cirrhosis need ongoing counseling to maintain normal glucose homeostasis, healthy weight and diet. NASH is a progressive chronic condition which can lead to chronic liver failure; however, it does not present with ALF [16].

## Wilson Disease

Wilson disease (WD) is a rare genetic disorder of copper metabolism characterized by excessive copper deposition predominantly in the liver and brain but also in other organ-tissues. WD can cause hepatic dysfunction as well as neuropsychiatric disorders. It was named after Samuel Wilson, an American-born British neurologist, who first described “hepatolenticular degeneration”. WD is an autosomal recessive

inherited disorder caused by a mutation in the Wilson disease protein ATP7B gene. ATP7B is a P-type ATPase which is responsible for transporting excess copper into bile. WD occurs in approximately 1 in 30,000 people. Most patients with WD present with clinical manifestation in younger life between the age of 5 and 35 years.

Patients with WD can present with chronic active hepatitis, cirrhosis and acute hepatitis with ALF. Most WD patients with chronic hepatitis have cirrhosis on initial presentation. Clinical manifestations are complications of portal hypertension such as ascites, hepatic encephalopathy, variceal bleeding. The distinct features of WD are low alkaline phosphatase level and Coombs-negative hemolytic anemia. Alkaline phosphatase:bilirubin ratio tends to be less than 4 and AST:ALT ration tends to be >2.2 in patients with WD. Neuropsychiatric manifestations are also common in WD such as classic "wing-beating tremor", ataxia, slurred speech, dystonia, bradykinesia, and behavioral changes such as impulsivity, impaired judgement, apathy, executive dysfunction, depression, anxiety and psychosis in extreme cases. Other organ-specific manifestations include Kayser-Fleischer rings (KF rings), copper deposition in Descemet's membrane in the cornea, type 2 renal tubular acidosis, cardiomyopathy, hypoparathyroidism, infertility and recurrent miscarriage.

The initial diagnostic workup for WD is to check serum ceruloplasmin level [13]. Ceruloplasmin level less than 20 mg/dL suggests a diagnosis of WD and warrant proceeding with 24-h urine copper confirmation test. Serum ceruloplasmin level less than 20 mg/dL with 24-h urine copper more than 40 mcg per day fulfills criteria for WD diagnosis. Presence of KF rings is pathognomonic for WD if detected on slit-lamp examination. However, only 50% of patients with WD develop KF rings. Patients with indeterminate findings of ceruloplasmin and urine copper levels need liver biopsy for definitive diagnosis. Dry weight of hepatic copper concentration more than 250 μg/g is a gold standard test to establish WD diagnosis. For patients with indeterminate findings, Leipzig scoring system [17] (Table 13.4) can be used to make the diagnosis of WD. Molecular testing for ATP7B gene mutation can be performed for screening in first- and second-degree relatives of patients with WD.

The management of WD includes avoiding copper-rich foods such as mushrooms, nuts, chocolate, dried fruit, liver and shellfish as well as copper chelation therapies. D-penicillamine or trientine can be used as a first-line chelating agent in WD. D-penicillamine has many potential adverse effects such as skin reactions, bone marrow toxicity with severe thrombocytopenia or neutropenia and proteinuria. Approximately 30% of patients who start on D-penicillamine discontinue it due to severe side effects. Trientine is found to be very effective in treating WD without serious adverse effects. Trientine should be considered as a first-line chelating agent. Zinc supplementation may be effective as a first-line therapy in treating WD with neurological symptoms.

2–5% of all ALF cases comprise of WD (WD-ALF) patients. Historically, WD-ALF has been considered uniformly fatal without a liver transplantation. Any WD patients who present with ALF should be promptly transferred to a liver transplant center for an immediate LT evaluation/and listing. New Wilson Index

**Table 13.4** Leipzig Score: Wilson Disease Diagnosis Scoring System

| Typical signs and symptoms | Scores |
|---|---|
| KF rings | |
| Present | 2 |
| Absent | 0 |
| Neurologic symptoms | |
| Severe | 2 |
| Mild | 1 |
| Absent | 0 |
| Serum ceruloplasmin | |
| Normal (>20 g/dL) | 0 |
| 10–20 g/dL | 1 |
| <10 g/dL | 2 |
| Coombs-negative hemolytic anemia | |
| Present | 1 |
| Absent | 0 |
| Other tests | |
| Liver copper (in the absence of cholestasis) | |
| >100 mcg/g | 2 |
| 20–100 mcg/g | 1 |
| <20 mcg/g | −1 |
| Rhodanine-positive granules | 1 |
| Urinary copper | |
| Normal | 0 |
| 1–2× upper normal limit | 1 |
| >2× upper normal limit | 2 |
| Normal, >5× upper normal limit after D-penicillamine | 2 |
| Mutation analysis | |
| On both chromosomes detected | 4 |
| On 1 chromosome detected | 1 |
| No mutation detected | 0 |

Total score: 4 or more—diagnosis established; 3—diagnosis possible, more tests needed; 2 or less—diagnosis very unlikely

Adapted from Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease. Liver Int. 2003;23(3):139–142; with permission

(Table 13.5) scoring system can be utilized in predicting clinical outcome in patients with WD-ALF. WD-ALF patients with new Wilson Index score > 10 have very high risk of mortality without liver transplantation. According to the recent ALFSG registry study, the prognosis of WD patients with severe acute liver injury (ALI) without hepatic encephalopathy can differ from WD-ALF. Some patients with WD-ALI survived without requiring liver transplantation. It is essential to identify patients with WD-ALI among patients presenting with fulminant picture and to initiate medical chelating therapy promptly in order to avoid liver transplantation. New Wilson Index score > 10 provides a predictor of poor outcomes in WD-ALI patient [18].

**Table 13.5** Revised Wilson Disease Index

| Albumin | AST | Bilirubin | INR | White cell count ($10^9$/L) | Scores |
|---|---|---|---|---|---|
| 4.5 | 0–100 | 0–1 | 0–1.29 | 0–6.7 | 0 |
| 3.4–4.4 | 101–150 | 1–2 | 1.3–1.6 | 6.8–8.3 | 1 |
| 2.5–3.3 | 151–300 | 2–2.5 | 1.7–1.9 | 8.4–10.3 | 2 |
| 2.1–2.4 | 301–400 | 2.6–3.5 | 2–2.4 | 10.4–15.3 | 3 |
| <2 | >401 | >3.5 | >2.5 | >15.4 | 4 |

A score ≥ 11 using the new Wilson Index has a sensitivity and specificity of 93% and 97%, and positive predictive value and negative predictive values of 92% and 97%, respectively
*INR* international normalized ratio
Adapted from Dhawan A, Taylor RM, Cheeseman P, et al. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. Liver Transpl. 2005;11(4):441–448; with permission

## Pregnancy-Associated Acute Liver Diseases

Pregnancy-associated acute liver diseases (PAALD) are rare pregnancy-specific conditions characterized by acute liver injury or ALF occurs in pregnant women. However, 50% of ALF cases in pregnancy accounts for acetaminophen overdose. PAALDs include acute fatty liver of pregnancy (AFLP); hemolysis, elevated liver enzymes, low platelet counts (HELLP) syndrome and mixed conditions and pre-eclampsia. Intrahepatic cholestasis of pregnancy (ICP) usually presents with chronic liver injury, therefore ICP will not be discussed in this chapter. While preeclampsia can occur in the second and third trimester of pregnancy while pregnant patients with HELLP syndrome and AFLP classically present in the third trimester. PAALD imposes serious risks to both the mother and the fetus. Maternal complications include placental abruption, disseminated intravascular coagulopathy (DIC) and death. Possible fetal complications are intrauterine growth retardation (IUGR), hypoxic neurologic injury with long-term consequences, preterm delivery, fetal demise and perinatal death.

## Preeclampsia and HELLP Syndrome

Preeclampsia is the most common cause of PAALD. Approximately 3% of pregnant women develops preeclampsia. The pathophysiology of preeclampsia is secondary to the maternal reaction to the placenta. Risk factors for preeclampsia include Obesity, advanced maternal age, nulliparity, multifetal gestation and prior history of preeclampsia. Lower extremity edema, proteinuria and hypertension are the three cardinal manifestations of preeclampsia. Approximately 20% of patients with pre-eclampsia can progress to HELLP syndrome. Hemolysis, elevated liver enzymes, thrombocytopenia are the hallmark of HELLP syndrome. The fatal complication of severe preeclampsia and HELLP syndrome is hepatic rupture and capsular hematoma (Glisson capsule). Hepatic artery embolization by Interventional Radiology is

the preferred first-line treatment of hepatic rupture and hematoma. If unsuccessful, surgery may be required to control hemorrhage. Corticosteroids, magnesium sulfate and systolic blood pressure control with anti-hypertensive agents have been used to improve maternal outcomes in HELLP syndrome. More recent data by a Cochrane review demonstrated that there was no maternal morbidity or mortality benefit as well as fetal demise risk in patients with HELLP syndrome who were treated with corticosteroids. Therefore, corticosteroids such as dexamethasone should be used only to induce fetal lung maturity by producing surfactant. The principal management of severe preeclampsia, eclampsia with seizures or HELLP syndrome is urgent delivery after 34 weeks of gestation. Patients with HELLP syndrome can progress to ALF and liver transplantation is seldomly necessary as the last resort lifesaving treatment [19].

## Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare entity which can affect 1 in 10,000 to 15,000 pregnant women in the third trimester or during the postpartum period. AFLP is characterized by severe liver injury due to microvascular steatosis and it can progress to ALF. AFLP presenting with ALF can be fatal and those patients require liver transplantation. Maternal mortality rate of AFLP can range from 2% to 11%. The underlying pathophysiology of AFLP is due to mitochondrial defects in fetal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD). These defects can result in excessive accumulation of fatty acids in the maternal hepatocytes which cause oxidative stress, lipotoxicity, inflammation and finally hepatocyte necrosis. It is critical to identify AFLP early to avoid fetal and maternal bad outcomes. Children of patients with AFLP should be monitored LCHAD deficiency.

Patients with AFLP present with abdominal pain, vomiting, elevated aminotransferases, jaundice, hypoglycemia, leukocytosis and acute kidney injury. AFLP with ALF can manifest with hepatic encephalopathy, hyperammonemia, coagulopathy and signs of portal hypertension such as ascites. The diagnosis is based on clinical findings. The Swansea criteria [16] (Table 13.6) can be used to establish the diagnosis of AFLP if 6 or more parameters are present. The Swansea criteria provides 85% positive predictive value and 100% negative predictive value.

Approximately 10–37.5% of AFLP patients can present with signs and symptoms of ALF. Compared to other PAALD, patients with AFLP are likely to have greater chance of hepatic encephalopathy, requirement of ventilation due to hypoxic respiratory failure, severe coagulopathy and acute kidney failure. The management of AFLP includes adequate dextrose/glucose intake (>2000 kcal/day), adequate blood transfusion support prior to delivery, broad-spectrum antibiotic prophylaxis and urgent cesarean section delivery. The algorithmic management protocol for AFLP is outlined in Fig. 13.2. Sometimes, hepatic dysfunction and liver injury of AFLP patients can continue to deteriorate in early postpartum period even after the delivery.

**Table 13.6** Swansea criteria for diagnosis of acute fatty liver of pregnancy

| **Six or more following features in the absence of another cause** | |
|---|---|
| 1. | Abdominal pain |
| 2. | Vomiting |
| 3. | Encephalopathy |
| 4. | Elevated aminotransferases (AST or ALT) >42 mg/dL |
| 5. | Elevated bilirubin >1.5 mg/dL |
| 6. | Elevated BUN >34 mg/dL |
| 7. | Leukocytosis $11 \times 10^6$ |
| 8. | Elevated ammonia >47 mcg/L |
| 9. | Renal impairment with creatinine >1.5 mg/dL |
| 10. | Coagulopathy with prothrombin time > 14 s |
| 11. | Presence of ascites or bright liver on ultrasound |
| 12. | Microvesicular steatosis son liver biopsy |

Kingham JG. Swansea criteria for diagnosis of acute fatty liver of pregnancy [published online ahead of print, 2010 Oct 11]. Gut. 2010;https://doi.org/10.1136/gut.2010.222240

Based on ALFSG registry data, AFLP patients who underwent liver transplantation may have higher rates of graft rejection and graft survival compared to pregnant patients with other etiologies. These patients tend to have higher aminotransferases in post-transplant period compared to others and it is indicative of ongoing insult to the allograft from residual circulating toxic fatty acid metabolites. Nonadherence to immunosuppression could contribute to higher rejection rate in this population as new mothers may not comply with immunosuppressive regimens [20].

**Summary**

Patients with ALF are at high risk for morbidity and mortality. Recent advancements in surgical techniques in liver transplantation, intensive care management and immunosuppression agents have been instrumental in improvement of clinical outcomes in ALF. Although common causes of ALF are alcohol hepatitis, acetaminophen overdose, viral etiologies and drug-induced liver injury, it is crucial to recognize, identify and manage nonviral nondrug-induced liver injuries such as AIH, BCS, WD, ischemic hepatitis and PAALDs as early recognition leads to disease-specific therapy to salvage liver function and avoid liver transplantation. However, some patients with ALF will require liver transplantation as a life-saving treatment. Therefore, understanding of clinical manifestation, pathophysiology, diagnostic work up and treatment options for nonviral, inflammatory, vascular and metabolic causes of acute liver injury is necessary.

**Conflicts of interest** Authors declare no conflicts of interest pertinent to this manuscript.

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# Chapter 14
# Alcoholic Hepatitis and Alcohol-Related Acute on Chronic Liver Failure

**Joseph C. Ahn and Vijay H. Shah**

**Key Concepts**

- Severe alcoholic hepatitis (AH) is defined by Maddrey discriminant function ≥32 or MELD score ≥ 20, and is associated with a high risk of acute-on-chronic liver failure and 30–40% risk of 1-month mortality.
- Alcohol-related acute-on-chronic liver failure (ALD-ACLF) is defined by presence of hepatic and extrahepatic organ system failures. For patients with ALD-ACLF, the CLIF-C ACLF scoring system should be used for predicting outcomes.
- A clinical diagnosis of probable AH can be made in patients with history of heavy drinking and typical liver enzyme abnormalities, but a liver biopsy is needed to make a definitive diagnosis of AH.
- Corticosteroids remain the only approved pharmacologic therapy for severe AH, but their utility is limited by lack of long-term survival benefit, significant portion of non-responders, and increased risk of infection and GI bleeding.
- The role of corticosteroids is unclear in ALD-ACLF, as the response rate significantly decreases with worsening grade of ACLF. ALD-ACLF patients who do respond to corticosteroids appear to receive survival benefits.
- Early liver transplantation prior to the traditional 6-month sobriety period can be an effective curative option in select patients with severe AH and ALD-ACLF.

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## Introduction

Alcoholic hepatitis (AH) is a distinct clinical syndrome which occurs in patients with chronic and active heavy alcohol consumption. Patients present with symptoms and signs of liver disease such as jaundice, right upper quadrant pain and elevated liver enzymes, as well as systemic inflammatory response syndrome (SIRS) [1]. Those with severe AH can progress to alcohol-related acute-on-chronic liver failure (ALD-ACLF) with hepatic and extrahepatic organ system failures, and have up to 30–40% risk of death within a month from the initial presentation [2]. Given the high morbidity and mortality associated with this condition, accurate diagnosis and assessment of disease severity are essential in order to identify patients who are candidates for specific therapeutic options. The management of AH is primarily supportive, consisting of alcohol abstinence, nutritional supplementation, and treatment of superimposed infections. The only available pharmacologic therapy for severe AH is corticosteroids, but they have no proven long-term mortality benefit beyond one month. Moreover, corticosteroid use is often limited by a significant proportion of non-responders, as well as increased risk of infections and gastrointestinal bleeding [3]. New therapies and molecules targeting different pathways in the AH and ALD-ACLF pathophysiology are being investigated, and many clinical trials are underway. Recently, early liver transplantation prior to the traditional 6-month sobriety period has emerged as a promising curative option for certain patients with severe AH and ALD-ACLF. This chapter will review the currently available diagnostic and therapeutic options for AH and ALD-ACLF, and also outline the recent advancements in treatment, role of liver transplantation, as well as emerging novel biomarkers.

## Pathophysiology of AH and ALD-ACLF

The pathophysiology of AH and ALD-ACLF involves a complex interplay of various pathways which involve direct hepatocyte injury as well as indirect liver damage from intestinal dysbiosis (Fig. 14.1) [4]. Chronic alcohol consumption leads to small intestinal bacterial overgrowth (SIBO) by destroying Paneth cells which are key effectors of innate mucosal defense in the small intestine [5]. In addition to SIBO, there may be intestinal dysbiosis of fungi and viruses as well [6]. Alcohol also increases gut permeability by disrupting the integrity of the gut mucosa, through both the direct action of alcohol on the intestinal epithelium and/or through indirect effects of circulating blood alcohol. The combination of intestinal dysbiosis and increased gut permeability leads to increased translocation and delivery of bacterial products through the portal vein into the liver. In the liver, the bacterial

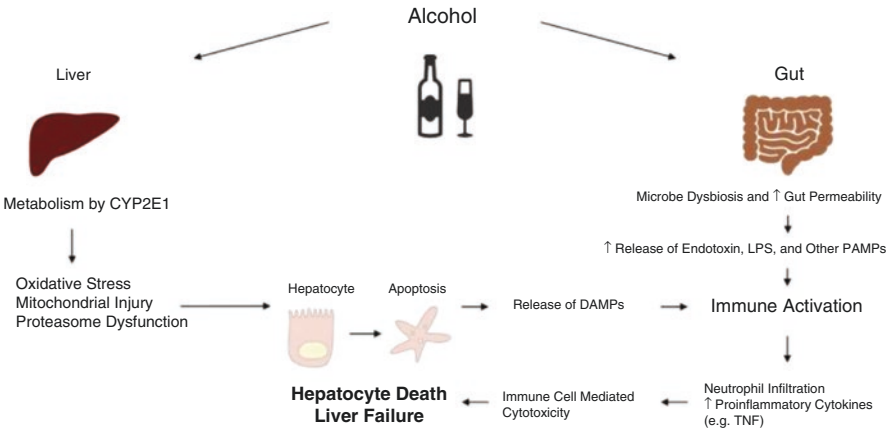


**Fig. 14.1** Pathophysiology of alcoholic hepatitis. Source: Liu M, Shah VH. New Prospects for Medical Management of Acute Alcoholic Hepatitis. Clin Liver Dis (Hoboken). 2019;13 (5):131–5

products cause a sterile necrosis response mediated by pathogen associated molecular patterns (PAMPs). Bacterial lipopolysaccharide (LPS) stimulates toll-like receptors (TLR-4) on macrophages and cause them to release pro-inflammatory cytokines, triggering an inflammatory cascade in the liver [7]. Alcohol and its metabolite, aldehyde, can also cause direct oxidative stress and injury to the liver. This leads to apoptosis and necrosis of hepatocytes with release of damage associated molecular patterns (DAMPs) which also stimulate liver macrophages to promote even more inflammation [7].

The inflammatory cascade in AH involves both pro- and anti-inflammatory pathways, and the complex interplay of these pathways may ultimately determine whether the disease eventually resolves or leads to ALD-ACLF and death [8]. Pro-inflammatory cytokines such as TNF-alpha and interleukin-1 (IL-1) are upregulated in AH and responsible for increased release of reactive oxygen species (ROS), causing hepatocyte death and severe depletion of glutathione. In response to this, Kupffer cells activate factors such as IL-8 and chemokines which recruit neutrophils, and IL-10, IL-22, and INF-gamma which promote hepatocyte regeneration [1, 9]. AH also causes liver fibrosis and portal hypertension by activation of hepatic stellate cells. When activated by hepatic macrophages, Kupffer cells or bacterial LPS, stellate cells increase collagen tissue production and decrease endothelial nitric oxide synthase. Ethanol can also block natural killer (NK) cells' ability to combat hepatic fibrogenesis [9]. With worsening severity of ALD-ACLF, there appears to be a shift of the balance in immunity towards an anti-inflammatory phenotype, leading to a very high risk of infection and death [10].

## Clinical Manifestations

AH is suspected in patients with known alcoholic liver disease or history of heavy alcohol use who present with rapid onset of jaundice and clinical decompensation. Many patients with AH drink until the day of presentation and require treatment for concurrent alcohol withdrawal, while other patients with AH may have been abstinent for up to 60 days prior to presentation. Patients commonly complain of upper abdominal pain, nausea, vomiting, malaise and loss of appetite. On physical examination, there may be findings suggestive of cirrhosis or its complications such as jaundice, ascites, sarcopenia, palmar erythema and hepatic encephalopathy. Those with severe AH often exhibit features of systemic inflammatory response syndrome (SIRS) as defined by two or more of the following criteria: temperature >38 °C or <36 °C; heart rate >90 beats/min; respiration >20/min; WBC >12,000/μL or <4000/μL or >10% immature forms. SIRS is frequently seen in AH even in the absence of infection, but presence of SIRS warrants a proper infectious work up as around 25% of AH patients with SIRS have concurrent infection, mainly spontaneous bacterial peritonitis (SBP), bacteremia and urinary tract infection [11, 12].

Patients with severe AH are at risk of developing ALD-ACLF, a syndrome of acute deterioration with organ system failures and high short-term mortality which occurs in patients with underlying chronic liver disease [10]. ALD-ACLF have been reported in 65% of patients with severe AH either at the time of severe AH diagnosis or within a six-month follow-up period [13]. Bacterial infection and continued alcohol consumption are the most common precipitants of ALD-ACLF in AH patients, but superimposed viral hepatitis, drug-induced liver injury or ischemic events can also lead to ALD-ACLF [14].

## Diagnosis of AH

Clinical diagnosis of AH requires presence of hepatitis with documented history of heavy alcohol use as the most likely etiology, and exclusion of other known causes of liver disease. Hepatitis manifests with rapid onset of jaundice and liver enzyme abnormalities including serum bilirubin ≥3 mg/dl, aspartate aminotransferase (AST) >50 IU/ml and <500 IU/ml, and an AST: alanine aminotransferase (ALT) ratio of >1.5.1 [15]. A detailed history must be obtained to quantify alcohol consumption and time of last drink, often with corroboration of information from family members or close friends [16]. In general, average consumption of three or more drinks (40 grams) per day for women and four or more drinks (50–60 g) per day for men is accepted as a minimal threshold for diagnosis of AH. Duration of alcohol use is typically for years, and for diagnosis of AH should include the period within two months of presentation [2]. Additional blood tests should be performed to exclude autoimmune, metabolic, viral and other causes of liver disease. A useful score which can assist with the diagnosis of AH in the setting of uncertain history is the

Alcohol-associated Liver Disease (ALD)/Non-Alcoholic Fatty Liver Disease (NAFLD) Index (ANI) [17]. ANI was generated based on logistic regression using variables such as MCV, AST/ALT ratio, BMI and gender, with ANI of greater than 0 incrementally favoring ALD, and ANI of less than 0 incrementally favoring NAFLD, thus making ALD unlikely. ANI of >2.2 or less than −2.2 provides a relatively clear diagnosis, corresponding to a 92.4% or 8.2% probability of ALD, respectively [17]. The National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded Alcoholic Hepatitis Consortia stratified diagnosis of AH according to degree of certainty as following: (1) *Definite AH*: Clinically diagnosed and biopsy proven; (2) *Probable AH*: Clinically diagnosed AH without confounding variables (patients with heavy alcohol use and typical liver tests, along with exclusion of other liver diseases); and (3) *Possible AH*: Clinically diagnosed but with potential confounding variables including other possibilities and atypical laboratory tests [15]. Figure 14.2 reviews an algorithm for diagnosis of alcoholic hepatitis according to the above criteria [2].

The European Association for Study of Liver (EASL) recommends a liver biopsy to establish a definitive diagnosis of AH [18], since up to 30% of patients clinically diagnosed with AH are found to have an alternative diagnosis on liver biopsy [19]. The American College of Gastroenterology recommends a transjugular liver biopsy in patients with suspected AH when the clinical diagnosis is confounded by another liver disease etiology or there is uncertainty on alcohol consumption history [16]. Diagnostic findings of AH on histology include macrovesicular steatosis, neutrophil infiltration, hepatocyte injury (ballooning), and Mallory-Denk bodies [2, 3, 20]. Fibrosis is always present to varying degrees, and follow a "chicken-wire" pattern

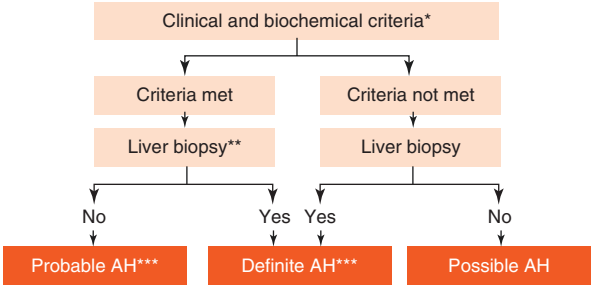


**Fig. 14.2** Algorithm for diagnosis of alcoholic hepatitis. Algorithm for diagnosis of alcoholic hepatitis. *Clinical criteria: Heavy alcohol use (>2 drinks in females and >3 drinks in males) for >5 years; Active alcohol use until at least 8 weeks prior to presentation; Recent (<1 month) onset or worsening of jaundice; Exclude other liver diseases, biliary obstruction, HCC. *Biochemical criteria: Serum bilirubin >3 mg/dl, AST >50 and <500, AST > ALT by 1.5:1; **Transjugular route preferred for obtaining the liver tissue. **Characteristic histological findings: Cell ballooning, neutrophil infiltration, cholestasis, varying degree of steatosis and fibrosis. ***Needed for inclusion in clinical trials and before starting specific pharmacologic therapy. *AH* alcoholic hepatitis; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *HCC* hepatocellular carcinoma. Source: Singal AK, Louvet A, Shah VH, Kamath PS. Grand Rounds: Alcoholic Hepatitis. Journal of hepatology. 2018;69(2):534–43

with fibrotic tissue deposition in the pericellular and/or perivenular spaces; the majority of patients with severe AH have cirrhosis [1, 20]. In addition to providing a definitive diagnosis, liver biopsy may also provide useful prognostic information. AH histologic score, a scoring system based on the degree of fibrosis, degree of neutrophil infiltration, type of bilirubin stasis and presence of mega mitochondria, helps identify patients with high 90-day mortality [20]. A more recent study also showed that certain histological parameters in severe AH, ballooning degeneration, and Mallory-Denk bodies can reliably identify patients who are non-responders to corticosteroids [21].

Transjugular approach is preferred over percutaneous approach for liver biopsy, as patients with AH often have ascites and coagulopathy [16]. Transjugular liver biopsy is successful at providing histological diagnosis in 96.1% of specimens, and has an excellent safety profile with 0.09% mortality (hemorrhage in 0.06%; ventricular arrhythmia in 0.03%) [22]. Transjugular approach also allows measurement of hepatic venous pressure gradient (HVPG), which has been shown to provide important prognostic information on the short-term outcome of patients with severe AH [23]. In practice, however, the use of liver biopsy is limited by the reluctance of both physicians and patients and is mostly reserved for patients whose diagnosis is *Possible AH* according to the NIAAA criteria.

## *Non-invasive Biomarkers for AH Diagnosis*

In practice, the use of liver biopsy is limited by the reluctance of both physicians and patients and is mostly reserved for when the clinical diagnosis of AH is uncertain. Therefore, there is a clear need for non-invasive biomarkers for diagnosis of AH. Researchers have investigated various markers of inflammation as biomarkers for AH. For example, CCL20 is a pro-inflammatory cytokine implicated LPS-induced liver injury and its levels are increased in patients with AH [24]. Elevation of M1 Kupffer class over M2 Kupffer class of macrophages is associated with AH and liver damage [25]. Novel liquid biopsy techniques also suggest association of certain types of microRNAs (miRNAs) and extracellular vesicles with AH [26]. For example, the release of CD-40 containing extracellular vesicles are significantly increased when hepatocytes are exposed to alcohol [27]. Mitochondrial oxygen consumption rate can stratify patients with decompensated ALD into those with and without AH. In addition, breath levels of volatile substances such as trimethylamine and pentane demonstrated high sensitivity and specificity for diagnosing AH [28]. Mainly studied in patients with non-alcoholic steatohepatitis, three-dimensional magnetic resonance elastography (3D-MRE) has an ability to discriminate inflammation from fibrosis and could be a valuable imaging biomarker in patients with AH [29]. Though promising, most of the non-invasive biomarkers to date are limited by their availability, cost and lack of validation in large studies [1].

## Predicting Disease Severity and Prognosis

Several scoring systems have been used to identify AH patients with severe disease and higher risk of ALD-ACLF and mortality who may benefit from specific therapeutic options. Developed in the 1970s, the Maddrey discriminant function (MDF) is calculated using two variables as following: 4.6 × (patient's prothrombin time − control) × serum bilirubin (mg/dL). The MDF has been extensively validated with a score of ≥32 predicting mortality of over 50% within two months, and the MDF score of ≥32 has been widely used to select patients for corticosteroid treatments [30]. However, the MDF is limited by the variability of prothrombin time, a lower but significant risk of death in patients with MDF < 32, and cannot be used to assess response to treatment [2].

The model for end-stage liver disease (MELD) score uses three variables of INR, serum creatinine and serum bilirubin and can also reliably estimate the severity of AH [31]. The INR used in the MELD score is more reproducible than the prothrombin time which is used in the MDF [2]. A MELD score of ≥20 is used as the threshold for diagnosis of severe AH and is associated with 20% mortality at 90 days. Patients with MELD score <11 are classified as having mild AH, and their risk of mortality is negligible [31]. The American Association for the Study of Liver Diseases (AASLD) suggests using serial calculation of the MELD score as a method of evaluating a patient's condition over time [32]. The newer version of MELD, MELD-Na is not superior to the MELD score in AH patients without ascites, as hyponatremia in AH is often due to beer potomania instead of truly reflecting the degree of hepatic decompensation [33]. The Age, serum Bilirubin, INR, and serum Creatinine (ABIC) score is a variation of MELD score used to stratify risk of death in patients with AH at 90 days and 1 year. An ABIC score <6.71 predicts survival rate close to 100% at 90 days, while an ABIC score >9 is associated with 90-day survival rate of only 25% [34]. Another prediction model, the Glasgow alcoholic hepatitis score (GAHS) uses age, white cell count, urea, prothrombin ratio or INR, and serum bilirubin with a score ≥9 predicting a poor outcome [35]. In 2014, a comparison of nine prognostic models showed that MELD, MDF, GAHS, ABIC and scores of corticosteroid response all proved to be valid in an independent cohort of biopsy-proven alcoholic hepatitis, with the MELD score being superior to all other scores in determining 30-day mortality as well as 90-day mortality [36].

The presence of SIRS during hospitalization, as well as serum markers of inflammation such as LPS, procalcitonin, and C-reactive protein can predict ACLF and death in AH patients [13]. Other novel biomarkers that are being studied to estimate disease severity and prognosis in AH include extracellular vesicles [27], byproducts of lipid peroxidation such as malondialdehyde (MDA) [37], lipidomic profile with evidence of triglyceride lipolysis [38], inflammatory markers such as IL-6 [39] and CCL-20 [24], CK-18 fragments [40], matrix proteins such as osteopontin [41] and circulating microbiome [42].

For patients with ALD-ACLF, the CLIF-C ACLF score uses parameters of following organ system failures: hepatic (bilirubin), renal (creatinine and renal

replacement therapy), neurologic (West-Haven grade for hepatic encephalopathy), hematologic (INR), circulatory (mean arterial pressure and use of vasopressors), and respiratory (PaO2 and mechanical ventilation) [43]. Based on the number and the severity of organ system failures, the CLIF-C ACLF score categorizes patients into following categories: no ACLF, ACLF grade 1, ACLF grade 2 and ACLF grade 3. When used in patients with ACLF and cirrhotic patients admitted to the intensive care unit, the CLIF-C ACLF score demonstrated significantly superior prediction of short and medium-term mortality compared to the classical scores including MELD, MELD-Na, and Child-Pugh scores [43].

## Treatment of AH and ALD-ACLF

### *General Measures*

Regardless of the severity, the cornerstone of therapy and the most important determinant of long-term prognosis in AH is alcohol abstinence [18]. In order to prevent relapse, combination of both behavioral and pharmacologic therapy is encouraged. Patients with recent history of drinking should also be monitored and treated for symptoms/signs of alcohol withdrawal and supplemented with B-complex vitamins to prevent Wernicke's encephalopathy. In addition, patients should be treated for events of hepatic decompensation such as hepatic encephalopathy, ascites, variceal bleeding and renal failure. Of note, AH patients with acute kidney injury (AKI) have significantly higher 90-day mortality compared to those without AKI [44]. Therefore, providers must take measures aimed at preventing the development of AKI such as volume expansion and avoidance of diuretics and nephrotoxic drugs [18]. Patients with AH are also at significantly higher risk of developing infections, and complete infectious work up including work up for underlying spontaneous bacterial peritonitis is recommended.

### *Nutrition*

Protein-calorie malnutrition is present in almost every patient with severe AH, and the severity of malnutrition is correlated with disease severity and outcomes [45]. AH patients are also universally deficient in vitamins and trace minerals, including vitamin A, vitamin D, thiamine, folate, pyridoxine, and zinc [46]. Several clinical trials of anabolic steroids, nutritional supplementation, or aggressive enteral feeding showed improvement in biochemical markers but were mostly unable to demonstrate an improvement in short-term survival [47]. In some trials, however, subgroups of patients who achieved nutritional goals and positive nitrogen balance did have improved survival compared to those who did not [48]. More recently, a

multicenter randomized controlled trial studied the effects of intensive enteral nutrition via tube feeding in patients with severe AH receiving corticosteroids [49]. Although patients in the intensive enteral nutrition group did not have improved survival compared to those receiving conventional nutrition, it was noted that half of the patients in the intensive enteral nutrition group prematurely withdrew the feeding tube [49]. Moreover, a post hoc analysis of this study showed that, regardless of the assigned group, patients with a daily calorie intake below 21.5 kcal/kg of body weight had significantly higher 1- and 6-month mortality as well as risk of infections. Thus, practice guidelines recommend nutritional optimization of severe AH patients by targeting 35–40 kcal/kg of BW and a daily protein intake of 1.2–1.5 g/kg [18]. Parenteral nutrition is currently not recommended given lack of sufficient evidence and increased risk of infection, but may be used in patients who cannot tolerate enteral nutrition.

## *Pharmacologic Treatment*

Corticosteroids are the most extensively studied and widely adopted pharmacologic treatment in severe AH. They suppress cellular immunity, thereby reducing cytokine signaling and inflammation in the liver [1]. However, survival benefit has been observed in only about 50–60% of patients and limited to 1–2 months [50]. Also, close to 50% of patients with severe AH may have contraindications to corticosteroids such as infections, uncontrolled diabetes, gastrointestinal bleeding, and renal failure [13, 51]. Between 2011 and 2014, a large randomized controlled study of over 1,100 patients from 65 centers in the United Kingdom (STOPAH) was conducted to compare the survival benefits of corticosteroids (prednisolone 40 mg/day) and pentoxifylline in patients with severe AH [52]. While neither corticosteroids nor pentoxifylline provided statistically significant survival benefit over placebo, corticosteroids did demonstrate a trend for mortality benefit (13.8 vs 18%, $p = 0.06$), with 40% reduced risk of 28-day mortality [52]. There were no improvements in outcome at 90 days or 1 year, which was confirmed in a subsequent network meta-analysis [53]. Based on the evidence of short-term survival benefit, oral prednisolone 40 mg/day or intravenous methylprednisolone 32 mg/day for a maximum duration of 28 days is recommended as first-line therapy in patients with severe AH who do not have contraindications to corticosteroids [16].

However, approximately 40% of patients with severe AH do not respond to steroids, and continued steroid use is associated with increased risk of infection and gastrointestinal bleeding. Therefore, all patients with severe AH needed to be systematically screened for infection using tests including chest radiograph, ascitic fluid studies, blood and urine cultures prior to initiation of corticosteroids. Also, steroid non-responders need to be identified early so that unnecessary exposure can be limited. Notably, the probability of response to corticosteroids appears to be reduced in patients with ALD-ACLF compared to severe AH patients without

ACLF, with progressively decreasing response rate with increasing ACLF grades (52% for ACLF grade 1, 42% for ACLF grade 2, and 8% for ACLF grade 3) [54]. A subgroup analysis of STOPAH trial indeed confirmed the overall diminished response to corticosteroids and increased risk of infection in ALD-ACLF patients, but ALD-ACLF patients who did respond to corticosteroids received survival benefit regardless of their ACLF grades [55]. Thus, the role of corticosteroids in ALD-ACLF remains unclear based on the currently available data and patients should be considered on a case-by-case basis [14].

A 25% decrease in serum bilirubin at one week is considered to be a reasonable marker of steroid response [56]. Developed on biopsy proven severe AH patients, the Lille score is calculated at day 7 after initiation of the corticosteroid therapy to determine treatment response [50]. The Lille score is a linear score between 0 and 1 and is derived using age, renal function, prothrombin time, and albumin at initiation of treatment and the decrease in serum bilirubin at seven days [50]. If the Lille score of <0.45 indicates that the patient is responding to therapy and should be continued on corticosteroids for 28 days. On the other hand, a Lille score of ≥0.45 indicates non-response to corticosteroids with a high risk of death. Figure 14.3 illustrates an algorithm for surveillance of infection and starting/stopping of corticosteroids in patients with severe AH [2].

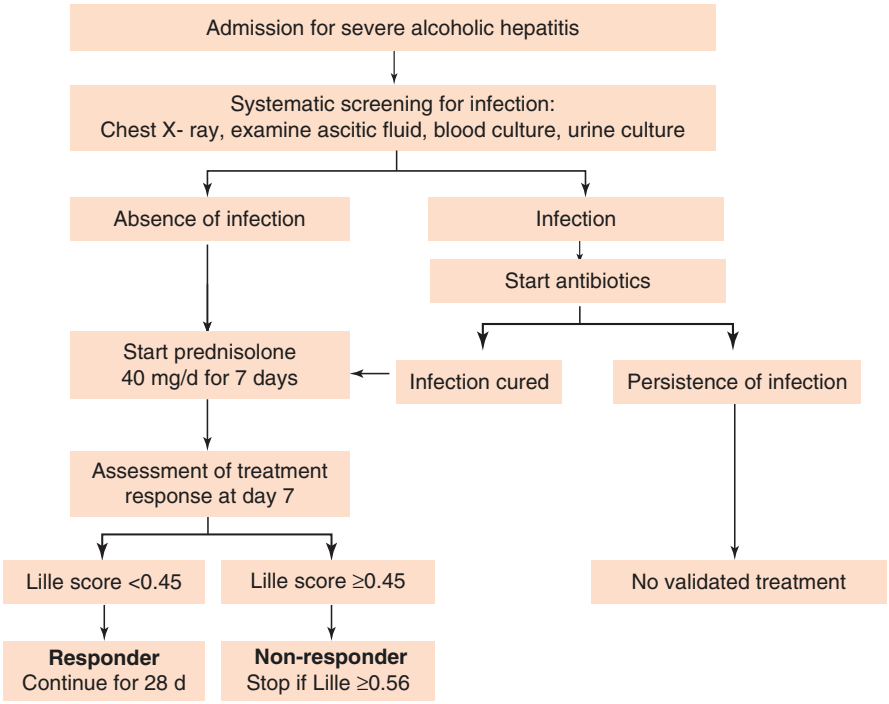


**Fig. 14.3** Algorithm for surveillance of infections and starting/stopping corticosteroids in patients with severe alcoholic hepatitis. Source: Singal AK, Louvet A, Shah VH, Kamath PS. Grand Rounds: Alcoholic Hepatitis. Journal of hepatology. 2018;69(2):534–43

Pentoxifylline is a phosphodiesterase inhibitor with an ability to inhibit TNF production, and has been extensively evaluated in the treatment of severe AH. The initial randomized trial comparing pentoxifylline to placebo showed that severe AH patients treated with PTX 400 mg three times a day for four weeks had significantly lower mortality during the index hospitalization (24.5% vs. 46.1%, p = 0.037), mainly due to a marked reduction in the incidence of hepatorenal syndrome rather than significant changes in liver function [57]. However, subsequent trials evaluating pentoxifylline failed to show improved survival [58]. The Corpentox study showed that pentoxifylline also did not improve the Lille score at 7 days or 6-month survival compared to placebo when used as an adjunct to prednisolone [59]. Pentoxifylline was also ineffective as a salvage therapy in non-responders to corticosteroids [60]. Finally, the STOPAH trial, the largest randomized controlled trial in AH to date, again demonstrated no survival benefit by pentoxifylline [52]. Therefore, societies recommend no role of pentoxifylline in the treatment of severe AH and ALD-ACLF [16, 18]. Other drugs including glutathione, anti-TNF agents, androgenic steroids, propylthiouracil, and vital therapy have failed to show any clinical benefit and have no role for treatment of AH [61–63].

## Emerging Treatment Strategies

### *Antioxidant Therapy*

As oxidative stress plays a key role in alcohol-mediated hepatotoxicity and leads to depletion of endogenous antioxidants, antioxidant therapy is of high theoretical interest in the treatment of severe AH. *N*-acetylcysteine (NAC) restores the body's glutathione store and is an effective first-line therapy for acetaminophen-induced hepatotoxicity. NAC was studied either alone or in combination with other antioxidants in several trials of severe AH, but most studies did not demonstrate survival benefit of NAC compared to standard medical therapy [64–66]. However, in A multicenter French trial comparing the effects of the combination of NAC and prednisolone to prednisolone and placebo, patients receiving five days of intravenous NAC plus prednisolone had significantly lower one month mortality compared to the prednisolone plus placebo arm (8% vs. 24%, p = 0.006) [67]. Importantly, NAC combined with prednisolone, also significantly reduced the incidence of hepatorenal syndrome and infections. Although the combination of NAC and prednisolone did not result in long-term survival, this combination is being investigated in clinical trials to confirm its efficacy.

### *Hepatic Regeneration Therapy*

The regenerative capacity of the liver after any acute or chronic insult is an important determinant of outcome [68]. In animal models, administration of granulocyte colony stimulating factor (GCSF) was shown to mobilize hematopoietic stem cells

into the bloodstream, which would then travel to the damaged liver to induce liver regeneration and improve survival [69]. GCSF administered subcutaneously for five days in patients with AH results in mobilization of CD34+ stem cells, increased circulating hepatocyte growth factor and proliferation of hepatic progenitor cells [70]. GCSF is easy to administer and is well-tolerated. Several randomized placebo controlled trials from Asia demonstrated GCSF's effects in improved disease severity, complications of ACLF and patient survival [71–73]. However, these results have not been validated in the Western hemisphere and further trials are required before GCSF can be recommended as a treatment in severe AH and ALD-ACLF.

Another molecule of interest is IL-22, a cytokine which plays a key role in preventing liver injury, promoting liver regeneration, and suppressing bacterial infection [74]. Administration of recombinant IL-22 protein generated minor side effects in healthy humans, and a placebo controlled randomized clinical trial is being planned to assess 90-day survival in patients with moderate and severe AH with MELD score <28 [75].

## *Gut Liver Axis*

As intestinal dysbiosis contributes to the inflammatory cascade in AH by increased production and delivery of bacterial products through the portal vein, there is a heightened interest in altering gut flora through antibiotics, probiotics, or efforts to neutralize bacterial endotoxin and the LPS [2]. In an open-label study, eight patients with severe AH ineligible for corticosteroids underwent fecal microbiota transplantation from healthy relatives, and demonstrated significant improvements in parameters of liver disease, complication rate, and survival compared to historical controls (87.5% vs. 33.3%, $p = 0.018$) [76]. There are ongoing clinical trials investigating the potential benefits of antibiotics, probiotics, or IgG antibodies against bacterial LPS in patients with severe AH.

## *Drugs Targeting Inflammatory Cascade*

A variety of drugs targeting different points of the inflammatory cascade are being investigated for the treatment of AH. In a phase II randomized clinical trial of severe AH patients, a combination regimen consisting of IL-1 receptor antagonist anakinra (100 μg subcutaneously for 14 days), zinc (220 mg twice daily for 6 months) and pentoxifylline (400 mg three times daily for 28 days) showed a non-statistically significant trend towards improved 6-month survival compared with corticosteroids (70% vs. 56%, $p = 0.28$) [1]. Researchers have also evaluated inhibitors of caspase activation such as emricasan, but a randomized placebo-controlled study within the NIAAA consortium was stopped due to issues with high blood levels of the caspase inhibitory compound [77]. Selonsertib, an oral inhibitor of apoptosis signaling

kinase1 (ASK1), has been studied as an adjunct to corticosteroids, but did not improve mortality or liver function when compared to prednisolone alone. Other anti-inflammatory agents under investigation include farnesoid X receptor (FXR) agonist obeticholic acid, CCR2/5 antagonist cenicriviroc, and various miRNAs.

## Role of Liver Transplantation

Until recent years, liver transplantation (LT) as a treatment for severe AH has been a taboo due to concerns about limited donor organ supply and the assumption that the AH LT recipient will return to harmful drinking [78]. For a long time, the "6-month rule," an arbitrary time frame used as a proof of commitment to abstinence by LT candidates with alcoholic liver disease, effectively excluded patients with severe AH. The 6-month rule was widely unpopular among some experts, who believed that it was not an accurate predictor of post-LT relapse, and that reliance on the 6-month rule discriminated against patients with favorable psychosocial profiles who have low risk of relapse despite recent drinking [78]. A review of over 70 psychosocial studies concluded that the main predictors of relapse are patient's psychosocial status, polysubstance abuse, underlying severe psychiatric disorder, repeated alcohol-treatment failures, and younger age. Duration of preoperative abstinence was a poor predictor [79].

Improved understanding of risk factors for relapse and continued challenges to the 6-month eventually led to attitude changes starting in Europe, where a French consensus conference in 2005 concluded that a therapeutic trial of early LT in corticosteroid non-responders was recommended "despite the brevity of the required abstinence" [80]. This eventually led to the landmark French-Belgian trial published in 2011, a multicenter prospective study of LT for severe AH at 7 liver transplant centers (6 across France, 1 in Belgium) that included severe AH not responding to medical therapy [81]. The trial had very stringent selection criteria: no prior decompensation episodes, supportive family members, commitment to abstinence and complete consensus amongst relevant providers [81]. Overall, 26 severe AH patients with median Lille score of 0.88 and median MELD score of 34 at listing underwent LT. The survival benefit of LT was evident compared to matched controls without LT, with a markedly superior 6-month survival (77% vs. 23%, $p < 0.001$). After a 2-year follow up, 3 of the 20 surviving patients returned to some alcohol use but none of them had graft dysfunction [81].

In response to the French-Belgian trial demonstrating the efficacy of LT for treatment of severe AH, several retrospective and prospective studies have confirmed benefits of early LT in select patients with AH [82–84]. In the United States, the response was slower than in Europe, with a few centers initiating single-center pilot studies. The first U.S. single-center study from Mount Sinai Medical Center was published in 2016, where 94 patients with severe AH not responding to medical therapy were evaluated for early LT using stringent selection criteria similar to the French-Belgian study, with nine patients eventually undergoing LT. The outcomes

were excellent with eight (89%) of the nine early LT patients surviving at 6 months, compared to 11% survival in the control group ($p < 0.001$) [84]. Relapse was seen in one patient with poor insight and prior liver decompensation. In 2018, Johns Hopkins reported on another single-center study from 2012 to 2017 comparing 46 severe AH patients who underwent early LT to a control group of 34 alcoholic cirrhosis patients who met the traditional 6-month sobriety requirement [85]. The outcomes were excellent in both groups, with 1-year survival of 97% in the AH group and 100% in the cirrhosis group [85]. Relapse rates were also similar in both groups at 24% and 28% respectively, and it is noted that the selection criteria in this study were more liberal, allowing inclusion of patients with mental health disorder [85]. Again, it was clear that the interval of pre-transplant sobriety was not predictive of survival or relapse in either group.

A meta-analysis of 11 retrospective and prospective studies of early LT for severe AH has again found that, severe AH patients who receive early LT have significantly improved 6-month survival compared to corticosteroids non-responders who are not transplanted (OR = 16.69, 95% CI = 6.21–44.81, $p < 0.001$), and the rates of relapse to alcohol consumption after LT over 2–3 years were similar at 15–20% between severe AH patients who undergo early LT and alcoholic cirrhosis patients who undergo elective LT [86]. In addition, a large observational multicenter study by a U.S. consortium (ACCELERATE-AH) retrospectively analyzed 147 patients with severe AH (median MELD 39, Lille score 0.82) who underwent early LT from 11/2006 to 3/2017at 12 centers, and found excellent 1- and 3-year survival (94% and 84%, respectively) [87]. Sustained alcohol use after LT was seen in 11% of patients at median follow-up of 1.6 years, and was associated with significantly increased mortality (HR 4.59, $p = 0.01$) [87]. Based on such encouraging data, major societies including ACG and EASL now recommend consideration of LT for select severe AH patients not responding to corticosteroids [16, 18]. Figure 14.4 illustrates a proposed algorithm for optimal management of patients with severe AH, including the consideration of LT as a salvage therapy in corticosteroid non-responders [2]. Between 2014 and 2017, the number of LT centers that had performed more than one LT for AH increased from 11 to 23, and now represent more than 40 centers with a case from every UNOS region [78].

As the practice of using LT as a salvage therapy for patients with severe AH and ALD-ACLF becomes more universal, there are potential concerns about its ethics and patients' risk of recidivism. Therefore, it is critical to develop standardized selection criteria acceptable to the patients, the providers, and the public, and post-transplant follow-up and management protocols to minimize relapse. Currently, the criteria for patient selection in most centers are based on the prospective French-Belgian study which were: excellent psychosocial status as agreed upon by the treating team, social worker, surgeons, and anesthesiologists; first episode of hepatic decompensation and of AH, non-response to corticosteroids, and signed document by the recipient for maintaining abstinence after LT and take rehabilitation therapy

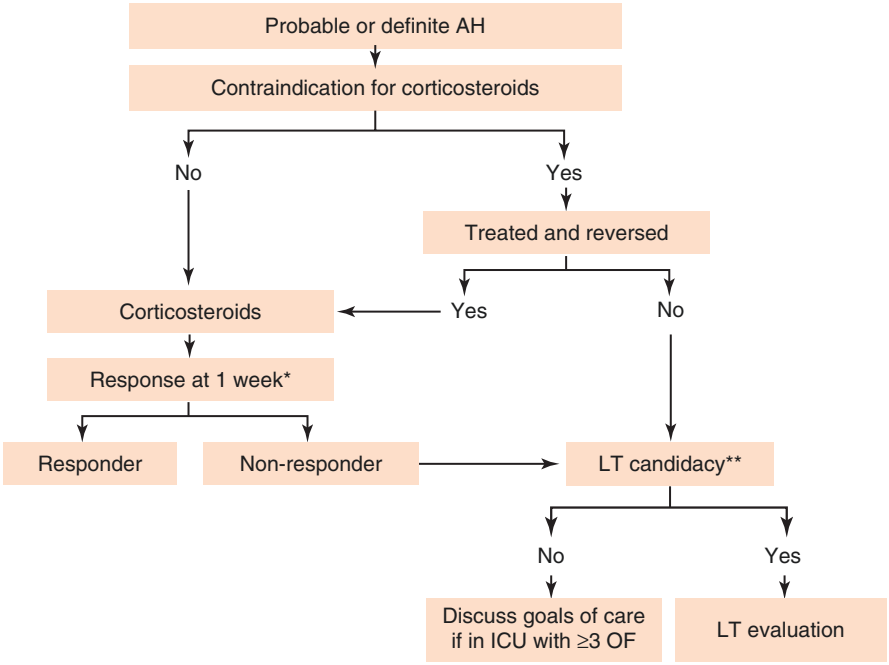


**Fig. 14.4** Algorithm for optimal management of patients with alcoholic hepatitis. *Using Lille score. **Excellent psychosocial support in a patient with first episode of AH. *AH* alcoholic hepatitis; *ICU* intensive care unit; *LT* liver transplantation; *OF* organ failure. Source: Singal AK, Louvet A, Shah VH, Kamath PS. Grand Rounds: Alcoholic Hepatitis. Journal of hepatology. 2018;69(2):534–43

if directed by the treating team [81]. Figure 14.5 lists common inclusion and exclusion criteria used by many centers for LT in AH patients [78]. Based on this criteria, only about 2–3% of all AH patients would be eligible for LT, with no major impact on the donor pool [83]. It should also be noted that the majority of AH patients are younger individuals in their prime productive years. Nevertheless, public opinions and survey findings of LT centers still show that there remain barriers to accepting LT as a treatment modality for severe AH patients [83]. Living donor LT could be an option to overcome the barrier of donor shortage with outcomes comparable to LT using deceased donors, but incurs substantial risks for the donors and can raise ethical concerns such as coercion of unwilling family members [2]. In summary, LT for patients with AH has evolved from a taboo in the early 2000s to now becoming an emerging and effective option for highly selected severe AH patients not responding to medical therapy. Further studies on the use of LT for AH are warranted to better refine the selection criteria and reduce the risk of relapse.

**Inclusion criteria**
- Maddrey Discriminant Function >32
- Non-responder to (according to Lille ≥0.45) or ineligible for medical therapies (mainly corticosteroids)
- First liver-decompensating event
- Favourable psychosocial profile
- Good social support
- Agreement of transplant selection committee

**Exclusion criteria**
- Uncontrolled infection
- Comorbid systemic illness likely to prevent recovery
- Poor prognostic profile: failure to accept addiction as a problem; history of previous failed alcohol use disorder treatments
- Lack of social support: no home, supporting family or friends, lack of transport
- Prior liver-decompensating events
- Severe, uncontrolled psychiatric disorder

**Fig. 14.5** Common study criteria in liver transplantation for alcoholic hepatitis. Source: Im GY, Cameron AM, Lucey MR. Liver transplantation for alcoholic hepatitis. Journal of hepatology. 2019;70(2):328–34

## Conclusion and Future Directions

Severe AH carries a significant risk of ALD-ACLF and high rates of mortality within 1 month of presentation. Corticosteroids remain the only currently available pharmacologic therapy for severe AH, but their utility is limited by lack of long-term survival benefit, a significant proportion of patients with contraindications, as well as steroid non-responders. Researchers are investigating novel biomarkers for diagnosis and prognostication in patients with severe AH and ALD-ACLF. Also, clinical trials are underway to evaluate new therapeutic options. During the past decade, significant progress has been made in using early LT as a curative option for patients with severe AH not responding to corticosteroids. Despite the successes of several single-center studies, there continue to be significant concerns and barriers to accepting LT as a standard treatment for severe AH patients. Additional multicenter, prospective studies with large patient population using uniform selection criteria for LT will be needed to better establish the role of LT in severe AH and ALD-ACLF patients.

**Questions**

1. Which statement is true?

   (a) A definitive diagnosis of alcoholic hepatitis can be made based on history of heavy drinking and characteristic liver enzyme abnormalities.
   (b) Infectious work up is seldom needed in alcoholic hepatitis patients with features of systemic inflammatory response syndrome (SIRS), since SIRS can be explained by inflammation of the liver.
   (c) Maddrey discriminant function ≥32 or MELD score ≥20 are used to prognosticate severe alcoholic hepatitis.
   (d) Percutaneous approach is the preferred method to obtain liver biopsy in patients suspected of having alcoholic hepatitis.

2. Which statement is true?

   (a) Corticosteroids should be given to all patients with Maddrey discriminant function ≥32 or MELD score ≥20.
   (b) Lille score ≥0.45 at day 7 of corticosteroid therapy is an indicator of non-response to corticosteroids.
   (c) Pentoxifylline is an effective second-line therapy for severe alcoholic patients who do not respond to corticosteroids.
   (d) Alcoholic hepatitis is an absolute contraindication for liver transplantation.

**Answers**

1.

(a) A probable diagnosis of alcoholic hepatitis can be made based on history of heavy drinking and characteristic liver enzyme abnormalities, but a definitive diagnosis of alcoholic hepatitis requires a liver biopsy. Diagnostic findings of AH on histology include macrovesicular steatosis, neutrophil infiltration, hepatocyte injury (ballooning), and Mallory-Denk bodies.
(b) A thorough infectious work up should be obtained in all alcoholic hepatitis patients with features of systemic inflammatory response syndrome, as these patients have a significantly increased risk of infection.
(c) **CORRECT ANSWER**. Maddrey discriminant function ≥32 or MELD score ≥20 are used to diagnose severe alcoholic hepatitis. In 2014, a comparison of nine prognostic models showed that MELD, MDF, GAHS, ABIC and scores of corticosteroid response all proved to be valid in an

independent cohort of biopsy-proven alcoholic hepatitis, with the MELD score being superior to all other scores in determining 30-day mortality as well as 90-day mortality.

(d) Transjugular approach is the preferred method to obtain liver biopsy in patients suspected of having alcoholic hepatitis.

2.

(a) Corticosteroids cannot be given to close to 50% of patients with severe AH, due to presence of contraindications to corticosteroids such as infections and GI bleeding.

(b) **CORRECT ANSWER.** Lille score of ≥0.45 calculated at day 7 of corticosteroid therapy indicates non-response to corticosteroids with a high risk of death.

(c) Although pentoxifylline was previously thought to have a beneficial role in severe alcoholic hepatitis by reducing the risk of hepatorenal syndrome, multiple trials including the STOPAH trial, the largest randomized controlled trial in alcoholic hepatitis to date, have failed to show any survival benefit by pentoxifylline. Major society guidelines recommend no role of pentoxifylline in the treatment of severe AH.

(d) Although still a topic of debate, early liver transplantation is now an option for a select population of severe alcoholic hepatitis patients. The criteria for patient selection in most centers include: excellent psychosocial status as agreed upon by the treating team, social worker, surgeons, and anesthesiologists; first episode of hepatic decompensation and of AH, non-response to corticosteroids, and signed document by the recipient for maintaining abstinence after LT and take rehabilitation therapy if directed by the treating team

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# Chapter 15
# Liver Transplantation for Acute and Acute on Chronic Liver Failure

**Flavio Paterno, Raquel Olivo Salcedo, Nikolaos Pyrsopoulos, and James V. Guarrera**

**Key Concepts**

- Liver transplantation is a life-saving treatment for both severe acute liver failure (ALF) and severe acute on chronic liver failure (ACLF). The survival rates after liver transplant are above 80% at 1 year for both conditions which is remarkable considering the emergent nature of transplant and the severity of these conditions.
- Both ALF and ACLF patients need prioritization in the waiting list and expedite organ allocation due to the high mortality rate in the waiting list. Their disease severity and mortality risk is not accurately represented by the MELD score.
- Some ALF patients improve spontaneously with a recovery of their liver function, about half of ALF patients require liver transplantation.
- Early referral to a liver transplant center and expedite evaluation of ALF and ACLF patients is highly recommended in the effort to improve their outcomes.
- Proper pre-transplant and perioperative care, patient selection, careful donor organ selection, early transplantation are necessary for the final success of transplantation in both ALF and ACLF patients.

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## Introduction

Both acute liver failure (ALF) and acute on chronic liver failure (ACLF) represent two emergency conditions with acute decompensation of the liver function complicated by high morbidity and mortality. ALF consists of an acute deterioration of the liver function that occurs in days or few weeks in patients without pre-existing liver disease. Its severity may range in a wide spectrum from milder forms that recover with medical treatment to severe forms complicated by encephalopathy, multiorgan failure and high mortality. ACLF is defined as a syndrome with acute deterioration of liver function in patients with cirrhosis complicated by other organ system failures, and high short-term mortality [1]. ACLF is staged in grades based on the number of organ failures. ACLF grade 3 is the highest grade with 3 or more organ system failures. In the severe forms of ALF and ACLF, liver transplantation represents the only effective treatment. Both ALF and ACLF may progress and deteriorate rapidly, therefore, it is critical early referral to a liver transplant center, expedite liver transplant evaluation, listing, and prioritization in liver allocation.

## Acute Liver Failure (ALF)

### *Background on ALF*

Although about 12% remains indeterminate, it is critical to identify the cause that triggered ALF (Table 15.1), to start specific therapies that can improve the outcomes [2]. In the US and Europe, the most common cause of ALF remains acetaminophen overdose, while in developing countries, the most common cause is acute viral hepatitis.

#### Acetaminophen Toxicity

Acetaminophen toxicity is the most common cause of ALF in the western world and requires an urgent liver transplant in less proportion than other causes [2, 3]. Accidental acetaminophen overdose is more common that suicidal overdose [4]. Clinically, there is an acute onset of jaundice and encephalopathy usually within

**Table 15.1** Common causes of ALF

| |
|---|
| Acetaminophen toxicity |
| Drug induced liver injury (DILI) |
| Viral hepatitis |
| Ischemic hepatitis |
| Autoimmune hepatitis (AIH) |

hours. Biochemically, acetaminophen overdose presents with a rapid and severe increase in aminotransferases and international normalized ratio (INR) within 8–12 h with a peak around 72 h [2]. If the ingestion occurred within 1 h, activated charcoal could be used. The standard of care is the administration of *N*-acetylcysteine (NAC) as early as possible [5].

### Drug Induced Liver Injury (DILI)

DILI is the second most common cause of ALF in the US. As an idiosyncratic reaction, DILI is thought to be related to autoimmune processes and genetic predisposition. Multiple drugs or supplements can cause DILI, but only around 10% of those patients will develop ALF. Careful and detailed drug history and exclusion of other potential causes are paramount for the diagnosis. DILI presents within days since drug exposure, with aminotransferases around 500 IU/L and a markedly increased bilirubin. DILI has a worse prognosis with a transplant-free survival of 25% [4]. The treatment is to stop the suspected agent; NAC may improve outcomes [6].

### Viral Hepatitis

Viral hepatitis is an infrequent cause of ALF in Western countries, accounting for 12% of the cases in the US. Hepatitis B causes 8%, Hepatitis A 4%, other culprits of ALF, although in much less proportion are Hepatitis E, Hepatitis C, Varicella Zoster, and Herpes Simplex Virus [4]. Diagnosis is based in serologies. In developing countries, Hepatitis B is one of the principal causes of ALF [7]. Hepatitis E is relatively frequent in Asia and carries a bad prognosis when the patient is pregnant. The majority of ALF related to Hepatitis B is caused by a de novo infection; one third is related to reactivation. The later carries worse prognosis and requires liver transplant more often.

### Ischemic Hepatitis

Ischemic injury is among the top five causes of ALF in the Acute Liver Failure Study Group Registry. The liver injury occurs due to lack of perfusion of the liver due to various reasons. It can be secondary to severe heart disease, hypovolemic or septic shock, hypoxia, and cocaine use. The liver injury is characterized by elevated aminotransferases and low bilirubin and can be reversible once the underlying cause is corrected [4]. Therefore, ALF due to ischemic hepatitis rarely requires liver transplantation, either because it is resolved or because the underlying etiology precludes liver transplantation.

### Autoimmune Hepatitis (AIH)

Autoimmune hepatitis remains a frequent cause of ALF, and it is more prevalent in women. It is mediated by autoimmune reactions. The diagnosis can be made by elevated IgG, and positive anti-smooth antibody (ASMA), antinuclear antibodies or ultimately by biopsy. Similar to DILI, the onset is slow, with significantly elevated bilirubin and moderately elevated aminotransferases. Steroids can be used mainly in the early stages. Nevertheless, the prognosis is poor with only around 15% of patients surviving without transplant; thus, these patients should be considered for transplant early on [4, 5].

### Other Causes

Wilson disease can rarely present as an ALF in undiagnosed cases. Almost all patients will need a liver transplant since the prognosis without one is very poor. Others causes of ALF includes HELLP syndrome and Budd-Chiari syndrome. Finally, infiltrative neoplastic processes can cause ALF in a small proportion of patients, in those cases, a liver transplant is not an option, and the overall prognosis is poor.

## *Liver Transplant Evaluation for ALF*

Liver transplant is a lifesaving procedure for ALF. In the US and UK, 25% of patients with ALF receive a liver transplant decreasing the overall mortality from 80% in the past to 30% in the most recent studies [3, 4]. The decision to place an ALF patient in the wait-list for liver transplant is complex and needs to consider the chances of spontaneous recovery, the risks that the disease is already too advanced to be treated with a transplant, the potential adverse outcomes that may occur in an acute and severely ill patient. Having a patient died when he or she could have had a liver transplant is a result that we want to avoid as much as having a transplanted patient when he or she could have recovered on their own. Prognostic scores can assist in the evaluation of ALF. The most common used are the King's College Criteria, the Clichy Criteria, the APACHE II score, and more recently the Acute Liver Failure Study Group (ALFSG) Index. Some other poor prognostic factors include certain etiology (DILI, AIH), clinical progression of the disease (encephalopathy and multiorgan failure), patient age (>50 years old) and laboratory markers of severity (high lactate, phosphate, and factor VIII; low factor VII) and volumetric CT findings (liver volume < 1000 $cm^3$) [2, 8]. Although there is a variation among transplant centers, contraindications for liver transplantation in ALF settings usually include brain death from cerebral herniation, severe infection, septic shock requiring vasopressors, severe heart and lung comorbidities, and malignancies [8].

It is paramount to thoroughly evaluate these patients and maximize medical management in a transplant center. This evaluation needs to be expedited due to the acuity of the disease and the high mortality. We favor the approach to evaluate patients by a multidisciplinary team and list the patients that fulfill the criteria for listing at the time of the presentation. Thereafter, reassess the clinical condition of the patient often, and, if clinical deterioration occurs or if there is a significant improvement, the patient can be delisted. Evaluation for transplantation should involve a hepatologist, transplant surgeon, cardiologist, psychiatrist, and infectious disease specialist if warranted, as well as a social worker, transplant coordinators, financial coordinators, and any other required consultant. Financial and social support also needs to be established [9]. Another possible caveat in the evaluation may be the ethical issues in situations like suicidal acetaminophen overdose or hepatitis B flare up due to medication non-compliance or hepatitis B de novo related to intravenous drug use. In those cases, careful social and psychological evaluation is warranted.

## *Surgical Considerations in ALF*

Patients with acute liver failure usually benefit of prioritization in the organ allocation to facilitate their transplantation and decrease their waiting time [10]. In the US, ALF patients are listed as status 1A that allows them to have priority in the waiting list regardless their Model of End-Stage Liver Disease (MELD) score. According to the United Network for Organ Sharing (UNOS) policy, patients with ALF can be listed for liver transplant with status 1A if they fulfill to the definition of fulminant liver failure:

- no pre-existing liver disease
- onset of hepatic encephalopathy within 56 days of the first signs or symptoms of liver disease
- currently admitted in the intensive care unit
- and at least one of the following criteria: ventilator dependent, need for dialysis, continuous veno-venous hemofiltration (CVVH), or international normalized ratio (INR) greater than 2.0

The waiting time for transplantation for most ALF patients with this policy has been between 2 and 4 days [11]. The priority of liver allocation is very important for these patients and despite that 20% of patients with ALF expire while waiting for a liver allograft [12].

In many Asian countries, deceased donors are rare and liver transplantation rely mainly on living—donation [13]. As expected, the time constraints of acute liver failure impose an expedite evaluation of living donors [14]. Excellent outcomes in terms of patient and graft survival have been reported after living donor liver transplant for ALF [14, 15]. Moreover, there was no difference in postoperative morbidity between emergency living donors and elective living donors [13].

Liver transplantation for ALF patients implies some specific surgical operative considerations. ALF patients undergoing liver transplants are usually very ill with severe coagulopathy, jaundice, acute renal failure, hemodynamic instability requiring vasopressors. The transplant procedure is at risk of severe blood loss due to the coagulopathy. During surgery, it is recommended to check frequently the coagulation tests including thromboelastogram (TEG), to keep a continuous communication between anesthesia and surgery teams about the degree of bleeding in the operative field and prompt transfuse the necessary blood products (fresh frozen plasma, cryoprecipitate, platelets…).

Upon intra-abdominal exploration, most of ALF patients do not present the typical findings of cirrhosis and portal hypertension. The liver does not look cirrhotic but necrotic, pale. In most patients there is no evidence of portal hypertension, venous collaterals, varices, or splenomegaly. Patients may not tolerate clamping of the portal vein due to the lack of venous collaterals, therefore, the portal venous clamping may cause systemic hypotension, bowel swelling, and congestion. If patient does not tolerate the portal venous clamping or the portal vein needs to be clamped during the early stages of the hepatectomy, it may be necessary to perform a temporary porto-caval shunt that will be taken down during the implantation of the liver just before the portal venous anastomosis. One of the major causes of hemodynamic instability is attributed to the release of toxins from the necrotic liver, therefore, a rapid hepatectomy with removal of the necrotic liver is sometimes necessary to remove the major source of hypotension and hemodynamic instability.

In some selected cases, the patient is made anhepatic even before a liver allograft is available in order to decrease hemodynamic instability. Patients with severe liver necrosis who develop a “toxic liver syndrome” with severe hypotension and multiple organ failure despite all resuscitation efforts and supportive care measures, may benefit from the removal of the necrotic liver even before a liver allograft is available. In these cases, a two stage procedure is performed. Patient undergoes hepatectomy with a temporary portocaval shunt (Fig. 15.1). In most patients the hemodynamic conditions improve after removal of the necrotic liver. Afterwards, liver transplantation is performed as soon as the allograft becomes available. In previous reports, liver transplantation was performed between 6 and 41 h after hepatectomy. During the anhepatic phase patients are monitored and treated for any metabolic disturbances: patients receive continuous veno-venous hemofiltration (CVVH), bicarbonate, fresh frozen plasma, albumin [16, 17]. However, this is a risky procedure as patient may expire while anhepatic waiting for the availability of a new allograft.

From anesthesia standpoint, the most critical step during liver transplantation occurs when the caval and portal clamps are released with reperfusion of the allograft as a post-reperfusion syndrome may occur. Post-reperfusion syndrome is characterized by marked decrease in systemic blood pressure, cardiac output and increase in pulmonary pressure. This syndrome has been reported in about 20% of all liver transplants and almost 40% of liver transplants performed for fulminant hepatic failure. ALF patients are often hemodynamically unstable already during the hepatectomy phase, moreover it is possible that they are subject to more acidosis

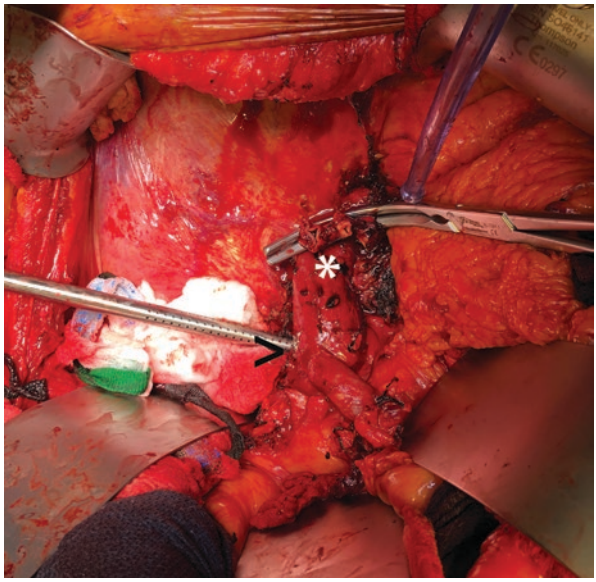

**Fig. 15.1** Temporary porto-caval shunt: intraoperative picture of a temporary porto-caval shunt with total hepatectomy in patient with severe ALF. The asterisk indicates the inferior vena cava, the arrowhead points to the porto-caval anastomosis

from the portal clamping due to the lack of porto-systemic collaterals and varices that are usually present in cirrhotic patients [18, 19]. Careful patient monitoring, prompt treatment of hypotension, arrhythmias, electrolytes alterations, slow and modulated portal flow release may help to alleviate this occurrence.

## *Postoperative Care in ALF*

The postoperative care after liver transplant for ALF is usually challenging because these patients are often hemodynamically unstable with multiple organ failure. Most patients require continuous dialysis due to renal failure and volume overload. Infections represent a major cause of morbidity, therefore, adequate antibiotic prophylaxis, prompt sepsis work-up, and early treatment of infections are the paramount [9].

In most transplant centers, the immunosuppression after liver transplant is based a combination of immunosuppressive agents such as a calcineurin inhibitor (tacrolimus, cyclosporine) and mycophenolate mofetil. Most patients receive a steroid induction with intraoperative steroid bolus followed by a steroid taper. In ALF recipients, the management of immunosuppression is more complex as it needs to keep in consideration that these patients are usually younger and less immunocompromised than cirrhotic patients. On the other side, the immunosuppression regimen needs to be adjusted to allow the recovery of neurologic function and renal function. Calcineurin inhibitors are known for some nephrotoxic effects and especially tacrolimus for some neurotoxic effects. In most patients the use of calcineurin inhibitiors

(tacrolimus, cyclosporine) is delayed to allow time for neurologic and renal recovery. An induction agent (for example, basiliximab or anti-thymocyte globulin) is sometimes used to achieve adequate immunosuppression while the calcineurin inhibitor is delayed.

### *Outcomes after Liver Transplantation for ALF*

Data from the Scientific Registry of Transplant Recipients (SRTR) database in the United States have shown that the post-transplant patient survival was similar in ALF patients and in cirrhotic patients. ALF patients presented a lower survival at 1 year follow-up but the survival rates were similar between ALF and cirrhotic patients by the fourth year follow-up [6]. Infections were the most common cause of death/graft failure regardless the etiology of ALF [20].

Several donor and recipient predictors have been associated with outcomes. The most common recipient predictors associated with patient mortality and/or graft failure were older recipient age (older than 50 years), vasopressor requirement, renal failure, certain causes of ALF (autoimmune and drug-induced liver disease) [6, 10, 12, 20, 21]. Donor predictors associated with worse patient and graft survival were increased donor age (especially >60 years), steatotic graft, incompatible ABO blood type, reduced size graft [6, 10, 12, 20]. These findings are relevant as in ALF patients there is usually a dilemma between proceeding with an emergency transplant with a marginal donor or waiting for unknown time until a better donor becomes available. The use of a marginal donors may carry an increased risk for graft failure up to a 13% of primary nonfunction in these patients [21].

## Acute on Chronic Liver Failure (ACLF)

### *Background on ACLF*

Acute-on-chronic liver failure (ACLF) is an acute deterioration of the liver function with organ system failures in a patient with preexisting cirrhosis, diagnosed or not, and carries a very high short-term mortality and a significant disease burden [22]. ACLF may complicate up to 30% of end-stage liver patients, and it is associated with a severe inflammatory response [23]. The mortality associated with ACLF is roughly 50%. It is crucial to identify and treat the cause the triggered the decompensation since the process can be reversed and treated in many cases (Table 15.2). The usual culprits are infections, variceal bleeding, alcoholic hepatitis, and surgeries. Still, more than 40% remains indeterminate [24].

Infections are by far the most common precipitating event in ACLF. Cirrhotic patients are considered functionally immunocompromised patients. Most common

**Table 15.2** Common triggers of ACLF

| |
|---|
| Infections |
| Variceal bleeding |
| Alcoholic hepatitis |
| Surgeries |
| Hepatotoxic drugs |
| Liver ischemia |

infections are spontaneous bacterial peritonitis, pneumonia, and urinary tract infections. In case of variceal bleed, the primary treatment is based on resuscitation and endoscopic procedures. Patients with variceal bleeding are prone to infections and need to be started on prophylaxis as well [24]. ACLF is more prevalent in patients with alcoholic cirrhosis and active drinking. The medical treatment is usually based on corticosteroids if there is no contraindication [23]. Other triggers of ACLF includes surgeries, superimposed hepatotoxic drugs, liver ischemia and acute infections like hepatitis A and B, or hepatitis B flare-up [24].

## *Liver Transplant Evaluation for ACLF*

Patients with ACLF can be assigned to two different groups regarding liver transplant evaluation: patients who are already listed and patients who are not listed yet. In both circumstances, patients should be referred to a transplant center early on. In patients with chronic liver disease who present with a decompensation, the MELD score tends to rise quickly, improving the patient position in the transplant wait-list. Nevertheless, careful reassessments must be done frequently as since infections, septic shock, and other complications can preclude an emergent transplant. In fact, 48% of patients listed, died during an acute illness requiring intensive care admission [25], reflecting the severity and acuity of the disease. The CLIF-C score can aid in the assessment and prognosis of those patients [26]. If the patient is not listed at the moment of the decompensation, then an expedite inpatient evaluation is started including a hepatologist, transplant surgeon, cardiologist, psychiatrist, any other required consultant, as well as a social worker, transplant coordinators, financial coordinators (Fig. 15.2). Nevertheless, due to the progression of the disease, only 9% of patients with ACLF are transplanted within 28 days of admission and 15% within 90 days [23].

## *Surgical Considerations in ACLF*

Patients with ACLF carry high risk of mortality while they are in the waiting list for liver transplantation. In these patients, the severity of disease is not accurately captured by the Na-MELD score. It has been shown that patients with ACLF grade 3,

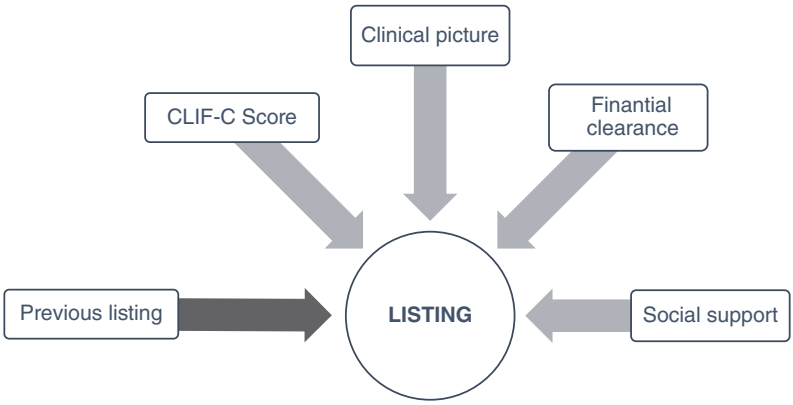


**Fig. 15.2** Model for liver transplant evaluation in ACLF

defined as 3 or more organ failures, have increased risk of mortality regardless the Na-MELD score [27]. Patients with ACLF grade 3 exhibit high short-term mortality rate of 44% at 1 month from listing even with a Na-MELD score < 25 [27]. Liver transplantation is the only effective treatment for these patients. The timing of transplantation is critical as it has been shown that transplantation within 30 days of listing is associated with increased patient survival at 1 year (HR 0.89, 95%CI: 0.81–0.98) [27]. Careful donor selection is critical for the final success of liver transplantation in these sick patients. A previous study showed that ACLF patients transplanted with marginal donor allografts (higher donor risk index, DRI) presented worse survival rates [27].

ACLF patients undergoing liver transplant are usually very ill with severe coagulopathy and underlying portal hypertension (splenomegaly, varices, thrombocytopenia). Cirrhosis, portal hypertension, varices increase the complexity of surgical dissection and operative technique. Patients usually present increased blood transfusion requirements [1] due to significant bleeding related to coagulopathy and portal hypertension. Early portal vein ligation with temporary porto-caval shunt may facilitate the hepatectomy and decrease bleeding. Concomitant renal failure, electrolyte unbalances, hemodynamic instability may complicate the perioperative anesthesiologic management.

In some patients, the acute decompensation is precipitated by infections, therefore, it advisable to send ascites fluid culture and intraoperative tissue cultures in case of suspected infections.

Two-stage liver transplant with total hepatectomy followed by liver transplantation has been also described for highly selected ACLF patients complicated with liver necrosis and "toxic liver syndrome" with severe hypotension, metabolic acidosis, and multiorgan failure. The rationale for this approach is to remove the cirrhotic, necrotic liver, in order to improve patient's hemodynamic and metabolic conditions [28].

## *Postoperative Care in ACLF*

The postoperative management after liver transplant for ACLF is complex due to the concomitant multiorgan failures. These patients often require longer stay in the intensive care unit, mechanical ventilation, CVVH or hemodialysis, and vasopressors [1]. It is advisable to keep a careful balance between volume fluid resuscitation and vasopressor weaning. The new allograft and the intestine may not tolerate high dose vasopressors for long time, on the other side, high volume resuscitation may cause allograft congestion leading to liver injury, and pulmonary edema leading to respiratory failure. Antibiotic prophylaxis is very important in these critically ill patients and it is woth to keep a low-threshold for sepsis work-up, cultures and antibiotic treatment as these patients are at high risk of infection before and after transplantation.

The immunosuppression regimen will be adjusted to allow the recovery of renal function and potential ongoing infections. The start of calcineurin inhibitors (tacrolimus, cyclosporine) is often delayed in patients with severe renal failure and a reduction in immunosuppression, especially mycophenolate mofetil, is usually considered in patients with infectious complications.

## *Outcomes After Liver Transplantation for ACLF*

Liver transplantation is the only effective treatment for severe ACLF as it improves significantly patient survival compared to non-transplanted patients (83.6% vs 7.9%, $p < 0.01$) [1]. The prognosis of patients transplanted for ACLF is associated with the ACLF grade/staging. Patients with ACLF grade 3 (defined as 3 or more organ failures) exhibited worse 1-year patient survival when compared to patients without ACLF or lower stages of ACLF (81.8% vs 91.9% $p < 0.0010$ [27]. A large study based on the SRTR database showed that predictors associated with 1-year patient mortality after transplantation were mechanical ventilation at time of transplant (HR 1.49, 95%CI: 1.22–1.84), increased donor risk defined as donor risk index (DRI) >1.7 (HR1.22, 95%CI: 1.09–1.35), while transplantation within 30 days of listing was predictive of lower mortality (HR: 0.89; 95%CI: 0.81–0.98) [27]. Patients with grade 3 ACLF also presented increased risk of post-transplant complications (pulmonary, renal, infectious) and prolonged hospital stay [1]. Careful patient selection, optimization of pre-transplant care, early transplantation, and accurate donor organ selection are all important measures to improve these patient outcomes.

**Summary**

Both ALF and ACLF are emergent conditions characterized by acute deterioration of liver function with high risk for morbidity and mortality. Both conditions require early referral to a liver transplant center for assessment and expedite liver transplant evaluation. Liver transplantation represents the only effective treatment for severe forms of ALF and ACLF. Emergent liver transplant for ALF and ACLF patients may present increased blood transfusion requirements, increased morbidity and mortality compared to elective liver transplantation performed in cirrhotic patients.

ALF patients do not exhibit cirrhosis of liver or signs of portal hypertension while ACLF patients usually have some degree of cirrhosis and portal hypertension (varices, splenomegaly) with significant implications in surgical operative technique and strategy.

In both ALF and ACLF patients, Na-MELD score does not reflect the severity of disease and the prognosis. In the US, the organ allocation for ALF and ACLF is different (Table 15.3). ALF patients benefit of prioritization and are listed as status 1A while ACLF patients are listed according their MELD score. There is evidence that grade 3 ACLF patients present higher mortality rate in the waiting list compared to ALF patients [29].

**Table 15.3** Comparison between ALF vs ACLF

| | ALF | ACLF |
|---|---|---|
| Acute liver decompensation | Yes | Yes |
| Pre-existing cirrhosis | No | Yes |
| Concomitant portal hypertension | No | Yes |
| Possible recovery in some patients | Yes | No |
| High-mortality without transplant | Yes | Yes |
| Recommended early referral and OLT evaluation | Yes | Yes |
| Specific prioritization in the waiting list (status 1A) | Yes | No |
| Recommended accurate donor selection | Yes | Yes |

## Self-Study

**Questions**

1. Which one is <u>not</u> contraindications to liver transplantation for ALF?
   (a) severe hemodynamic instability requiring multiple vasopressors at high dose
   (b) invasive fungal infection

(c) encephalopathy
(d) both pupils fixed and dilated

2. What are the risk factors for worse survival after liver transplant for ACLF?

(a) grade 3 ACLF, need for mechanical ventilation, poor donor quality, delayed transplantation
(b) grade 3 ACLF, need for mechanical ventilation, poor donor quality, early transplantation
(c) any ACLF grade, need for mechanical ventilation, good donor quality, delayed transplantation
(d) need for vasopressors, good donor quality, delayed transplantation

**Answers**

1.

(a) severe hemodynamic instability requiring multiple vasopressors at high dose is a contraindication to liver transplantation
(b) severe infections are definitely contraindication to transplantation due to potential risks of worsening with surgery and immunosuppression
(c) CORRECT ANSWER. Encephalopathy is actually a sign of fulminant hepatic failure and is an indication for liver transplantation for ALF.
(d) Brain stem herniation with loss of brain stem reflexes is definitely irreversible neurologic condition and is a contraindication to liver transplantation

2.

(a) CORRECT ANSWER. Grade 3 ACLF, need for mechanical ventilation, poor donor quality, delayed transplantation are all predictors of worse survival after transplant
(b) Early transplantation is not a risk factor for worse survival but actually is associated with better survival
(c) There is difference in post-transplant survival between grades of ACLF. Grade 3 ACLF has worse survival compared to lower grades of ACLF
(d) Good donor quality expressed by low donor risk index is not associated to worse survival

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# Chapter 16
# Cellular and Non-Cellular Liver Assist Devices in Management of Acute and Acute on Chronic Liver Failure

**Jan Stange**

**Key Concepts**
- Need and expectations from liver support.
- Technologies available for liver support in the US and/or in the EU.
- Clinical results of liver support.
- Recommendation for clinical implementation.

## Introduction

Liver Failure is associated with a loss of synthesis of proteins, metabolic regulation and the accumulation of toxins. While proteins can be partly substituted and the metabolism can be supported for some time by parenteral nutrition the removal of toxic substances accumulating in liver failure has been challenging for a long time due to the heterogeneity of the toxins in terms of molecular weight, water solubility and albumin binding rate. Toxins include water soluble toxins such as ammonia, lactate and more lipophilic molecules such as elevated aromatic amino acids and their phenolic metabolites, tryptophan and their indole metabolites such as 5-kyonorenin, bilirubin, bile acids, middle chain fatty acids such as caprylate, mercaptans, prostacyclins and leucotriens, histamines, digoxine like endogenous substances, endogenous benzodiazepines, endogenous cannabinoids, endogenous opioids and nitric oxide in the form of S-nitroso-thiols bound to albumin and middle molecules such as pro-inflammatory cytokines and inhibitors of liver regeneration.

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This was even more challenging since the toxins are major players in the development of secondary organ failures, such as circulatory dysfunction, renal failure, hepatic coma and further deterioration of liver function.

Therefore detoxification with a satisfying risk/benefit ratio was the major expectation towards extracorporeal liver support for the practicing clinician. In order to be effective, the extracorporeal toxin removal needs to control the rebound from tissues, otherwise the therapy would be considered quantitatively underdosed (Fig. 16.1). Ideally, the whole spectrum of toxins needs to be addressed, an isolated removal of bilirubin will be ineffective and should be considered qualitatively under-dosed (Fig. 16.2). Only if the broad spectrum of toxins can be removed quicker than they are forming in the circulation the liver support therapy can be considered effective (Fig. 16.3).

Since it is almost impossible to monitor single toxins, one can use the patients albumin binding capacity for clinical development purposes, a procedure that is based on measuring marker binding (Fig. 16.4).

Cellular Liver Assist Devices-are Liver Assist Systems that consist usually of an extracorporeal blood processing device which contains metabolically active cells mimicking hepatocellular function. Therefore, the term "Device" is actually misleading and there are regulated as biologicals or advanced therapeutic medicinal products. Until today, there are no available Cellular Liver Assist Systems but

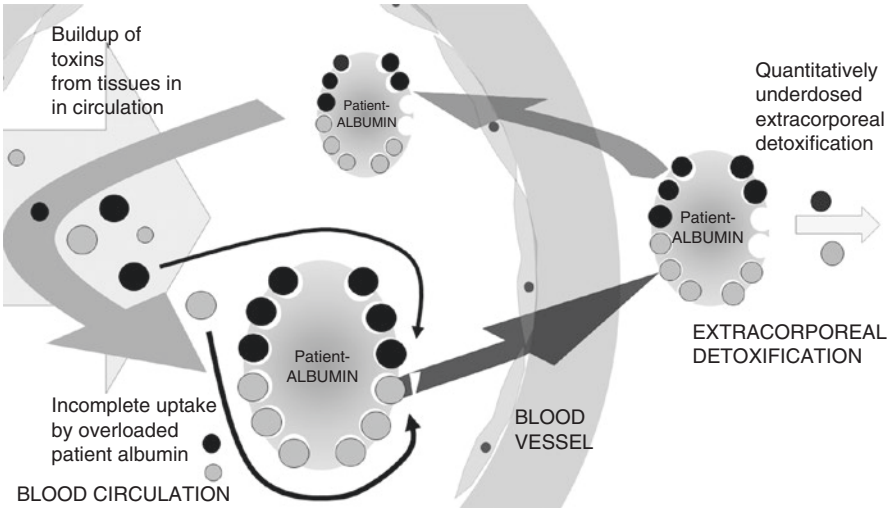



**Fig. 16.1** Figure shows the balance between the build up of toxins in the body during liver failure entering the circulation at a high rate (from the left). The different colors of the toxins point out at the fact that there are different toxins which also occupy different binding sites. It also displays the incapacity of the albumin in the circulation to take up lipophilic toxins if the toxins cannot be removed at least at the same rate (quantitatively under dosed detoxification). This imbalance leads to an overload of albumin in the patient (which can be measured by detecting the patients albumin binding capacity-ABiC) and an increase of biologically available and active toxins in the circulation which results in secondary organ failures

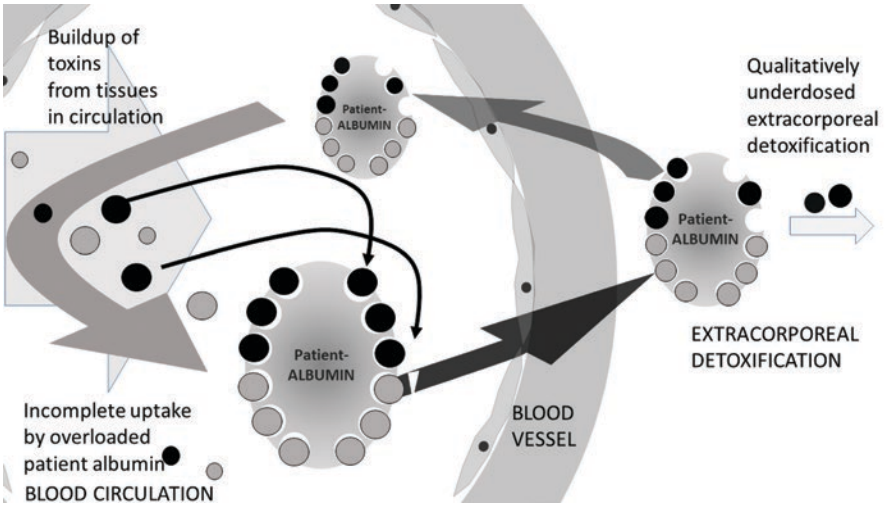



**Fig. 16.2** Figure shows the balance between the build up of toxins in the body during liver failure entering the circulation at a high rate (from the left). The different colors of the toxins point out at the fact that there are different toxins which also occupy different binding sites. It also displays the incapacity of the albumin in the circulation to take up one group of lipophilic toxins (e.g. bile acids-here gray-binding at the benzodiazepine binding site of albumin) if the this group of toxins cannot be removed at least at the same rate while another group (e.g. bilirubin-black) can (qualitatively under dosed detoxification). This imbalance leads to an overload of albumin in the patient at the binding site for the group of toxins that cannot be removed (which can be measured by detecting the patient's albumin binding capacity-ABiC at this site) and an increase of specific biologically available and active toxins in the circulation which also can result in secondary organ failures. This scenario would occur if a bilirubin adsorbent would be used for liver support

several are in clinical development. Since they have no impact on clinical practice yet there status will be discussed shortly at the end of this chapter.

Non-Cellular Liver Assist Devices represent evolutions of membrane- and/or adsorbent based extracorporeal detoxification devices. Table 16.1 lists technologies that are commercially available in either the US or the EU or in both at the edition of this chapter.

It is very important to realize that these techniques are not necessary competing technologies and may even be more effective if used in combination in parallel or consecutively. As a matter of fact, the most successful therapy for Liver Failure, Extracorporeal Albumin Dialysis (ECAD) represents in its most successful brands a combination of diafiltration and adsorption.

Several versions of dialysis-like technologies have been used to treat complications of liver failure. A flow scheme and a depicturing of the molecular mechanism is shown in Figs. 16.5a and 16.5b.

A common denominator of dialysis-like technologies is that only molecules smaller than albumin can be removed and therefore the removal of toxins accumulating in liver failure is very low, since most of them are lipophilic and have a high albumin binding rate. However, smaller molecules not bound to albumin, such as

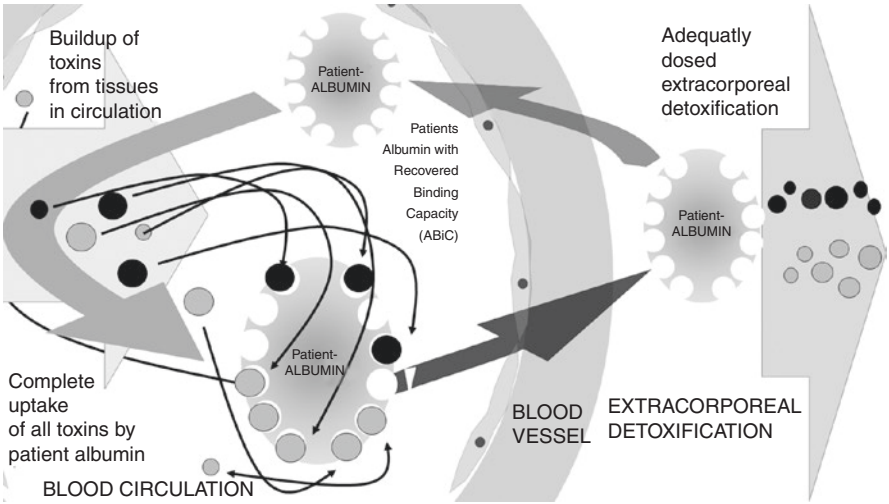



**Fig. 16.3** Figure shows the balance between the build up of toxins in the body during liver failure entering the circulation at a high rate (from the left). The different colors of the toxins point out at the fact that there are different toxins which also occupy different binding sites. It also displays the capacity of the albumin in the circulation to take up lipophilic toxins if the toxins can be removed at a faster rate (adequately dosed detoxification). This leads to a restoration of albumin binding function in the patient (which can be measured by detecting the patients albumin binding capacity-ABiC) and a reduction of biologically available and active toxins in the circulation which can prevent or reverse secondary organ failures

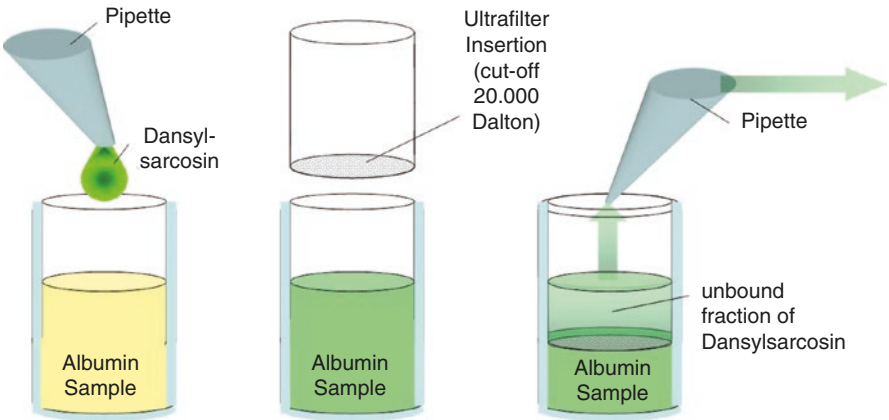



**Fig. 16.4** Figure shows the principle of albumin binding capacity measurement. The patient's blood sample will be mixed with a marker molecule (MW < 20 kDa) that binds to the binding site that is investigated and after that an ultrafiltrate using an ultrafiltration membrane with a cut off of 20 kDa is made. The concentration of the unbound marker is put in relation to the total marker concentration and the Albumin Binding Function can be calculated. ABiC has been published using dansylsarkosin as a marker which binds to the benzodiazepine binding site (Sudlow II), the major binding site for bile salts, caprylate, tryptophane, endogenous benzodiazepines and other toxins of clinical relevance. Patient's outcome correlates with that binding site; a low binding site is associated with poor outcome, improvement with a better outcome [1–4]. It is the binding site that is compromised by stabilizers (sodium caprylate and *N*-acetyl-tryptophan) in commercial albumin and removal of those improves the effect of albumin. Interestingly, bilirubin does not bind to that site and may therefore be a less reliable marker for success of extracorporeal liver support

**Table 16.1** Term, brand name, technology, function targeted, commercially approved/available[a] (US, EU, ROW)[b]

| Term | Adopted or brand-names | Primary blood purification | Secondary toxin removal | Availability |
|---|---|---|---|---|
| Extracorporeal Albumin Dialysis (ECAD) Type 1 | MARS[c] | Figure 16.11a | Figures 16.11c and 16.11d | EU, ROW, US[d] |
| | OPAL[e] | Figure 16.11g | Figure 16.11f | EU |
| ECAD) Type 2 | ADVOS[f] | Figure 16.11i | Figure 16.11j | EU |
| ECAD Type 3 | SPAD[g] | Figure 16.11h, 16.11k | Not applicable | EU, ROW, US |
| Apheresis PE | PE/HVPE[h] | Figure 16.9 | Not applicable | EU, ROW, US |
| Apheresis SEPET[i] | SEPET/Dialive[j] | Figure 16.6a plus Figure 16.10 | Not applicable | Under study |
| Apheresis Plasmaperfusion | BR350 | Figure 16.7a | Figure 16.7b | EU, ROW |
| | N350 | Figure 16.7a | Figure 16.7b | EU, ROW |
| Apheresis FPSA[k] | Prometheus | Figure 16.8a | Figure 16.8b | EU, ROW |
| Hemoperfusion | Adsorba 300C[l] | Figures 16.6a and 16.6b | Not applicable | EU, ROW, US |
| | Cytosorb | Figures 16.6a and 16.6b | Not applicable | EU, ROW |
| Continuous/Extended Hemodiafiltration | Prismaflex/-max System One | Figures 16.5a and 16.5b | Not applicable | EU, US, ROW |
| | Multifiltrate | Figures 16.5a and 16.5b | Not applicable | EU, ROW |

[a]Clinical reports in a listed Journal with an Impact Factor (IF), searchable on ISI web of science or on clinical trials.gov
[b]As of the edition of this book
[c]MARS-Molecular Adsorbent Recirculating System
[d]As of the edition of this book MARS has no label for the treatment of liver failure or bridge to transplant in the US. It has been re-classified as class III for treatment of liver failure by FDA
[e]OPAL-Open Albumin Dialysis
[f]ADVOS-Advanced Organ Support
[g]SPAD-Single Pass Albumin Dialysis
[h]PE/HVPE-Plasma Exchange/High Volume Plasma Exchange
[i]SEPET-Selective Extracorporeal Plasma Exchange Therapy
[j]Under clinical study
[k]FPSA-Fractionated Plasma Filtration and Adsorption
[l]The program was initiated with Haemocol 100 (Smith and Nephew) and continued with Adsorba 300 C after the initial product was no longer available

ammonia or glutamine and the unbound fraction of aromatic amino acids and tryptophan can be removed which is why some effect in improving severe hepatic encephalopathy has been suggested. More importantly, secondary kidney failure is a frequent complication of liver failure, therefore extended or continuous modalities with high efficiency dialysis membranes represent an important component of the tool box available for extracorporeal liver support.

A more detailed description of the meanings of high-efficiency- and high-flux hemodialysis, hemofiltration and hemodiafiltration has been published by Ambalavanan et al. [10].

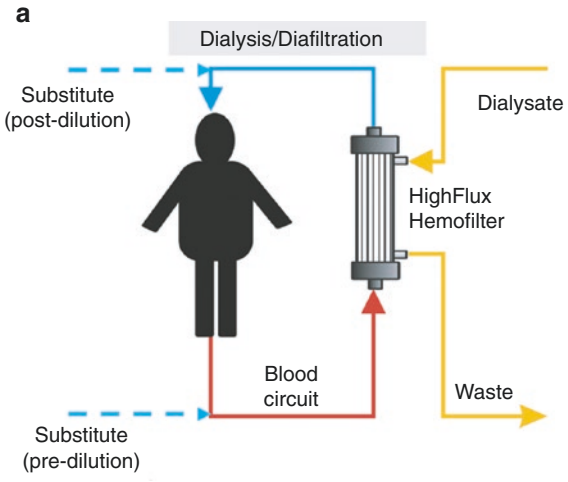



**Fig. 16.5a** Figure shows the principle of dialysis like methods. Blood is perfused through semi-permeable membranes (mostly hollow fibers) and detoxified by interacting with clean, physiologic dialysate solution on the other side of the membrane by diffusion (dialysis). Larger molecules have a slower diffusion rate and can be removed more effectively (if permeable based on size) by adding convective flow (filtration) by applying pressure from the blood side. To prevent fluid loss the filtered fluid should be replaced by infusion before the filter (pre-dilution) or after the filter (post dilution). If only filtration occurs and no dialysis based diffusion (outlet on the dialysis side closed) it is called hemofiltration, if dialysis and filtration are used in combination the technique is called hemodiafiltration. The common denominator is that all three types do not allow for clinically relevant albumin passage through the membrane. For the molecular mechanism see Fig. 16.5b

In short, a more open pore structure improves the removal of molecules in the range up to 50 kD and can support the removal of pro-inflammatory cytokines, especially when the filter is used in filtration mode (convective solvent drag through the membrane by ultrafiltration).

Due to the inefficacy of dialysis like membranes to reduce the amount of albumin bound toxins dialysis like procedures are ineffective as standalone liver support systems.

The need to remove albumin bound toxins was the main intention for the development of adsorption devices which enable the direct contact of albumin and albumin-bound toxins with the surface of adsorbents.

A flow scheme and a depicturing of the molecular mechanism of adsorption is depictured in Figs. 16.6a and 16.6b. Direct interaction of an adsorbent with blood or plasma does allow for the removal of albumin bound substances and may allow for other molecules to be removed, especially when unspecific adsorbents, such as charcoal are used.

This may be beneficial if the removed substances may be harmful, such as pro-inflammatory cytokines or inhibitors of liver regeneration or it may be problematic if the removed substances are growth factors, essential vitamins or nutrients or hormones, which has been described for hemo- or plasma perfusion using activated charcoal. Also, some adsorbents, such as charcoal have been shown to interact

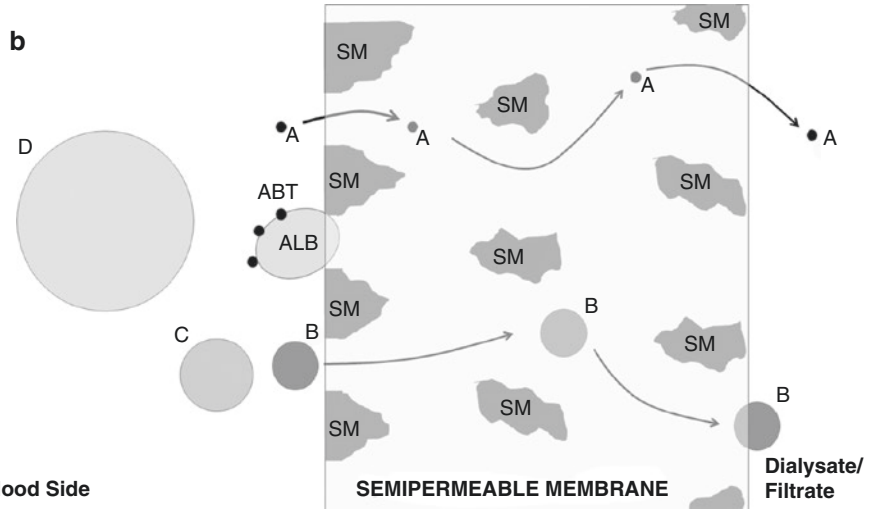
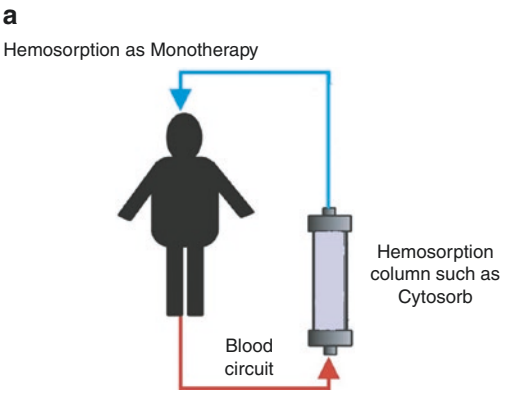



**Fig. 16.5b** Figure shows the molecular mechanism of dialysis like membranes. Most dialysis like procedures in the critical care world are based on so called high flux membranes, which means that they allow for high ultrafiltration rates based on pressure. Usually this also means that the pore size allows not only small molecules (Type A such as ammonia, urea and creatinine) but also middle molecular weight sized molecules (Type B e.g. beta 2 microglobulin, 11 kDa) and potentially smaller cytokines, such as IL6 (17 kDa) to pass. Larger proteins such as Albumin (ALB), Fibrinogen (C) or Alpha-Makroglobulin (D) do not pass. Therefore, dialysis like technologies are insufficient to remove Albumin Bound Toxins (ABT), which represent the major challenge for extracorporeal liver support systems. Therefore, dialysis like technologies are ineffective as stand-alone but represent a valuable tool in combination to manage ammonia and potential secondary renal failure. Also, dialysate solutions contain physiological concentrations of electrolytes, calcium and glucose, which supports metabolic homeostasis

**Fig. 16.6a** Figure shows the flow scheme of hemosorption, which allows for blood contact with an adsorbent that can adsorb albumin bound toxins from blood albumin. The molecular mechanism is described in Fig. 16.6b




significantly with the coagulation and complement system, thereby increasing the risk of DIC development.

Since the latter has been described as a cause for failed studies investigating the efficacy of charcoal perfusion in liver failure, several attempts have been made to

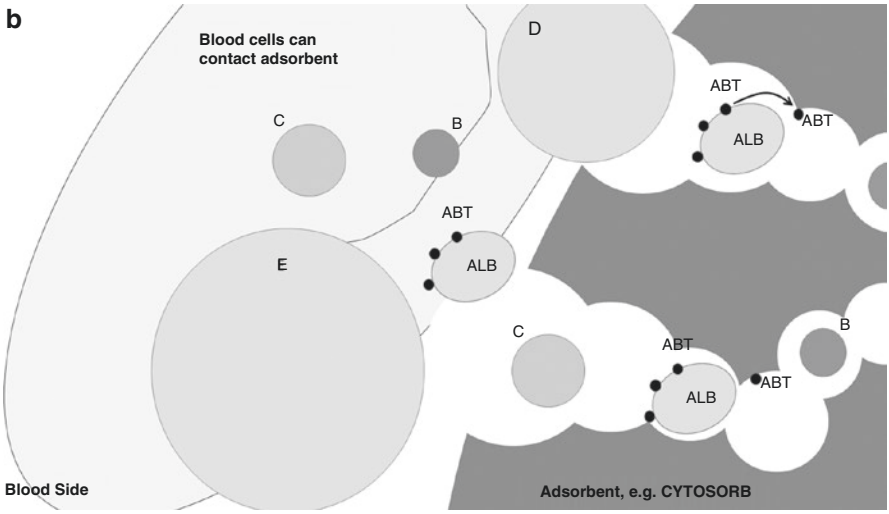



**Fig. 16.6b** Figure shows the molecular mechanism of hemosorption. Full blood including blood cells interact with the adsorbent which allows for direct adsorption of albumin bound toxins (ABT) from Albumin (ALB). Usually other proteins such as beta 2 microglobulin and IL6 (B) and larger proteins such as Albumin (ALB), Fibrinogen (C) or Alpha-Makroglobulin (D) can be adsorbed at a potentially meaningful rate, depending on the physicochemistry of the adsorbent. Also, direct contact can be associated with platelet and leucocyte activation. Since the potential effects can be broad, hemosorption devices are classified as Class C devices by the FDA in terms of requirements for risk/benefit data. The unspecific adsorption characteristics of uncoated activated charcoal and the activation of leucocytes and platelet loss led to failed trials for uncoated charcoal, but newer, more biocompatible and semi-selective (based on lipophilicity and size) hemosorbents did show promising performance in a liver support model [9]

improve the selectivity and biocompatibility, including separating blood cells before adsorbent perfusion to prevent platelet loss and leucocyte activation (plasma perfusion, Figs. 16.7a and 16.7b) or even larger proteins representing vulnerable components of the coagulation system (e.g. in the initial version of the Prometheus system (Figs. 16.8a and 16.8b).

A more recent adsorption technology that has been introduced in the EU is based on polymer beads that remove molecules with a molecular large spectrum of molecular size up to the size of albumin [9] and that are more selective towards less hydrophilic domains. Due to the biocompatibility of the product, it can be used in direct blood contact and it had been used as a stand alone or in combination with hemodiafiltration in liver failure in the EU.

A similar concept as plasma perfusion or selective plasma perfusion using a filtration process to isolate albumin bound toxins with albumin is the plasma exchange therapy (PE) or the selective plasma exchange therapy (SEPET), in which the filtrate is not regenerated by adsorbents but simply discarded and replaced by human plasma (mostly fresh frozen plasma-FFP) or human serum albumin (HSA) or a combination of both (Fig. 16.9).

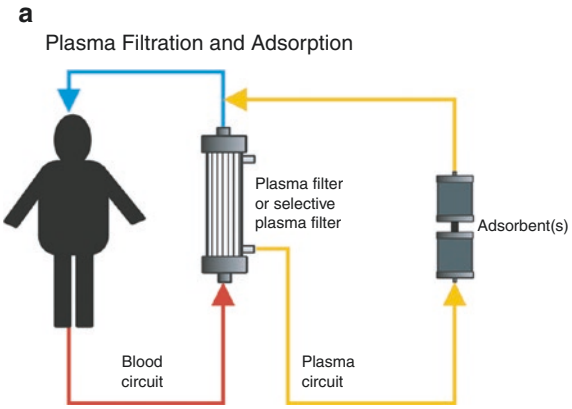



**Fig. 16.7a** Figure shows the flow scheme of plasma adsorption or selective plasma filtration and adsorption. In order to increase the selectivity and the biocompatibility of adsorption the plasma or a fraction (based on molecular size) is separated from blood before perfused over one (e.g. charcoal) or multiple (e.g. combination of charcoal with anion exchanger resin or neutral resin with anion exchanger resin) for adsorption and reinfusion into the blood return line. The molecular mechanism is described in Fig. 16.7b

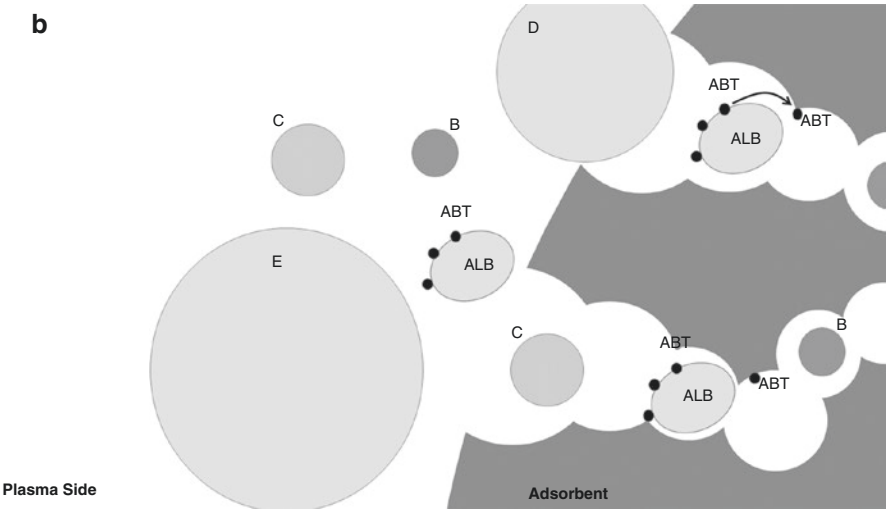



**Fig. 16.7b** Figure shows the molecular mechanism of plasma adsorption or selective (fractionated) plasma filtration and adsorption. Since blood cells are separated by the membrane the unspecific loss or activation does not occur. All these techniques aim at a high rate for albumin filtration which allows for direct adsorption of albumin bound toxins (ABT) from Albumin (ALB). Also proteins in the size of albumin or smaller (B) filter at high rates and may be adsorbed at least in part. Also, depending on pore size even larger proteins than albumin, such as fibrinogen (C) alpha-2-Macroglobulin (D, not shown) or multimeres of smaller molecules presenting larger (E) interact with the adsorbent and may be adsorbed in part

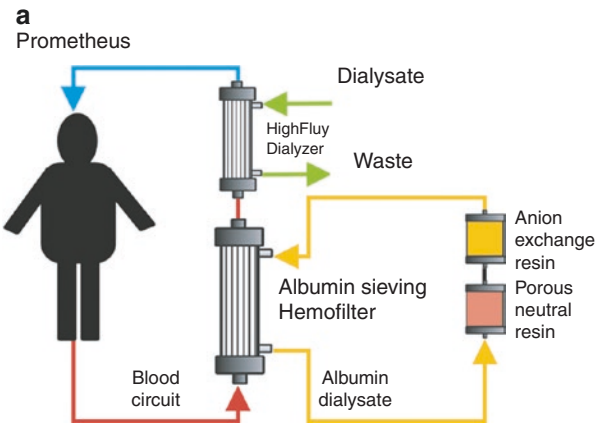



**Fig. 16.8a** Figure shows the flow scheme of selective (fractionated) plasma filtration and adsorption of the Prometheus therapy. In essence, it represents a combination of selective (fractionated) plasma filtration and adsorption (FPSA) and dialysis in consecutive order. The molecular mechanism is shown in Fig. 16.8b

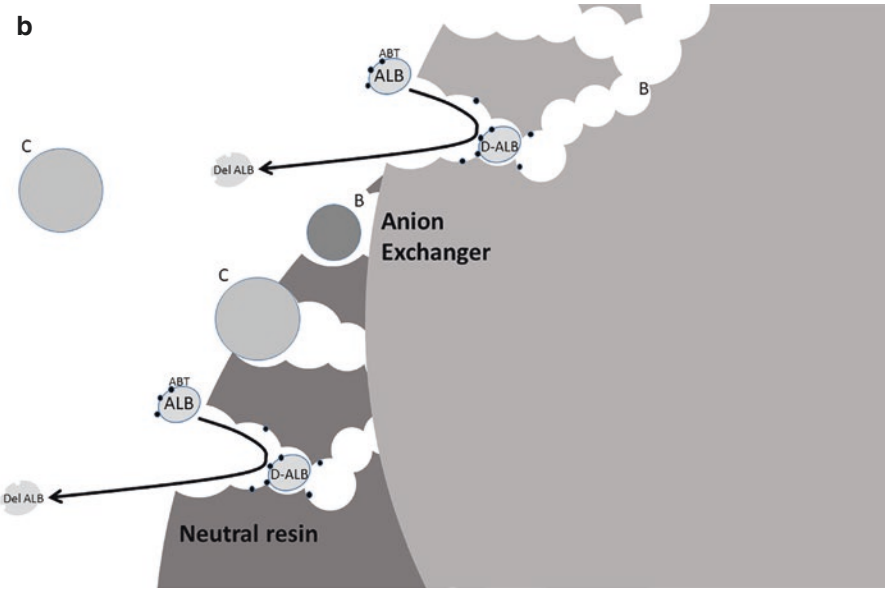



**Fig. 16.8b** Figure shows the molecular mechanism of adsorption after selective plasma filtration and adsorption. Since larger molecules (D such as Alpha-Makroglobulin or E multimeres of smaller molecules presenting larger) and blood cells are separated by the membrane the unspecific loss of super large proteins or activation of blood cells does not occur. The technique aims at a high rate for albumin filtration which allows for direct adsorption of albumin bound toxins (ABT) from Albumin (ALB). Therefore, albumin sized or smaller proteins such as Interleukins (B) and even larger proteins than albumin, such as fibrinogen (C) interact with the adsorbent and may be adsorbed in part

Selective Plasma Exchange is based on a more selective filtration of the Albumin-Toxin Complex by using membranes with pores that allow for the filtration of albumin [11].

Both replacement products bare some problems for patients with liver failure. FFP contains significant amounts of citrate for anticoagulation, which can cause

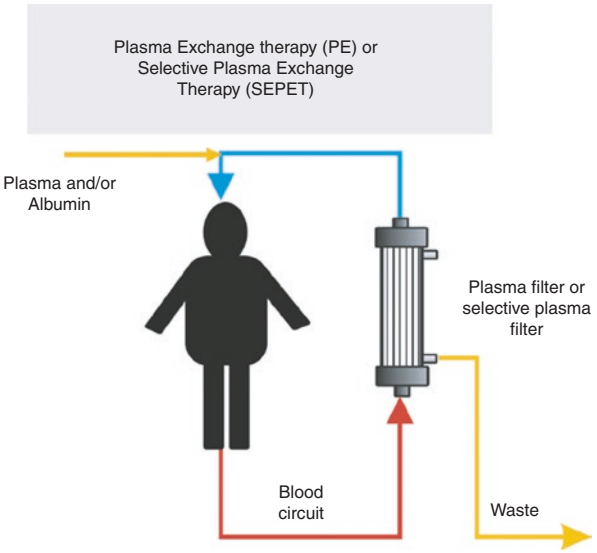



**Fig. 16.9** Figure shows the flow scheme of plasma or selective plasma filtration. In order to increase the selectivity and retain blood cells the plasma or a fraction (based on molecular size) is separated from blood and simply discarded. The loss of the passing molecular spectrum is complete and is replaced with plasma, albumin or a mixture of both. If the replacement fluid is based on albumin, new versions of selective plasma filtration implement albumin filtration (Fig. 16.10)

ionized hypocalcemia and metabolic alkalosis if large volumes are exchanged, the latter potentially exacerbating the metabolic alkalosis which can be present in liver failure.

Commercial human serum albumin contains significant amounts of albumin bound caprylate and in most preparations also *N*-acetyl-tryptophan (as stabilizers), both molecules occupying binding sites of albumin and displaying clinically relevant challenges in patients with liver failure and reduced capacity to metabolize both molecules [1]. Therefore, newer versions of plasma- or selective plasma exchange therapies are combined with pre-adsorption in order to remove the stabilizers and "activate" the albumin molecule for better toxin binding (Fig. 16.10).

In these therapies based on filtration merely, the clearance for any toxin to be removed is limited by filtration rate and the total amount of the toxin removed is limited by the exchanged volume and the sieving coefficient of the membrane for the toxin, which is the main limitation of these technologies. However, if used over longer periods of time or if higher volumes are exchanged, Plasma Exchange Therapy has been used successfully in acute liver failure patients.

Dialysis-like therapies, plasma filtration, plasma exchange and hemo- and plasma perfusion are principles that have been used clinically before the nineties of the last century, but have improved over time in terms of usability and biocompatibility until today.

A newer and very different concept for removing albumin bound toxins without the need to filter the albumin/toxin complex from blood is extracorporeal albumin dialysis (ECAD), which was introduced 1992 [12]. The molecular mechanism is depicted in Fig. 16.11a, and flow schemes of various products based on this principle as well as the molecular mechanism to recycle the albumin dialysate if applicable are given in Figs. 16.11a–k. The common denominator of all ECAD treatments is that blood is dialyzed against an albumin containing dialysate using a dialysis

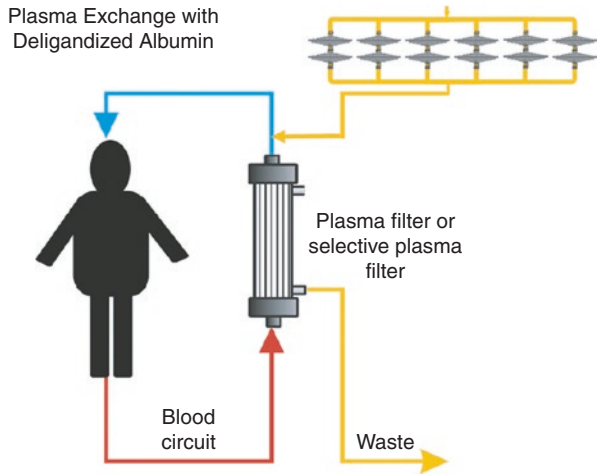



**Fig. 16.10a** Figure shows the flow scheme of selective plasma filtration. In order to increase the selectivity and retain blood cells the plasma fraction (based on molecular size) is separated from blood and simply discarded. The loss of the passing molecular spectrum is complete and is replaced usually with albumin implementing albumin filtration to remove the stabilizers and "activate" albumin binding sites. The molecular mechanism of the membrane filtration process is described in Fig. 16.10b

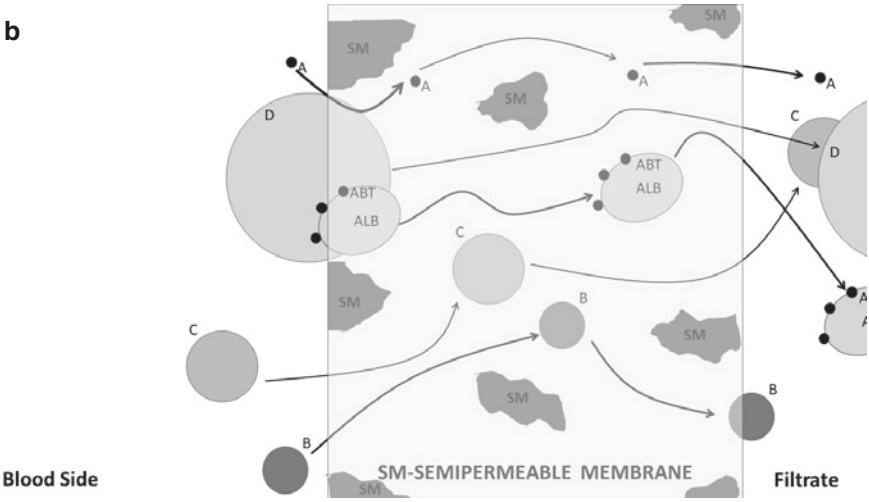



**Fig. 16.10b** The figure shows a plasma filtration membrane that allows the albumin toxin complex (ABT) to pass through. Smaller toxins (A) pass freely, also middle molecules such as cytokines can pass (B, C). Depending on the Cut off of the membrane very large molecules, such as IgM may be retained at a higher rate, which makes the process semi-selective

membrane which is essentially impermeable to patients and dialysate albumin but allows dialysate albumin to enter the inner pore structure of the membrane from the dialysate side (Fig. 16.11a).

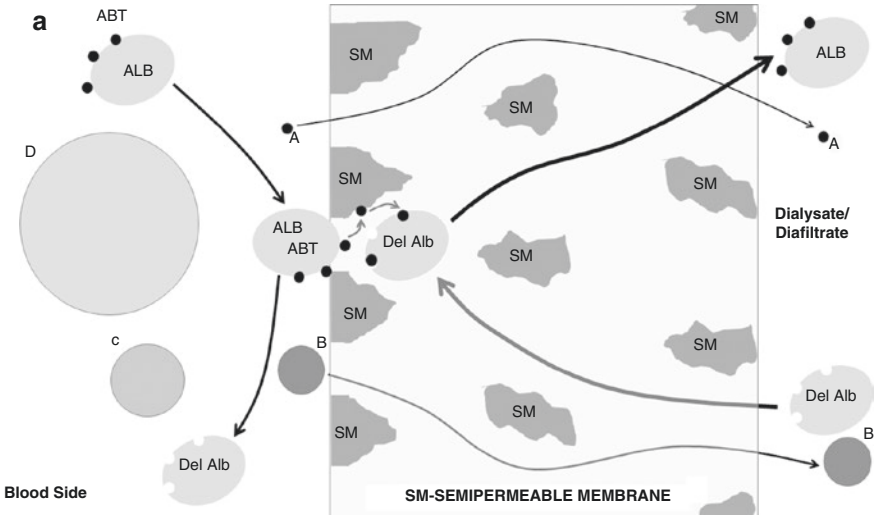



**Fig. 16.11a** Figure shows the molecular principle of extracorporeal albumin dialysis. Blood is perfused through semipermeable membranes (mostly hollow fibers) and detoxified by interacting with clean, physiologic dialysate solution on the other side of the membrane by diffusion (dialysis) containing albumin. The separation of proteins is identical with dialysis like techniques (Figs. 16.5a and 16.5c). However, due to the addition of albumin in the dialysate which can actually enter the larger entry of pores from the dialysate side and travel towards the blood side over 90% of the membrane thickness it can interact with blood albumin by taking over albumin bound toxins from blood but not patient's albumin. The pore size allows not only small molecules (Type A such as ammonia, urea and creatinine) but also middle molecular weight sized molecules (Type B e.g. beta 2 microglobulin, 11 kDa) and potentially smaller cytokines, such as IL6 (17 kDa) to pass. Larger proteins such as Albumin (ALB), Fibrinogen (C) or Alpha-Makroglobulin (D) do not pass. ECAD allows to manage ammonia and potential secondary renal failure. Also, dialysate solutions contain physiological concentrations of electrolytes, calcium and glucose, which supports metabolic homeostasis. The common denominator of all ECAD therapies is that all three types do not allow for clinically relevant albumin passage through the membrane. There are 3 Types of ECAD explained in in Figs. 16.11b, 16.11c, 16.11d, 16.11e, 16.11f, 16.11g, 16.11h, 16.11i, 16.11j, and 16.11k

Since the beginning of the twentieth-century ECAD methods evolved to the most frequently used, studied and published procedure for extracorporeal liver support in liver failure.

Based on the method to maintain the binding properties of the dialysate albumin there are three types of ECAD that are available in the US and/or the EU at this point:

- ECAD Type 1: Recirculation using adsorbents (MARS, OPAL) (Figs. 16.11d and 16.11e)

In these procedures the dialysate albumin is recycled by perfusion of the toxin-enriched used albumin dialysate over adsorbents (similar to adsorbents used for blood—or plasma perfusion). The procedure can be combined with dialysis by implementing a dialyzer in the albumin dialysis circuit simultaneously; or by

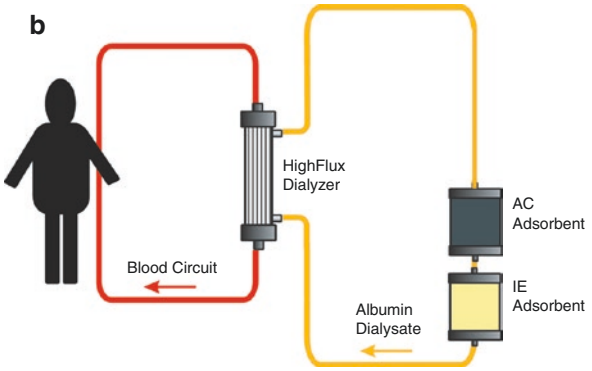



**Fig. 16.11b** Figures 16.11b–16.11g show ECAD Type 1 therapies, in which the common denominator is that adsorbents are used on the dialysate side. Figure 16.11b shows that the used albumin dialysate is reused with a combination of charcoal and an anion resin adsorbents, such as the commercial versions in MARS (AC-250 and IE-250). The molecular mechanism of adsorption is shown in Fig. 16.11c

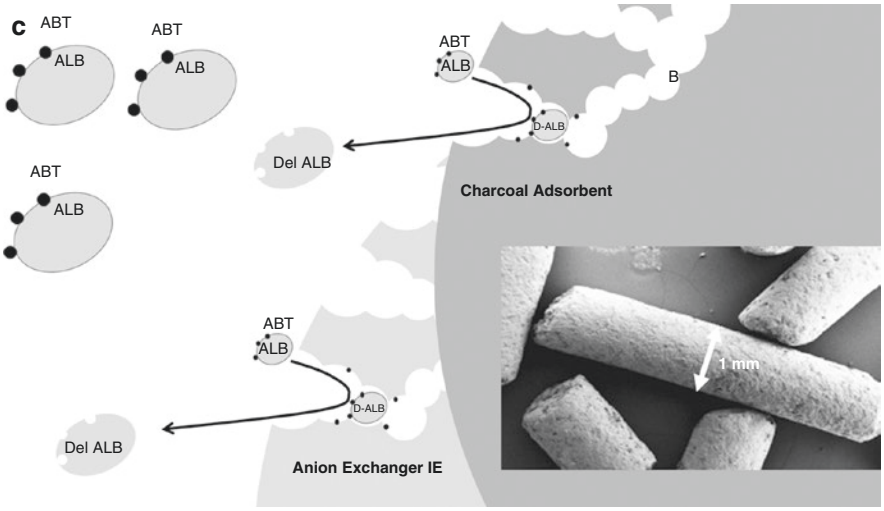



**Fig. 16.11c** Figure shows the molecular mechanism of adsorption for reuse of dialysate albumin in commercial ECAD Type 1 therapies such as MARS. All molecules as large or larger than albumin are separated by the membrane therefore the unspecific loss of proteins or activation of blood cells does not occur. The charcoal has a broad adsorption spectrum, but does not effectively bind bilirubin which is why an anion exchanger is also implemented. Also, the size of the charcoal particles is macroscopic (1 mm thick sticks), therefore large channels provide the flow through space for albumin. Since albumin diffuses slowly and the flow rates in ECAD are high, not all albumins reach the surface, which limits clearance Fig. 16.11d

switching between albumin recirculation over adsorbents to dialysis continuously in intervals (Fig. 16.11g). In the MARS set, macroscopically visible charcoal "sticks" and an anion-exchanger resin are combined since the charcoal does not bind bilirubin effectively, in the OPAL system, a micro-particle sized charcoal is used,

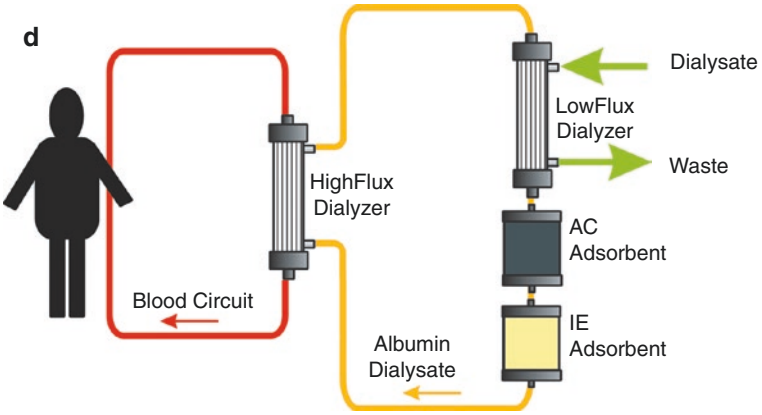



**Fig. 16.11d** The shows ECAD Type 1 as commercialized under MARS, in which used albumin dialysate is reused with a combination of charcoal and an anion resin adsorbent and dialysis

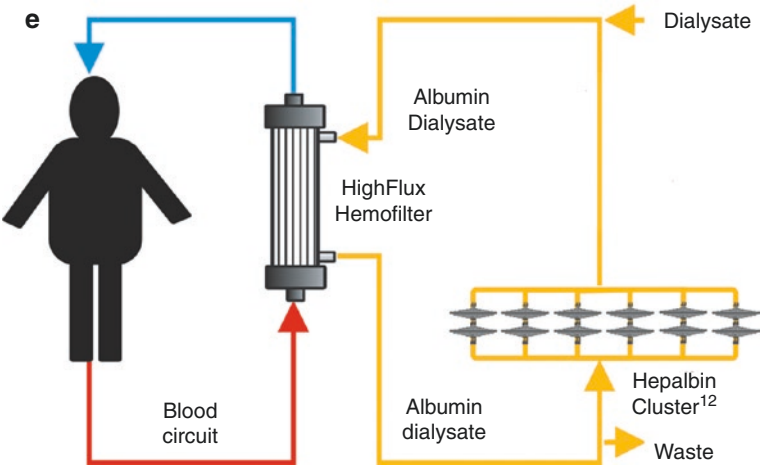



**Fig. 16.11e** Figure 16.11e shows ECAD Type 1 as commercialized under Microparticle Charcoal (Hepalbin)-Adsorbent recirculation, in which used albumin dialysate is reused by a micro-particle sized charcoal, embedded in a cellulose/resin scaffold creating much smaller diffusion channels. The adsorbent also eliminates bilirubin and, more importantly, the stabilizer caprylate significantly more effective, which is why the procedure has shown to be more effective in removing albumin bound toxins [5–8]. In a recent prospective multicenter randomized controlled cross-over study comparing the efficacy of MARS versus OPAL based on the biomarker albumin binding function (ABiC) for efficacy OPAL was superior to MARS, which is simply based on a higher adsorbent performance. The molecular mechanism of the microparticle charcoal adsorption is shown in Fig. 16.11f. If combination with dialysis is desired it can be performed consecutively by switching from recirculation to single pass dialysis

embedded in a cellulose/resin scaffold creating much smaller diffusion channels. In the latter case, the adsorbent also eliminates bilirubin and, more importantly, the stabilizer caprylate significantly more effective, which is why the procedure has shown to be more effective in removing albumin bound toxins [5–8]. In a recent

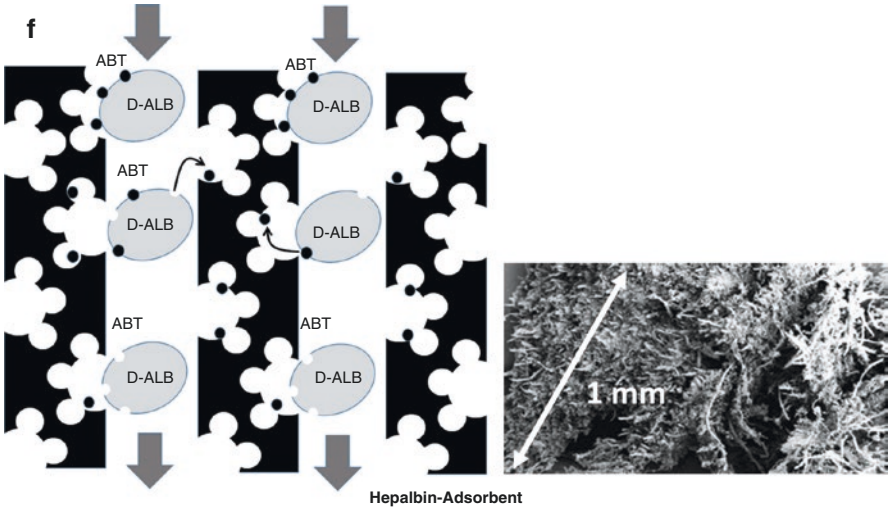



**Fig. 16.11f** Figure shows the molecular mechanism of adsorption for reuse of dialysate albumin in microparticle charcoal (Hepalbin)-Adsorbent recirculation. As in MARS, all molecules as large or larger than albumin are separated by the membrane therefore the unspecific loss of proteins or activation of blood cells does not occur. The charcoal adsorbent has a broad adsorption spectrum and binds effectively bilirubin and albumin stabilizers. The channels for albumin perfusion are microscopic, which forces all albumin molecules to interact with the surface of the adsorbent, similar to toll roads forcing every car to pass a toolbooth

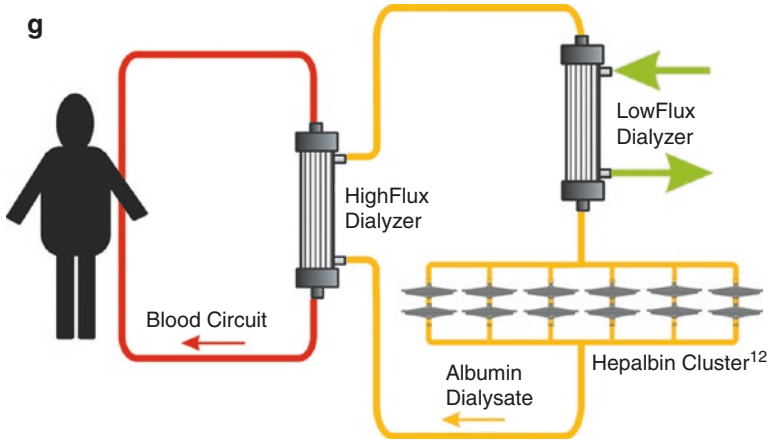



**Fig. 16.11g** Figure 16.11g shows ECAD Type 1 as commercialized under OPAL, which is equivalent to MARS (implementing simultaneous dialysis) but using the microparticle charcoal (Hepalbin)-Adsorbent for albumin dialysate reuse

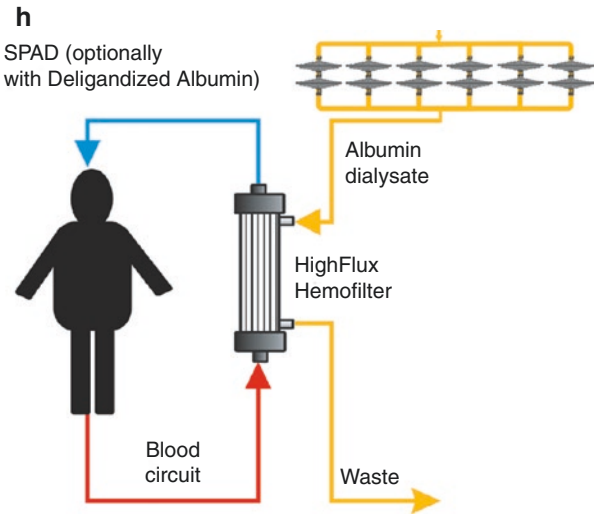



**Fig. 16.11h** This figure is essentially an ECAD therapy type 3 (single pass albumin dialysis) but as in Fig. 16.10, the commercial dialysate albumin is used implementing albumin filtration to remove the stabilizers and "activate" albumin binding sites as described in [2]

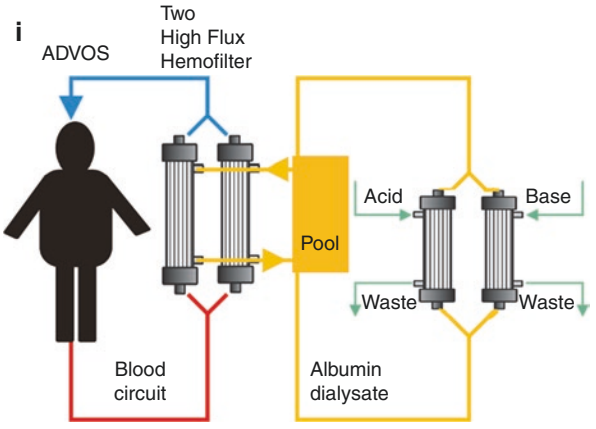



**Fig. 16.11i** This figure shows the flow scheme of ECAD Type 3 (ADVOS) in which the albumin dialysis process from blood into the albumin dialysate is equivalent to other ECAD devices, however, the recycling process is fundamentally different. Based on the observation, that the binding rate of albumin bound toxins can be lowered by manipulating the pH value, the albumin dialysate is split in to half and while one half is filtered in an alkaline milieu the other one is filtered in an acidic milieu before the two flows re-join for another uptake of toxins via albumin dialysis. The molecular mechanism of this recycling process is explained in Fig. 16.11j

prospective multicenter randomized controlled cross-over study comparing the efficacy of MARS versus OPAL based on the biomarker albumin binding function (ABiC) for efficacy OPAL was superior to MARS, which is simply based on a higher adsorbent performance.

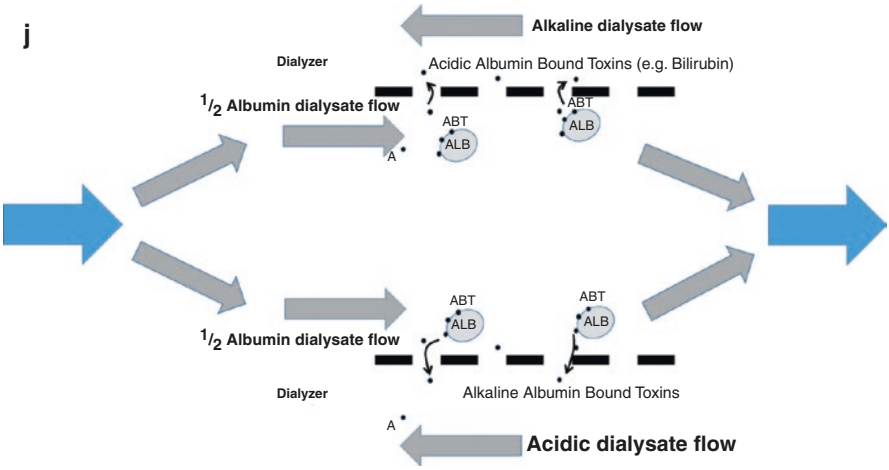



**Fig. 16.11j** The binding rate of albumin bound toxins can be lowered by manipulating the pH value, the albumin dialysate is split in to half. One half is filtered in an alkaline milieu the other one is filtered in an acidic milieu before the two flows re-join for another uptake of toxins via albumin dialysis. Since alkaline pH manipulation is loosening other toxins than acidic pH manipulation and both procedures are done in parallel one must assume that the clearance *from dialysate* for both types is 50%. The procedure is relatively new and technically interesting

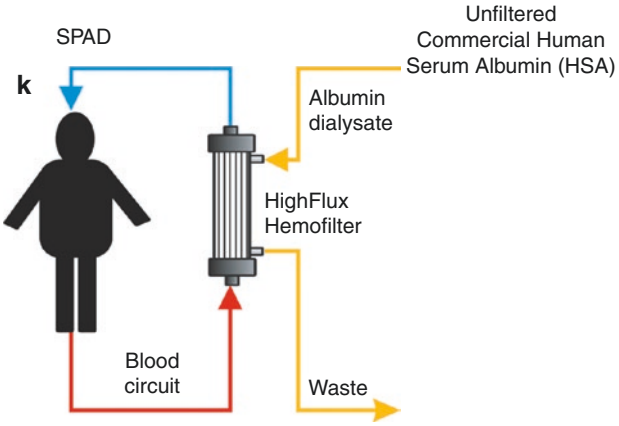



**Fig. 16.11k** This figure shows the ECAD therapy type 3 (single pass albumin dialysis) in its most simple version but in contrast to in Fig. 16.11h, the commercial dialysate albumin is not filtered and stabilizers limit the efficacy of dialysate albumin's binding site (Sudlow II) which resulted in lesser improvement compared to MARS [1, 2]. It is reasonable to assume that this limitation can be resolved by applying version 11h, since the molecular mechanism of the membrane separation of toxins is equivalent to ECAD type 1 and since the albumin is discarded, the removal of toxins from dialysate is practically 100%

- ECAD Type 2: Recirculation using secondary albumin filtration under pH manipulation to "loosen" the albumin binding of toxins (ADVOS) (Fig. 16.11i)

While the albumin dialysis process from blood into the albumin dialysate is equivalent to other ECAD devices, the recycling process is fundamentally different. Based on the observation, that the binding rate of albumin bound toxins can be lowered by manipulating the pH value, the albumin dialysate is split in to half and while one half is filtered in an alkaline milieu the other one is filtered in an acidic milieu before the two flows re-join for another uptake of toxins via albumin dialysis (Fig. 16.11j). Since alkaline pH manipulation is loosening other toxins than acidic pH manipulation and both procedures are done in parallel one must assume that the clearance from dialysate for both types is 50%. The procedure is relatively new and no controlled clinical data have been published at the time of the edition of this chapter, so substantial equivalence to MARS and OPAL is unclear, however, a first 14 patient case series did show reduction of albumin bound albumin [13].

- ECAD Type 3: Discarding used dialysate albumin (single pass albumin dialysis-SPAD Figs. 16.11h and 16.11k)

A very simple and universally applicable version of ECAD does not require albumin regeneration but is based on discarding used albumin and supplying fresh dialysate with fresh albumin. Although human serum albumin is expensive, one saves the costs for recycling disposables which can be costly and the procedure is simple and can be performed with any critical care dialysis machine by simply adding the albumin into the dialysate bags. However, since the rate of albumin waste correlates with dialysate flow and albumin concentration, users of this version usually use low dialysate albumin concentration (between 2% and 4%) and low flow rates. In one prospective randomized controlled cross-over study comparing MARS versus SPAD, the investigators concluded that SPAD is less effective than MARS. Especially using patients albumin binding function (ABiC) as a biomarker for ECAD efficacy SPAD was inferior to MARS. Considering earlier publications the inferiority of SPAD despite the constant use of "fresh" albumin can only be explained by the overload of commercial albumin with caprylate and *N*-acetyltryptophan, a fact that has been shown to affect commercial albumin function in liver patients.

In ECAD therapies of Type 1 the content of stabilizers is reduced significantly before therapy by MARS and even more so by OPAL during the pre-circulation of albumin dialysate via the adsorbents [14].

Since newer Selective Plasma Exchange Therapy procedures such as DiaLive pre-purify the substitute albumin by online adsorption via charcoal filtration one could also utilize the same method to pre-purify dialysate albumin during SPAD [2, 15].

In conclusion, the vast majority of clinical data over the last 20 years have been generated by ECAD procedures based on ECAD Type I and as long as clinical data do not support substantial equivalence for the dialysate albumin quality equal safety/

efficacy outcomes as outlined in the following chapter may be possible but are not guaranteed.

Finally, new concepts based on cellular therapies and tissue engineering have been emerging. However, since there are no approved or cleared devices available yet, the status of biological liver assist systems will be summarized in the outlook paragraph of this chapter.

The following paragraphs relate to non-cellular liver assist devices that are commercially available in the EU and/or in the US.

## Indications

There are four domains of liver failure, where Liver Assist devices have been used with documented improvements of clinically meaningful endpoints:

- Acute Liver Failure
- Acute on chronic Liver Failure
- Post surgery (primary poor liver transplant function and post resection)
- Cholestasis with intractable pruritus

Liver failure can occur without preexisting liver disease as a consequence of intoxication or acute viral hepatitis (Acute Liver Failure), but in the vast majority it is caused by a superimposed precipitating event on the basis of an underlying chronic liver disease (Acute on Chronic Liver Failure). The latter represents by far the most frequent indication for Liver Assist Devices.

If Liver function does not recover within 2–4 weeks, the only therapy improving long or even middle term survival is liver transplantation. ECAD Type 1 has been studied most extensively in subjects with acute on chronic liver failure.

If the transplant takes too long to take over liver function or doesn't function properly (Primary poor liver transplantation), temporary liver support has been tested in order to support transplant recovery or bridge to re-transplant.

A key area of use for extracorporeal liver support systems is evolving around liver transplantation, either to bridge to in acute and acute on chronic liver failure or to support primary poor transplant function.

Also, after extensive liver surgery (mostly resection) a rapid deterioration of liver function can occur, which also has been investigated clinically, although controlled studies in this area are very difficult to design.

During the studies in patients with acute on chronic liver failure an unexpected observation was made in a subpopulation with cholestatic liver disease (mostly in PBC and PSC) with pruritus. Even in non-responders to conventional drug therapy (intractable pruritus) pruritus was reduced significantly or disappeared within 2–3 treatments and remained bearable for 2–3 months, which identified an additional potential use of ECAD, intractable cholestatic pruritus.

In the following subchapters the indications, precautions, endpoints and the evidence presented in these areas will be laid out.

Indications for extracorporeal albumin dialysis devices in diseases that are not primarily related to Liver dysfunction or failure, such as drug overdose and poisoning will not be discussed in this Chapter.

## *Acute Liver Failure*

Acute Liver Failure is a syndrome in which liver failure occurs in patients without pre-existing liver disease and is associated with the development of hepatic encephalopathy. It is a rare condition and a detailed description is given in chapter (…) of this book.

Since it was realized that non-dialyzable toxins play an important role in the clinical manifestation of liver failure multiple attempts of extracorporeal detoxification where reported which lead to the ground breaking effort of the group of Professor Roger Williams using charcoal hemoperfusion for liver support in acute liver failure [16]. Although this study could not show an improvement of survival it laid the ground work for the entire field of extracorporeal liver support.

The next significant effort was undertaken by the group of Professor Achilles Demetriou investigating a hybrid device containing a similar charcoal used in plasma perfusion mode in combination with a cartridge containing 50 g of porcine hepatocytes [17]. Although the study did not show a significant improvement of survival in the total population which included transplanted subjects with primary non function, there were strong trends for improvement in significant subgroups. In the twenty-first century, a prospective multicenter randomized controlled study in French transplant centers investigated the efficacy of MARS in fulminant liver failure. Since the majority of treated subjects received a liver transplant within 24 h the overall survival was very high which made an assessment for the effect on survival impossible, however, in subjects with a longer waiting time for the transplant there was a better outcome for subjects on MARS [18]. Finally, a prospective randomized controlled multinational study conducted by Fin Larsen et al. [19] in order to investigate the effect of High Volume Plasma Exchange (HVPE) did show an improvement of survival by extracorporeal liver support.

An important observation made by all the studies is that these treatments proved to be quite safe, especially if used with citrate anticoagulation which is a regional anticoagulation and has only minor effects on patient's coagulation. Based on these studies and considering an acceptable safety profile when used by skilled sites it can be suggested to consider Liver Support Therapy in subjects where a longer waiting time for the transplant (based on allocation or blood group) must be expected.

ECAD in acute Liver failure has also been associated with clinically meaningful improvements of brain edema and circulatory dysfunction [20–23].

The largest compilation of the use of ECAD for stabilizing patients with acute liver failure before transplantation in the US so far has been published by Hanish et al. [24]. The authors report a significant improvement of INR, creatinine,

bilirubin, lactate, liver enzymes GOT and GPT, the Apache Score and hepatic encephalopathy.

In a specific and rare form of ALF associated with Copper toxicity, albumin dialysis was also effective, which may be additionally caused by the ability of dialysate albumin to remove copper itself [25, 26].

## *Acute on Chronic Liver Failure*

Acute on chronic Liver Failure is a syndrome in which liver failure develops in patients with pre-existing liver disease based on a precipitating event in which secondary organ failures manifest themselves within 4 weeks. A detailed description of the disease can be found in this book.

Secondary organ failures may include the brain, the circulation, lung function, renal function, coagulation and the liver itself, displaying acute deterioration.

While there is consensus in the international liver community about the concept of ACLF and need for therapies there are different grading systems between the North American Consortium for the Study on End Stage Liver Disease (NACSELD), the European Chronic Liver Failure Consortium (CLIF) and the Asian Pacific Association for the Study of Liver Disease (APASL) based on secondary organ failure definitions, which are laid out in a consensus paper on the definition of ACLF [27].

### Effects on Secondary Organ Failures

Prospective randomized studies have shown the following effects of liver support on liver and secondary organ functions in ACLF:

**Hepatic Encephalopathy**
An improvement of Hepatic Encephalopathy by ECAD has been shown consistently in multiple controlled studies in patients with cirrhosis and superimposed acute liver injury [28–33].

Also, a combination of ECAD with Plasma Exchange [34] was reported to be effective in ACLF.

The mechanism of action of ECAD to improve hepatic encephalopathy is based on multiple synergistic effects [31, 35, 36].

The improvement of hepatic encephalopathy by ECAD has been reported so consistently, that recently the group of Hicks et al. [37] suggested the procedure also as a potential diagnostic tool to assess the reversibility of hepatic coma prior to transplantation.

**Circulatory Dysfunction**
ACLF is frequently associated with marked circulatory dysfunction which is frequently triggered by portal hypertension and systemic inflammation. Although the

primary intention of the development of liver support systems was the prevention and treatment of hepatic coma in liver failure, multiple controlled studies have repeatedly reported a significant improvement of hemodynamic parameters, such as the systemic vascular resistance index and the mean arterial pressure [28, 38, 39].

As for the improvement of hepatic encephalopathy, multiple parallel mechanisms of action have been discovered to explain the reason for improvement of this clinically meaningful endpoint, including removal of vasodilators such as bile acids, caprylate, prostaglandins, the reduction of NO either in the albumin bound form of a Nitrosothiol or by reducing inducible NO-Synthase and the reduction of pro-inflammatory molecules. Also, a reversal of arteriole vasodilation by the reduction of the portal vein pressure has been suggested which would explain improvements of hepatorenal syndrome [40, 41].

Interestingly, the hemodynamic improvements during extracorporeal liver support were significantly more prominent during ECAD when compared to selective plasma filtration and adsorption (Prometheus), pointing at the importance of the difference in the mechanism of action in terms of membrane separation and adsorbent between MARS and Prometheus. This is important, since the removal rates for bilirubin and bile acids in Prometheus were even better than for MARS due to direct plasma perfusion, however, virtually none of the hemodynamic parameters such as SVRI and MAP improved during Prometheus but in MARS and only MARS was associated with a reduction of plasma renin activity, vasopressin, aldosterone, norepinephrine and nitrate/nitrite levels. On the other hand, there was a strong trend of INR in Prometheus while it remained unchanged in MARS, an indicator that even selective plasma perfusion affects the coagulation system more than dialysis [42].

One explanation for this significantly different effect despite similar removal rates would be that there are other molecules that would be more effectively removed by ECAD than by Prometheus. A good parameter to detect the removal of unknown albumin bound toxins would be to measure changes of the remaining patient's albumin capacity as a "mirror image" of accumulation of albumin bound toxins (Fig. 16.4). When comparing selective plasma filtration (Prometheus) with ECAD (MARS), ECAD using MARS but not FPSA using Prometheus could improve patients albumin binding function measured by ABIC [3, 4].

This might very well explain the stronger effect of ECAD using MARS on the improvement of hemodynamics because many of the relevant vasodilators in Liver Failure bind to albumin and binding sites are required to bind an excess of vasodilators in inflammation in order to make them biologically unavailable rendering them inactive.

This hypothesis of mechanism of action to improve hemodynamics by albumin dialysis is supported by the fact, that ECAD Type 3 (SPAD) was even more effective in improving blood pressure and reducing need for pressor support in patients at the ICU with liver failure on pressor therapy when the dialysate albumin was purified from caprylate prior to use which also resulted into an even more prominent improvement of patients albumin binding function [2].

These data lead to the development of OPAL, which contains a new generation of charcoal based adsorbents that remove caprylate from dialysate albumin prior to treatment more efficiently and have shown statistically significant improvement of patients albumin binding function measured by ABiC and also by Electron Spin Resonance (ESR) in one single center [6] and another multi center prospective randomized controlled cross over study when compared to MARS [7, 8].

The improvement of circulatory dysfunction has crystallized as one of the leading clinically meaningful benefits of ECAD, which makes sense, since circulatory dysfunction as a consequence of portal hypertension and systemic inflammation has an additional tertiary effect on almost any other organ system including the brain and even the liver itself, but the most sensible organ towards hemodynamic dysfunction are the kidneys, which explains additional beneficial effects of albumin dialysis on kidney dysfunction, although they are not just based on improved renal perfusion.

**Renal Function**

Renal function in ACLF can be affected by multiple risk factors, such as circulatory dysfunction caused by portal hypertention, splanchnic arterial vasodilation and systemic inflammation, but also inflammation itself and jaundice have a direct toxic effect on renal tubular cells [43, 44].

In general, lipophilic bile acids typically accumulating in the circulation in liver failure are known to be quite toxic. In hepatocytes, apoptosis has been observed already at exposure of relatively low concentrations as 25–50 μmol/l [45].

Therefore, not just the improvement of hemodynamics discussed above, but also the removal of nephrotoxic endogenous molecules suggest a clinically meaningful effect of extracorporeal detoxification in renal failure.

Significant improvement of renal function has been reported in two prospective randomized controlled studies [28, 30, 33, 46] and several case series [47–49].

Especially in subjects with hepatorenal syndrome type I one has to bare in mind, that once the tubular cells are irreversibly damaged by ischemia or toxic effects of accumulating toxins of liver failures including, but not limited to bile acids, fast recovery of renal dysfunction in HRS-1 may be difficult to achieve [50].

Therefore, especially in patients with a chance for hepatic recovery (such as in patients with acute alcoholic hepatitis and only mild cirrhosis) and potential transplant candidates, it is fundamentally important to continue with liver support therapy until the liver and the kidneys either recover or until a transplant is available.

In general, ECAD is looked at as an additional tool in the treatment of intractable HRS [51, 52].

**Liver Function**

Since accumulated toxic bile acids do affect hepatocellular function and circulatory dysfunction may affect the whole liver, multiple studies have investigated the effect of extracorporeal liver support on liver function.

Hetz et al reported an improvement of the Indocyanin Green Clearance, which is a function of liver perfusion, hepatocellular uptake and bile excretion [48].

Hepatocellular recovery is also suggested by the reduction of plasma toxicity of liver failure patients on cultivated hepatocytes viability and p450 function [53].

Therefore, several authors have investigated clinically if potential recovery of hepatocytes is associated with an improvement of protein synthesis and have reported several indicators, such as factor VII improvement [54], INR improvement [53, 55], AT III improvement [53], and cholinesterase increase [56].

Although the reports are optimistic, it appears obvious that the opportunity to recover liver function in ACLF is dependent on the degree of underlying cirrhosis (which may be not even very high in even severe acute alcoholic hepatitis, where recovery is possible). In order to assess the effect of liver support on the improvement of liver function a stratification based on the underlying functional liver capacity would be needed in future studies. Especially in end stage cirrhosis and severe inflammation, extracorporeal therapies may actually trigger disseminated extracorporeal coagulation (DIC) which may deteriorate coagulation.

However, in severe alcoholic hepatitis as a special form of ACLF where recovery is possible if the patient commences alcohol consumption, ECAD has been suggested as a useful tool to either bridge to recovery or to transplant by stabilizing cerebral function and hemodynamic stability [57].

Effects of ECAD Type 3 (SPAD) in AoCLF have also been reported as similar, but larger prospective randomized controlled data missing [58].

There are also not many data on the effect of plasma exchange in ACLF since the syndrome has been described, however, due to the encouraging results of high volume plasma exchange therapy in Acute liver failure, a multicenter prospective randomized controlled study has been initiated to investigate the effect of plasma exchange in ACLF (APACHE Study).

The largest data set on the effects of Selective Plasma Filtration and Adsorption (FPSA-Prometheus) in patients with ACLF has been published on the Helios Study which will be discussed in the following section.

## Effects on Extracorporeal Liver Support on Outcome in ACLF

In prospective controlled studies ECAD has been associated with an improved survival in hepatorenal syndrome [46], cirrhosis with superimposed acute liver injury and progressive jaundice, almost exclusively due to alcoholic hepatitis [28] and in severe hepatic encephalopathy in patients with MELD > 30 [30].

Between 2000 and 2010, ECAD using MARS and FPSA using Prometheus have been investigated for their efficacy and safety to improve the one month outcome of patients with decompensated cirrhosis. At this time, the definition and the classification and stratification of ACLF had not been developed since prospective observational studies on risk factors and the natural history of ACLF were missing. Therefore, subjects were enrolled based on hepatic encephalopathy and/or jaundice and/or renal dysfunction.

Also, while the primary endpoint was the one month outcome, the treatment was in general commenced within the first two weeks. Unfortunately both studies failed the primary endpoint and considered dose administration and study design limitations as potential reasons [33, 59].

Also, in the early phase of the studies citrate anticoagulation had not yet been established as a standard, which has later resulted into a significant reduction of potentially severe adverse effects due to bleeding.

In the meantime, pioneered by the Chronic Liver Failure Consortia, ACLF as a syndrome is much better understood and rules for stratification have been developed [60–62].

Re-Analysis of the RELIEF data by two independent groups suggested, that in patients with ACLF ≥ 2 the effect of ECAD using MARS on 30 days survival was significant [63] which was validated by an separate historical population and a separate and independent Metaanalysis of the entire data concluded that in subjects receiving 5 or more sessions 30 day survival was also significantly improved in the ECAD group [64].

A prolongation of survival time in the 4 week range would make ECAD a valuable tool for the managements of patients who are potential transplant candidates due to ACLF and who could recover (as in severe alcoholic hepatitis).

A most recent review and meta-analysis including 25 randomized controlled trials including 1796 patients [65] concluded that extracorporeal liver support was associated with a reduction of mortality (RR 0.84; 95% CI 0.74, 0.96).

However, since patient stratification and the definition of ACLF remain a moving target and are subject to the need for further harmonization and also since the next generation of ECAD systems are under clinical development, further studies should be encouraged [66].

### *As a Bridging Tool for Liver Surgery and Transplant Centers*

Based on the accumulation of encouraging reports and since there is urgent need for surgeons to manage patients with liver surgery and before and potentially after surgery or transplantation and due to the improved safety profile of liver support especially for ECAD, there are many reports supporting the use of extracorporeal liver support, mostly ECAD around liver surgery [48, 67–72], however, one must consider, that in this area controlled studies will be almost impossible to design, due to the overwhelming covariate of liver transplantation or the underlying disease in liver surgery.

Since the safety profile of liver support, especially for ECAD Type I has been consistently improving and reported to be safe if used in skilled centers, the use in pediatric liver surgery and transplantation has also been increasing over the last years [73–75].

### *Cholestatic Liver Disease and Intractable Pruritus*

An early observation of patients treated with extracorporeal liver support therapies removing albumin bound toxins was the rapid improvement of pruritus in patients

with severe cholestasis. Although bile acids correlate with the degree of pruritus, the effect of liver support on pruritus is also on multiple levels, since besides bile acids, also prostaglandins, precursers and metabolites of histidine, endogenous opioids and phospholipids are affected by albumin dialysis.

Due to the good safety profile of ECAD, reports on using this form of liver support in desperate cases that do not respond to medical therapy reports on successful treatment of intractable pruritus have accumulated quickly, even in children and also in an ambulatory setting [75–97].

Since LCAT activity as a potential player in pruritus development is dependent on albumin binding of a metabolite a connection between pruritus and patients albumin binding function can be assumed, therefore ECAD Type I therapies improving patients albumin binding function even more effective have been used and seem to have a more prominent effect on pruritus improvement [8, 98].

**Contraindications**

There are no absolute contraindications for extracorporeal liver support, but patients with active bleeding or hemodynamic instability due to septic shock have been excluded from most controlled studies and are more prone to severe adverse effects.

Also, patients with INR > 2.5 or platelets less than 50 GPT/l should be considered with caution, especially if thrombocytopenia progresses already quickly before treatment as it could be a manifestation of dissiminated intravascular coagulation (DIC). If platelets drop rapidly during first treatment (more than 30%), one should re-evaluate and exclude or address DIC before continuation of therapy.

## Recommendations for Technical Excellence

### *General Recommendations*

As with all complex therapies, center based analysis has shown that Liver Support results were better in sites that do more cases than sites that do low numbers. A minimum number for a site should be 20–30 treatments a year, preferably more. The best documented systems are ECAD Type 1 so far (Fig. 16.12).

#### Catheter Access

Due to the higher risk of bleeding and infection catheters should be placed by experienced physicians, preferably under support of interventional radiology. Jugular catheters had less complications than subclavian or femoral. Sterile handling is imperative due to the higher susceptibility of liver patients towards infections, antibacterial coatings of catheters will reduce the probability of catheter sebsis.

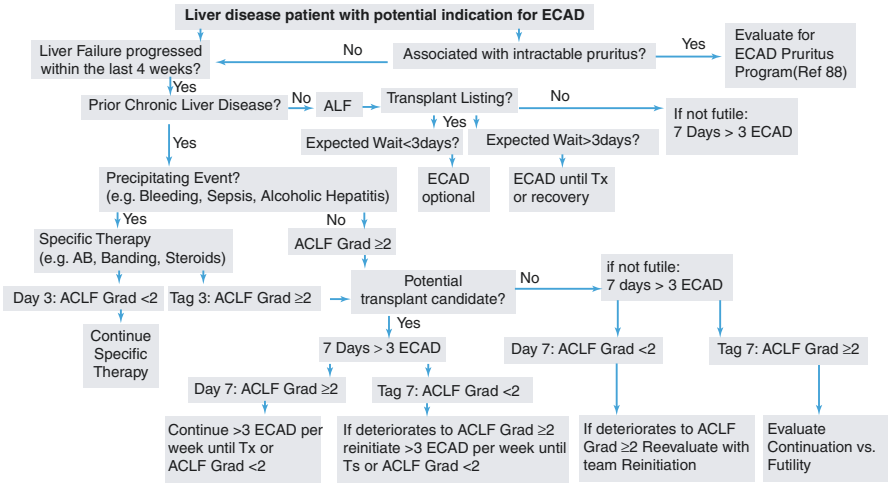



**Fig. 16.12** Displays the suggested implementation of ECLS* (Extracorporeal Liver Support) in subjects with liver failure based on the current evidence in Acute Liver Failure (ALF), Acute on Chronic Liver Failure (ACLF), and intractable cholestatic pruritus. Especially in subjects with cholestatic pruritus that have failed all medical therapy (intractable) several sites have established ECAD pruritus programs for outpatient treatment, which means subjects receive sessions of 2–3 ECAD treatments within 2–5 days and return after rebound of pruritus. While evidence for prolongation of survival in ACLF exists for ECAD Type 1 but not for Plasma Exchange, the suggested ECLS method for ECAD as of the time of the edition of this chapter is ECAD. For Acute Liver Failure (ALF), the data for Plasma Exchange Therapy are reliable if High Volumes are exchanged. Based on the FULMAR Study, ECAD represents a good alternative if listed candidates look at a waiting time of more than 3 days for urgent liver transplantation

## Anticoagulation

If heparin is used a strict protocol is recommended steering the pTT between 50 and 80 s. Antithrombin III application might be needed if less than 50% and heparin induced thrombocytopenia needs to be excluded. Preferably, citrate anticoagulation is used, with a post filter target of less than 0.34 mmol/l ionized calcium and a systemic ionized calcium of no less than 1 mmol/l.

## Medication

In intermittent therapy modes (4–12 h a day, depending on patients size and severity, medications should be given AFTER the therapy in the interval, in continuous therapies important drugs such as antibiotics or immune-suppressants should be considered to be drug-monitored.

### Monitoring of Success

As a biomarker, bilirubin is a mediocre marker for therapy success, since some Liver support Systems may remove Bilirubin only and may show great bilirubin data but no clinical benefit whatsoever. If possible, plasma bile acids should be kept below 5 μmol/l. Patients albumin binding capacity is a very good biomarker correlating with survival, but is currently only available in studies for retrospective analysis.

## Complications

Extracorporeal Liver Support can be associated with all complications associated with any extracorporeal therapy, the most prominent being catheter related complications or bleeding, which should be manage as if those were dialysis patients. Albumin dialysate should be prepared by Pharmacy, using standard dialysate or isotonic electrolyte solution as a base. Potassium and Calcium concentration should be adjusted based on consultation with an expert on extracorporeal therapy and dialysis.

**Future Trends**

**Non-Cellular Liver Support Systems**

Although ECAD Type I systems have evolved and will probably show more and more prolongation of survival time in the bridge to transplant field based on better technology, usability and better patient stratification, ECAD Type I systems do not address very effectively systemic inflammation. Although Interleukin 1 can be removed by ECAD, the membranes are impermeable to albumin and are therefore essentially also impermeable to TNF alpha, at least to the degree that they are not having an effect on in vivo levels. Recent new technologies such as the combination with high permeability membrane filtration, adsorption (Cytosorb or Endotoxin Adsorbents) or simply with plasma exchange are options currently under study.

**Cellular Liver Support Systems**

Since extracorporeal liver support only covers a part of liver functions several attempts have been made to apply cellular based systems. In fact, the ultimate therapy for end stage liver failure, liver transplantation is at the end a cellular therapy.

Hybrid devices using porcine cells have been discussed in the section about Acute Liver Failure, more recently two larger prospective randomized controlled studies showed promising trends in severe alcoholic hepatitis without secondary organ failures but failed statistical significance. However,

plasma biomarkers indicated that cellular therapies were able to modulate severe systemic inflammation and hepatic regeneration not only by removing pro-inflammatory cytokines or inhibitors of regeneration such as SEPET or plasma exchange therapy, but also adding anti-inflammatory proteins and growth factors [99]. It can be assumed, that with the explosive development of regenerative medicine, stem cell technologies, 3-D printing, organ perfusion technologies and repopulation of decellularized scaffolds cell based liver support technologies will undergo clinical development again in the near future. However, it is assumed that even then, non-cellular liver support systems such as ECAD will remain valuable tools to stabilize the patients while new biologicals will take their effect.

## Self Study

### Questions

Question 1

Which one of the following statements is incorrect?

(a) Detoxification by ECAD has been shown to effectively remove ABT and improves circulatory dysfunction, hepatic encephalopathy and renal dysfunction due to liver failure
(b) Plasma exchange therapy removes toxins effectively at high volume exchange in ALF
(c) High Volume Plasma Exchange Therapy has improved survival in ALF
(d) Recent metanalysis support that by ECAD in AoCLF survival can be extended by 2–4 weeks
(e) Extracorporeal Liver Support is associated with severe complications that outweigh potential benefits
(f) ELS should be performed by specialized experts.

Question 2

Which of the following answers are correct?

(a) The largest body of evidence for efficacy in liver failure exists for Plasma perfusion
(b) The largest body of evidence for efficacy in liver failure exists for Extracorporeal albumin dialysis in recirculation over adsorbents
(c) The largest body of evidence for efficacy in liver failure exists for single pass albumin dialysis
(d) The largest body of evidence exists for Plasma Exchange in ACLF

### Answers

1. e
2. b

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# Chapter 17
# Looking Past Orthotopic Liver Transplantation: A Review of Emerging Strategies for Managing Acute and Acute-on-Chronic Liver Failure

**Robert Brumer, Seyedehsan Navabi, and Nikolaos Pyrsopoulos**

**Key Points**
- Several artificial liver support devices that have been tested in patients with Acute and Acute-On-Chronic Liver Failure, but as of yet no clear survival benefit noted based on current evidence with any of these devices in clinical setting.
- Hepatocyte transplantation and stem cell therapy could serve as potential treatments for ACLF with limited but promising supportive data.
- Semisynthetic organs may offer novel therapeutic management of ALF and ACLF in future.

## Introduction

Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) are both characterized by an acute insult leading to dysfunction of the liver and often other organs. Acute liver failure is defined by coagulopathy (INR > 1.5) and hepatic encephalopathy in the context of a new hepatic insult within the past 26 weeks [1]. It is relatively rare, with approximately 2000 cases per year diagnosed in the United

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**Table 17.1** Commonly used ACLF definitions

| Definition | Characteristics |
|---|---|
| APASL [3] | Bilirubin >5.0 and either INR > 1.5 or prothrombin activity (PTA) < 40% with ascites and/or encephalopathy in patients with chronic liver failure |
| EASL-CLIF [4] | Defined by organ failure, with severity increasing with number of organs failing. Organ failure is measured on a modified sequential organ failure assessment (SOFA) scale:<br>• Liver failure: Bilirubin ≥12.0 mg/dL<br>• Renal failure: Creatinine ≥2.0 mg/dL OR patient requiring renal replacement therapy<br>• Cerebral failure: Hepatic encephalopathy grade 3 or 4<br>• Coagulopathy: INR ≥2.5 OR platelet count ≤20,000/μL<br>• Circulatory failure: Requirement for vasopressors<br>• Respiratory failure: $P_{aO2}/F_{IO2} \leq 200$ OR $Sp_{O2}/F_{IO2} \leq 214$ OR need for mechanical ventilation<br>**Grade 1:** Renal failure OR creatinine 1.5–1.9 in the context of another single organ failure and hepatic encephalopathy<br>**Grade 2:** Two organ failures<br>**Grade 3:** Three or more organ failures |

States [2]. ACLF refers to an acute decompensation of chronic liver disease, but lacks a single clear definition [1]; the definitions used the most in studies discussed herein are reviewed in Table 17.1. Orthotopic liver transplant (OLT) is a valuable therapy for both conditions, but as with chronic liver failure, the demand for organs exceeds the supply. In the absence of liver transplant, the mortality of ALF has been estimated at >80% in some studies [1]. While the inconsistent definition makes ACLF mortality difficult to determine, a review based on the Asian Pacific Association for the Study of the Liver (APASL) and the European Foundation for the Study of Chronic Liver Failure (EASL-CLIF) definitions found a 90-day transplant-free mortality of about 50% [5].

With this high mortality in the absence of transplant, there is a need for alternative medical strategies that can support these patients—either until they recover sufficiently or until they receive a liver graft. One category of treatment comes in the form of hepatic assist devices, which are designed to exogenously support liver function through artificial or bioartificial means. Artificial devices such as the Molecular Adsorbent Recirculating System (MARS®) mostly target metabolic detoxification through dialysis techniques, while bio-artificial devices like HepatAssist® make use of human or animal cell lines to provide some synthetic capacity. There are also hybrid devices combining dialysis techniques and bioartificial support. Several of these hepatic assist devices have been tested in patients with ALF and/or ACLF, with mixed results.

Transplantation of hepatocytes allows cells to be prepared from livers that are suboptimal for transplantation and enables the treatment of multiple patients with cells from a single donor organ. There are also techniques under development to generate new and usable donor organs, though these remain at the preclinical stage of research. Decellularizing and repopulating organs allows for the transformation of a suboptimal or even porcine liver into one populated with the recipient's cells,

while 3-D printing and stem cell organoids are promising techniques for the *de novo* production of liver tissue. We will discuss each of these strategies and, when available, the evidence regarding its use in patients with ALF or ACLF.

## Artificial Liver Support Systems

The artificial liver support systems apply dialysis techniques to filter protein-bound and water-bound metabolites from the bloodstream. There are three major modalities that have been tested in patients: the Molecular Adsorbent Recirculating System (MARS®), the Prometheus® system, and single-pass albumin dialysis (SPAD®) [6]. These systems all operate on the principle of filtering whole blood or plasma against a dialysate containing albumin, which may or may not be then regenerated and recycled.

### *Molecular Adsorbent Recirculating System*

The MARS system was developed in Germany in 1993, and was commercialized and available for clinical use by 1998 [7]. A stream of whole blood is filtered against a stream of albumin-enriched dialysate via a high flux membrane filter, allowing the passage of hydrophobic, albumin-bound metabolites. The albumin-rich stream is then dialyzed against a stream of normal dialysate and regenerated with an adsorption column and an ion exchanger. This regenerated stream is then again passed against whole blood from the patient (Fig. 17.1). The MARS system has been tested in a number of clinical scenarios, including ALF, ACLF, severe hepatic encephalopathy (grade > II), elevated intracranial pressure, acute hypoxic hepatitis with bilirubin >8 mg/dL ("shock liver"), hepatorenal syndrome, progressive intrahepatic cholestasis, and graft dysfunction after liver transplant [9–11]. In 2005, it was approved by the FDA for use in drug overdose and poisonings so long as the agent is dialyzable and bound by charcoal [12]. It was also approved in 2012 for use in hepatic encephalopathy caused by a decompensation of chronic liver disease [13]. However, the device is not indicated by the FDA as a bridge to liver transplant, and it is additionally not approved for use in patients who are sedated [13].

MARS has been shown to reduce elevated bilirubin and creatinine levels in the case of ALF or ACLF, but no significant mortality benefit has been demonstrated. The RELIEF trial was a multi-center randomized controlled trial that compared MARS plus standard medical therapy (SMT) to SMT alone in patients with ACLF [14]. In this study, ACLF was defined as a known insult in the setting of chronic liver disease causing an increase in serum bilirubin >5 mg/dL and either hepatorenal syndrome, hepatic encephalopathy Grade > II, or bilirubin >20 mg/dL at the time of admission. There was no observed difference in short-term or long-term transplant-free survival in this trial. However, a more recent retrospective cohort study in a

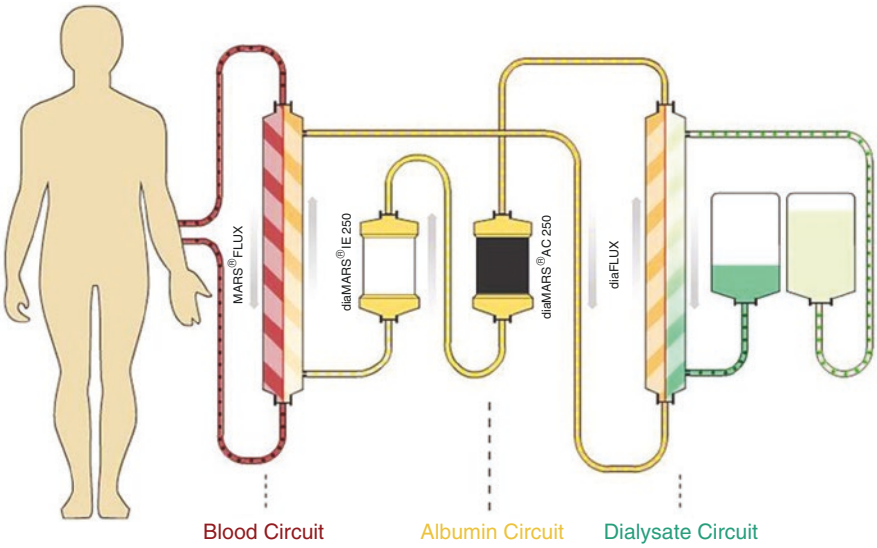



**Fig. 17.1** Molecular adsorbent recirculating system (MARS). Whole blood is filtered against a dialysis solution containing albumin. This solution is then filtered against a traditional dialysis solution to remove water-bound solutes, regenerated online with a neutral resin, filter, and anion exchanger to remove the protein-bound solutes, and finally recycled against the whole blood stream. Image is open access, reproduced via the Creative Commons License [8]

similar-sized population found that MARS + SMT had a survival benefit compared to SMT alone in patients with more severe ACLF as defined by Grade 2 or greater on EASL-CLIF criteria for ACLF [15]. Additionally, this group re-analyzed the patient data from the RELIEF trial and found an increase in 14-day survival among patients with ≥Grade 2 EASL-CLIF ACLF, but no difference in longer-term survival. These data suggest that MARS may in fact play a therapeutic role in the sickest patients with ACLF and may in fact be valuable as a bridge to OLT.

In the setting of ALF, however, there is less convincing evidence. A multi-center randomized controlled trial found no benefit in 6-month survival after using MARS in patients with ALF, including a subgroup analysis based on the etiology of liver failure [16]. A case-control study by Gerth et al. examined patients with ALF or graft failure and found no survival benefit after using MARS [17]. Although there were improvements in laboratory values—decreased bilirubin, blood urea nitrogen, creatinine, and lactate—the lack of mortality benefit makes the efficacy of this device in ALF questionable. Additionally, there are some adverse effects associated with MARS, similar to those seen with hemodialysis: an increase in bleeding risk and decrease in platelet count and fibrinogen, both of which may be clinically concerning in liver patients with an underlying coagulopathy [18].

### *Prometheus Device*

Another artificial liver support system that has received attention in clinical trials is the Prometheus device, which operates by generating an albumin-rich ultrafiltrate from the patient's own blood and cleansing this stream with an adsorption column and anion exchanger. This is combined with the retentate to reconstitute the patient's blood, which is then filtered through a traditional hemodialysis system to remove water-soluble toxins.

The only large multi-center randomized controlled trial evaluating Prometheus ACLF was performed by the HELIOS group and found that there was no significant difference in 28-day or 90-day survival in patients treated with Prometheus + SMT vs. SMT alone [19]. However, in subgroup analysis there was a significant improvement in survival in patients with a MELD score of >30, indicating severe failure. There are limited data surrounding the use of this device in ALF, and only cohort studies rather than randomized controlled trials. One larger cohort study showed that 33% of ALF patients treated with Prometheus were downgraded from needing a transplant [20].

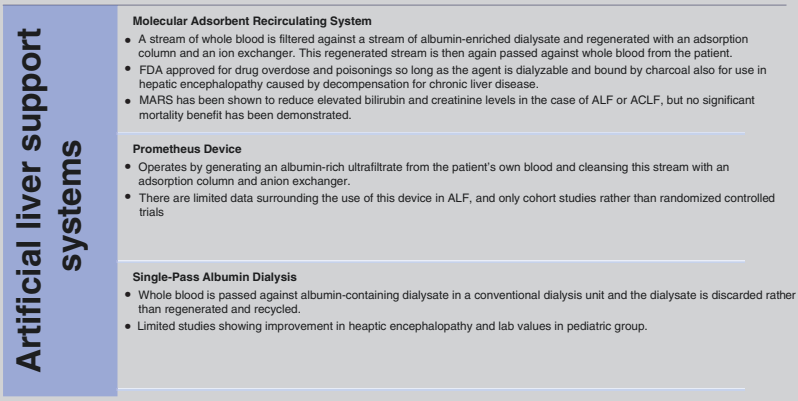
### *Single-Pass Albumin Dialysis*

The last major methodology of artificial hepatic support device is single-pass albumin dialysis (SPAD), wherein whole blood is passed against albumin-containing dialysate in a conventional dialysis unit and the dialysate is discarded rather than regenerated and recycled. There are very limited data regarding the use of SPAD in liver failure, and no randomized controlled trials. There is a crossover study comparing the effect of SPAD and MARS on laboratory values in patients with ALF and ACLF, which showed no difference in mortality between the two devices, but there is no comparison to a control [21]. Although there are some retrospective studies, including a recent one in pediatric patients showing a significant improvement in hepatic encephalopathy and laboratory values [22], these are also uncontrolled.

**Summary**

There are several artificial liver support devices that have been tested in patients with ALF and ACLF, but as of yet there is no clear survival benefit with any of these devices in either clinical setting. Tsipotis et al. published a systematic review and meta-analysis of albumin dialysis strategies that evaluated the efficacy of MARS and Prometheus in patients with liver failure across several trials; there were no studies of SPAD compatible with the analysis [23]. With 239 patients given MARS + SMT vs. 222 given SMT alone, there

was no significant survival benefit (OR 0.97, 95% CI 0.85–1.11). There were 91 patients treated with Prometheus + SMT vs. 82 treated with SMT alone, and no significant survival benefit (OR 0.87, 95% CI 0.66–1.14). It is apparent that the data do not support the systematic use of these devices in patients with liver failure. However, data from large randomized controlled trials suggest that the patients with the most severe disease (defined by MELD score or the EASL-CLIF grade of ACLF) may benefit from albumin dialysis [14, 15, 19]. These artificial liver support devices may eventually offer a method to support the sickest patients either as a bridge to transplant or as supportive therapy until the patient recovers on their own.




## Bioartificial Liver Support Systems

Bioartificial liver support systems combine aspects of the artificial liver support devices, but the addition of hepatocytes allows for some replacement of the liver's synthetic functionality. There are two systems that have received the most research: The Extracorporeal Liver Assist Device (ELAD®), which uses human cells, and the HepatAssist®, which uses porcine hepatocytes. There are several other bioartificial liver systems in development, but these have yet to be tested with an RCT.

### *Extracorporeal Liver Assist Device (ELAD)*

The bioreactor in the ELAD consists of human hepatoblastoma cells (cell line C3A) in hollow cartridges. These cells serve a synthetic role, synthesizing proteins normally produced by hepatocytes, and their functional CYP450 system allows for some detoxification of metabolites [24]. The initial device passed whole blood

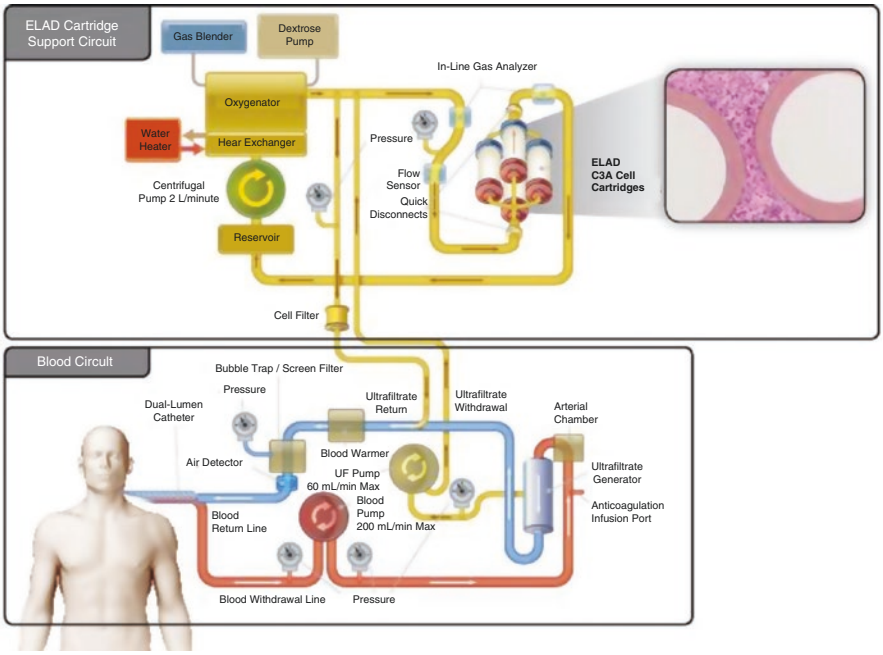



**Fig. 17.2** Extracorporeal liver assist device. Ultrafiltrated plasma is generated from the patient's whole blood and passed into the ELAD circuit. Within the device, plasma is heated and oxygenated before passing through the four cartridges containing C3A human hepatoblastoma cells. Ultrafiltrate is passed through a cell filter before being mixed back with the retentate to reconstitute the patient's blood, which is returned to the patient. This image is reproduced from open access literature via the Creative Commons License [25]

through the bioreactor, but most applications have instead generated an ultrafiltrate of plasma which is then oxygenated and warmed and exposed to the cells (Fig. 17.2). There is theoretically a risk of these hepatoblastoma cells making it back to the patient, but a number of membranes and valves make this unlikely.

An RCT by Duan et al. in China compared ELAD + SMT to SMT alone in patients with ACLF and found a significant benefit to transplant-free survival with ELAD, with the length of treatment time correlating to survival benefit [26]. Conversely, a phase III clinical trial evaluating the device in patients with severe alcoholic hepatitis—liver failure secondary to alcohol use, which is tacitly considered ACLF due to the history of alcohol abuse—found no effect of ELAD on overall survival [25]. Although subgroup analysis in this trial suggested a survival benefit in patients with less severe disease (MELD < 28), a phase III pivotal trial of the device in patients with alcoholic hepatitis was recently terminated due to failure to achieve the primary endpoint of increased overall survival [27]. As for ALF, the original pilot study of ELAD found no survival benefit regardless of transplant listing status [24]; per a recent systematic review, this remains the only RCT of ELAD in the setting of ALF [28]. From these results, the only survival benefit from ELAD was shown in the trial by Duan et al., in which 65% of the patients had ACLF secondary

to chronic hepatitis B; it is possible that the varying etiology of ACLF may contribute to the difference in outcomes.

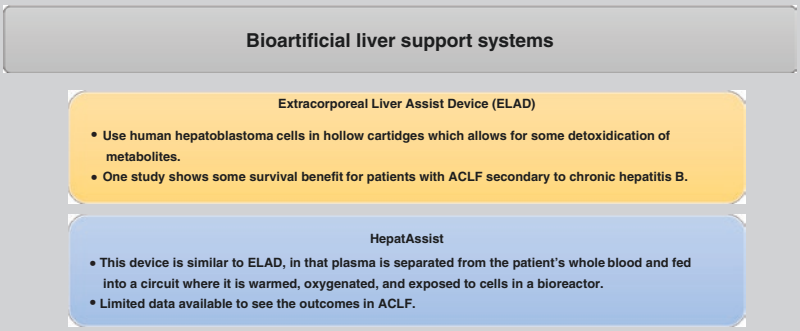
## *HepatAssist*

There are several bioartificial liver support systems based on the use of porcine hepatocytes in a bioreactor. Although some of these are being tested in phase 1 clinical trials, the only such device that has been evaluated with an RCT in human patients is HepatAssist [28]. This device is similar to ELAD, in that plasma is separated from the patient's whole blood and fed into a circuit where it is warmed, oxygenated, and exposed to cells in a bioreactor.

In the RCT by Demetrious et al. patients with ALF or post-OLT graft failure were treated with either HepatAssist + SMT or SMT alone and there was no significant difference in 30-day survival; this resulted in early termination of the trial [29]. However, in subgroup analysis of patients with ALF (excluding the graft failures), there was a significant reduction in mortality (RR 0.56, $p = 0.048$) and a significantly longer time to death within the first 30 days. Although immune reactions and zoonosis are major concerns when animal tissue is used in human patients, these adverse events were not reported. Based on these findings, further research into the application of HepatAssist in ALF could be promising. Additional trials should be performed to determine whether this device is helpful in improving outcomes in ACLF.

**Summary**

The limited available data suggest that bioartificial liver support systems may have value in the treatment of ALF and ACLF. Although it is based on a retrospective subgroup analysis, a survival benefit was observed in ACLF patients with a low MELD treated with ELAD and in ALF patients treated with the HepatAssist device. The potential role of these devices in the treatment of liver failure can only be determined by further trials assessing their efficacy in patients.



## Cell Transplantation

The transplantation of hepatocytes or stem cells into patients with liver failure aims to aid in liver regeneration to facilitate recovery from the acute insult. Using primary human hepatocytes allows many recipients to receive cells from a single donor, while the use of stem cells is not limited by the availability of donor organs. In addition, transplantation of cells into the spleen or portal vein is a much less traumatic procedure than OLT, reducing the risk of surgical complications and the high cost associated with transplant.

### *Hepatocyte Transplantation*

There have been numerous trials testing the efficacy of human hepatocyte transplantation (HT) across a spectrum of liver disease [30]. Primary human hepatocytes are harvested from a donor organ with collagenase and cryo-preserved until they are ready to be used. This allows for the immediate availability of cells—therapy can be given as needed without the need for waiting on a transplant list. There are numerous inborn errors of metabolism that result in failure of the liver to fulfill its metabolic role. While some of these conditions can be treated with diet and/or medical therapy, the morbidity and mortality is usually high unless these children receive an OLT. There are case reports describing the use of HT in patients with a variety of metabolic defects.

Ornithine transcarbamylase (OTC) deficiency is an X-linked urea cycle defect that can present in the first several days of life as severe hyperammonemia with metabolic encephalopathy [31]. In one case series, children with OTC deficiency who were poor candidates for OLT were treated with HT and showed a marked reduction in hyperammonemia [32]. Two of the children were treated neonatally with the goal of avoiding the developmental defects associated with the disease. Out of four children treated in the series, three survived until the end of the study period and showed sustained clinical improvement. Two of these three were on the list for OLT at the time the series was published. Crigler-Najjar syndrome is a defect in UDP-glucuronosyltransferase (UTG), the enzyme required to conjugate bilirubin [33]. One form of the disease presents neonatally as severe unconjugated hyperbilirubinemia that can cause kernicterus, resulting in permanent brain damage. Several cases have been reported of these patients receiving HT, resulting in a significant reduction of bilirubin and increased UGT activity; however, these patients inevitably require OLT [30, 34].

In the settings of ALF and ACLF, there are also only case reports describing the therapeutic use of HT. There is great disparity in the number of hepatocytes transplanted to patients (from $10^6$ cells to $10^{10}$ cells transplanted) and the reports include liver failure from a variety of etiologies [35]. In the setting of ALF caused by drugs or viral infection or idiopathic ALF, outcomes following HT were either OLT or death. The only report of HT as therapy for ACLF treated 7 patients with an expected survival of 8 weeks via intrasplenic injection of donor hepatocytes [36]. Of these

patients, 3 died, 1 required OLT, and 3 survived without the need for transplant. In surviving patients, viable hepatocytes were observed in the spleen 48 months after HT. The limited data available suggest that HT may be a viable therapy for patients with ACLF, but there is currently insufficient evidence to determine this clearly. The available data do not suggest that HT is a potential replacement for OLT in ALF, although it is possible that it may be useful as a bridging therapy as with the metabolic diseases.

A major limitation of HT is the availability of donor hepatocytes. The most viable organs are allocated for OLT, so hepatocytes in these studies were almost universally isolated from poor quality livers; this may have affected the outcomes [30]. Additionally, further study is needed regarding the immune response to these transplanted cells and the immunosuppressive strategies needed to prevent their destruction. Although cells were detected 4 years post-HT in the ACLF case series, most reports indicated that cells were no longer detectable after 6–9 months [35]. Current work aims to enhance the engraftment and proliferation of transplanted cells, optimize immunosuppression, and circumvent the supply issues by generating functional hepatocyte-like cells from stem cells [30]. HT may be a promising technique for treating ACLF or bridging ALF patients to OLT, and further study is required.

## *Stem Cell Transplantation*

There are numerous ongoing clinical trials testing the efficacy of stem cell transplantation in liver failure. Although most of these studies focus on chronic liver failure, there have been several RCTs testing stem cell transplantation in the setting of ACLF [37]. Most studies apply either bone marrow or umbilical cord blood derived mesenchymal stem cells (BMSCs and UMSCs, respectively). These multipotent progenitor cells can self-renew and differentiate into cells from the mesenchymal lineage. Administration of these cells through the hepatic artery or portal vein aims to repopulate damaged tissue and facilitate recovery.

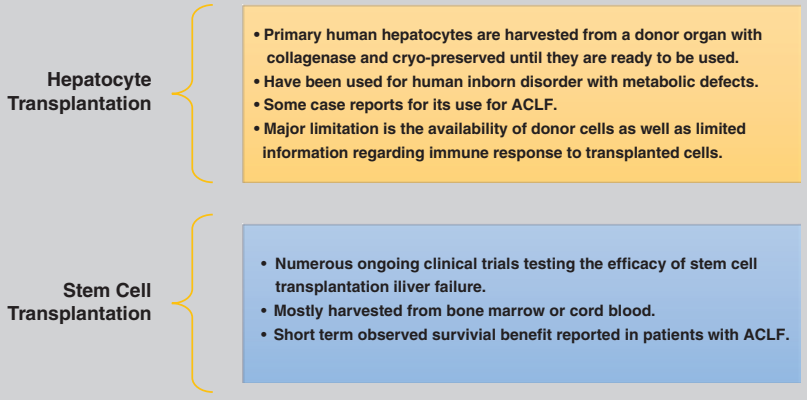
A recent meta-analysis by Xue et al. characterized the efficacy of stem cell transplantation in ACLF [38]. The survival analysis was performed on a pooled data set from trials using different cell types, with different etiologies of ACLF, and administering the cells through either the hepatic artery or portal vein. Most of these trials were performed in China, and as a result about 75% of all ACLF patients had chronic hepatitis B. On this heterogenous data set, stem cell therapy was found to significantly improve survival up to 6 months after the therapy. Between 9 months and 2 years, there was a non-significant trend towards improved survival after stem cell therapy. Improvement in clinical markers was variable, but significant improvements in total bilirubin, albumin, and MELD score after stem cell transplant were reported in another meta-analysis [39]. However, the observed survival benefit indicates that stem cell transplantation has promise as therapy for ACLF.

As for ALF, only animal data are currently available to support the efficacy of stem cell therapy, but the results are promising. In rat models of liver failure, injection of BMSCs significantly improved serum ALT and AST levels and reduced hepatocyte apoptosis [40, 41]. A mouse model of acetaminophen-induced liver injury had significantly improved survival and reduced liver damage following adipose tissue-derived stem cell (ASC) transplantation [42]. The application of human BMSCs to a pig model of ALF showed a significant survival benefit and reduction in serum cytokine levels [43]. Numerous other studies have shown benefits of stem cell therapy in animal models [44], but a translational effort is needed to determine whether this treatment will be valuable for humans with ALF.

There are limitations to stem cell therapy that must be overcome before it can be possible used routinely in human disease. A sustainable and consistent source of cells is necessary, and there are ethical concerns surrounding stem cell acquisition and research [45]. Additionally, a great deal of study is needed to determine the long-term safety and efficacy of this therapy. The available data suggest that stem cell transplantation is a promising strategy for the treatment of ACLF, and possibly for ALF.

**Summary**

There is a limited amount of evidence regarding cell transplantation as therapy for ALF or ACLF, but the available data support both hepatocyte transplantation and stem cell therapy as potential treatments for ACLF. The efficacy of HT in ALF is questionable, and there are currently no reported trials of stem cell therapy for ALF. These therapies offer great potential for life saving therapy that can defer the need for OLT or replace transplant entirely. More research into these therapies will hopefully continue to yield positive results and lead to the routine application in patients with liver failure.



## Other Medical Therapies

### *Granulocyte Colony-Stimulating Factor*

Similar to the direct administration of mesenchymal stem cells aimed to support liver functionality through regeneration, the administration of granulocyte colony-stimulating factor (G-CSF) to patients with liver failure aims to mobilize these stem cells from the patient's own bone marrow. There is not a great deal of evidence regarding its application, but a meta-analysis of two trials showed a significant improvement in overall survival when patients with ACLF were treated with G-CSF + SMT vs. SMT alone [46]. Additionally, several trials of GCSF in patients with severe alcoholic hepatitis—which is tacitly ACLF—have showed a survival benefit without major adverse events [47–49]. These data support the administration of GCSF in patients with ACLF. There are no clinical data available supporting the use of GCSF in ALF, but there have been animal models showing its efficacy. In a rat model of ALF, administration of GCSF significantly improved survival and reduced hepatic injury [50]. A study with a pig model of ALF had a dramatic survival benefit—6/6 control animals died, while 5/6 animals given GCSF survived indefinitely [51]. Based on the demonstrated benefit of G-CSF in ACLF, the supportive animal data, and the relative tolerability of G-CSF therapy, it would be reasonable to trial G-CSF in human patients with ALF. This may eventually offer a readily available medical therapy that provides some of the benefit of stem cells without as many limitations.

### *Plasma Exchange*

High volume plasma exchange (HVP) operates on the same principle as the artificial liver support systems, removing toxic metabolites from the patient's bloodstream. One trial found that HVP significantly improves biomarkers such as INR, total bilirubin, and albumin and significantly boosts transplant-free survival in patients with ALF [52]. Based on the patient population in this study, it is likely that the most benefit came from patients in severe condition with ALF caused by acetaminophen toxicity [53]. A nested cohort study within this trial found that HVP reduced serum levels of proinflammatory cytokines, including TNF-α and IL-6. This suggests that HVP may act to suppress the systemic inflammatory response that is characteristic of ALF. Although there are no data regarding the use of HVP in ACLF, the apparent anti-inflammatory effect of this therapy may provide a benefit. More extensive trials should be performed to assess the efficacy of HVP in liver failure.

## Semisynthetic Organs

The construction of a synthetic organ from a patient's own cells is a major target in transplant research, as it will provide a means to acquire organs independent of human donors. There is still much work to be done before organ synthesis will be a viable and readily applicable methodology, but that work is ongoing. A major limitation in the generation of solid organs has been maintaining nutrient and oxygen delivery within the structure [54], and efforts to synthesize a vascular tree have been unsuccessful [55]. One strategy involves removing the cells and immunogenic particles from an animal organ and repopulating it with stem cells from the patient. Another possibility is using 3D-printed organ scaffolds that can be populated with stem cells. There is also work being done on the implantation of organoids produced from stem cells, in which the cells produce their own vascular and biliary trees.

### *Decellularized and Repopulated Organs*

Decellularization techniques clear the organ of cellular contents and leave behind a scaffold of extracellular matrix including an intact vascular and biliary tree [56]. This scaffold can be used to reconstruct a functional organ using stem cells, hepatocytes, or hepatocyte-like cell lines. If stem cells from a patient awaiting liver transplant were used, it may be possible to produce an organ that can be implanted without the need for immunosuppression. Proof of concept was first obtained using a rat model, with repopulated organs successfully implanted into animals to rescue them from hepatectomy [56]. Since then, the technique has been employed in a wide variety of animal livers, including porcine livers that are of comparable size to human [57, 58]. The proteins making up the extracellular matrix are well conserved between species [59], meaning that a scaffold produced from pig livers and repopulated with human cells could possibly be used in human patients.

Currently, the biggest limitation of this technique lies in the recellularization of the organ scaffolds. It is necessary to line the organ's vasculature with endothelial cells and to reconstruct the organ's parenchyma. Earlier attempts using hepatocytes and cell lines were met with limited success [57], but better results were obtained with the use of mesenchymal stem cells, with transplantation of repopulated organs rescuing mice from acute liver failure [60]. Another possible method is the direct implantation of the decellularized scaffold, as in situ repopulation with liver parenchymal cells has been reported in a rat model [61]. If development continues on this technique, it is foreseeable that porcine livers—which are in much greater supply than human livers—could be used to provide scaffolding for large-scale production of semisynthetic human livers.

## *3D Printing of Organs*

The technique of 3D printing relies on a computer-controlled nozzle that extrudes material in layers to form a 3-dimensional shape and has been widely used with thermoplastics. Advances in this technology have allowed for the development of bioprinters that can extrude viable biological matter, offering a new route for organ engineering [62]. Production of artificial liver tissue via 3D bioprinting is has been approached from several different angles [63]. Some techniques are based on artificial scaffolds, wherein a bio-ink containing cells and support proteins is extruded into tissue. One group used a human cell line with alginate, gelatin, and human extracellular matrix proteins to produce liver tissue that produces albumin and has a functional CYP450 system [64]. This has been applied in animal models, with another group reporting that 3D printed liver tissue produced from a human cell line and a hydrogel significantly improved survival in a mouse model of acute liver damage [65]. Scaffold-free techniques have also been employed, with one group reporting that hepatocyte spheroids constructed from primary hepatocytes can be assembled into liver tissue that produces glucose and bile and detoxifies drugs [66]. Another group engineered different lines of liver cells to express linking proteins on their surface that allow cells to stay adhered long enough to secrete their own extracellular matrix, producing functional 3-dimensional tissue [67].

These advances are promising, but there are still major limitations, including the production of vasculature to deliver nutrients to cells in a 3D structure. The source of cells is also a concern, as primary human hepatocytes have the same limitations as organ transplant while immortalized cell lines do not adequately reproduce hepatocyte functionality. One possible inroad is the usage of stem cells from the patient, which would allow for the avoidance of immunosuppression, and there are many groups working with induced pluripotent stem cells to produce 3D liver tissue [68]. Optimization of this technique may eventually allow for the widespread production of artificial liver tissue.

## *Organoid Implantation*

Targeted differentiation of induced pluripotent stem cells (iPSCs) allows for the *in vitro* production of organ-like structures called organoids. One group differentiated iPSCs into hepatic endoderm cells, which they then co-cultured with endothelial cells and mesenchymal stem cells [69]. These cells organized themselves into a 3D liver-like structure that the group called an organ bud. These buds produced their own vasculature and biliary trees and became natively perfused after implantation into mice. This same group later reported scalable mass production of liver organoids entirely from human iPSCs, and found that implantation of these organoids significantly improved survival in a mouse model of ALF [70]. There is much more preclinical research to be done on this topic, but the available results suggest that it

is an encouraging avenue for synthesizing organs. The self-organization of vascular and biliary trees overcome one of the major difficulties of tissue engineering, and the ability to use iPSCs produced from the patient's own fibroblasts avoids the need for immunosuppression.

**Summary**
Organ engineering, when optimized and fully deployed, will change the field of transplant medicine. Production of an organ from a patient's own cells removes the need for a transplant wait list and the reliance on cadaveric transplantation. It is also likely that it would significantly reduce the incidence of rejection, as the new organ should be detected as the patient's own tissue. There is a great deal of progress that needs to be made before this can become a reality, but the preclinical research that is available suggests that these techniques may 1 day significantly improve survival of patients with liver failure.

## Early Prevention of ACLF

Preventing ACLF before it can fully develop has the potential to significantly improve mortality. ACLF is thought to be present in 24–40% cirrhotic patients admitted to the hospital [71] and increases the risk of mortality almost 20-fold [4]. The Asian Pacific Association for the Study of the Liver identified a "golden therapeutic window," a period between the acute onset of liver failure and the onset of multi-organ failure, during which preventative measures can reverse the pathology in a patient [3]. It is important to clinically identify patients at risk for ACLF by taking proactive measures. Bacterial infection is a common cause of ACLF, which is part of why diagnostic paracentesis is commonly performed in cirrhotic patients who are hospitalized. In the absence of a known etiology, therapies that can control the systemic inflammatory response associated with ACLF may also prove beneficial [71].

**Summary**
The best therapy to improve survival in ALF and ACLF is OLT, but there are not enough livers available to meet the demand. We have discussed therapies that are under development for these disease states that largely aim to support the functionality of the liver to either allow full recovery or bridge a patient to transplant. The extracorporeal liver support systems offer some hepatic functionality, and the current data support a survival benefit for some of these systems in subsets of patients with ALF and ACLF. Administration of G-CSF has also been shown to have a survival benefit for ACLF and has not been tested in patients with ALF.

More novel strategies such as hepatocyte transplantation and stem cell therapy have limited evidence surrounding their use but may show promise. There are also efforts being made in tissue engineering that may eventually allow for the production of semisynthetic livers. There is still much work to be done to improve the survival of these patients, but it is possible that one of these avenues will prove successful.

**Questions**

1. Which of the following artificial liver support systems has been approved by FDA for management of hepatic encephalopathy due to decompensation of chronic liver disease?

   A) MARS
   B) Prometheus Device
   C) Single-Pass Albumin Dialysis

2. Based on current available data which of the following statements is true:

   A) ELAD would improve the survival in patients with ACLF due to alcoholic hepatitis
   B) HepatAssis has 30 days survival benefit in patients with post-OLT graft failure.
   C) A survival benefit was shown from ELAD in patients with ACLF with chronic hepatitis B infection.

**Answers**

Question 1—The answer is A.
Question 2—The answer is C.

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