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REVIEW

# Mechanisms and aetiology-dependent treatment of acute liver failure

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## Abstract

This review compiles the mechanisms of acute liver failure (ALF) as well as the current and potential therapeutic approaches, including aetiology-specific treatment, and the issues encountered with such approaches. On a cellular level, ALF is characterized by massive hepatocyte death due to different types of cellular demise. Compensatory hyperplasia and functional recovery are possible when the regenerative capacity is sufficient to sustain hepatic function. ALF has a high mortality of about 30% and can lead to death in a very short time despite maximum therapeutic intervention. Besides aetiology-specific therapy and intensive care, the therapeutic option of emergency liver transplantation has significantly improved the prognosis of patients with ALF. However, due to limiting factors such as organ shortage, many patients die on the waiting list. In addition to graft assessment, machine perfusion may have the potential to recondition marginal organs and thus expand the organ donor pool.

**KEYWORDS**
acute liver failure, aetiology, liver transplantation, prediction of prognosis, rebalanced haemostasis, survival markers

## 1 | INTRODUCTION

Acute liver failure (ALF), while considered rare, has a notable incidence of approximately 800–1000 cases annually in Germany between 2014 and 2018. This condition predominantly affects adults, with women slightly more affected than men (52% vs. 48%, $p < .001$).[1] ALF has a high mortality of about 30% and despite aggressive therapeutic intervention, it can lead to death in a very short time. The primary focus of ALF treatment is addressing the underlying cause and managing complications arising from liver failure. A timely diagnosis and assessment of the clinical course of the disease are critical for optimizing treatment. A multidisciplinary approach involving specialists in hepatology, critical care medicine and transplant surgery is required for effective management. Emergency liver transplantation (ELT) may be necessary in some cases, but its availability is limited by organ shortage and extensive healthcare resources, and graft rejection remains a significant concern. This underlines the importance of prognostic tools to predict the individual course of ALF and the requirement for ELT. Although the recent years have seen much progress in ALF diagnosis and treatment, challenges for clinical practice remain. This review intends to describe the mechanisms of ALF in adults as well as the current and emerging potential therapeutic approaches, with a focus on aetiology-specific treatment modalities, and potential associated issues. For those interested in paediatric ALF, we recommend referring to recent overview articles.[2,3]

## 2 | DEFINITION AND CLINICAL PRESENTATION OF ALF

The definitions of ALF provided by international professional societies (EASL, AASLD and APASL) all include four typical clinical

symptoms: elevated serum transaminases and bilirubin, impaired coagulation (INR > 1.5), and the presence of hepatic encephalopathy (HE).[4,5] ALF excludes the presence of any chronic liver disease in the affected patient prior to its onset. Consequently, ALF must be clearly differentiated from other entities in which the sudden loss of liver function occurs against a background of preexisting liver disease. One of these conditions is known as acute-on-chronic liver failure (ACLF) and has been defined as a clinical syndrome where patients with preexisting chronic liver disease, specifically cirrhosis, experience a sudden acute deterioration in liver function.[6–8] In our opinion, liver failure resulting from an acute injury in patients with preexisting liver injury or chronic disease but without cirrhosis and prior decompensation events ("acute-on-chronic" injury) should be clearly separated from patients with cirrhosis experiencing an additional acute injury ("acute-on-cirrhotic" injury), as these present differently and have probably distinct outcomes.

The US American ALF Study Group (ALFSG) classifies ALF into hyperacute (<7 days), acute (7–28 days) or subacute (28 days to 6 months) based on the period between symptom onset and occurrence of coagulopathy and encephalopathy.[4] Mortality rates are influenced by the latency periods, with higher latencies associated with higher mortality.

The clinical situation of ALF is triggered by significant loss of functional liver mass due to the demise of large quantities of hepatocytes upon the acute injury (Figure 1). The predominant mechanism of hepatocellular death (i.e, necrosis, apoptosis, necroptosis) and the overall outcome vary depending on the underlying aetiology.[9]

The widespread hepatocyte death initiates several intrinsic regenerative processes aimed at maintaining or restoring hepatic architecture and function. Lost hepatocytes can be replaced by healthy hepatocytes undergoing cell division or via the proliferation of ductular structures. Additionally, Kupffer cells, newly infiltrating bone marrow-derived macrophages and hepatic stellate cells (HSCs) play a crucial role in clearing apoptotic bodies and debris from dying cells. Usually, quiescent HSCs are activated upon uptake of apoptotic bodies or cell debris and induced to produce collagen.[10,11] This helps restore or maintain the structural integrity of the organ.

However, in cases of extensive injury and widespread hepatocellular death, the regenerative capacity may not be sufficient to sustain hepatic function. Although the progenitor cell compartment is typically activated, the differentiation into hepatocytes is a time-consuming process.[12] Moreover, the continuous activation of HSC leads to extensive deposition of the extracellular matrix and to scar formation, impairing the repopulation of the tissue by hepatocytes.[13]

The nod-like receptor protein 3 (NLRP3) inflammasome, one of the best-characterized inflammasomes (cytoplasmic multimeric protein complexes crucial for activating inflammatory responses) in humans, seems to play a critical role in the pathophysiology of ALF. Studies have demonstrated that the aberrant activation of the NLRP3 inflammasome is involved in various types of ALF and leads to different forms of programmed cell death (PCD).[14] For instance, Jimenez-Castro et al. showed that the interaction between the NLRP3 inflammasome and PCD is critical in cold ischaemia reperfusion associated with ELT.[15] A comprehensive understanding of these mechanisms could aid in developing new targeted inhibitors and new strategies for the treatment of ALF.

Some patients can recover from ALF with complete restoration of liver mass and function within a relatively short time frame. A central concern in clinical practice is identifying which patients possess sufficient regenerative capacity to recover from the sudden hepatocyte death and subsequent loss of function. Such patients would not have to be considered for ELT, alleviating pressure from attending physicians and health care resources.[12]

**Key points**

1. Acute liver failure (ALF) has a high mortality of about 30% and can quickly lead to death despite maximum therapeutic intervention.
2. On a cellular level, ALF is characterized by massive hepatocyte death due to different types of cellular demise.
3. In the past decades, there has been a shift concerning the predominant etiologies, with drug-induced liver injury as the most common cause in the Western World today.
4. Therapy of ALF comprises intensive care medicine, aetiology-specific therapies, and in cases where ALF is irreversible. emergency liver transplantation (ELT).
5. ELT as therapeutic option is strongly limited by organ shortage.

## 3 | GENERAL TREATMENT OF ALF

Effective management of ALF requires comprehensive intensive care, addressing ALF-specific symptoms, such as HE, and providing aetiology-specific interventions if feasible. However, due to the urgent nature of most cases and the high risk of mortality, clinical trials, especially randomized studies, on ALF and its treatments are scarce. Consequently, much of the available data is derived from retrospective studies.

### 3.1 | General treatment for ALF

Intensive care medicine plays a crucial role in managing ALF. The primary goal of general intensive care measures is to prevent complications, including metabolic disorders (e.g., hypoglycemia, hyponatremia), coagulation abnormalities, infections, neurological impairments, and the involvement of other organ systems (e.g., renal failure, acute respiratory distress syndrome).

A key aspect of treatment involves monitoring for infections, as patients with ALF are particularly susceptible to them. Infections, especially septic complications, pose a significant risk of mortality. Additionally, they can complicate postoperative management of ELT

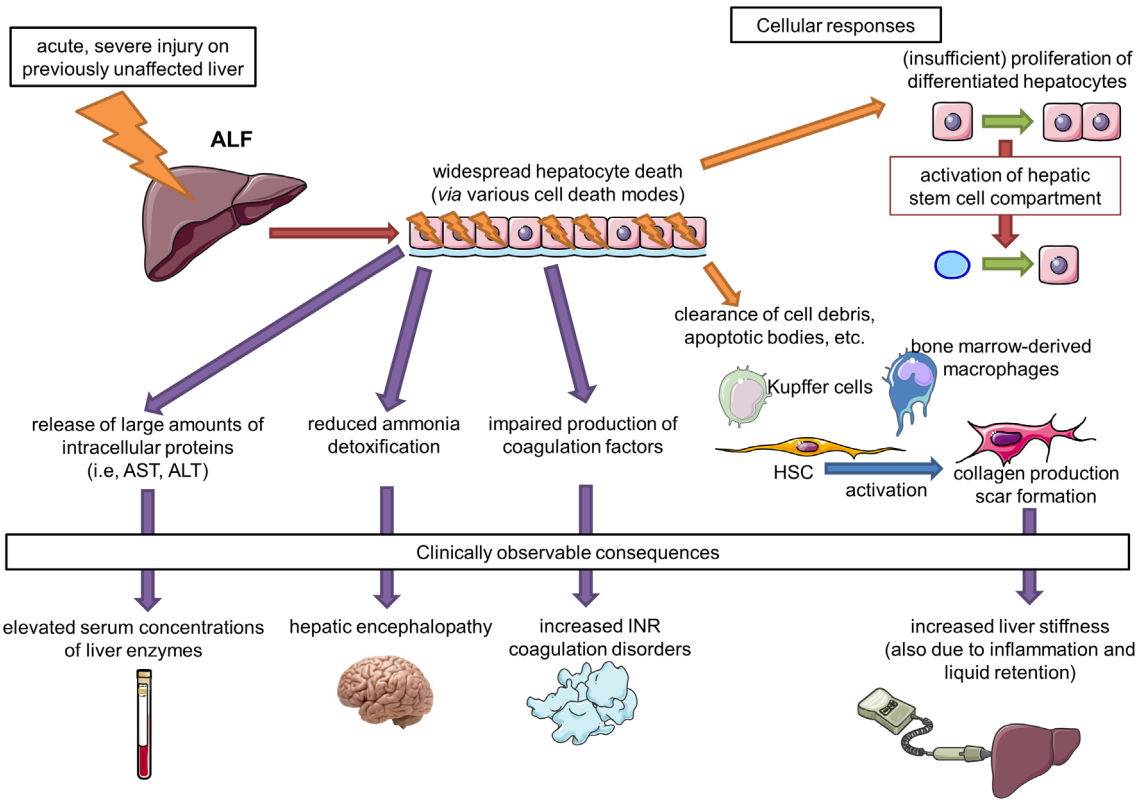


**FIGURE 1** Overview on mechanisms involved during acute liver failure. Acute liver failure (ALF) is characterized by severe acute liver injury resulting in extensive hepatocyte cell death and loss of liver function, occurring suddenly without prior injury or chronic disease. Various modes of hepatocyte cell death, including apoptosis, necrosis, and necroptosis, potentially modulated by the NLRP3 inflammasome, contribute to this process. The widespread demise of hepatocytes triggers the proliferation of differentiated hepatocytes as an initial compensatory response, which might be inadequate to counterbalance the cell loss. Consequently, activation of the hepatic stem cell compartment ensues. Elimination of cellular debris and apoptotic bodies originating from the deceased hepatocytes is handled by resident Kupffer cells, infiltrating bone marrow-derived macrophages and hepatic stellate cells (HSCs). Activated HSCs adopt a fibroblast-like phenotype and produce collagen to promote tissue integrity in the damaged liver. Persistent injury, if unabated, and uncontrolled collagen production by HSCs lead to the formation of scar tissue and fibrogenesis, replacing functional liver mass with extracellular matrix. The extensive hepatocyte cell death results in the release of enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), causing a significant elevation of their serum concentrations. The diminished number and compromised function of hepatocytes impairs ammonia detoxification, thereby contributing to the development of hepatic encephalopathy (HE). Moreover, the reduced hepatocyte capacity to synthesize both pro- and anticoagulant factors manifests as increased International Normalized Ratio (INR) and coagulation abnormalities. Pictograms/cartoons taken from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 France Licence.

or render ELT unfeasible.[16] Diagnosing infections in patients with ALF can be challenging due to reduced synthesis of serum-derived inflammatory parameters like C-reactive protein and procalcitonin. To aid in early detection, regular microbiological monitoring should include taking urine and blood cultures, alongside close clinical observation.[17] While general prophylactic antibiotic or antifungal therapy should be avoided, empirical anti-infective therapy is warranted when clinical signs of infection arise (e.g., fever, first episode or worsening of HE[18]), keeping in mind the increased risk of fungal infection during prolonged hospitalization.[19]

Additionally, mechanical liver support procedures, such as bilirubin adsorption, the Molecular Adsorbent Recirculating System (MARS®; Baxter, Deerfield, IL, USA), or the Prometheus® system (Fresenius Medical Care, Bad Homburg, Germany), can be considered if available. However, since these are not yet established therapeutic procedures, they should only be applied within the context of clinical studies.[20] For more in-depth information on these specialized therapeutic procedures, interested readers are encouraged to refer to excellent review articles in journals of intensive care medicine.[21,22]

Of particular importance is plasma exchange (PE), a treatment strategy recognized in the EASL Clinical Practical Guidelines.[23] The efficacy of PE was demonstrated in a 2016 randomized controlled trial (RCT) conducted by Larsen et al. This trial utilized PE, replacing plasma with fresh frozen plasma in a 1:1 ratio. The study's findings indicated a substantial decrease in mortality among patients with ALF who did not receive ELT. Interestingly, this survival advantage was also observed in patients with unfavourable prognostic factors but who were not suitable for ELT listing due to existing comorbidities. Beyond its immediate benefits, PE appears to influence monocyte immune function, potentially providing an explanation for

the observed survival benefit. This transformative effect on the immune response, coupled with the immediate removal of mediators and replenishment of plasma-derived factors, contributes to PE's potential therapeutic impact.[24]

Another potential therapeutic option, irrespective of the aetiology, involves the use of adipose-derived stem cells (ASCs). These mesenchymal stem cells (MSCs) can be obtained from human adipose tissue and lipoaspirate.[25] Notably, they possess the ability to differentiate into various cell types, including hepatocytes, making them a promising cell source for enhancing regeneration from ALF.[26,27] For instance, Götze et al. administered ASC intravenously (in physiologic salt solution) to three individuals with alcohol-triggered ALF or ACLF under compassionate use. Remarkably, all three cases demonstrated a reduction in serum transaminases and an improved general condition after this treatment.[28] However, the therapeutic effect of MSCs is probably not solely based on their differentiation into hepatocytes. These stem cells also influence immune cell regulation and other co-factors.[29] However, MSC or ASC treatment for ALF is still an experimental approach suited for individual cases only. As such, further studies are warranted to gain a comprehensive understanding of the therapeutic effect, potentially unwanted immune reactions and inflammatory processes, and to optimize the application of MSCs for ALF treatment.

### 3.2 | Treatment of HE

The clinical manifestations of HE comprise irritability, confusion, agitation, reduced consciousness and coma. The West Haven criteria classify HE into four stages, all of which can be transitional and reversible. However, a progression from stage II (lethargy or apathy) to stage III (somnolence) is considered indicative of irreversible liver damage. In such cases spontaneous recovery is rare, necessitating immediate transfer to a tertiary care centre with the option of ELT as a viable treatment option.[30,31] Ideally, such a transfer should be initiated earlier. The pathogenesis of HE involves multiple mechanisms, including neurotoxins, increased serum ammonia and systemic and neuroinflammation. In ALF, hepatic detoxification of ammonia becomes impaired. The resulting elevated serum ammonia concentration leads to osmotic and cellular dysregulation in the brain, resulting in cerebral oedema and increased intracranial pressure. Intracranial hypertension (>25 mmg) may predispose individuals to cerebral herniation and death.[32] However, with advancements in critical care management and improved treatment options for ammonia detoxification, cases of intracranial hypertension are now much less common than in the past.[33]

### 3.3 | Diagnosis and treatment of impaired coagulation in ALF

Over the last decade, our comprehension of the coagulation system in hepatic failure patients has significantly evolved. The concept of "rebalanced haemostasis" has emerged, recognizing that the synthesis of coagulation factors and inhibitors in the liver leads to a lower-level equilibrium of coagulation.[34] While classic coagulation parameters such as INR, aPTT, fibrinogen and platelet count are often employed to gauge bleeding tendencies in patients with ALF, these measurements can be misleading due to the reduction of both anticoagulant and coagulation factors.[35] Hence, these parameters should only be considered as a measure of hepatic synthesis.[35,36]

In most cases of liver failure, there is a shift towards a procoagulant state. Unnecessary transfusion of coagulation factors can be costly and even trigger complications such as portal vein thrombosis and other thrombotic events. Thus, the use viscoelastic test (VET) methods, such as the ROTEM® analysis, is gaining traction for managing liver failure patients[34] and perioperative care.[37] VET methods enable more precise coagulation status assessment, guiding decisions regarding fibrinogen, platelets, or prothrombin complex, or the need for fibrinolytic treatment. Moreover, these methods provide rapid point-of-care testing, outpacing conventional laboratory diagnostics.[38]

Studies have demonstrated that pre-intervention ROTEM® analysis can significantly reduce the amount of substituted coagulation factors in patients with ACLF without heightening bleeding or thrombotic risk.[39] This finding is supported by an increasing number of patients with ALF, who undergo liver transplantation without blood product administration.[40] Nonetheless, prospective studies are required to firmly establish the benefit of VET methods across various liver failure forms. Further research should also focus on the role of distinct hepatic cell species, especially HSCs and Kupffer cells, in producing and activating pro- and anticoagulant factors. In clinical practice, a cautious approach to coagulation factor transfusion for patients with ALF is advised, and a thorough actual coagulation status assessment is recommended.

## 4 | AETIOLOGY-SPECIFIC TREATMENT OF ALF

As mentioned above, ALF can be triggered by a variety of causes, making it crucial to focus on diagnostic procedures to identify the causative factors. The early administration of specific therapies is essential, as their efficacy is highly dependent on prompt intervention.[4] The most common causes of ALF are acute hepatitis B virus (HBV) infection and drug-induced liver injury (DILI). Although rare, ALF can also occur in the context of other viral hepatitis (e.g., hepatitis A/E), autoimmune diseases (including autoimmune hepatitis [AIH]), Wilson's disease (WD), pregnancy, Budd-Chiari syndrome (BCS), Amanita phalloides ("Death cap") poisoning and congestive heart failure. Overviews of causes and specific therapies for ALF are presented in Table 1 and Figure 2.

### 4.1 | Advancements in treatment and diagnostic assessment for DILI

Over the past few decades, the predominant etiologies of ALF have shifted. While acute HBV infection was once considered the most

**TABLE 1** Specific therapy/measures of acute liver failure.

| | |
|---|---|
| Paracetamol intoxication | N-acetylcysteine<br>General rule: first 10 g as a short infusion over 20 min, then further 10 g over 24 h, if bodyweight >70 kg (5 g over 24 h, if bodyweight <70 kg), administered intravenously, for 3 days |
| Acute hepatitis B | Antiviral therapy with Entecavir 0.5–1 mg/day or Tenofovir disoproxil (TDF) 245 mg/day or Tenofovir alafenamide (TAF) 25 mg/day, administered perorally |
| Acute hepatitis E | Possibly Ribavirin by body weight, up to 1200 mg/day |
| Death cap intoxication | Silibinin 20–50 mg/kg bodyweight/day, administered intravenously |
| Autoimmune hepatitis | Methylprednisolone 1–2 mg/kg bodyweight/day, administered intravenously |
| Budd-Chiari syndrome | Anticoagulation and transjugular intrahepatic portosystemic shunt |
| Acute fatty liver of pregnancy (AFLP) | Prompt delivery |
| Herpes simplex hepatitis | Acyclovir 3 × 10 mg/kg bodyweight/day, administered intravenously |

*Note*: Table according to Lemmer et al.[6]

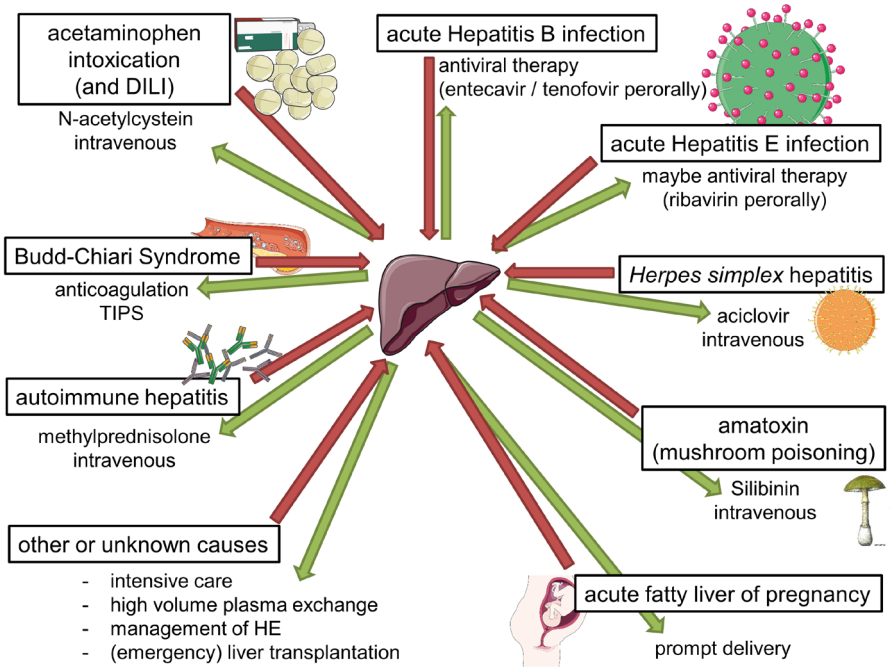


**FIGURE 2** Etiologies and specific treatments for acute liver failure. This schematic overview illustrates various causative factors that can lead to severe acute liver tissue damage, culminating in acute liver failure (ALF). Depending on the specific underlying cause, immediate and tailored therapeutic approaches can effectively address the ALF, potentially obviating the need for (emergency) liver transplantation, which serves as a last-resort measure in cases where ALF lacks spontaneous remission or when the cause remains unidentified. For comprehensive treatment protocols, refer to Table 1. DILI, drug-induced liver injury; HE, hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt. Pictograms/cartoons taken from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 France Licence. Death cap picture from Danny Cicchetti, CC BY-SA 4.0 https://creativecommons.org/licenses/by-sa/4.0, via Wikimedia Commons.

frequent trigger in the early 1980s, there has been a significant increase in ALF cases due to toxic liver injury, particularly DILI, in the Western world.[41] Diagnosing DILI, even in tertiary care centres, remains challenging and is often based solely on the exclusion of other potential causes. DILI can be categorized into two major types: idiosyncratic and intrinsic. An idiosyncratic liver injury arises from an unpredictable dose-independent interaction between a drug and a susceptible individual. In contrast, intrinsic liver injury results from drug overdosing. A well-known example of intrinsic liver injury is acetaminophen (paracetamol) or N-Acetyl-p-aminophenol (APAP). In cases of APAP intoxication, timely administration of the antidote N-acetylcysteine is crucial. When initiated before the onset of liver damage, N-acetylcysteine treatment can effectively prevent liver failure.[41]

Notably, a systematic review conducted by Sanabria-Cabrera et al. revealed that N-acetylcysteine therapy has a therapeutic effect

in non-paracetamol-induced DILI as well.[42] However, it is essential to acknowledge that no RCTs are currently available on this matter.

In everyday clinical practice, corticosteroids are often employed in the treatment of DILI. While several studies suggest that patients with moderate to severe DILI, particularly those with DILI-induced AIH (DI–AIH), may benefit from steroid therapy, the observational nature of these studies and their comparison with historical controls present challenges in drawing definitive conclusions.[43] Therefore, the precise role of corticosteroids in DILI requires further elucidation through additional RCTs.

Recent progress in assessing the extent of liver injury caused by drugs, especially in idiosyncratic DILI, includes the development of the diagnostic scoring algorithm Revised Electronic Causality Assessment Method (RECAM). This evidence-based update of the RUCAM (Roussel Uclaf Causality Assessment Method), developed in the early 1990s, demonstrates better sensitivity, as judged by experts, especially in detecting extreme diagnostic categories (i.e., DILI highly likely or high probable and unlikely/excluded).[44]

Furthermore, the identification of drug-specific HLA associations has proven valuable in confirming or excluding DILI in individual patients.[45] For instance, DILI caused by amoxicillin-clavulanic acid (AC), one of the drugs with the highest incidence of DILI,[46] is associated with specific HLA variants, including HLA-A*02:01, HLA-DRB1*15:01 and a missense variant in PTPN22 (rs2476601). These HLA variants have been incorporated into a genetic risk score (GRS), which demonstrates high predictability for AC-DILI risk.[47] As genetic analysis becomes more available and cost-effective, such scores are likely to be increasingly utilized in differential diagnostic considerations, reducing the incidence of DILI.

### 4.2 | Treatment of ALF induced by viral hepatitides

In the case of ALF triggered by hepatitis B virus (HBV), early antiviral therapy with entecavir or tenofovir for highly viremic severe acute hepatitis B may obviate the need for ELT.[4]

Over the past 10–20 years, Hepatitis E (HEV) has garnered significant attention. Originally classified as a tropical disease in the 1980s, the status of this infectious disease has evolved in industrialized countries since the turn of the century. In industrialized nations like Germany, HEV's genotype 3 is prevalent, primarily spread through the consumption of undercooked meat, particularly from domestic and wild pigs, which serve as the primary animal reservoir.[48] The clinical course of hepatitis E infection varies significantly, ranging from mostly asymptomatic cases to potentially fatal liver failure. The latter is most common in individuals with chronic liver disease.[49] Developing countries bear the highest burden of Hepatitis E-related ALF, where the hepatitis E virus (genotypes 1 and 2) is predominantly transmitted through faecal contamination of water and food.[50] While the administration of ribavirin is an established treatment option for chronic hepatitis E, there is currently no data on its efficacy in treating severe acute hepatitis E to prevent ALF, yet.[51]

### 4.3 | Treatment of AIH-induced ALF—A diagnostic challenge

AIH is characterized as a chronic inflammatory hepatic disorder, initiated by unidentified stimuli that trigger a predominantly T-cell-dependent immunological attack against the liver. Despite extensive research, the primary auto-antigen responsible for this reaction remains unidentified.[52] Establishing a diagnosis for AIH poses significant challenges due to the absence of definitive, disease-specific diagnostic tests. While diagnostic scoring systems based on the presence of autoantibodies offer some assistance in numerous cases, they have limitations, particularly when dealing with acute disease manifestations.[53] In the early stages of AIH, antibodies might not be present and may only appear as the disease progresses. Conversely, autoantibodies like ANA and SMA are often identified in cases of acute severe hepatitis, regardless of the underlying aetiology, including DILI. Consequently, diagnosing acute severe AIH remains problematic despite its critical clinical implications, especially regarding the timely initiation of immunosuppressive therapy to prevent hepatic damage and the consideration of ELT if treatment proves non-responsive.[54]

The appropriateness of administering high-dose steroids, particularly intravenous prednisolone at a dose of 1 mg/kg body weight per day (standard-of-care medical treatment for inducing remission in AIH), to all of these patients remains uncertain. Moreover, it is unclear if there is any stage in ALF where treatment could be more harmful than beneficial. Another point of ambiguity lies in the optimal time point to recognize steroid non-responders, necessitating the consideration of ELT.[55] Addressing these challenges is essential in optimizing existing diagnostic scoring systems.

### 4.4 | ALF associated with WD—Treatment challenges and advances

WD, an uncommon autosomal recessive disorder characterized by abnormal hepatocellular copper accumulation, is often fatal if left untreated, primarily due to liver disease and, in some cases, advancing neurological disorders. The introduction of medical interventions like chelators and zinc salts has notably enhanced survival rates in the majority of cases.[56] However, when WD leads to ALF, the effectiveness of medical therapy is markedly diminished. This is primarily attributed to the extensive duration required for copper removal from the body. Consequently, in such critical situations, ELT often remains the only viable treatment option.[57] Although efforts have been made to eliminate copper through albumin dialysis, empirical support for this method remains limited. Maintaining a high level of suspicion for acute WD is crucial in patients displaying symptoms such as severe jaundice, low haemoglobin, reduced cholinesterase activity and diminished alkaline phosphatase levels.[58]

### 4.5 | Acute fatty liver of pregnancy (AFLP)—A rare obstetric problem

AFLP is an infrequent yet potentially life-threatening obstetric disorder primarily characterized by varying degrees of hepatic failure, typically occurring in the third trimester of pregnancy.[59] Experts widely advocate the use of the Swansea criteria for the clinical diagnosis of AFLP, which comprise clinical, laboratory, ultrasonographic and histologic features.[60] Central to AFLP is hepatic dysfunction, the hallmark of acute fatty liver. It's understood that liver failure persists until the fetus is delivered. Therefore, upon identification, the management of AFLP depends on meticulous delivery planning and comprehensive supportive care, which also includes addressing any concurrent coagulopathy. Post-delivery, the patient generally experiences a gradual restoration of metabolic equilibrium encompassing both hepatic and renal functions. This recovery process often necessitates extensive supportive care spanning several days to weeks.[59]

### 4.6 | Treatment of BCS—Eliminating outflow obstruction

BCS is a rare yet potentially life-threatening pathology characterized by the blockage of the hepatic venous outflow tract. This obstruction is typically attributed to thrombosis or primary conditions affecting the venous wall.[61] Approximately three-quarters of diagnosed cases can be linked to an underlying disorder, notably hereditary or acquired hypercoagulable states. The most prevalent underlying condition in this category is myeloproliferative neoplasm. Other causative factors include hormonal influences, like use of oral contraceptives, and local factors such as abdominal trauma. However, around 20% of suspected BCS cases remain unexplained despite comprehensive evaluation, leading to their classification as idiopathic BCS.[62]

Therapeutic strategies for BCS primarily revolve around addressing the underlying prothrombotic disorder and restoring the hepatic venous outflow. Until this goal is achieved, meticulous management of portal hypertension is crucial. Consistent with universal treatment protocols, long-term anticoagulant therapy is crucial to impede thrombosis progression. The favoured approach involves the initial administration of low-molecular-weight heparin followed by a vitamin K antagonist once the patient's condition stabilizes. However, pregnant women are an exception due to the teratogenic risks linked with vitamin K antagonists.[63]

If the disease continues to progress despite these efforts, the next step is relieving pressure on the liver by altering the portal system into an outflow tract. Currently, the preferred method to achieve this is through the placement of a transjugular intrahepatic portosystemic shunt (TIPS). In cases where BCS leads to ALF, ELT remains the final treatment option. It's worth noting that the use of a TIPS prior to transplantation does not negatively impact the post-transplantation prognosis.[64]

### 4.7 | Amatoxin-containing mushroom poisoning—Immediate treatment by toxin uptake inhibition

Over 35 mushroom species across three genera (Amanita, Galerina and Lepiota) are known to contain the deadly toxin amatoxin. Among these, *Amanita phalloides* ('Death cap') is one of the most toxic mushrooms. Its potent liver toxicity accounts for the majority of human fatalities caused by mushroom poisoning. Identification of amatoxin-containing mushroom poisoning relies on clinical symptoms and should be considered as a potential diagnosis for patients exhibiting delayed onset of gastrointestinal symptoms or hepatotoxicity after ingesting mushrooms.[65] Ideally, the clinical diagnosis should be confirmed through amatoxin detection in the urine.[66] However, therapeutic measures should be promptly initiated without awaiting test results. This involves managing fluid losses resulting from vomiting and diarrhoea, conducting gastrointestinal decontamination with activated charcoal and administering the amatoxin uptake inhibitor silibinin dihemisuccinate intravenously.[67] Importantly, silibinin appears most effective within 24 h of ingestion.[68] Severely poisoned patients may develop irreversible hepatic failure 2–4 days after mushroom consumption, often accompanied by acute renal failure.[69] Therefore, if the clinical signs of hepatic injury range from moderate to severe, transfer to a tertiary healthcare facility capable of performing ELT should be promptly arranged.

### 4.8 | ALF of unidentified reason—Limited therapeutic options

In a significant proportion of ALF cases, about 15% in adults and 50% in children, the underlying causes remain unidentified.[70] As emphasized previously, the ultimate curative recourse in progressive ALF is ELT, which is the sole therapeutic option when the aetiology remains undefined. Given the scarcity of organs, it's crucial to differentiate ALF from the more prevalent chronic liver failure forms, as patients with ALF may be prioritized as "high urgency" (HU) candidates, granting them preferential access to organs.

## 5 | PREDICTION OF ALF OUTCOME

Improved specific therapies for certain etiologies, availability of ELT and notable advances in critical care medicine have consistently reduced the mortality rates of ALF in recent decades.[71] ELT and liver transplantation (LTx) have substantially improved short-term survival in ALF, exceeding 80% after 1 year and over 70% after 5 years.[72]

However, ELT has inherent limitations, including organ shortage, resource consumption and risk of graft rejection.[4] To optimize outcomes and resource allocation, accurate prognostic indicators are essential to identify patients who may not necessitate ELT or would not gain substantial benefits from it. Currently, the King's College (KCC)

and Clichy criteria are applied to assess prognosis in specific ALF causes and are widely recognized tools. Nonetheless, both systems display limited accuracy in predicting patient outcomes.[73] Alternative markers like the Model for End-Stage Liver Disease (MELD) may offer superior prognostic precision.[74,75] ALF is characterized by hepatocyte cell death in various forms (apoptosis, necrosis and necroptosis).[76] Research suggests incorporation of M65, a marker for overall cell death, into the MELD formula, could enhance its predictive ability.[77] The ALFSG index, incorporating M30 (an apoptotic cell death marker), alongside established indicators like coma grade, INR and bilirubin levels, outperformed KCC and MELD in a large cohort of US patients.[78] Short-lived hepatocellular products such as hepcidin might also serve as useful predictors of ALF progression, offering real-time insight into liver synthetic capacity.[79] Refer to Table 2 for a summary of presently utilized outcome assessment scores for ALF.

ALF initiates a regenerative response from the remaining hepatocytes. When hepatocyte regenerative capacity falls short, resident liver progenitor cells (LPC) become activated.[80] Given the positive correlation between LPC activation, severity of liver injury and the clinical outcome of ALF,[81] the extent of LPC response could potentially serve as a biomarker for regenerative capability.[12]

## 6 | THE SHORT- AND LONG-TERM OUTCOMES OF ALF DEPEND ON DIFFERENT CLINICAL FACTORS

Short-term outcomes after LTx in ALF have improved due to refinements in therapy concepts, donor and recipient evaluation, surgery procedures and immunosuppression.[72] In contrast, the highly variable long-term prognosis after LTx still depends on factors that are difficult to control (co-morbidities, infectious complications, relapse of the underlying condition and development of malignancy). Despite optimization of individualized immunosuppressive therapy, graft rejection remains a major concern, impacting long-term prognosis negatively. Managing and averting graft rejection through tailored immunosuppression selection and protocols post LTx stands as a considerable challenge. It is crucial to balance the use of immunosuppressive drugs against their potential side effects, which encompass impaired renal function, heightened risk of de novo malignancies and worsened cardiovascular profiles.[82]

To further improve long-term survival after ELT/LTx, continuous refinement of immunosuppressive medications and personalized treatment protocols is imperative. A promising approach is

**TABLE 2** Scoring systems for severity of acute liver failure/necessity of transplantation and novel candidate factors.

| Scoring system/criteria/candidate | | Evaluation/prognostic factors |
|---|---|---|
| Kings' College criteria | Acetaminophen toxicity | Arterial pH <7.25 (independent of stage of hepatic encephalopathy)<br>OR two out of three of the following criteria and clinical deterioration:<br>• INR < 6.5<br>• creatinine >300 μmol/L<br>• hepatic encephalopathy grades 3–4 |
| | Other causes | INR > 6.5 (independent of hepatic encephalopathy) OR<br>three out of five of the following criteria (independent of stage of encephalopathy):<br>• age < 10 or > 40 years<br>• aetiology: unclear, medication-toxic<br>• time from icterus to encephalopathy >7 days<br>• INR > 3.5<br>• Bilirubin >300 μmol/L |
| Clichy criteria | | Hepatic encephalopathy grade 3 or 4 and<br>• factor V < 20% (age < 30 years) or<br>• factor V < 30% (age > 30 years) |
| MELD | | $10 \times (0.957 \times \ln_{\text{serum creatinine}} + 0.378 \times \ln_{\text{bilirubin}} + 1.12 \times \ln_{\text{INR}} + 0.643)$ |
| CK-18/modified MELD | | $10 \times (0.957 \times \ln_{\text{serum creatinine}} + 0.378 \times \ln_{\text{serum CK-18/M65}} + 1.12 \times \ln_{\text{INR}} + 0.643)$ |
| BILE score | | Bilirubin (μmol/L)/100 + lactate (mmol/L)<br>+4 (for cryptogenic ALF, Budd-Chiari syndrome, or phenprocoumon toxicity)<br>−2 (for acetaminophen toxicity)<br>±0 (for other etiologies of ALV) |
| ALFSG index | | Coma grade, Bilirubin, INR, phosphorus, $\ln_{\text{M30}}$ |
| ALFED model | | Dynamic of variables over 3 days:<br>HE 0–2 points; INR 0–1 point;<br>Arterial ammonia 0–2 points; serum Bilirubin 0–1 point |
| Thyroid hormones | | Low T3 levels are associated with worse outcome in acute liver failure |
| Lipid metabolism | | Low HDL levels associated with worse outcome in acute liver failure |
| Ferritin/Transferrin | | High ferritin and low transferrin levels are associated with worse outcome in acute liver failure |

*Note*: Table according to Lemmer et al.[6]

the detection of donor-specific cell-free DNA by liquid biopsy, a technique already employed for the detection of cancer and metastases.[83] In the context of ELT/LTx, this method could facilitate identification of subclinical rejections by detecting circulating cell-free donor DNA, thereby enabling optimization of immunosuppressive dosages.[84]

## 7 | CAN MACHINE LIVER PERFUSION RESOLVE THE ISSUE OF ORGAN SHORTAGE?

Liver transplantation has achieved remarkable success; however, many patients succumb while awaiting a transplant.[85] This applies to both regular waiting list patients and those on the HU-list. The global transplant community grapples with the increasing need for liver grafts.[86] To address this issue, donor selection criteria have been expanded, encompassing liver grafts with significant steatosis or from circulatory death donors. Notably, the utilization of donation after Circulatory Death (DCD) is still prohibited in some countries, including Germany.[87] However, these marginal livers carry an increased risk of graft-associated complications, such as primary nonfunction, delayed graft function or late biliary injuries. Therefore, comprehensive assessment and reconditioning of these grafts are essential.

Mechanical liver perfusion, a procedure developed 50 years ago, has shown promising results in expanding the pool of viable grafts and improving recipient outcomes.[88–91] In many institutions, machine perfusion of donor livers is now a mandatory procedure prior to liver transplantation. There are two different types of perfusions: hypothermic (<12°C) and normothermic (35–37°C). Hypothermic perfusion reduces metabolism by a factor of 6–12, while normothermic perfusion requires continuous nutritional support. Many transplant centers employ both procedures, sometimes sequentially, to assess, improve or recondition the graft. Both hypothermic and normothermic perfusion play pivotal roles in assessing graft vitality and improving its quality.[89]

The success of liver transplantation depends heavily on graft functionality. Unfortunately, non-anastomotic biliary strictures are a common complication post-transplantation. This condition can cause cholestasis, cholangitis, and occasionally requires further biliary intervention or retransplantation.[92] Compelling evidence underscores that livers from DCD donors are three times more likely to result in non-anastomotic biliary strictures than livers from brain-dead donors.[93] However, due to the scarcity of available organs, the number of DCD transplants is increasing. To assess the impact of machine liver perfusion, van Rijn et al conducted a randomized trial.[90] Seventy-eight patients underwent liver transplantation with hypothermic perfusion, and 78 patients with cold storage of the donor graft (control arm). The primary study objective was to determine the incidence of biliary strictures 6 months after transplantation. The results showed that biliary strictures occurred in 6% of patients with hypothermic perfusion and in 18% of patients in the control arm ($p = .03$). Additionally, reperfusion syndrome (12% vs. 27%) and graft dysfunction (26% vs. 40%) were significantly lower with hypothermic graft perfusion. The cumulative incidence of biliary strictures was fourfold lower in the machine arm than in the control arm, and with comparable side effects in both groups. Overall, machine perfusion reduced post-transplant complications compared to conventional cold organ storage.

## 8 | SUMMARY AND CONCLUSIONS

The management of ALF, characterized by rapid hepatocyte demise and subsequently impaired liver function, requires a multidisciplinary approach, involving specialists in hepatology, critical care medicine and transplant surgery. Improvements in therapy and management, specific therapies for certain etiologies, the availability of ELT, and advances in critical care medicine have reduced the mortality of ALF over the last decades. Timely identification of the causal factors remains pivotal, since effectiveness of specific treatments often depends on prompt application. When ALF reaches an irreversible stage, ELT remains the only curative option.

Viscoelastic test methods show promise in managing patients with ALF with complex coagulation disorders. Though, further studies are needed to confirm their utility in therapeutic decision-making. ELT has significantly improved the prognosis of patients with ALF, but donor organ shortages and overstretched healthcare resources highlight the need for robust prognostic outcome indicators. Adaptations to established prognostic tools like the MELD, alongside markers of cell death and donor-specific circulating DNA for graft rejection, hold potential. A better understanding of the regenerative process and of involved cell death mechanisms in liver failure may also provide novel survival markers. Prospective studies are needed to evaluate the performance of new markers and to harness the regenerative potential of the liver during ALF's rapid progression.

### AUTHOR CONTRIBUTIONS

Study concept and design: Peter Lemmer, Ali Canbay. Drafting of the manuscript: Peter Lemmer. Critical revision of the manuscript for important intellectual content: Peter Lemmer, Jan-Peter Sowa, Pavel Strnad, Ali Canbay. Obtained funding: Ali Canbay. Study supervision: Ali Canbay. All authors approved the final draft submitted.

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The authors have no conflict of interest to disclose.

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## ETHICS STATEMENT

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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