HEPATOLOGY

A clinical textbook

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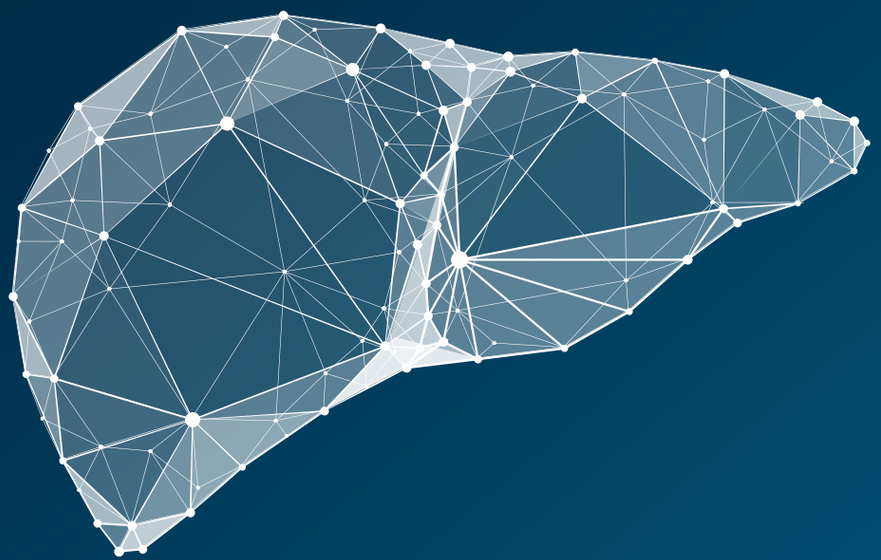
11th Edition **2024–2025**



16. Acute liver failure

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Introduction

Acute liver failure (ALF), characterized by elevated liver enzymes in addition to hyperbilirubinemia, coagulopathy, and/ or hepatic encephalopathy, is a potentially life-threatening clinical condition that develops in the presence of a healthy liver. Preexisting chronic liver issues must be ruled out because the management and outcome of acute-on-chronic liver failure differ from ALF (Lemmer 2023).

The classical clinical picture is extensive hepatocyte death followed by loss of liver functions displaying prolonged INR and elevated bilirubin levels (Rutherford 2008). In animal studies, targeting ferroptosis, in addition to previously documented cell deaths of apoptosis, necrosis, and necroptosis, was recently found to have a limiting effect on acetaminophen-induced ALF (Yamada 2020). NLRP3 inflammasome was shown to play a crucial role in ALF by causing various cell deaths (Jiménez-Castro 2019). ALF is a potentially reversible disease that occurs in the body's most regeneratively skilled organ. In this dynamic process, the lost hepatocytes undergo healthy hepatocyte cell division and ductular structure proliferation while apoptotic bodies and cell debris are cleared out by inmate and newly recruited macrophages, along with the activated hepatic stellate cells, which play an important role in the progression of fibrosis (Cardoso 2017). The balance between the degree of cell death and the ability of hepatocytes to regenerate, as well as the severity of neutrophil infiltration and the amount of collagen produced, would define where the liver ends up. As a result, predicting which patients require more aggressive intervention, such as emergent liver transplantation, is in clinical practice difficult yet valuable.

Epidemiology

The overall incidence of ALF is estimated to be one to six cases per million people each year, and it accounts for up to 8% of all adult liver transplants (Bernal 2010, Rovegno 2019). Germany, with 800-1000 ALF cases annually, was found to be comparable with the US but significantly lower than East Asian countries such as Taiwan and Thailand (Weiler 2020). In Thailand, the incidence of ALF in was reported as 62.9 per million population per year, with just 0.005% of ALF patients undergoing liver transplantation

(Thanapirom 2019). However, comparing the results by income level would be inaccurate due to a lack of reliable data and some misclassifications, including alcohol-related liver failure labeled as ALF in middle- and low-income countries (Weiler 2020, Thanapirom 2019). The establishment of a registry in Asia to collect ALF-related data should be promoted.

In high-income countries, acetaminophen intoxication remains the most common cause of ALF (about 50%), whereas viral hepatitis and herbal medications are in low- and middle-income nations (Bernal 2010, Stravitz 2023, Vento 2023). Surprisingly, the Argentinian registry revealed that nearly half of ALF patients had indeterminate etiology or autoimmune hepatitis (Mendizabal 2019). The etiology, as well as the outcome, varied greatly depending on the country's income level. The more than 90% ALF-related deaths in the 1980s dropped to 29% in Western countries, however it still double the rate within the low-income regions (Vento 2023). Receiving timely and accurate diagnoses, as well as meeting general standards of care in ICU settings with transplantation options, makes a significant difference in outcome. The survival rates following liver transplantation continued to improve (e.g., 5 years survival rate was 63%) even though the age of the donors and recipients was advancing in Europe (Müller 2020).

With acetaminophen as the major cause, drug-induced ALF does have a central role with only minor changes in Western countries. Painkillers, such as acetaminophen, ibuprofen, and diclofenac, are comparable to the group of antibiotics followed by some herbal medicines (Weiler 2020, Tujios 2022). In the United States, 22% of ALF patients waiting for liver transplant had seronegative or indeterminate etiology, 34% as drug-induced etiology and 15% had viral hepatitis (Karvellas 2023). In Asia, the most common drugs for drug-induced ALF are herbals, traditional and anti-tuberculosis medicines (Jindal 2022). According to the literature, almost half of the acetaminophen-related ALF cases are unintentional (not suicidal), and half of them involve a combination with opioids (Larson 2005). Interestingly, in the United States, after limiting the dose of acetaminophen in this combination, the rate of ALF secondary to acetaminophen has decreased by 16% every year (Orandi 2023).

Viral hepatitis B and E, particularly HEV in pregnant women, which are still the leading causes of ALF in middle- and low-income countries, have begun to rise again following a steady drop thanks to widespread immunization campaigns. This recent spike was mostly attributed to the opioid crisis, injection drug use, and homelessness (Tujios 2022). There is always a need for updated approaches to prevent HBV reactivations as new biological, immune-suppressive, or immuno-modulatory therapies become available (Papatheodoridis 2022). Hepatitis A, on the other hand, is closely related to socioeconomic development level, poor access to healthcare or clean water, a rising number of immigrants, intravenous drug use, and sexual orientation (e.g., males having sex with men). Even though ALF occurs in less than 1% of HAV patients, once established, the mortality rate among adults can reach 30% and the outcome following liver transplantation, compared to HBV-induced ALF, is much worse (Jindal 2022, Manka 2016). HCV has not been identified as a cause of ALF; on the other hand, HDV requires the presence of HBV and is commonly identified as a cause of acute-on-chronic hepatitis/ liver failure.

Acute-onset severe AIH presentation is a rare cause of ALF (ranging from 7% to 32%), but transplant-free survival with the presentation of ALF was as low as 15% in U.S. and 20% in Brazil (Mendizabal 2019, Jindal 2022, Enke 2023).

Other causes of ALF, such as amanita toxin, Wilson's disease, Budd-Chiari syndrome, and acute fatty liver of pregnancy, may account for nearly 1% of all causes (Table 1) (Stravitz 2023). In Western countries, however, indeterminate, or idiosyncratic etiologies account for 7- 43% of ALF cases (Stravitz 2023, Mendizabal 2019, Müller 2020, Hadem 2012).

Table 1. Aetiology-specific diagnostic and treatment methods of ALF

Aetiology	Diagnostic method	Treatment method
Acetaminophen	Drug concentration in serum	Oral active charcoal N-acetylcysteine
Idiosyncratic drug toxicity	Drug concentrations in serum Eosinophil count in serum	N-acetylcysteine Corticosteroid Ursodeoxycholic acid
Acute viral hepatitis A	HAV Ig M	No specific therapy
Acute viral hepatitis B	HBsAg, HBc Ig M, HBV DNA	Entecavir, Tenofovir disoproxil or alafenamide
Acute viral hepatitis E	Anti- HEV, HEV RNA	Ribavirin
Herpes Simplex virus	HSV Ig M, HSV RNA	Acyclovir
Autoimmune hepatitis	ANA, ASMA, Ig G, LKM, SLA	Methylprednisolone
Wilson's disease	Urinary copper, ceruloplasmin in serum, slit-lamp examination	No specific therapy
Alpha 1 antitrypsin deficiency	AT level in serum, AT genotyping	No specific therapy
Haemochromatosis	Ferritin in serum, transferrin saturation	No specific therapy
Budd-Chiari syndrome	Ultrasound	Anticoagulation, transjugular intrahepatic portosystemic shunt
Acute fatty liver of pregnancy	Swansea criteria	Immediate delivery
Amanita	Amatoxins in urine, history	Oral active charcoal Silibinin

General standard of care

Traditionally, the time interval between the onset of symptoms and the development of coagulopathy and encephalopathy I used to classify patients as hyperacute (<7 days), acute (8-28 days), or subacute (28 days-6 months) groups. This classification would be useful in predicting not only the etiology, which is usually linked with hyperacute presentations such as APAP and ischemic etiologies, but also the outcome, as the longer the delay, the worse the outcome (O'Grady 1993). Recognizing ALF earlier and distinguishing it from acute-on-chronic liver diseases, transferring the patient to an intensive care unit (ICU), preferably in a specialized transplant center, defining the cause and initiating a specific therapy in addition to the standards of care, could be lifesaving. Therefore, the management plan should prioritize timely and evidence-based medicine treatment methods for ALF, including etiology-specific approaches as well as general standards of care with multi-disciplinary teams.

A race against the clock starts immediately after a presumed diagnosis of ALF. Preventing metabolic complications such as hypoglycemia or hyponatremia should be supported by monitoring for potential organ failures due to renal or lung involvement. As a result, monitoring urine output, ammonia and lactate levels, repeating finger stick glucose levels as well as electrolytes, kidney, and hepatic functions, and avoiding nephrotoxic agents, is critical in the management of ALF.

The initial workup should also include searching for possible underlying infections with a detailed physical evaluation, routine urinalysis, urine and blood cultures, and chest images. Providers should also bear in mind that the interpretation of inflammatory markers such as C-reactive protein (CRP) and procalcitonin may be challenging due to altered synthetic capacity of the liver. Routine antibiotic use without any evidence of infection is usually advised; nevertheless, given the high risk of infection evolving in sepsis and multi-organ failure quickly, the bar for initiating an empirical broad-spectrum antibiotic should be low (Lemmer 2023).

Close monitoring of vital signs alongside neurological impairments is essential in the context of ALF management. The most common used hepatic encephalopathy (HE) classification is the West Haven criteria which divided HE into 4 category where minimal and grade 1 represents clinically covert HE, whereas grade 3 and 4, clinically overt HE, present with somnolence or coma, respectively, are indicative for emergent liver transplantation in the setting of irreversible liver injury (Lemmer 2023, Weissenborn 2019). Because the elevated serum ammonia levels related to cerebral edema may result in cerebral herniation and death if intracranial pressure (ICP) exceeds 25mmHg, obtaining cranial computed tomography (CT) in patients with advanced hepatic encephalopathy and repeating the imaging in the event of neurological deterioration is now standard of care. It was reported that these complications of ALF are seen much less than before with the improvements in the standard of care and the modalities to detoxify ammonia. Furthermore, because of increased mental alteration and neurological dysfunction, avoiding aspiration risks is as important as avoiding benzodiazepines, particularly long-acting formulations.

Monitoring INR, aPTT, fibrinogen, and platelet counts in ALF patients is still part of assessing the severity of underlying hepatic functions and the risk of bleeding. However, given the recent concept of “rebalanced hemostasis,” it is widely agreed that the decision to transfuse any type of coagulation factor or blood products has not been made without obtaining viscoelastic tests (VET) such as ROTEM analyses (Lemmer 2023, Cohen 2020, Stravitz 2018). There is an overall decreased synthesis of both pro- and anti-coagulant factors in the context of ALF. Furthermore, despite having coagulopathy due to a pro-coagulant state, both mechanical and medical DVT prophylaxis, as well as routine vitamin K supplementation in the context of prolonged cholestasis, is recommended (Pereira 2005). On the other side, the risk of bleeding is mostly attributable to stress-induced GI mucosal injury and has been reported to be 10%, although only 2% relates to death (Stravitz 2018). Of note, platelet count could be a predictor of a poor outcome (Stravitz 2023).

Some scoring systems have been widely utilized predict the outcome of ALF (Table 2). The model for end-stage liver disease (MELD), which was originally designed to predict the outcome of cirrhotic patients undergoing transjugular portacaval shunt (TIPS) procedure, was found to be a better tool than King’s College (KCC) and Clichy criteria, and has since been widely used as an allocation tool in Europe and the United States (Lemmer 2023). While KCC outperformed MELD in predicting mortality from acetaminophen-related ALF, MELD was shown to be superior to KCC in non-acetaminophen-drug-related cases (Craig 2010, Fontana 2021). The ALFSG index was demonstrated to be better than the KCC and Clichy criterion (Koch 2016). In a recent observational cohort study, a bedside noninvasive breathing test (13C-methacetin) representing the metabolic function of the liver was shown to be a promising tool (Fontana et al. 2021). The combination of MicroRNAs combination in addition to clinical data was also found to be better than the ALFSG index, MELD, and KCC criteria (Tavabie 2021). Because the outcome of ALF is primarily defined by the impaired balance between the amount of hepatocyte cell death, the regenerative capacity of the hepatocytes and the synthetic function of the liver, incorporating the apoptotic or overall cell death markers of M30 or M65, respectively, into scoring systems, including a short-lived liver product of hepcidin or an activated liver progenitor cell marker reflecting the regenerative capacity of liver, could display better accuracy (Lemmer 2023). There is ongoing interest in and need for a more

accurate prognostic scoring method (Stravitz 2023).

Liver biopsy has been mostly replaced by non-invasive tests. However, in such circumstances, a liver biopsy is required to determine the presence of Ebstein-Barr virus (EBV), Herpes simplex virus (HSV), or Cytomegalovirus (CMV), or to diagnose autoimmune hepatitis or malignancies, or with the indeterminate cases when the prompt diagnosis may lead to a specific treatment. A liver biopsy could still be of benefit in predicting the outcome and the need for emergent liver transplantation in individualized cases.

Table 2. Current widely used and promising new scoring systems

Scoring systems	Aetiology specific	
King's College criteria	Acetaminophen	Arterial pH 7.25 or Two of the following criteria: INR <6.5, creatinine >300 µmol/L, grade 3-4 hepatic encephalopathy
	Non-acetaminophen	INR>6.5 or Three of the following criteria: age <10 or >40 years, unclear or drug-induced aetiology, onset-time between jaundice and encephalopathy >7 days, INR>3.5, bilirubin >300 µmol/L
Clichy criteria*		Grade 3-4 hepatic encephalopathy and factor V level <20% if <30 years old, or <30% if >30 years old
MELD		10 x [0.957 x ln (serum creatinine) + 0.378 x ln(total bilirubin) +1.12 x ln(INR+0.643)]
Modified MELD with CK-18		10 x [0.957 x ln (serum creatinine) + 0.378 x ln(CK18/ M65) + 1.12 x ln(INR + 0.643)]
BILE score	Addition or subtraction of point(s) based on aetiology	Bilirubin (µmol/L)/100 + Lactate (mmol/L) + 4 (for cryptogenic ALF, Budd-Chiari or Phenprocoumon induced) –2 (for acetaminophen-induced) +0 (for other causes)
ALFSG index		Coma grade, bilirubin, INR, phosphorus, $\log_{10}$ M30
ALFED model		Dynamic of variables over 3 days: HE 0–2 points; INR 0–1 point; arterial ammonia 0–2 points; serum bilirubin 0–1 point
Additionally,		Low T3, low HDL, or high ferritin and low transferrin levels were found to be related to worse outcome

* Validated to HBV aetiology
Adapted from Lemmer P et al. (1)

Aetiology specific approach

Drug-induced

This Western society's nightmare is nevertheless often an exclusion diagnosis either from an idiosyncratic reaction or a predicted acetaminophen dose-related liver damage. Acetaminophen intoxication is typically caused by suicidal intent, roughly half of the cases, and causes a dose-related hepatocellular liver injury (Larson 2005). Therefore, monitoring the drug concentration in serum would mostly be beneficial in the context of suicide attempt. If acetaminophen-induced ALF occurs after a suicide attempt, activated oral charcoal (1 g/kg) if appears within 4 hours accompanied by N-acetyl cysteine infusion to restore glutathione if presents within 24-36 hours can be beneficial (Table 1) (Hoofnagle 2019). N-acetyl cysteine intravenous infusion protocol involves 10 grams over 20 minutes followed by 10 grams over 24 hours or 5 grams if the body weight is less than 70 kg.

On the other hand, most of the non-acetaminophen-drug-induced ALFs have a significant latency period, even up to one year, making the diagnosis challenging. Thus, there is continued interest in developing scores such as the Revised Electronic Causality Assessment Method (RECAM) to obtain a diagnosis with a better sensitivity (Hayashi 2022). In the future, drug-specific HLA-based genetic analysis could play a role in reaching a precise diagnosis (Fontana et al. 2023a; Nicoletti 2023). Corticosteroids are frequently used in non-acetaminophen-drug-related ALF cases (Sanabria-Cabrera 2022). Despite the need for randomized controlled trials to assess the actual role of corticosteroids, it is suggested to use in patients presenting with moderate-severe ALF or with autoimmune hepatitis features (Björnsson 2022). Even though the usefulness of three days of N-acetylcysteine infusion in the context of non-acetaminophen-drug-induced ALF is still debated, it is commonly employed given the non-harmful feature along with possibility of benefit (Andrade 2019, Fontana 2023). Of note, there is no harm or any supportive benefit for the use of ursodeoxycholic acid even in the setting of cholestatic presentation of drug-induced liver injury (Bernal 2010, Andrade 2019).

Viral hepatitis

The impact of the recent large population migration should be observed closely in Western countries. The majority of immigrants are from the areas where national vaccination programs are less likely to be implemented or where access to clean water, sanitation, and healthcare is limited (Bernal 2010). Furthermore, young generations from recently industrialized

countries such as South Korea, may lack HAV-protective antibodies HAV (Yoon 2017). On the other hand, HEV infection should be considered in every ALF case because it is the most prevalent viral cause of ALF in Asian countries (20- 40%) and is becoming more common in developed nations (up to 10%) (Manka 2016). Initiating one of the oral anti-viral agents for acute severe acute hepatitis (entecavir 0.5- 1 mg per day or tenofovir disoproxil 245 mg per day or Tenofovir alafenamide 25 mg per day) has been demonstrated to be effective in decreasing mortality rate (Stravitz 2019). Moreover, there is no effective anti-viral medication against HAV, and the most often used anti-viral for HEV is ribavirin (up to 1200 mg per day per body weight) (Gabrielli 2023).

ALF can be caused by viruses other than the conventional A- E viral hepatitis viruses, such as herpes simplex virus (HSV), CMV, EBV, VZV, and Dengue virus. Disseminated primary HSV (type 1 or 2) infections or reactivation secondary to the use of various monoclonal antibodies (e.g., tocilizumab) has been shown to be a cause of ALF, with nearly 90% mortality rates if untreated (Busani 2021, Chaudhary 2017). The absence of mucocutaneous lesions may make the diagnosis more difficult. The standard treatment for HSV-induced ALF is intravenous acyclovir with a dose of 10 mg/ kg three times per day.

Autoimmune related

Earlier accurate diagnosis and initiation of steroid treatment can reduce the need for emergent liver transplantation in individuals with acute onset severe AIH patients. However, given the lack of precise diagnostic markers, the absence of classical autoimmune markers in the majority of the cases (almost 40% seronegativity rates), the difficulties in obtaining a liver biopsy, the significant limitations in applying the standard AIH diagnostic scoring systems to the acute settings, and the confusion with prior suspicious drug usage may prevent timely initiation of therapy (Weiler-Normann 2014). Even though there are still some debates about the definition of responsiveness, the treatment of AIH-induced ALF should begin as soon as underlying sepsis is excluded. The standard of care is administration of intravenous methylprednisolone 1-2 mg/kg per day.

Amanita intoxication

Administering activated charcoal enterally for gastrointestinal decompensation, accompanied by silibinin intravenously (20- 50 mg/ kg per day) as an amatoxin uptake inhibitor, are the major modalities to fight against Amanita phalloides-related poisoning (Olano 2021). Without obtaining urine test positivity for amatoxins, particularly in spring and early summer, the treatment should be initiated based on the mushroom consumption history. The first 24 hours are important for initiating treatment for the greatest efficacy, however since the days of 2-4 are critical for developing irreversible liver failure, monitoring these patients closely and transferring them to an institute capable of emergent liver transplantation is critical (Lemmer 2023).

Wilson disease

The presence of prominently high bilirubin levels alongside low alkaline phosphatase, relatively low transaminases with reduced hemoglobin levels secondary to Coomb's negative hemolysis, and cholinesterase activity may raise the suspicion of Wilson disease without awaiting the typical clinical presentation of Wilson disease. Because the classical treatment options for Wilson's disease, chelators and zinc tablets, are ineffective in the setting of ALF due to time limitation to take in action, practically almost all patients die without liver transplantation (Lee 2009). This uncommon reason for ALF, reportedly 1% in the US, is an autosomal recessive disease (Stravitz 2023).

Acute fatty liver of pregnancy

It is an uncommon (in 1 out of 7000-15000 pregnancies), but potentially fatal obstetric complication that typically seen in the third trimester of the pregnancy (Verma 2021). The diagnosis is determined when 6 out of 14 Swansea criteria met, and extreme precautions, including immediate delivery regardless of gestational age, should be taken. Newborns should be monitored for hypoglycemia and fatty liver carefully, while mothers should be monitored for liver failure, requiring emergent liver transplantation. Both mom and newborn may undergo long-chain 3-hydroxyacyl-coenzyme A dehydrogenase enzyme deficiency afterward.

Budd- Chiari syndrome

This rare cause of ALF, around 1%, occurs in the context of underlying hereditary or acquired hypercoagulable state (one-third), or secondary to oral contraceptive use or abdominal trauma, or idiopathic (one-fifth) (Stravitz 2023, Parekh 2017). Therefore, diagnostic investigations should

include myeloproliferative disorders, which vary from 30% to 50% of Budd-Chiari syndrome cases, and of utmost importance, the search for an undiagnosed malignancy before moving forward to emergent liver transplantation (Costa 2020).

Once the diagnosis of Budd-Chiari syndrome is established, the general standard of care is initiation of long-term anticoagulation therapy with low molecular weight heparin followed by vitamin K antagonists, if there is no contraindication such as pregnancy. If attempts to reduce the portal system outflow pressure with trans-jugular intrahepatic portosystemic shunt (TIPS) placement fail and ALF progresses, emergent liver transplantation is inevitable. Despite the advances in treatment modalities, even hospital mortality was almost 60%, and the classical scoring systems (MELD and King's College) were found to be inaccurate in predicting the survival of these patients with Budd-Chiari syndrome (Parekh 2017).

In addition to Continues Renal Replacement Therapy (CRRT), which has been linked to an improved neurological and overall outcome if initiated earlier, there are certain artificial liver support systems, promising plasma exchange therapy, and developing stem cell therapies (Lemmer 2023; Stravitz 2023). The common characteristic of these modalities is their non-etiology-specific features. They should be considered as part of the overall ALF management strategy.

Despite the fact that acute kidney injury is not rare in ALF patients, the success of CRRT is independent of AKI occurrence, and defined as efficacious in the context of sustained high ammonia levels (>150 mmol/L) (Cardoso 2018, Nanchal 2020, Tsipotis 2015). Albumin-bound toxin-adsorbing systems such as MARS and Prometheus could also be beneficial. However, given the conflicting data in the literature, it could be considered a bridge therapy to liver transplantation, particularly under clinical trials (Tsipotis 2015). Circuit thrombosis could be a possible issue to deal with when it comes to these systems.

An alternative to these liver support systems with the capacity to adsorb large amounts of protein-bound toxins is plasma exchange therapy (Stravitz 2023). Likely related to its capability to decrease the amount of damage-associated molecular patterns and the impact on monocyte function, plasma exchange was found to improve overall survival, even in patients who are too sick to undergo liver transplantation (Larsen 2016). MARS and plasma exchange were shown to be beneficial as a bridge to liver transplantation in Wilson disease patients (Jindal 2022). Given the high mortality rate of ALF presentation of Wilson disease, identifying even a bridge therapy toward emergent liver transplantation is important.

To enhance liver cell regeneration, adipose-derived stem cells are being used as promising hepatocyte cell sources and to enrich the immunological environment in individuals, whereas allogeneic macrophages were found to be limiting necrosis via increased clearance of apoptotic and necrotic cells in the liver in a mouse model (Götze 2019, Lewis 2020).

Liver transplantation

The main goal of ALF treatment is to prevent death and improve transplant-free survival. Access to emergent liver transplantation in the setting of ALF necessitates major resources, such as institutions with specialized human resources and advanced units, long-term follow-up with close social and medical support, and useful organ donors. The pressing concern for high-income countries is the limited number of liver donors. There are ongoing efforts to broaden the donor criteria by accepting livers from persons with advanced steatosis, as well as livers from circulating death donors, or by employing split grafts or living donors (Sharma 2022). While the percentage of living liver donors increased from 2.3% to 5% between 2017 and 2020 in the United States, the global average is 23% (Terrault 2023). Applying mechanical liver perfusion to increase graft viability and decrease posttransplantation complications has the potential to impact on the liver transplantation process (Da Sousa Silva 2022).

In other words, emergent liver transplantation is a game changer, particularly for ALF patients who do not respond to the standard of care. Predicting the outcome and taking precautions towards emergent liver transplantation in an earlier setting is an important step in the management of ALF. Therefore, the necessity of emergent liver transplantation should be assessed every day starting from admission day until the day of discharge.

It should be taken into account that, irrespective of etiology, overall survival in the context of ALF is around 65- 70%, with acetaminophen-induced ALF representing the highest possibility of transplantation-free recovery as well as the highest risk of death in the waitlist (Reddy et al. 2016). The transplant-free survival dropped to 20-30% with the etiologies of DILI, autoimmune, and HBV (Stravitz 2023).

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