Management of Acute and Acute-on-Chronic Liver Failure in the ICU
CCM and EASL 2023 Guidelines

Acute liver failure (ALF)

Defined by the presence of acute liver injury, hepatic synthetic dysfunction (elevated INR >1.5), and encephalopathy within 26 weeks of the first symptoms of liver disease in a patient without evidence of chronic liver disease.

Acute on chronic liver failure (ACLF)

Clinical syndrome characterized by acutely decompensated cirrhosis resulting in one or more extrahepatic organ failures.

- ACLF is caused by an excessive systemic inflammatory response triggered by precipitants that are clinically apparent or not.
    - Common precipitants: infection, severe alcohol-related hepatitis, GI bleed, sedatives, and drug-induced AKI.
- The presence of organ failure distinguishes ACLF from acute decompensation of cirrhosis (acute development of ascites, variceal bleeding, and hepatic encephalopathy). See figure 1.

Prognosis

Assessment of the risk of death

- The risk of death should be evaluated 3-7 days after starting full organ support and not at admission. See figure 2.

Potential rules for stopping organ support

- The presence of 4 or more organ failures or a CLIF-C ACLF score (available in MDCalc) >70 points 3-7 days after ICU admission should lead to a re-evaluation of the adequacy of maintaining organ support in the absence of liver transplant options.

Neurology Section

Treatment of Hepatic Encephalopathy

- Treatments with lactulose, rifaximin, and L-ornithine L-aspartate (LOLA) are recommended in critically ill ACLF patients with hyperammonemia.
    - Use lactulose as first-line agent in critically ill ACLF patients.
    - Use oral rifaximin as adjunctive therapy in critically ill patients ACLF patients with overt hepatic encephalopathy.
    - Suggest using LOLA (provides substrates for both ureagenesis and glutamine synthesis) in critically ill ACLF patients with overt hepatic encephalopathy (conditional recommendation, very low quality of evidence).
- Lactulose, rifaximin, and LOLA used in ACLF, have not demonstrated benefit in ALF.

Treatment of intracranial Hypertension (ICH)

Cerebral edema and ICH are common in ALF but not in ACLF. There is no evidence supporting the need for ICP monitoring.

- Unlike ACLF, ALF patients are not preconditioned to cope with hyperammonemia or SIR and are more susceptible to ICH.

Risk factors for ICH include:

- Severe hyperammonemia defined as >150 umol/L.
- III-IV high-grade hepatic encephalopathy.
- Evidence of multiple organ failure.

CRRT

- Usually delivered over 24 h, remains the first-line treatment for severe hyperammonemia and is often used in the absence of AKI.

Plasma exchange

- Suggest using plasma exchange for severe hyperammonemia in ALF (conditional recommendation, very low quality of evidence).
    - Typical plasma exchange treatment 1 to 1.5 times the patient's estimated plasma volume, approximately 3 L in an average sized adult for 3 consecutive days.
    - Descriptions of the safety and feasibility of the combined CRRT and plasma exchange are limited to case reports and case series.

3% hypertonic saline

- Suggest using 3% hypertonic saline in critically ill ALF patients who are at risk of developing intracranial hypertension to maintain sodium levels between 145 and 155 mmol/L (conditional recommendation, low quality of evidence).

Infectious Diseases Section

- Antibiotic prophylaxis in critically ill ACLF patients with any type of upper gastrointestinal bleeding (UGIB).
    - Typically, third generation cephalosporins/ceftriaxone.
- Empirical antifungal therapy (mainly echinocandins) in patients with ACLF- cirrhosis associated immunodeficiency and septic shock at risk of fungal infections.
    - Prolonged ICU stay, broad-spectrum antibiotics, TPN, DM, and renal replacement therapy
    - The empirical strategy should be followed by a rapid de-escalation if fungi are not identified
        - Two negative determinations of 1,3-b-D-glucan in blood samples can be used to safely discontinue antifungals.
- SBP treatment
    - Use albumin in critically ill ACLF patients with SBP.
    - Not performing large volume paracentesis (LVP) defined as removing greater than 4L of ascitic fluid in critically ill ACLF patients with SBP.
        - Although can be mitigated with albumin as a plasma expanders (8 g/L ascites removed) LVP may induce circulatory dysfunction.
    - Use broad spectrum antibiotic agents for the initial management of SBP in critically ill ACLF patients.
        - Third generation cephalosporins/ceftriaxone as the initial empirical treatment to low-risk community acquired SBP patients.

        - Piperacillin/Tazobactam and vancomycin as the initial empirical treatment to high-risk community acquired SBP patients (there is a trend of increased MRSA, VRE, and ESBL).
        - Risk factors associated with multidrug resistant SBP include:
            - Advanced liver disease.
            - Severe critical illness.
            - Receiving prophylactic antibiotics.
- Hepatitis B infection
    - In patients with HBV-related ACLF, the use of nucleotide analogues reduces mortality and should be started immediately
    - Antiviral therapy with a nucleotide analogue may be beneficial in patients with acute liver failure from acute hepatitis B virus infection.

Gastroenterology Section

- Recommend performing EGD no later than 12 hours of presentation in critically ill ACLF patients with portal hypertensive bleeding.
- Use of proton pump inhibitors in portal hypertensive bleeding.
- Use octreotide in portal hypertensive bleeding.
- TIPS for variceal bleeding.
    - Both the CCM and EASL guidelines recommended TIPS for recurrent variceal bleeding for patients with ACLF who do not have a contraindication.
    - The EASL guidelines recommended considering both pre-emptive and rescue TIPS and the CCM although in favor stated that continues to be challenging.
    - The Baveno Consensus Conference recommends the use of pre-emptive TIPS within 24-72 hours in patients with Child-Pugh class C <14 points or Child-Pugh class B >7 and active bleeding at initial endoscopy or HVPG >20 at the time of bleeding.
    - In patients with ACLF, the presence of hepatic encephalopathy or hyperbilirubinemia should not be considered an absolute contraindication to TIPS.
- Large volume paracentesis in intra-abdominal hypertension in critically ill ACLF patients with tense ascites and intraabdominal hypertension or hemodynamic, renal, or respiratory compromise.
- Alcohol-related hepatitis
    - The EASL do not recommend corticosteroids in patients with severe alcohol-related hepatitis and ACLF-3, nor in patients with uncontrolled bacterial infection.
- Autoimmune hepatitis (AIH)
    - The evidence for the role of corticosteroids in patients with AIH and ACLF is very limited
    - The benefit-risk ratio of the introduction of corticosteroid treatment should be evaluated on a case-by-case basis but corticosteroids should be avoided in case of concomitant uncontrolled infection
- The routine use of extracorporeal liver support or plasma exchange in ACLF is not recommended outside investigative trials
    - Although albumin dialysis can improve the severity of hepatic encephalopathy, there is no evidence it improves survival.
- Oral intake should be preferred whenever possible; if oral intake is not possible, enteral nutrition ideally using a naso-jejunal tube should be attempted.

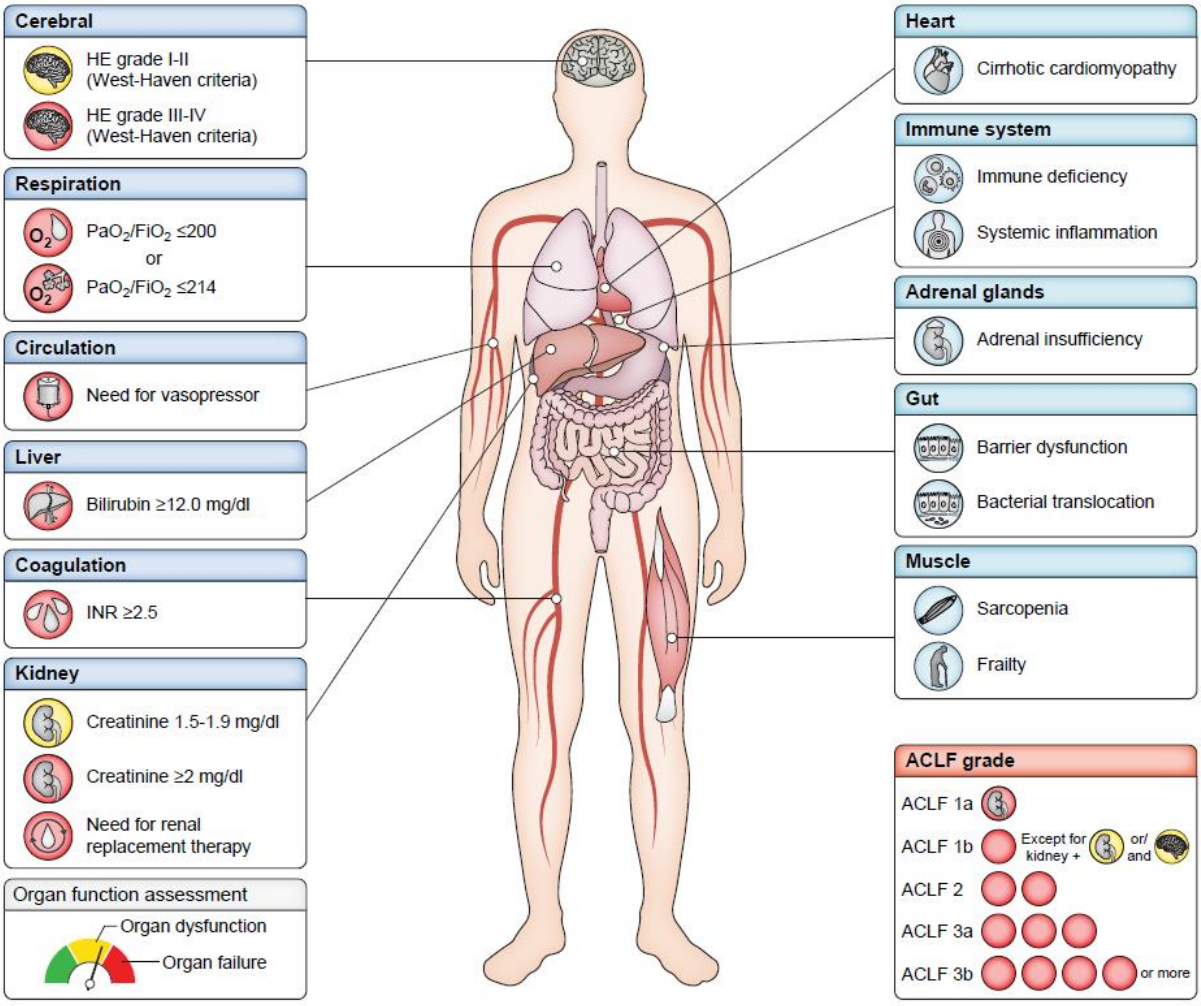
    - Should be started within 24–48 hours of the hospitalization
    - If enteral nutrition is not tolerated, parenteral nutrition can be used as for other critically ill patients
    - Refeeding syndrome which is characterized by hypophosphatemia, hypokalemia and hypomagnesemia
        - Common in patients with ACLF in setting of alcohol abuse and treatment with insulin and diuretics
        - Should be prevented, recognized early, and treated, since it can lead to fatal complications
    - Use of non-selective beta-blockers (NSBBs) patients with ACLF
        - In patients with cirrhosis the use of NSBBS is associated with a significant reduction in the risk of variceal bleeding or of other decompensating events.
        - The decision to continue using NSBBs in patients who were receiving them should be made a case-by-case basis with careful dose titration based on close monitoring of the mean arterial pressure and renal function
        - No specific study has addressed the safety and efficacy of starting NSBBs in patients who recover from an episode of ACLF. Therefore, the effect of NSBBs on outcomes is not known
        - If the decision is to initiate NSBBs should be done cautiously, with close monitoring of blood pressure
        - Dose increases should be guided by the mean arterial pressure; below a threshold of 65 mmHg, beneficial effects are limited
- The use of statins may decrease portal pressure and improve overall survival and should be encouraged in patients with advanced chronic liver disease
- An early assessment for liver transplantation should be proposed for all patients with severe ACLF

Summary of Management of ALF – not discussed in the 2023 CCM

- Balanced IV crystalloids to keep MAP >65 mmHg and UO >0.5 ml/Kg/h.
- If vasopressors are necessary, norepinephrine is preferred.
- If patients with ALF require renal replacement therapy, CRRT is recommended to limit the changes in cardiac index, mean arterial pressure, and increase in ICP that can occur with intermittent dialysis.
- Intubation should be considered by hepatic encephalopathy grades ≥3 to manage the airway.
- Adequate sedation and pain control are essential to limit intracranial hypertension; however, sedatives and narcotics may worsen hepatic encephalopathy. Propofol is recommended over benzodiazepines. Analgesics with a shorter half-life such as fentanyl are preferred over those with longer half-lives.
- Vitamin K intravenously should be given.
- Prophylactic transfusion of FFP is not recommended except in the case of invasive procedures and profound coagulopathy.
- A platelet count of 10 to 20 000/mm3 is generally safe unless an invasive procedure is planned in which case platelets should be transfused for a goal of >50.000.
- Cryoprecipitate should be given if fibrinogen <100 mg/dL for invasive procedures or active bleeding.
- Gastrointestinal prophylaxis with proton pump inhibitor is recommended.

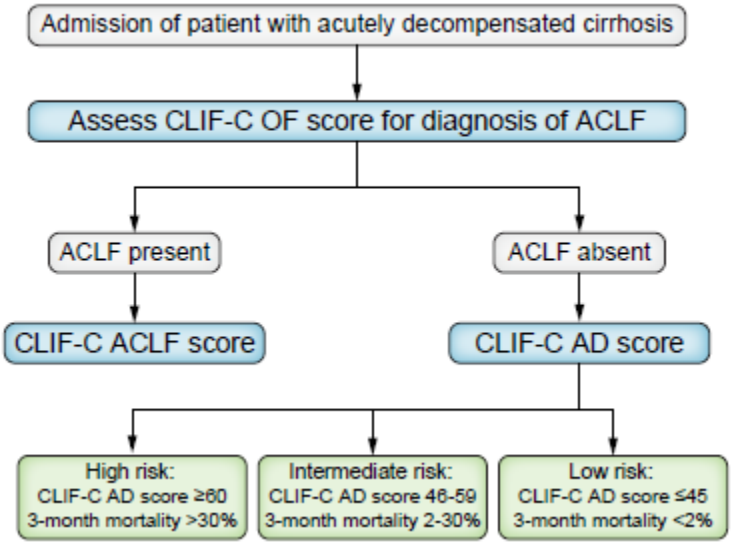
- Prophylactic antibiotics are not routinely recommended although should be considered in patients with worsening HE, SIRS, or hypotension.
- N-acetylcysteine (NAC) is the drug of choice for the treatment of acetaminophen-related ALF and is also considered beneficial for non-acetaminophen-related ALF.
    - NAC IV infusion within 72 h of suspected ingestion: 150 mg/kg over 1 hour followed by an infusion of 12.5 mg/kg/h for 4 hours, then 6.25 mg/kg/h for at least 16 hours.

Figure 1. Organs systems involved in ACLF.



On the left are shown each of the 6 organ systems explored by CLIF-C OF scoring system; the red color indicates the criteria for organ failure and the orange color indicates criteria for kidney or cerebral dysfunction.
Box in the right bottom corner shows the criteria established by the EASL-CLIF Consortium to define the presence of ACLF and its grade. On the right, in light blue, are shown additional organ systems whose function is altered in patients with ACLF.
Journal of Hepatology, July 2023. https://doi.org/10.1016/j.jhep.2023.04.021

Figure 2. Algorithm for the sequential use of the EASL-CLIF consortium predictive scores in patients with cirrhosis admitted to hospital with acute decompensation.



Journal of Hepatology, July 2023. https://doi.org/10.1016/j.jhep.2023.04.021