**DEFINITION**

Acute on chronic liver failure (ACLF) is a common entity in cirrhotics hospitalized for acute decompensation. Diagnostic criteria include acute decompensation of some form, presence of organ failure, and high 28 day mortality rate exceeding 15%. It is a distinct and separate entity from acute decompensation alone. [1]

**Comparison of ALF versus ACLF versus decompensated cirrhosis [2]**

**ACUTE DECOMPENSATION IS DIFFERENT THAN ACLF**

Includes acute development of large ascites (either first episode or new episode) within 2 weeks but not those with chronic refractory ascites, acute development of hepatic encephalopathy (either first episode or new episode after previous good control), acute GI hemorrhage (upper or lower), or development of any bacterial infection including SBP.

**CLINICAL CHARACTERISTICS OF ACLF**

Patients with ACLF tend to be younger and more frequently alcoholic. Precipitating events leading to higher occurrence of ACLF include bacterial infections (SBP and pneumonia), active alcoholism within past 3 months, large volume paracentesis without use of albumin resulting in hypotension/hypoperfusion.
of the liver, TIPS, major surgery inducing an inflammatory state or hypoperfusion of the liver, and acute toxic or viral hepatitis. However, in approximately 40% of patients with ACLF, no precipitating event is identifiable although the patients often present with a septic-like or inflammatory response. [1]

Patients with ACLF also have a higher degree of systemic inflammation as evidenced by increased WBC and CRP regardless of whether there is an active bacterial infection. [1] CRP should be done at baseline in all cirrhotics with a change in their clinical status.

Prior decompensated cirrhosis is NOT needed in order to develop ACLF. Approximately half of patients who develop ACLF will not have had preceding decompensated cirrhosis. Those patients who develop ACLF without preceding decompensated cirrhosis often have more severe ACLF and higher mortality.

Clinical course of ACLF [3]
Acute and chronic insults in ACLF and outcome [2]

Fig. 2 Acute and chronic insults in ACLF and outcome

What constitutes chronic insult?

- NASH
- Chronic Hepatitis
- Cirrhosis

What constitutes the acute insult?

- Hepatotrophic insults
  - Alcohol
  - Viral
  - DILI
  - Autoimmune hepatitis
  - Wilson’s

- Non hepatotrophic insults leading to primary hepatic failure
  - Infections
  - Surgery
  - Bleed

Acute-on-chronic liver failure

- Hepatic failure
  - Jaundice to ascites
  - Coagulopathy

- Extra-hepatic organ failures
  - Hepatic encephalopathy
  - Acute Kidney injury
  - Sepsis
  - Circulatory dysfunction

DIAGNOSIS OF ORGAN FAILURE

There are two “schools” of thought to define ACLF. Criteria for diagnosis are similar but differ somewhat between the American Association for the Study of Liver Disease and European Association for the Study of Liver Disease (AASLD-EASL) and the Asian Pacific Association for the Study of the Liver (APASL).

- APASL Definition: Acute hepatic insult manifesting as jaundice (bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28 day mortality.

- AASLD-EASL Definition: Acute deterioration of preexisting chronic liver disease/cirrhosis usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure.

As well, there are several scoring systems that have been developed recently to help determine organ failure and severity of illness in patients specifically with underlying cirrhosis.
The CLIF-SOFA score is a modified version of the SOFA score which is commonly used to assess severity in any patient in the ICU. This was developed as part of the CANONIC study from which the initial definition of ACLF was derived. [1]

<table>
<thead>
<tr>
<th>Organ/system</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (bilirubin, mg/dL)</td>
<td>&lt;1.2</td>
<td>≥1.2 to &lt;2.0</td>
<td>≥2.0 to &lt;6.0</td>
<td>≥6.0 to &lt;12.0</td>
<td>≥12.0</td>
</tr>
<tr>
<td>Kidney (creatinine, mg/dL)</td>
<td>&lt;1.2</td>
<td>≥1.2 to &lt;2.0</td>
<td>≥2.0 to &lt;3.5</td>
<td>≥3.5 to &lt;5.0</td>
<td>≥5.0</td>
</tr>
<tr>
<td>Cerebral (HE grade)</td>
<td>No HE</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>Coagulation (international</td>
<td>&lt;1.1</td>
<td>≥1.1 to &lt;1.25</td>
<td>≥1.25 to &lt;1.5</td>
<td>≥1.5 to &lt;2.5</td>
<td>≥2.5 or platelet count ≤20 x 10^9/L</td>
</tr>
<tr>
<td>Circulation (mean arterial</td>
<td>≥70</td>
<td>&lt;70</td>
<td>Dopamine ≤5 or</td>
<td>Dopamine &gt;5 or</td>
<td>Dopamine &gt;15 or</td>
</tr>
<tr>
<td>pressure, mm Hg)</td>
<td></td>
<td></td>
<td>dobutamine or</td>
<td>E ≤0.1 or</td>
<td>E &gt;0.1 or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>terlipressin</td>
<td>NE ≤0.1</td>
<td>NE &gt;0.1</td>
</tr>
<tr>
<td>Lungs PaO₂/FiO₂ or</td>
<td>≥400</td>
<td>≥300 to ≤400</td>
<td>≥200 to ≤300</td>
<td>&gt;100 to ≤200</td>
<td>≤100</td>
</tr>
<tr>
<td>SpO₂/FiO₂</td>
<td>≥512</td>
<td>≥357 to ≤512</td>
<td>≥214 to ≤357</td>
<td>≥89 to ≤214</td>
<td>≤89</td>
</tr>
</tbody>
</table>

NOTE: The original SOFA score is described by Vincent et al. Like the SOFA score, the CLIF-SOFA score includes subscores ranging from 0 to 4 for each of 6 components (liver, kidneys, brain, coagulation, circulation, and lungs), with higher scores indicating more severe organ impairment. Aggregated scores range from 0 to 24 and provide information on overall severity. The text in bold indicates the diagnostic criteria for organ failures (see also Supplementary Materials and Methods).

HE, hepatic encephalopathy; E, epinephrine; NE, norepinephrine; PaO₂/FiO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen; SpO₂, pulse oximetric saturation.

The CLIF-OF score is a more simplified organ function scoring system with equal mortality predictive value as the CLIF-SOFA score. [4]

The CLIF-C ACLF score is a prognostic score, which incorporates the CLIF OF score as well as age and WBC, which is used in those with a definitive diagnosis of ACLF and not simply acute decompensation. This score has been shown to be superior to MELD, MELD-Na, and CTP scores in determining mortality in those patients admitted for ACLF. [4]

\[
\text{CLIF-C ACLF} = 10 \times [0.33 \times \text{CLIF-OF} + 0.04 \times \text{age} + 0.63 \times \ln(\text{WBC}) - 2]
\]

The CLIF-C AD score is a prognostic score used in those without ACLF but presence of acute decompensation. [5]
CLIF-C AD = 10 x [0.03 x age + 0.66 x Ln(Cr) + 1.71 x Ln(INR) + 0.88 x Ln(WBC) - 0.05 x Na + 8]

An on-line calculator to determine CLIF-OF, CLIF-C ACLF, ACLF grade, CLIF-C AD and predicted death rate at specific time (1 month, 3 month, 6 month, 12 month) can be found at www.clifconsortium.com.

GRADE of ACLF [1]

Patients with higher grades of ACLF have increased number of organ failure and higher 28 day and 90 day mortality.

Patients with specific organ failures including acute kidney injury, cerebral injury manifesting as hepatic encephalopathy and refractory ascites are known to have higher grades of ACLF and thus higher mortality rates than those with other organ failures.

1. **No ACLF**: Patients with no organ failure; patients with single “non-kidney” organ failure with serum Cr <1.5 and no hepatic encephalopathy; patients with single cerebral failure with serum Cr <1.5.

2. **Grade 1 ACLF**: Patients with single kidney failure; patients with single failure of the liver, coagulation, circulation or respiration with a serum Cr 1.5-1.9 and/or mild to moderate hepatic encephalopathy; patients with single cerebral failure with serum Cr 1.5-1.9.

3. **Grade 2 ACLF**: Patients with 2 organ failures.

4. **Grade 3 ACLF**: Patients with 3 organ failures.

<p>| Table 2 |
|----------------------|----------------------|----------------------|</p>
<table>
<thead>
<tr>
<th><strong>Subgroups</strong></th>
<th><strong>Mortality rate at 28 days</strong></th>
<th><strong>Mortality rate at 90 days</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>ALD alone</td>
<td>4.7%</td>
<td>14%</td>
</tr>
<tr>
<td>ACLF grade 1</td>
<td>22.1%</td>
<td>40.7%</td>
</tr>
<tr>
<td>ACLF grade 2</td>
<td>32%</td>
<td>52.3%</td>
</tr>
<tr>
<td>ACLF grade 3</td>
<td>76.7%</td>
<td>79.1%</td>
</tr>
</tbody>
</table>

MANAGEMENT OF ACLF

Central to management of ACLF is early diagnosis given short golden therapeutic window, control of precipitating factor, if able to be identified, and support to each of the organs with failure.

- Specific management for various precipitating factors
  - Hepatitis B reactivation: Tenofovir or entecavir
  - Alcoholic hepatitis: Steroids, ?G-CSF
  - Autoimmune hepatitis flare: Steroids
DILI: Remove offending agent
Infections: Antibiotics

“Golden therapeutic window” is a short period of about one week before the onset of extra-hepatic organ failure and SIRS/sepsis in those with ACLF during which therapeutic interventions are more likely to prevent organ failure and possibly reverse underlying hepatic injury. [2]

**Hepatic Encephalopathy**

- Hepatic encephalopathy is present in about 40-50% of patients with ACLF but as opposed to those with ALF rarely develop Grade 4 hepatic encephalopathy or cerebral edema. [6]

- Hyperammonemia plays a critical role in pathogenesis of HE and cerebral edema (CE), though venous ammonia has a poor correlation with clinical status (see figure below). Arterial ammonia can be used very selectively, due to cost and painful sampling (>200g/dL associated with higher risk cerebral herniation) and incredible inaccuracy. The role of conventional treatment for HE in chronic liver disease (lactulose and/or rifaximin or sodium benzoate) remains unclear but can be considered on a case-by-case basis and treatment directed according to encephalopathy grade, not blood ammonia level. Additional therapies currently being explored include Miralax/PEG as well as probiotics. Neomycin should never be used for HE.

- **Lactulose** 30-60 ml PO every 2-6 hrs titrated to maintain 3-4 soft stools (~800ml liquid stool/day). Alternative: Lactulose 150ml enema + 350ml tap water PR every 6-8 hours.
  - Particular caution should be used to avoid over-distention of the bowel in ALF patients in need of liver transplant to reduce risk of surgical complications

- **Miralax/PEG** at a dose of 4L purge over 4 hours can be substituted for standard dose lactulose with a lower rate of ileus, pain and abdominal distension [7]

- **Rifaximin** 550mg PO/per NGT every 12 hours

- **Sodium Benzoate** 2 to 5 gm PO every 12 hours, be administered via NG tube, when given PO, best administered with a soft drink such as a sprite or coke.

- **Probiotics** VSL#3 twice daily in hospital or ICU.
  - Probiotics have been not only been shown to improve hepatic encephalopathy [8] but also reduce infections in patients that ultimately receive liver transplant [9]

**Management of Cerebral Edema (CE) & Intracranial Hypertension (ICH)**

- See ALF Protocol for specific management as cerebral edema is less common in those with ACLF compared to ALF.

**Correction of the Bleeding Diathesis**

- Patients with ACLF are often coagulopathic, but spontaneous, clinically significant bleeding is uncommon. Liver patients may have both a hyper- and hypocoagulation profile simultaneously.

- TEG is recommended to best characterize coagulopathy in this patient population so as to target appropriate factor administration and minimize transfusions that may result in unnecessary IV
volume, expense, and risk for complications. [10]

- See TEG protocol and algorithm for further details.

- TEG measures time to initial fibrin formation, rate of clot formation, quality/strength of clot, and clot lysis.

- Prophylactic FFP to improve coagulopathy in ACLF is NOT recommended, as it does not reduce the risk of significant bleeding nor transfusion requirements, obscures the trend of INR as a prognostic marker, and risks volume overload as well as TRALI (transfusion related acute lung injury).

- Cryoprecipitate is administered to keep fibrinogen in the low normal range (adjusted according to TEG results), fibrinogen tests can be ordered to supplement TEG and guide dosing of cryoprecipitate

**Infection Prophylaxis and Surveillance**

- Infection remains one of the principal causes of acute insult leading to ACLF and may be subtle in clinical presentation. Obtaining infectious evaluation including blood cultures, urinalysis/urine culture and chest X-ray is important in those with ACLF. [11]

- Empiric administration of antibiotics is recommended when infection or likelihood of impending sepsis is high (any one of the following conditions are met):
  - Progression of, or advanced stage (III/IV), hepatic encephalopathy
  - Refractory hypotension
  - Presence of systemic inflammatory response syndrome (SIRS) components (temperature >38 or <36°C, WBC >12,000 or < 4,000/mm³, pulse >90 beats/min
  - High CRP in the setting of unstable blood pressure, leukopenia, hypothermia

- Evaluate all patients for hepatoadrenal syndrome (see circulatory dysfunction section below) who have hypotension, regardless of electrolyte status. Consider hydrocortisone administration for any patient who is hypotensive and pressors are considered

- Empiric antimicrobial coverage for patients hospitalized < 72 hours
  - **Piperacillin/tazobactam** 3.375gm IV q8h (adjust for renal fxn) infused over 4 hours
  - **Vancomycin** 20-25mg/kg IV loading dose followed by vancomycin 1gm IV q12h (adjusted by pharmacy to maintain target trough ~ 15), adjust quickly for GFR under 60, Creatinine assessment is notoriously inaccurate in patients with liver failure
  - **Fluconazole** 200mg PO/IV x1 dose followed by 100mg/day

- For patients hospitalized > 72 hours and/or in those with complex medical history, ID consultation should be called for any suspected sepsis

- Remove and replace any central IV lines placed at an outside hospital

**Acute Kidney Injury**
• AKI is prevalent in a majority of patients with ACLF
  o Definition of AKI: Abrupt (within 48 hours) increase in serum Cr in more ≥0.3 mg/dL or percentage increase of serum Cr ≥50%. [12]
  o Staging of AKI [12]
    ▪ Stage 1: Increase in serum Cr ≥0.3 mg/dL or increase in serum Cr ≥1.5 to 2 fold from baseline
    ▪ Stage 2: Increase in serum Cr ≥2-3 fold from baseline
    ▪ Stage 3: Increase in serum Cr >3 fold from baseline or serum Cr ≥4 mg/dL with an acute increase of at least 0.5 mg/dL

• There is a higher prevalence, more rapid progression to tubular damage and higher mortality in those with ACLF compared to decompensated cirrhosis indicative of a different pathogenesis of renal dysfunction likely related to altered circulatory and immune dysfunction seen in those with ACLF [12]

• Patients with ACLF that develop hepatorenal syndrome are less likely to respond to vasopressors and have higher mortality than decompensated cirrhotic with hepatorenal syndrome [13]

Renal replacement therapy is required to treat fluid, electrolyte and acid-base abnormalities but does not improve outcome in hepatorenal syndrome

• Treatment of hepatorenal syndrome should include IV albumin 10-20 grams per day, SQ octreotide up to 200 mcg TID, and midodrine up to 12.5 mg TID to achieve increase in mean blood pressure of 15 mm Hg. Alternatively, if patient is in ICU, norepinephrine in addition to IV albumin can be administered [14, 15]

**Treatment of Circulatory Dysfunction**

• Ensure adequate volume resuscitation

• Indications for vasopressors
  o SBP < 90 mmHg (MAP < 65) OR to maintain a cerebral perfusion pressure (CPP) of 50 – 80 mmHg. (CPP = mean arterial pressure [MAP] - intracranial pressure [ICP]) in cases where ICP monitoring is performed

• Norepinephrine is the preferred vasopressor since it may provide a more consistent and predictable increase in cerebral perfusion than other pressors [16]

• Hepatoadrenal Syndrome:
  o Definition: Adrenal insufficiency in patients with advanced liver disease with sepsis and/or other complication. Can be present in both compensated and decompensated cirrhosis without sepsis. Can also occur in post-liver transplant patients
  o Diagnosis: Consider in any cirrhotic with hypotension refractory to vasopressors and fluid
Best diagnostic criteria are values of baseline cortisol and/or delta cortisol with Cortrosyn stimulation:
- **Definite**: Basal level <250 nmol/L
- **Probable**: Basal level <414 nmol/L and can be confirmed with a delta <250 nmol/L after stimulation test

A trial dose of hydrocortisone should be considered in patients with ACLF with persistent hypotension despite volume challenge and norepinephrine. **Hydrocortisone** 50mg IV q6h or 100mg IV q8h have been shown to improve the vasopressor response to norepinephrine in hypotensive patients with sepsis and ACLF [17]

- Vasopressin and analogues are NOT recommended, as they directly cause cerebral vasodilation and may exacerbate intracranial hypertension [18]

- Epinephrine is NOT recommended. Epinephrine has been shown to decrease mesenteric blood flow in severe septic shock, and therefore may compromise hepatic blood flow in patients with ACLF. [19]

**Mechanical Ventilation**

- In general, the lowest level of PEEP that achieves adequate oxygenation should be applied in patients with ACLF.

**Sedation and Analgesia**

- **Analgesia/Anxiolysis**: Controlling pain and minimizing agitation is important in controlling ICP. Fentanyl continuous infusion is the analgesic of choice in ALF if needed.

- **Propofol** is relatively short-acting, decreases cerebral blood flow and lowers intracranial pressure. As such, it is generally considered the preferred agent for sedation in ALF when necessary.

- Avoid benzodiazepines, long-acting narcotics and central acting antiemetics.

**Liver specific therapies**

- Liver dialysis, or molecular adsorbent recirculating system, has recently been shown to be effective as a bridge to liver transplant in those with ACLF. [20] However, although it has been shown to reduce bilirubin and creatinine levels and improve hepatic encephalopathy when compared to standard therapy in those with ACLF, it was not found to improve transplant free survival or mortality rates. [21]

- Liver transplant is the only curative option that can salvage ACLF patients. Several small studies have shown good outcomes with greater than 80% 5 year survival in those with ACLF undergoing liver transplant. However, data in those undergoing liver transplant for ACLF is limited and the timing and indication for transplantation is not yet well defined. In one recent retrospective study, liver transplant was feasible in less than 25% of ACLF patients evaluated for liver transplant mainly due to high percentage with infections/sepsis. [22] A recent study proposed an algorithm for patient selection in those with ACLF who would benefit from liver transplant which included...
those with MELD >25, single organ failure only without sepsis and thus early referral (less than 7
days following diagnosis of ACLF) is crucial. [23]

- G-CSF, via restoration of neutrophil function which is felt to be dysfunctional in ACLF, has been
  shown to improve survival, improve liver function (CTP, MELD and SOFA scores), and prevent
  sepsis, hepatorenal syndrome and hepatic encephalopathy in patients with ACLF. [24]
  Therefore, G-CSF use should be strongly considered in those who present with ACLF. G-CSF
  plus darbopoietin has also been shown to improve survival at 12 months in those with
decompensated cirrhosis and should be considered in these patients. [25]

  o G-CSF 5 mcg/kg SQ daily for 12 days in those with ACLF
  o G-CSF 5 mcg/kg/d for 5 days and then every third day for total of 12 doses as well as
darbopoietin 40 mcg/week for 4 weeks in those with decompensated cirrhosis

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