ACUTE ON CHRONIC LIVER FAILURE
When and How to Approach

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INTRODUCTION

ACUTE LIVER FAILURE (ALF)

LIVER FAILURE

ACUTE-ON-CHRONIC LIVER FAILURE (ACLF)

CHRONIC DECOMPENSATION OF END-STAGE LIVER DISEASE

## DEFINITION

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Patient</td>
<td>With previously diagnosed or undiagnosed chronic liver disease (CLD)</td>
<td>With pre-existing chronic liver disease (CLD)</td>
</tr>
<tr>
<td>Manifestations</td>
<td>Jaundice &amp; coagulopathy</td>
<td></td>
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<tr>
<td>Complication</td>
<td>Ascites and/or encephalopathy within 4 weeks</td>
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<tr>
<td>Cause of mortality</td>
<td></td>
<td>Multi-system organ failure</td>
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</tbody>
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Jalan, R. et al; “Acute-on-chronic liver failure”; Journal of Hepatology; 2012; vol. 57:1336-1348
CONCLUSION

- ACLF is a distinct syndrome from AD based on the presence of organ failure(s), high mortality rate, age, precipitating events, and systemic inflammation.

- ACLF mortality is associated with loss of organ function and high leukocyte counts.

- ACLF is especially severe in patients with no prior history of AD.

Moreau, R. et al; “Acute on Chronic Liver Failure is a Distinct Syndrome that Develops in Patients with Acute Decompensation of Cirrhosis”, Gastroenterology; 2013; 144:1426-1437
The following are central in the definition of ACLF, whatever the precipitating event:

1. Existence of a precipitating factor
2. Rapid deterioration in liver function
3. Initiation of extra-hepatic organ failure(s)
4. High in-hospital or early mortality (28 days)

Moreau, R. and Durand F.; “Acute on Chronic Liver Failure”; 2011
Moreau, R., et al; “Acute on Chronic Liver Failure: Is the definition ready for prime time?”; Clinical Liver Disease; June 2013 Vol. 2; No. 3.
Sarin, S.K. et al; “Acute on Chronic Liver Failure Consensus Recommendations of APASL”; Hepatology International
Importance of ACLF

- MELD score based allocation system in liver transplantation
- Relies on a ‘sickest first’ policy
- Offers opportunity for ACLF patients to receive an allograft based on disease severity
- Bridges ALCF patients to ‘salvage’ transplantation

MELD Score (Model For End-Stage Liver Disease) (12 and older)
Calculates the MELD score to quantify end-stage liver disease for transplant planning.

- Serum Bilirubin
- INR
- Serum Creatinine
- Has the patient had dialysis at least twice in the past week? Yes

MELD Score

Model for End Stage Liver Disease (MELD)

MELD score = 10 \times [0.957 \times \log e (\text{creatinine}) + \log e (\text{bilirubin}) + 1.12 \times \log e (\text{INR})] + 6.43

3 month mortality according to MELD score

- MELD score
  - <=9
  - 10-19
  - 20-29
  - 30-39
  - >=40
- Hospitalized pt.
  - 4%
  - 27%
  - 76%
  - 83%
  - 100%
- Outpatient cirrhotic
  - 2%
  - 6%
  - 50%

Moreaur, R. and Durand F.; “Acute on Chronic Liver Failure”; 2011
Acute-on chronic liver failure: diagrammatic representation of the clinical concept.

DIFFERENCE BETWEEN ACLF & ESLD (PATHOGENESIS)

- **Compensated Cirrhosis**
  - Precipitating events:
    - Acute hepatitis
    - Drug
    - Virus
    - Ischemia

  - Acute on Chronic Liver Failure
    - Multiorgan Failure
      - Sepsis
        - Death
        - Recompensation

- ** Decompensated Cirrhosis**
  - Precipitating events:
    - Variceal bleeding
    - Infection

  - Sepsis
    - Multiple Organ Failure
      - Death

**End Stage Liver Disease**

*Moreaur, R. and Durand F.; “Acute on Chronic Liver Failure”; 2011
Jalan, R. et al; “Acute-on-chronic liver failure”; Journal of Hepatology; 2012; vol. 57:1336-1348*
Pathophysiology

PIRO concept of acute-on-chronic liver failure

**P**redisposition → Severity of cirrhosis

**I**njury → Precipitating event

**R**esponse → Inflammation

**O**rgan → Organ failure

**Assessment**
- Etiology
- Pugh score
- MELD
- [Biomarkers]

**Intervention**
- Early identification
- Risk stratification
- Preventive strategies
- [Novel interventions]

- Rapid intervention to treat event
- Bundles of care
- [Novel interventions]

- Vigilance, monitoring
- Goal directed approaches
- [Biomarkers and novel interventions]

- Intensive care, organ support
- Liver transplantation
- [Liver support, stem cell therapies]

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REMARKABLE FEATURES OF ACLF

- Marked persistent systemic inflammatory response (SIRS)
  - associated with activation of the inflammatory cytokine cascade
  - Causing transition from stable cirrhosis to ACLF.

- Proinflammatory cytokines
  - mediate hepatic inflammation, apoptosis and necrosis of liver cells, cholestasis and fibrosis.

- The presence of SIRS is associated with more severe encephalopathy, associated infection, renal failure and poor outcome.

- Central role of inflammation and neutrophil dysfunction in organ failure

Liver failure / bacterial translocation

- Endotoxemia
- Reduced protein/complement synthesis
- Reduced immune surveillance
- Reduced albumin function

Immune paralysis

Innate immunity
- Neutrophils: phagocytic defect
- Monocytes: DR loss
- NK cells

Adaptive immunity
- T-cell exhaustion
- Inability to proliferate
- Increased apoptosis

SIRS: Systemic inflammatory response

CARS: Compensatory anti-inflammatory response

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DIAGNOSTIC CRITERIA

MELD Score (Model For End-Stage Liver Disease) (12 and older)

- Child-Turcotte-Pugh Classification for Severity of Cirrhosis
  - **Clinical and Lab Criteria**
  - **Points***
    - **1**
      - Encephalopathy: None
      - Ascites: < 2
      - Bilirubin (mg/dL): < 3.5
      - Prothrombin time: < 4
      - International normalized ratio: < 1.7
    - **2**
      - Encephalopathy: Mild to moderate (grade 1 or 2)
      - Ascites: 2-3
      - Bilirubin (mg/dL): 2.8-3.5
      - Prothrombin time: 4-6
      - International normalized ratio: 1.7-2.3
    - **3**
      - Encephalopathy: Severe (grade 3 or 4)
      - Ascites: > 3
      - Bilirubin (mg/dL): > 3.5
      - Prothrombin time: > 6
      - International normalized ratio: > 2.3
  - **Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**
    - **Class A**: 5 to 6 points (least severe liver disease)
    - **Class B**: 7 to 9 points (moderately severe liver disease)
    - **Class C**: 10 to 15 points (most severe liver disease)

- **MELD Score**
  - Calculates the MELD score to quantify end-stage liver disease for transplant planning.

  **Serum Bilirubin**
  - mg/dL
  - **INR**
  - **Serum Creatinine**
  - mg/dL
  - **Has the patient had dialysis at least twice in the past week?**
    - **Yes**
  - **MELD Score**
    - [Click!]

- **The APACHE II Severity of Disease Classification System**

<table>
<thead>
<tr>
<th>Physiologic Variable</th>
<th>High Abnormal Range</th>
<th>Low Abnormal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature - rectal (°C)</td>
<td>≥41°</td>
<td>39 to 40.6°</td>
</tr>
<tr>
<td>Mean Arterial Pressure - mm Hg</td>
<td>≥160</td>
<td>110 to 119</td>
</tr>
<tr>
<td>Heart Rate (ventricular response)</td>
<td>≤180</td>
<td>140 to 149</td>
</tr>
<tr>
<td>Respiratory Rate (non-ventilated or ventilated)</td>
<td>≥50</td>
<td>35 to 49</td>
</tr>
<tr>
<td>Oxygenation: AaDO2 or PaO2 (mm Hg) a. FIO2 ≥0.5 record AaDO2 b. FIO2 &lt;0.5 record PaO2</td>
<td>≥500</td>
<td>350 to 499</td>
</tr>
<tr>
<td>Arterial pH (preferred)</td>
<td>≥7.7</td>
<td>7.4 to 7.69</td>
</tr>
<tr>
<td>Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABG)</td>
<td>≥52</td>
<td>41 to 51.9</td>
</tr>
<tr>
<td>Serum Sodium (mEq/l)</td>
<td>≥160</td>
<td>155 to 159</td>
</tr>
<tr>
<td>Serum Potassium (mEq/l)</td>
<td>≥7</td>
<td>6 to 6.9</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl) Double point score for acute renal failure</td>
<td>≥3.5</td>
<td>3.4 to 3.9</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>≥40</td>
<td>39.9 to 39.9</td>
</tr>
<tr>
<td>White Blood Count (total/mm³) (in 1000s)</td>
<td>≥40</td>
<td>39.9 to 39.9</td>
</tr>
<tr>
<td>Glasgow Coma Score (GCS) Score = 15 minus actual GCS</td>
<td>≥40</td>
<td>20 to 29.9</td>
</tr>
</tbody>
</table>

  - **A. Total Acute Physiology Score (sum of 12 above points)**
  - **B. Age points (years) <44=0; 45 to 54=2; 55 to 64=3; 65 to 74=4; >75=5**
  - **C. Chronic Health Points (see below)**

  **Total APACHE II Score (add together points from A+B+C)**

### Table 1. CLIF-SOFA Score

<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 ≤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 normalized ratio)</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 × 10^9/L</td>
</tr>
<tr>
<td>Circulation (mean arterial pressure, mm Hg)</td>
<td>≥70</td>
<td>&lt;70</td>
<td>Dopamine ≤5 or dobutamine or terlipressin</td>
<td>Dopamine &gt;5 or E ≤0.1 or NE ≤0.1</td>
<td>Dopamine &gt;15 or E &gt;0.1 or NE &gt;0.1</td>
</tr>
<tr>
<td>Lungs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO/FiO₂ or</td>
<td>&gt;400</td>
<td>&gt;300 to ≤400</td>
<td>&gt;200 to ≤300</td>
<td>&gt;100 to ≤200</td>
<td>≤100</td>
</tr>
<tr>
<td>SpO₂/FiO₂</td>
<td>&gt;512</td>
<td>&gt;357 to ≤512</td>
<td>&gt;214 to ≤357</td>
<td>&gt;89 to ≤214</td>
<td>≤89</td>
</tr>
</tbody>
</table>

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**Systemic Inflammatory Response Syndrome (SIRS)**

When 2 of the following criteria are met:

- Body temperature $>38^\circ\text{C}$ or $<36^\circ\text{C}$
- Heart rate $>90\text{bpm}$
- Respiratory rate $>20\text{cpm}$ or arterial hypocapnia $<32\text{mmHg}$
- WBC $>12,000/\mu\text{L}$ or $<4,000/\mu\text{L}$ or immature forms $>10\%$
## Most common promising indicators of ACLF and their association with mortality extracted from 13 studies

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Association/Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. AGE</td>
<td>Positively associated with mortality</td>
</tr>
<tr>
<td>2. BILIRUBIN</td>
<td>Cut-off: 23.1mg/dL</td>
</tr>
<tr>
<td>3. MELD</td>
<td>Cut-off: ≥ 30</td>
</tr>
<tr>
<td>4. HEPATIC ENCEPHALOPATHY</td>
<td></td>
</tr>
<tr>
<td>5. INR</td>
<td>Cut-off 1.5 - 2</td>
</tr>
</tbody>
</table>

Wlodzimirow, KA, et al; “A Systematic Review on prognostic indicators of acute on chronic liver failure and their predictive value for mortality.”; Liver International; 2012; 40-52
MANAGEMENT

TREATMENT OF THE PRECIPITATING EVENT

- BACTERIAL SEPSIS
- SEVERE ALCOHOLIC HEPATITIS
- ACUTE VARICEAL HEMORRHAGE
- HEPATITIS B VIRUS
- DRUG INDUCED ACLF

MANAGEMENT OF ORGAN FAILURES

- CIRCULATORY FAILURE
- ACUTE RENAL FAILURE
- ADRENAL FAILURE
- RESPIRATORY FAILURE
- HEPATIC ENCEPHALOPATHY / LIVER FAILURE
- COAGULATION FAILURE

Moreaur, R. and Durand F.; “Acute on Chronic Liver Failure”; 2011
Antiviral therapy should be initiated in patients with ACLF due to hepatitis B. (3b, C)

Lamivudine may be used for a short-term period, but other drugs such as entecavir or tenofovir may be preferred in view of the long-term need for viral suppression with low frequency of drug resistance. (3b, C)

Prophylactic therapy is recommended for HBsAg-positive patients undergoing chemotherapy. (3b, C)

There is insufficient data to recommend antiviral therapy for HBsAg-negative and anti-HBc-positive patients. (3b, C)
Use of liver support devices in ACLF

- Molecular adsorbent recirculating system (MARS) does not offer any survival benefit to patients with ACLF. (1a, A)

- Role of MARS as a bridge to transplantation in patients with ACLF is still to be defined. (2b, B)

- MARS may improve hepatic encephalopathy in patients with ACLF. (1a, A)

- Plasma exchange needs further validation for the treatment of ACLF. (3b, C)

Liver Transplant in patients with ACLF

Criteria when to transplant

1. Liver transplantation should be performed according to prognosis scores suggesting death within the next 3 months. (2b, B)

2. Earlier intervention if HRS develops. (2b, B)

2.1 Liver transplantation should not be performed when there is HRS with anuria. (3b, C)

2.2 Results of liver transplantation are better when HRS has been partially controlled by terlipressin. (2b, B)

# Criteria when not to transplant

1. Hemodynamic instability and high-dose inotrope requirement (sepsis, bleeding). (2a, B)

2. Severe bacterial infection. (2a, B)

3. Fungal infection. (2a, B)

4. Cerebral edema or intracranial bleeding. (1a, A)

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CONCLUSION

• ACLF is the acute deterioration of liver function in a patient with compensated or decompensated, but stable cirrhosis.

• ACLF is a highly prevalent, life-threatening disease (with higher mortality in a few days or weeks) with few therapeutic options at present.

• It is a potentially reversible complication of chronic liver disease if caught at an early stage.
CONCLUSION

• Precipitating acute events: bacterial infection, variceal hemorrhage or primary liver insult due to alcohol, virus, drugs

• It is associated/coincides with failure of extra-hepatic organs.

• Inflammation is the LINK between the triggering event and the development of organ failure.
CONCLUSION

• There is still NO established universally acceptable diagnostic criteria as of date

• Management includes treatment of the precipitating event and of organ failure(s), and eventually liver transplantation.

• Early recognition of the syndrome with a more pathophysiology-guided therapeutic approach results in better survival rates of patients with ACLF, reducing the need for liver grafts as an ultimate salvage therapy.
“Time to get to know the Filipino people … unbelievably resilient, long suffering, good natured, overfriendly, loyal, ingenious, and a bunch of survivors.

At the end of the day, the Filipinos will just shake off the dirt from their clothes and go about their business … and SMILE. They do not complain much, they will bear as long as they can.

Maybe this is why they were given the “privilege” of bearing the burden of the strongest typhoon ever recorded.

The indomitable human spirit at its finest.”

- Compliments of a netizen from Facebook
THANK YOU!