What is Acute-on-Chronic Liver Failure?

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Hofstra Northwell School of Medicine

Acute on Chronic Liver Failure

- New clinical entity
- Distinct from acute decompensated cirrhosis
- Relatively common
  - 31% of hospitalized patients with cirrhosis
- Most common cause of death amongst cirrhotic patients

Arroyo J Hep 2015
In Hospital Mortality: Cirrhosis vs other diagnoses

![Bar chart showing hospital mortality rates for cirrhosis and other diagnoses.](Arroyo J Hep 2015)

Cirrhosis: Mortality Factors

<table>
<thead>
<tr>
<th>Factor*</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU care**</td>
<td>13.94</td>
<td>12.84-15.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PSE</td>
<td>2</td>
<td>1.87-2.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>6.06</td>
<td>5.44-6.75</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ascites</td>
<td>1.14</td>
<td>1.07-1.21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Variceal Bleed</td>
<td>0.82</td>
<td>0.73-0.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1.5</td>
<td>1.24-1.77</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, race

** mechanical ventilation

Arroyo J Hep 2015
Acute on Chronic Liver Disease:
Definition

• Acute decompensation
• Organ Failure
• High short term mortality

ACLF vs Decompensated Cirrhosis

• The 2 conditions differ in:
  – Prognosis
  – Potential for reversibility
  – Requirement for liver support
  – Need for early transplantation
  – Course of disease
ACLF vs Decompensated Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>ACLF</th>
<th>Decompensated Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral edema</td>
<td>✓</td>
<td>No</td>
</tr>
<tr>
<td>SIRS</td>
<td>Prominent</td>
<td>Less common</td>
</tr>
<tr>
<td>Organ Failure</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Infection</td>
<td>After organ failure</td>
<td>Before organ failure</td>
</tr>
<tr>
<td>Mortality</td>
<td>8-30 days</td>
<td>&gt;31 days</td>
</tr>
</tbody>
</table>

Natural History

Cirrhosis
- Exaggerated inflammatory response
- Multi-Organ Dysfunction/Failure
- Recovery
- Death

Compensated cirrhosis
- Decompensation
- Early Transplant
- Death
- Transplantation

ACLF
- Natural History

Insult

Recovery
- Death
Acute on Chronic Liver Failure

ACLF: Disputed Definition

- APASL vs. EASL/AASLD
- Consensus meeting at World Congress of Gastroenterology reached compromise
ACLF: Consensus is Reached

• 3 types
  – A Non-cirrhotic acute disease
  – B Compensated cirrhosis after surgery, infection, alcoholic hepatitis
  – C Similar to type B with a history of previous episode of hepatic decompensation
Pathophysiology of ACLF

- Predisposition
- Injury caused by precipitating event
- Response to injury
- Organ failure

Jalan et al J Hep 2012

ACLF: Precipitating Factors

- Bacterial infections
  - Spontaneous bacterial peritonitis
  - Genetic predisposition
    - Polymorphic variants NOD2 and TLR 2
- Active alcoholism
- Acute viral infection
  - Acute HAV
  - Reactivation HBV
  - Acute HEV
- Ischemia
  - Hypotension
  - Surgery
  - Trauma
- Portal vein thrombosis
- No precipitating factor in 40% of cases
ACLF: Response to Injury

Immune Dysfunction

- Liver failure/bacterial translocation
  - Endotoxins
  - Reduced protein/complement synthesis
  - Reduced immune surveillance
  - Reduced albumin function

- Immune paralysis
  - Innate immunity
    - Neutrophils: phagocytic defect
    - Monocytes: DRII loss
    - NK cells
  - Adaptive immunity
    - T-cell exhaustion
    - Inability to proliferate
    - Increased apoptosis

SIRS: Systemic inflammatory response

CARS: Compensatory anti-inflammatory response

Role of Bacterial Translocation in ACLF

- Bacterial translocation
  - Bacterial infection

- Compensated cirrhosis
  - Increasing portal pressure, fibrosis and vasodilatation

- Decompensated cirrhosis
  - VH
  - Ascites
  - HE

- Worsening systemic and hepatic hemodynamics/liver function

- Multiorgan failure
  - Death

- Hypotension
- Renal failure
- Jaundice
- Coagulopathy
- Encephalopathy

Jalan et al. J Hep 2012
Clinical Feature of ACLF: Systemic inflammation

- Compared to acute decompensation:
  - Higher WBC
  - Higher C-reactive proteins

Moreau et al. Gastro 2013

ACLF: Definition of Organ Failure

<table>
<thead>
<tr>
<th>Organ</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Bilirubin &gt;12 mg/dL</td>
</tr>
<tr>
<td>Kidney</td>
<td>Cr &gt;2 mg/dL</td>
</tr>
<tr>
<td>Brain</td>
<td>Grade 3 or 4 PSE</td>
</tr>
<tr>
<td>Coagulation</td>
<td>INR &gt;2.5 and or platelet count &lt;20,000</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Ratio of partial pressure of arterial oxygen to the FiO₂ of 200 or less</td>
</tr>
<tr>
<td>Circulation</td>
<td>Use of catecholamines or terlipressin to maintain SBP &gt;90 mm HG</td>
</tr>
</tbody>
</table>

Moreau Clin Gastr Hep 2015
ACLF: Definitions of Grade

- **Grade 1**
  - Single organ failure
  - Cr 1.5 – 1.9 mg/dL
  - and/or
  - Grade 1-2 PSE

- **Grade 2**
  - 2 organ failures

- **Grade 3**
  - 3 organ failures

Arroyo J Hep 2015

ACLF: CANONIC Study

- Evaluated 1343 patients
- Prevalence of ACLF 30%
  - 20% on admission
  - 10% during hospitalization

<table>
<thead>
<tr>
<th>ACLF Grade</th>
<th>Prevalence</th>
<th>28-day mortality</th>
<th>90-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ACLF</td>
<td>1.9%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15.8%</td>
<td>22%</td>
<td>41%</td>
</tr>
<tr>
<td>2</td>
<td>10.9%</td>
<td>32%</td>
<td>55%</td>
</tr>
<tr>
<td>3</td>
<td>4.4%</td>
<td>73%</td>
<td>78%</td>
</tr>
</tbody>
</table>

Moreau Clin Gastr Hep 2015
CANONIC STUDY OVERVIEW DEFINING ACLF

Moreau et al. Gastro 2013

Clinical Features of ACLF

- Younger patients
- Organ failure
  - Renal 56%
  - Liver 44%
  - Coagulation 28%
  - Cerebral 24%
  - Circulatory 17%
  - Respiratory 9%

Moreau et al. Gastro 2013
CANONIC study: ACLF v no ACLF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No ACLF</th>
<th>ACLF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic liver disease</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>HCV</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>SBP</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>WBC</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>C-reactive protein level</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

Moreau et al. Gastro 2013

ACLF: Short Term Mortality

- 28 day mortality of ≥15%
- Mortality defined by presence of:
  - Renal dysfunction
  - Cerebral dysfunction

Arroyo J Hep 2015
CANONIC Study:
No Acute on Chronic Liver Failure

Factors
• Organ Failure (1)
  – Liver
  – Coagulation
  – Respiratory
  – Circulation
• No renal dysfunction
• No cerebral dysfunction

28 day Mortality
• 5-7%

Arroyo J Hep 2015

CANONIC Study:
No Acute on Chronic Liver Failure

Factors
• No renal dysfunction
• Cerebral dysfunction
  – Grade 3-4 encephalopathy

28 day Mortality
• 8%

Arroyo J Hep 2015
CANONIC Study: 
Acute on Chronic Liver Failure

Factors

• Organ Failure
  – Liver
  – Coagulation
  – Respiratory
  – Circulation
• Renal dysfunction
  – Cr > 2 mg/dL
• Cerebral dysfunction

28 day Mortality

• 16-30%

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Acute on Chronic Liver Failure: Grading System

Grade

• No ACLF
• ACLF 1 (1 OF)
• ACLF 2 (2 OF)
• ACLF 3 (3-6 OF)

28 day mortality

• <15%
• 22%
• 32%
• 73%

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CANONIC STUDY: 28 and 90 day mortality

- Course dependent on early clinical course
- 50% improve
- 20% worsen
- Patients with no history of decompensated cirrhosis developed a more severe ACLF with higher 28 day mortality (42% vs 28%)

Aclf: Prognosis

- In chronic liver disease with decompensation, all worsen

Arroyo J Hep 2015
Predictors of Survival

- CLIF-C organ failure score
- Age
- White blood cell count

The Chronic Liver Failure Consortium Organ Failure Score (CLIF-SOFA Score)

<table>
<thead>
<tr>
<th>System</th>
<th>Parameter</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Bilirubin mg/dL</td>
<td>&lt;1.2</td>
<td>≥1.2 - &lt;2</td>
<td>≥2 - &lt;6</td>
<td>≥6 - &lt;12</td>
<td>≥12</td>
</tr>
<tr>
<td>Kidney</td>
<td>Cr (mg/dL)</td>
<td>&lt;1.2</td>
<td>≥1.2 - 2</td>
<td>≥2 - &lt;3.5</td>
<td>≥3.5 - &lt;5</td>
<td>≥5</td>
</tr>
<tr>
<td>Cerebral</td>
<td>HE Grade</td>
<td>No HE</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Coagulation</td>
<td>INR</td>
<td>&lt;1.1</td>
<td>≥1.1 - &lt;1.25</td>
<td>≥1.25 - &lt;1.5</td>
<td>≥1.5 - &lt;2.5</td>
<td>≥2.5 or platelet ct &lt;20,000</td>
</tr>
<tr>
<td>Circulation</td>
<td>MAP, 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>Respiratory</td>
<td>PaO2/FiO2</td>
<td>&gt;400</td>
<td>≥300 - ≤400</td>
<td>≥200 - &lt;300</td>
<td>≥100 - &lt;200</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>SpO2/FiO2</td>
<td>≥512</td>
<td>≥357 - ≤512</td>
<td>≥214 - ≤357</td>
<td>≥89 - ≤214</td>
<td>&lt;89</td>
</tr>
</tbody>
</table>

A score of 3 is defined as failure for each system, except for the kidney, where a score of 2 is defined as organ failure.

SpO2 = peripheral capillary oxygen saturation

Moreau et al Gastro, 2015
Admission of cirrhotic patient with acute decompensation

Assess CLIF-C OF score for diagnosis of ACLF

ACLIF present

ACLIF absent

CLIF-C ACLIF score

CLIF-C AD score

High risk: CLIF-C ADs ≥60
3-month mortality >30%

Intermediate risk: CLIF-C ADs 46-59
3-month mortality 2-30%

Low risk: CLIF-C ADs ≤45
3-month mortality <2%

Probability of death at 28 days based on presence of ACLF, prior AD and Leukocyte count

Moreau et al. Gastro 2015
Management of ACLF

- Rapid identification of syndrome
- Treatment of potential causes
- Treatment in ICU setting
- Extracorporeal liver support systems based on albumin dialysis
- Transplantation
Non-selective beta blockers improve survival in ACLF

- 349 pts with ACLF in the CANONIC study were included
- 164 on NSBB’s, 185 not on NSBB’s
- More patients on NSBB:
  - Had lower grades of ACLF
  - Improved
- Survival on treatment
  - 40 (24.4%) on NSBB’s died on treatment
  - 63 (34.1%) not on NSBB’s died on treatment
  - Difference was significant (p <0.05)
- Improved survival was associated with a lower WBC

Mookerjee et al. J Hep 2015

ACLF: Summary

- ACLF is a new clinical entity
- Grading based on presence of organ failure
- Younger age
- Prevalence of certain triggers:
  - Alcoholism
  - Bacterial infections
- Cannot be explained by sepsis or severe alcoholic hepatitis
- High mortality rate with possible recovery
  - Treatment focus on causative factor