Acute on Chronic Liver Failure: Current Concepts

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Disclosures

• None to declare
Agenda

- Definition
- Prevalence and natural history
- Pathophysiology
- Prognostic factors, Predictive Models, Biomarkers
- Therapies, Liver Transplant

Is ACLF a distinct clinical entity?

What is Acute on Chronic Liver Failure (ACLF)?

- Concept has been proposed for the past 2 decades

- Several definitions exist (North American Consortium for End Stage Liver Disease (NACSELD), European Association for the Study of the Liver-CLIF (EASL-CLIF) Consortium, and Asia Pacific Association for the Study of the Liver (APASL)

- Consolidated definition proposed by working group on behalf of the World Gastroenterology Organization:
  - A “syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and 1 or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from it”

Natural history of chronic liver disease

Decompensations
- Ascites
- Encephalopathy
- Variceal bleeding
- Jaundice

Chronic injury
- Viral infection
- Alcohol
- NASH
- Autoimmune disorders
- Cholestatic disorders
- Metabolic diseases

Generic polymorphisms
- Epigenetic marks
- Collateral effects (such as obesity and alcohol)

5-50 years

Inflammatory damage
- Matrix deposition
- Parenchymal cell death
- Apoptosis

Early fibrosis
- Disrupted architecture
- Loss of function
- Abnormal hepatocyte regeneration

Cirrhosis
- Liver failure
- Portal hypertension

Hepatocellular carcinoma

Liver transplant

Normal liver

Resolution
- Removal of underlying cause
- Anti-fibrosis, drug or cell therapy

Regression

Concept of ACLF

Red = chronic decline in cirrhosis
Blue = ACLF in relatively stable pt

Acute Insult

Threshold for organ failure

Liver Function

0 100%

Months

Concept of ACLF

ACLF vs Decompensated Cirrhosis

Compared to the general population:
- **Compensated cirrhosis**: 5 fold higher risk of death (HR 4.7, 95% CI 4.4-5.0)
- ** Decompensated cirrhosis**: 10 fold (HR 9.7, 95% CI 8/9-10.6)
- **ACLF**: 90 day mortality rates 34% vs 1.9% for chronic liver disease

Fleming KM et al. Liver Int 2012; 32:79-84
What is Acute on Chronic Liver Failure (ACLF)?

- Key points common to all definitions
  - Multiple organ failure
  - Increased risk of mortality

- Now includes patients with compensated cirrhosis and patients with chronic liver disease without cirrhosis

- Underlying premise of defining ACLF – identify a subset of pts with chronic liver disease (with or without cirrhosis) who have an unexpected rapid and abrupt decompensation of hepatic function with extrahepatic organ failure.

<table>
<thead>
<tr>
<th>Study</th>
<th>ACLF</th>
<th>Components</th>
<th>Survival</th>
<th>Common precipitants/diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACSELD infection-related ACLF</td>
<td>≥2 extrahepatic organ failures</td>
<td>Shock, grade 3 or 4 HE, need for HD or ventilation</td>
<td>30-day mortality: 27%, 49%, 64%, and 77%; extrahepatic organ failure</td>
<td>Bacterial infection, 16% with nosocomial infection; varied etiology of liver dz</td>
</tr>
<tr>
<td>EASL-CLIF consortium</td>
<td>Hepatic or extrahepatic organ failure with &gt; 15% 28-day mortality</td>
<td>Grade 1: (a) pts with renal failure ± HE with single failure of liver, coag, circ, or respiration; Grade 2: ≥ 2 failures</td>
<td>28-day mortality 22%, 32%, and 77%</td>
<td>Bacterial infection Underlying liver disease: alcoholic liver disease and HCV</td>
</tr>
<tr>
<td>APASL</td>
<td>Acute hepatic insult with jaundice (bili &gt;5 mg/dL), coagulopathy (INR&gt;1.5) complicated within 4 weeks of onset by ascites and/or HE in pt with liver disease</td>
<td>Liver failure</td>
<td></td>
<td>Reactivation of HBV, superinfection with HEV Underlying liver dz: HBV, alcoholic cirrhosis, hepatotoxic drugs</td>
</tr>
</tbody>
</table>
Proposed Types of ACLF

Because organ failure is required to define ACLF, diagnosis can be made at a time when process is irreversible.

Jalan R, et al. Gastroenterol 2014;147:4-10

Prevalence and Natural History

- Difficult to assess prevalence due to differing definitions

- CLIF (Chronic Liver Failure Consortium) in Europe produced a multicenter study CANONIC (CLIF Acute on Chronic Liver Failure in Cirrhosis) – 1343 pts, 29 liver units, 8 European countries – prevalence 31%

- North American Experience – prevalence 24.3%

Natural History

- Follow-up data from CLIF consortium – 388 pts, 50% had resolution or improvement in their ACLF, 20% worsened and 30% had steady or fluctuating course

- Prognosis best in pts with grade 1 ACLF

- Time to assess improvement, resolution, or worsening could be determined within 48 hrs in 40%, within 3-7 days in 15% and within 8-28 days in 15%
Costs

• Little data exists on cost of ACLF

• One estimate is that mean cost per ACLF hospitalization is 2x that of pts with cirrhosis without ACLF ($32,000 vs $16,000)

• Many readmissions in cirrhosis are likely due to ACLF

Allen AM. Hepatology 2014;60:485a

Readmission Rates

Figure 1. Rates of Rehospitalization within 30 Days after Hospital Discharge.
The rates include all patients in fee-for-service Medicare programs who were discharged between October 1, 2001, and September 30, 2004. The rate for Washington, DC, which does not appear on the map, was 23.2%.

Hospital Readmissions Related to Cirrhosis

Advanced liver disease
- >150,000 hospitalizations/yr
  - >40,000 deaths/year
  - Costs ~$4 billion dollars/year
- ~20–37% of patients are readmitted to hospital within 30 days of discharge
- ~20% of these readmissions may be preventable
- Each readmission within 30 days costs $20,000–$28,000
- 2/3 of all patients covered by Medicare or Medicaid

1. WHAT IS CURRENT KNOWLEDGE?
- Cirrhosis is a complex chronic disease with high morbidity and mortality
- In other diseases, early re-hospitalizations are known to be costly and partially preventable

2. WHAT IS NEW HERE?
- Rates of hospital re-admission among patients with decompensated cirrhosis are higher than other diseases such as congestive heart failure
- Predictors of re-admission include MELD score, serum sodium, and the number of medications
- Frequent re-admissions are independently associated with increased mortality
- Nearly one quarter of early re-admissions are possibly preventable

Hospital Readmissions Related to Cirrhosis

- ≥1 non-elective readmission within...
  - 1 week: 14%
  - 1 month: 37%
- Mean costs for readmissions
  - Within 1 week: $28,898
  - Weeks 1–4: $20,581
- Predictors of readmissions:
  - MELD
  - Serum sodium
  - Number of medications at discharge
- Among 165 readmissions within 30 days
  - 22% were possibly preventable
  - Most common preventable reasons:
    - Hepatic encephalopathy
    - Fluid imbalance (hyper or hypovolemia)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score</td>
<td>1.05 (1.03, 1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>0.97 (0.94, 0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td># medications</td>
<td>1.05 (1.02, 1.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.27 (0.99, 1.62)</td>
<td>0.05</td>
</tr>
<tr>
<td># of cirrhosis complications</td>
<td>1.13 (0.94, 1.35)</td>
<td>0.21</td>
</tr>
<tr>
<td>On transplant list at discharge</td>
<td>1.35 (0.97, 1.86)</td>
<td>0.07</td>
</tr>
<tr>
<td>Discharge location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home health (vs self-care)</td>
<td>0.96 (0.72, 1.30)</td>
<td>0.79</td>
</tr>
<tr>
<td>Skilled nursing (vs self-care)</td>
<td>0.76 (0.48, 1.24)</td>
<td>0.24</td>
</tr>
</tbody>
</table>


Pathophysiology: PIRO concept of ACLF

The PIRO concept of acute-on-chronic liver failure

Assessment

- Aetiology
- Pugh score
- MELD
- [Biomarkers]

Intervention

- Early identification
- Risk stratification
- Preventative 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]

Jalan R et al. Journal Hepatol. 2012; 57:1336-1348
Pathophysiology: Immune Dysfunction of ACLF

- Under normal conditions, liver exerts important defensive role against pathogens and related antigens
- In cirrhosis, loss or damage of Kupffer cells and compromise of circulating immune cell function
- ACLF patients show significant cellular immune depression by TNF alpha, and monocyte HLA-DR expression after LPS stimulation

Pathophysiology – Bacterial Translocation

- Bacterial translocation
  - Worsening systemic and hepatic hemodynamics/ liver function
  - Compensated cirrhosis
  - Increasing portal pressure, fibrosis and vasodilatation
  - Decompensated cirrhosis
    - Vascular hypertrophy
    - Ascites
    - HE
  - Multiorgan failure
    - Hypotension
    - Renal failure
    - Jaundice
    - Coagulopathy
    - Encephalopathy

SIRS: Systemic inflammatory response

CARS: Compensatory anti-inflammatory response

Jalan R et al. Journal Hepatol. 2012; 57:1336-1348
Pathophysiology of ACLF

1. PREDISPOSITION
   - Cirrhosis

2. INJURY
   - Alcohol
   - Acetaminophen
   - Ischemic / reperfusion
   - Bacterial translocation
   - Infection (SBP, UTI, etc)
   - DAMPs
   - PAMPs

3. RESPONSE
   - Proinflammatory cytokines
   - TNFα, IL-1β, IL-6
   - Lymphocyte
   - Neutrophil

4. ORGAN FAILURE


Pathophysiology of HE in ACLF

- ACLF characterized by a paralysis of the immune response similar to that seen in pts with severe sepsis

- Cerebral edema encountered in pts with ACLF but rarely seen in decompensated cirrhosis without ACLF

Hepatic Encephalopathy

Prognostic factors

• Number of organ systems affected in multisystem organ failure has important prognostic value

• Organ systems most commonly affected: kidneys, brain, cardiovascular system, respiratory system, coagulation

Organ dysfunction as a prognostic factor

• 50% mortality in those with organ dysfunction
• Time from organ failure to death – mean 10 days

Of those who survive those with organ dysfunction still have increased mortality many years later
Predictive models

- Commonly used scoring systems in cirrhosis (Child-Turcotte-Pugh score and MELD score) assess kidney, brain, and coagulation systems in addition to the liver.
- An improved scoring system for ACLF needs to consider inflammation and other organ dysfunction.
- CLIF-C ACLF incorporates age and white blood cell count; superior to MELD and MELD-Na in predicting mortality in ACLF.

### 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 &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>Coagulation (international)</td>
<td>No HE</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>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 greater platelet count</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>NE &gt;0.1</td>
</tr>
<tr>
<td>Lungs</td>
<td>PaO2/FIO2 or</td>
<td>≥400 to &lt;400</td>
<td>≥200 to &lt;300</td>
<td>≥100 to &lt;200</td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td>SpO2/Hb</td>
<td>≥91</td>
<td>357 to ≤512</td>
<td>≥214 to ≤357</td>
<td>≥89 to ≤214</td>
</tr>
</tbody>
</table>


Predictive models

- Bajaj et al proposed a simpler model from US data in the NACSELD (North American Consortium for End Stage Liver Disease) database.
- Prospective study of ACLF in American tertiary care centers.
- Increasing the number of organ failures may be sufficient to predict short-term mortality amongst patients who develop an infection.
- Gustot et al. assessed ACLF grades at different time points and found grade at 3 to 7 days is a better predictor of severity independent of initial assessment.
- Pts with nonsevere early course had 28 day transplant free mortality of 6%-18% compared with 42%-92% in those with severe early course.
- Unclear if these organ failure scores are prognostic (allow early recognition and can improve outcome) or only reflective.

Relationship between leukocyte count and death

Modified CLIF score algorithm

Admission of cirrhotic patient with acute decompensation

Assess CLIF-C OF score for diagnosis of ACLF

ACLFF present

ACLFF absent

CLIF-C ACLF 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%

CLIF-C AD score

Arroyo V et al. 2015 Journal of Hepatol; 62:S131-S143
<table>
<thead>
<tr>
<th>Organ system</th>
<th>Score = 1</th>
<th>Score = 2</th>
<th>Score = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, bilirubin (mg/dl)</td>
<td>&lt;6</td>
<td>6-12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Kidney, creatinine (mg/dl)</td>
<td>&lt;2</td>
<td>2-3.5</td>
<td>≥3.5 or renal replacement</td>
</tr>
<tr>
<td>Brain, grade (West-Haven)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Coagulation, INR</td>
<td>&lt;2.0</td>
<td>2.0-&lt;2.5</td>
<td>≥2.5</td>
</tr>
<tr>
<td>Circulation, MAP (mmHg)</td>
<td>≥70</td>
<td>&lt;70</td>
<td>Vasopressors</td>
</tr>
<tr>
<td>Respiratory PaO₂/FiO₂</td>
<td>&gt;300</td>
<td>≤300 and &gt;200</td>
<td>≤200</td>
</tr>
<tr>
<td>or SpO₂/FiO₂</td>
<td>&gt;357</td>
<td>&gt;214 and ≤357</td>
<td>≤214</td>
</tr>
</tbody>
</table>

**CLIF-C OF Score**

<table>
<thead>
<tr>
<th>Number and types of organ failures</th>
<th>No kidney dysfunction and no mild-to-moderate hepatic encephalopathy</th>
<th>Kidney dysfunction and/or mild-to-moderate hepatic encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No organ failure</td>
<td>20/562 (3.6)</td>
<td>19/312 (6.2)</td>
</tr>
<tr>
<td>Single liver failure</td>
<td>488 (5.9)</td>
<td>1033 (30.3)</td>
</tr>
<tr>
<td>Single cerebral failure</td>
<td>25 (0.5)</td>
<td>1/5 (20.5)</td>
</tr>
<tr>
<td>Single coagulation failure</td>
<td>1/9 (5.3)</td>
<td>2/9 (22.2)</td>
</tr>
<tr>
<td>Single circulation or single lung failure</td>
<td>1/15 (6.7)</td>
<td>2/7 (28.6)</td>
</tr>
<tr>
<td>Single kidney failure</td>
<td>9/47 (15.8)</td>
<td>7/29 (24.1)</td>
</tr>
<tr>
<td>Two organ failures</td>
<td>19/86 (28.8)</td>
<td>12/41 (38.7)</td>
</tr>
<tr>
<td>Three organ failures or more</td>
<td>28/59 (98.2)</td>
<td>8/13 (61.5)</td>
</tr>
</tbody>
</table>

**CLIF, MELD, MELD Na and CP**
Diagnostic Criteria of ACLF

Diagnostic criteria of ACLF grades were those previously described. 4 ACLF grade 1 (ACLF-1) at diagnosis was defined by presence of kidney failure (serum creatinine ≥2 mg/dL) or other single organ/system failure (liver: serum bilirubin ≥12 mg/dL; brain: grade III-IV hepatic encephalopathy [HE] based on West Haven criteria; coagulation: international normalized ratio [INR] ≥2.5 or platelet count ≤20 ×10⁹/L; circulation: treatment with vasoconstrictors to maintain arterial pressure or inotropes to improve cardiac output; lungs: PaO₂/FiO₂ ≤200 or SpO₂/FiO₂ ≤214) if associated with kidney dysfunction (serum creatinine ranging from 1.5 to 1.9 mg/dL) and/or mild-to-moderate (grade I-II) HE. ACLF grade 2 (ACLF-2) and ACLF grade 3 (ACLF-3) were defined by the presence of 2 or ≥3 organ failures, respectively.


Fig. 1. (A) Examples of time-course profiles: very rapid (within <8 hours, red lines), rapid (between 3 and 7 days, yellow lines), and slow (between 8 and 28 days, purple lines) improvement or worsening, steady (green line) and fluctuating course with unchanged final grade (blue line). (B) Kaplan-Meier’s 28-day transplant-free survival curves of patients based on their final ACLF grade. (C) Estimated probability of severe early course of ACLF based on CUF-Consortium ACLF score (CUF-C ACLF) and absence or presence of liver failure (defined by total bilirubin ≥12 mg/dL).

Biomarkers

• Few potential biomarkers identified to date

• Lactate, pyruvate, etone bodies, glutamine, phenylalanine, tyrosine, and creatinine

• TNF-α, IFN-γ

• More data required

There’s an app for that

ACLF Score Calculator

Welcome to ACLF
This app will define the prognosis of a chronic patient admitted to the hospital with acute deterioration with a complication of cirrhosis. This app should not be used for patients who are admitted for routine investigations or scheduled therapies.

The app will help:
- Define whether the patient has Acute on Chronic Liver Failure
- If yes, what is their probability to 30-day/90-day and 1 year survival?
- If no, what is their probability of 20-day/60-day and 1 year survival?

The app can be used to input data sequentially on a daily basis.
ACLF Version: 1.302

CyberLiver
Therapies: PIRO concept of ACLF

The PIRO concept of acute-on chronic liver failure

- **Predisposition**
  - Severity of cirrhosis
  - Aetiology
  - Fibrosis score
  - MELD
  - [Biomarkers]

- **Injury**
  - Precipitating event
  - Hepatic
  - Extra-hepatic
  - [Therapies]

- **Response**
  - Inflammation
  - Immune failure
  - [Biomarkers]

- **Organ**
  - Organ failure
  - SOFA
  - APACHE
  - [Biomarkers]

Assessment
- Early identification
- Risk stratification
- Preventative strategies
  - [Novel interventions]

Intervention
- 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]

Jalan R et al. Journal Hepatol. 2012; 57:1336-1348

Therapies: Liver Transplantation

- Acute insult
- Survival with transplant (82-90%)
- Dependent on clinical status

Window of opportunity for transplant

- Threshold for reversibility
- ? Too late for transplant

Median Transplant free survival 48 days

Pamecha V. Hepatol Int. 2015 Jul 10 Epub ahead of print.
Therapies: Liver Transplantation – Key Questions

The need
Why transplant?

Case selection
Which patients might recover with medical treatment?
Who requires urgent transplant?
What are the contraindications for transplant?

Timing
What is the ideal point in the natural history for LT?
What if they have organ dysfunction/failure?
What is the role of bridging therapies?
Should they be given additional points on listing?
Should they be listed as super-urgent?

Prognosis
What are the early predictors of need for LT?
What are the predictors of post-transplant outcomes?

Outcome
Perioperative results
Long term results
How do they compare with LT in ALF and CLD?
Deceased donor LT versus living donor LT
Role of Simultaneous Liver Kidney Transplant in ACLF
Role of LT for ACLF with non-carbolic liver
Hepatitis B/C
Alcoholic hepatitis
NASH

Therapies: Liver Transplantation

ACLF (APASL)

Rapidly worsening circulatory/respiratory failure
Cerebral edema progressing to brainstem, dysfunction/intracranial bleed
Uncontrolled sepsis/coagulopathy

Not a transplant candidate

Intensive care with appropriate organ support + ALS Bridge

Recovery
Deterioration

Best supportive care

Medical management
Early elective LT

Urgent LT

Assessment on Day 3-7 with CLIF-C ACLF score

Clinical course not improving, rising bilirubin

Appropriate treatment, source control Blood, body fluid cultures negative

ACLF grade I/III, CLIF-C ACLF score < 40

ACLF grade I/III, CLIF-C ACLF score > 60

Emergent LT

Emergent LT

Grade II/IV HE MELD score > 30

No sepsis
No organ dysfunction/failure

Satisfying standard transplant criteria

Clinical course improving, falling bilirubin

Pamecha V. Hepatol Int. 2015 Jul 10 Epub ahead of print.
Key Points

- ACLF definitions vary but in general, it is a “syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and 1 or more extrahepatic organ failures that is associated with increased mortality

- Altered host response to injury such as deranged SIRS

- Bacterial infection can occur with immune paralysis

- Systemic, cardiac, hepatic hemodynamics important

- Survival is contingent upon severity of organ failure

- Predictive models exist

- Treatment is with organ support but hopefully better understanding will allow for biomarker discovery and improved therapeutic strategies including optimal timing of transplant

Thank you!