Acute-on-chronic liver failure: Prognosis and treatment

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ACD, Barcelona January 14 2016
CLINICAL COURSE OF CIRRHOSIS: PHASES

1. **Compensated cirrhosis (CC).** Slow (>10-15y) progression of fibrosis and portal hypertension

2. **Acute decompensation (AD):** 70% of patients admitted to hospital with cirrhosis. Acute development of ascites, gastrointestinal hemorrhage, hepatic encephalopathy and/or acute bacterial infection *(mean survival <3 y)*

3. **Acute-on-Chronic Liver Failure (ACLF):** 32% of patients admitted to hospital (22% present ACLF at admission; 10% during hospitalization). Characteristics: a). AD; b). Organ failure(s) (Liver, Kidney, Brain, Coagulation, Respiration, Circulation) and c). High short-term mortality (main cause of death in cirrhosis)

Moreau et al, Gastroenterology 2013
### Diagnostic Criteria of ACLF: Organ Failures. CLIF-Consortium Organ Failure Score (Canonic Study)

<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 (mg/dl)</td>
<td>Bilirubin &lt; 6</td>
<td>6 ≤ Bilirubin ≤ 12</td>
<td>Bilirubin &gt;12</td>
</tr>
<tr>
<td>Kidney (mg/dl)</td>
<td>Creatinine &lt;2</td>
<td>Creatinine ≥2 &lt;3.5</td>
<td>Creatinine ≥3.5 or renal replacement</td>
</tr>
<tr>
<td>Brain (West-Haven)</td>
<td>Grade 0</td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Coagulation</td>
<td>INR &lt; 2.0</td>
<td>2.0 ≤ INR &lt; 2.5</td>
<td>INR ≥ 2.5</td>
</tr>
<tr>
<td>Circulation</td>
<td>MAP ≥70 mm/Hg</td>
<td>MAP &lt;70 mm/Hg</td>
<td>Vasopressors</td>
</tr>
<tr>
<td>Respiratory: PaO₂/FiO₂ or SpO₂/FiO₂</td>
<td>&gt;300</td>
<td>≤300 - &gt; 200</td>
<td>≤200</td>
</tr>
<tr>
<td></td>
<td>&gt;357</td>
<td>&gt;214 - ≤357</td>
<td>≤214</td>
</tr>
</tbody>
</table>

Values at study enrolment. Highlighted area reflects the definition of each organ failure.

Moreau et al, Gastroenterology 2013
1. **High short-term mortality rate**: 28-day mortality rate > 15%*.

2. **Cerebral Dysfunction**: Grade 1-2 (West Haven) hepatic encephalopathy.

3. **Renal Dysfunction**: Serum creatinine 1.5-1.9 mg/dl

* 50% mortality rate of septic shock

Moreau et al, Gastroenterology 2013
# DIAGNOSIS AND GRADES OF ACLF (CANONIC Study)

<table>
<thead>
<tr>
<th>ACLF grades</th>
<th>TX-FREE PATIENTS (N=1287)</th>
<th>28-DAY DEATH RATE</th>
<th>No OF 879 (68.3%)</th>
<th>39/879 (4.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No OF</td>
<td>879 (68.3%)</td>
<td>39/879 (4.4%)</td>
<td>39/879 (4.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>128 (9.9%)</td>
<td>8/128 (6.3%)</td>
<td>8/128 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Single non renal OF, creatinine &lt;1.5 mg/dl, no HE</td>
<td>128 (9.9%)</td>
<td>8/128 (6.3%)</td>
<td>8/128 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Single renal failure</td>
<td>86 (6.68%)</td>
<td>16/86 (18.6%)</td>
<td>16/86 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>Single non-renal OF, creatinine 1.5-1.9 mg/dL and/or grade 1-2 HE.</td>
<td>54 (4.1%)</td>
<td>15/54 (27.7%)</td>
<td>15/54 (27.7%)</td>
<td></td>
</tr>
<tr>
<td>2 OF</td>
<td>97 (7.5%)</td>
<td>31/97 (32.0%)</td>
<td>31/97 (32.0%)</td>
<td></td>
</tr>
<tr>
<td>3 OF</td>
<td>25 (1.9%)</td>
<td>17/25 (68.0%)</td>
<td>17/25 (68.0%)</td>
<td></td>
</tr>
<tr>
<td>4-6 OF</td>
<td>18 (1.4%)</td>
<td>12/18 (88.9%)</td>
<td>12/18 (88.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Moreau et al, Gastroenterology 2013
28-DAY AND 90-DAY MORTALITY RATES ASSOCIATED TO ACLF (Canonic Study)

Moreau et al, Gastroenterology 2013
### Hepatic Encephalopathy

<table>
<thead>
<tr>
<th></th>
<th>28-day mortality</th>
<th>90-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No ACLF (n=285)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HE grades I-II (n=259)</td>
<td>5.8%</td>
<td>5.9%</td>
</tr>
<tr>
<td>HE grades III-IV (n=26)</td>
<td>7.6%</td>
<td>11.0%</td>
</tr>
<tr>
<td><strong>ACLF (n=174)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HE grades I-II (n=107)</td>
<td>30.0%</td>
<td>42.0%</td>
</tr>
<tr>
<td>HE grades III-IV (n=67)</td>
<td>50.7%</td>
<td>59.7%</td>
</tr>
</tbody>
</table>

### GI Bleeding

<table>
<thead>
<tr>
<th></th>
<th>28-day mortality</th>
<th>90-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No ACLF (n=181)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8%</td>
<td>7.6%</td>
<td></td>
</tr>
<tr>
<td><strong>ACLF (n=41)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46.3%</td>
<td>48.8%</td>
<td></td>
</tr>
</tbody>
</table>
## CLINICAL COURSE OF PATIENTS WITH ACLF
(Canonic Study)

<table>
<thead>
<tr>
<th>Initial Grade</th>
<th>Final Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No-ACLF</td>
</tr>
<tr>
<td>ACLF-1 (202)</td>
<td>55%</td>
</tr>
<tr>
<td>ACLF-2 (136)</td>
<td>34%</td>
</tr>
<tr>
<td>ACLF-3 (50)</td>
<td>16%</td>
</tr>
</tbody>
</table>

Gustot & Fernandez et al, Hepatology 2015
SURVIVAL ACCORDING TO DAY 3-7 CLINICAL COURSE

Gustot & Fernandez et al, Hepatology 2015
Survival probability after ACLF 2-3 diagnosis in patients receiving and not receiving an early LT (<28 days)

- **Early transplanted d3-7 ACLF-2 or 3 patients (n=21)**
  - Survival probability: 95.2% (95% CI: 86.1-100)

- **Non-transplanted d3-7 ACLF-2 or 3 patients (n=120)**
  - Survival probability: 90.5% (95% CI: 77.9-100)

The survival probability is significantly different between the two groups with a p-value of <.0001.

Gustot & Fernandez et al, Hepatology 2015
## FUTILITY CRITERIA FOR TREATMENT IN ACLF-3 PATIENTS ACCORDING TO THE NUMBER OF ORGAN FAILURES 3-7 DAYS AFTER DIAGNOSIS

<table>
<thead>
<tr>
<th>Number of organ failures 3-7 days after diagnosis</th>
<th>28-day Tx free mortality</th>
<th>90-day Tx free mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 (n=14)</td>
<td>1 (7%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>2-3 (n=29)</td>
<td>16 (55%)</td>
<td>22 (75%)</td>
</tr>
<tr>
<td>4-6 (n=25)</td>
<td>24 (96%)</td>
<td>25 (100%)</td>
</tr>
</tbody>
</table>

Gustot & Fernandez et al, Hepatology 2015
SUGGESTED FUTILITY RULES IN ACLF ACCORDING TO THE EARLY CLINICAL COURSE

**Diagnosis**

ACLF

- **Medical management**
  - ICU for organ support

**Day 3-7**

- **No ACLF**
- **ACLF-1**
- **ACLF-2**
- **ACLF-3**

**Mortality rate (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>Day 28</th>
<th>Day 90</th>
<th>Day 180</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ACLF</td>
<td>10% (5-16)</td>
<td>24% (17-31)</td>
<td>38% (30-46)</td>
</tr>
<tr>
<td>ACLF-1</td>
<td>21% (11-32)</td>
<td>42% (29-54)</td>
<td>47% (34-60)</td>
</tr>
<tr>
<td>ACLF-2</td>
<td>57% (42-72)</td>
<td>74% (29-54)</td>
<td>79% (66-91)</td>
</tr>
<tr>
<td>ACLF-3</td>
<td>87% (80-95)</td>
<td>95% (90-100)</td>
<td>96% (92-100)</td>
</tr>
</tbody>
</table>

**Assessment for regular LT**

**Contraindication for LT?**

- **No**
- **Yes**

**Assessment for early 28-day LT**

- **No**
- **Yes**

**Regular LT**

- **Survival rate (95% CI)**
  - Day 180: 85% (69-95)

**Early 28-day LT**

- **Survival rate (95% CI)**
  - Day 180: Continue treatment
  - 58% (51-65)
  - 79% (54-94)
  - 35% (23-48)
  - 0% (0-10)

**Futility**

- < 4 OFs and CLIF-C ACLFs < 64*
- ≥ 4 OFs or CLIF-C ACLFs > 64*
ACCURACY OF CLIF-C ACLF SCORE IN PREDICTING MORTALITY COMPARED TO OTHER LIVER SCORES

CLIF-C ACLFs = 10 x [0.33 x CLIF-OFs + 0.04 x Age + 0.63 x ln (WBC count)-2]

Jalan et al, J Hepatol 2014
Admission of Cirrhotic patient with acute decompensation

Assess CLIF-C OF score for diagnosis of ACLF

ACLIF present

CLIF-C ACLIF score

ACLIF absent

CLIF-C AD score

Arroyo et al, J Hepatol 2015
### Acute-on-Chronic Liver Failure (ACLF) classification and expected mortality rates

**CLIF-C ACLF Score and ACLF grade. Only for patients with ACLF**

#### Score Formulae

<table>
<thead>
<tr>
<th>DATA</th>
<th>SCORES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilirubin</strong></td>
<td>[mg/dl]</td>
</tr>
<tr>
<td><strong>Serum Creatinine</strong></td>
<td>[mg/dl]</td>
</tr>
<tr>
<td><strong>Renal replacement therapy</strong></td>
<td>[Yes/No]</td>
</tr>
<tr>
<td><strong>Use of vasopressors</strong></td>
<td>[Yes/No]</td>
</tr>
<tr>
<td><strong>(Hepatorenal syndrome indication)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>West-Haven grade for HE</strong></td>
<td>[0-4]</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MAP</strong></td>
<td>[mm/Hg]</td>
</tr>
<tr>
<td><strong>Use of vasopressors</strong></td>
<td>[Yes/No]</td>
</tr>
<tr>
<td><strong>(Circulatory failure indication)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Select one</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PaO₂ (preferred)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>SpO₂</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FiO₂</strong></td>
<td>[%]</td>
</tr>
<tr>
<td><strong>Mechanical Ventilation</strong></td>
<td>[Yes/No]</td>
</tr>
<tr>
<td><strong>Total Number Failures</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CLIF Organ Failure Score</strong></td>
<td></td>
</tr>
</tbody>
</table>

LIVER SUPPORT SYSTEMS

- Detoxification systems:
  - Hemodialysis
  - Hemofiltration
  - Plasma exchange
  - Albumin dialysis (MARS)
  - Prometheus (PSF)

- Bioartificial systems

- Hepatocyte transplantation
Molecular adsorbent recirculating system (MARS)

Fractionated plasma separation and adsorption (Prometheus)

They can clear water soluble toxins but also, in contrast to hemodialysis, albumin-bound toxins
MARS SYSTEM

Adsorbers
Activated charcoal and anion exchange resins

Albumin circuit

Blood pump

MARS

Low flow
Dialysis

Albumin pump
PROMETHEUS SYSTEM

Albumin circuit

High flux hemodyalysis
ACUTE LIVER FAILURE
“THE TOXIC THEORY”

Dysfuncion:
• Cerebral
• Renal
• Circulatory
• Immune

Liver injury
Necrosis
Apoptosis

Accumulation of albumin-bound and water soluble (vasoactive) toxins

Biliary acids
Bilirubin
Prostacyclins
NO
Fatty acids
Tiols
Digoxin
Diazepam-like substances
Ammonia
Lactate
...
MARS in AoCLF (HE) III/IV

A

% of patients with HE improvement (≥2)

P < 0.01

mean cum num of improvements/person

0 12 24 36 48 60 72 84 96 108 120

hours

MELD > 30

MELD < 30

MARS

SMT

p=0.066

NS

SMT

SMT+ MARS

Trasplant-free survival (%)

p=0.066

Hassanein, Hepatology 2007
ALBUMIN DIALYSIS IN ACLF
MARS RELIEF TRIAL

- 189 patients
- Definition of ACLF: cirrhosis + bilirubin >5 mg/dl and HRS or HE ≥ 2 or serum bilirubin >20 mg/dl:
  - MARS: n = 90
  - SMT: n = 89
- Primary endpoint: transplant-free survival
- Secondary endpoints: HE and some analytical changes

Bañares et al. Hepatology 2013
CHANGES IN BASELINE PARAMETERS: DAY 4

- **Serum Creatinine**: $p=0.02$
- **Bilirubin**: $p=0.0001$
- **Platelets**: $p=0.0001$
- **INR**: $p=0.098$
- **Hb**: $p=0.009$

**% change**

- **Serum Creatinine**: $-6.4$
- **Bilirubin**: $-8.9$
- **Platelets**: $-2$
- **INR**: $6.4$
- **Hb**: $-5$

Bañares et al. Hepatology 2013
EFFECTS ON RENAL FUNCTION IN PATIENTS WITH HRS AT DAY 4

Proportion of patients with Creatinine value < 1.5 mg/dL

- SMT: 10/34 (26.3%)
- SMT+ MARS: 16/34 (47.1%)

p = 0.06

Bañares et al. Hepatology 2013
EFFECTS ON HEPATIC ENCEPHALOPATHY AT DAY 4

\[ p = 0.07 \]

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMT</td>
<td>13/34</td>
<td>38.2%</td>
</tr>
<tr>
<td>SMT+ MARS</td>
<td>15/24</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

\[ p = 0.07 \]
EFFECT OF MARS ON 28 DAYS TRANSPLANT-FREE SURVIVAL

ITT population
Overall 28 days mortality:
SMT: 39.3%
SMT + MARS: 41.4%
Log-rank test: $P=0.79$

PP population
Overall 28 days mortality:
SMT: 40%
SMT + MARS: 41.2%
Log-rank test: $P=0.88$
ALBUMIN DIALYSIS IN ACLF
PROMETHEUS TRIAL

- 145 patients
- Definition of ACLF: CH + bilirubin >5 mg/dl + Child-Pugh >10 points
- Number of patients:
  - 68 SMT
  - 77 SMT+FPSA (fractionated plasma separation and adsorption)
- Primary endpoint: 28 day survival
- Predefined subanalysis in type-1 HRS and in high MELD score (> 30 p) groups

Kribben et al. Gastroenterology 2012
PROMETHEUS RCT: 90-day survival

Kribben et al. Gastroenterology 2012
47 patients

Definition of ACLF: bilirubin \( \geq 5 \) mg/dl and INR \( \geq 1.5 \) and ascites or hepatic encephalopathy (APASL criteria)

Exclusion criteria: sepsis, MOF, grade 3-4 hepatic encephalopathy

Blinded placebo controlled trial:
- 23 G-CSF 5 μg/Kg SBC (12 doses)+SMT
- 24 SMT

Primary endpoint: 60 day survival

Kribben et al. Gastroenterology 2012
GRANULOCYTE COLONY-STIMULATING FACTOR IN ACLF
PLASMA EXCHANGE IN ACLF

- Open label pilot study: 10 patients

- Inclusion criteria: ACLF defined by acute deterioration of liver function within the last 2-4 weeks with serum bilirubin ≥ 5 mg/dl and hepatic encephalopathy (≥ grade 2) and/ or renal failure (serum creatinine ≥ 2 mg/dl).

- Treatment schedule: 6 sessions/patient in 10 days; 5% albumin as the main replacement fluid (≈70% of plasma exchanged)

- Main endpoint: safety
EFFECTS OF PLASMA EXCHANGE ON THE PROBABILITY OF DEATH

<table>
<thead>
<tr>
<th></th>
<th>Plasma exchange</th>
<th>Controls</th>
<th>Survival p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality a 28 días</td>
<td>3(30,0)</td>
<td>23(57,5)</td>
<td>0,077</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>4(40,0)</td>
<td>26(65,0)</td>
<td>0,098</td>
</tr>
<tr>
<td>6 month mortality</td>
<td>4(40,0)</td>
<td>27(67,5)</td>
<td>0,078</td>
</tr>
</tbody>
</table>
A 52 year old man with alcoholic cirrhosis, previous history of ascites, on treatment with diuretics and actively working as civil engineering, was admitted to hospital with CA pneumonia and rapid deterioration of his clinical condition. On admission the patient showed ascites, jaundice (bilirubin 21 mg/dl), grade III hepatic encephalopathy, renal failure (serum creatinine 2.2 mg/dl) and coagulopathy (INR: 2.6)

Grade of ACLF at admission? Grade 3
Number of organ failures?
No vasopressors, MAP: 72 mmHg, PaFi02: 225
Number of organ failures: 4
Prognosis? 89% mortality at 28 days
The patient was admitted to the ICU: IV antibiotics, mechanical ventilation due to hepatic encephalopathy.

Four days later: progressive impairment of liver (bilirubin 30 mg/dl), renal (RRT), respiratory (PaFiO2: 150) and vascular function (noradrenalin), INR: 2.7

Futility?
CLIF-C ACLF score?
CLIF-C ACLF score: 79

Treatment withdrawal
CLINICAL CASE 2

A 56 year old man with alcoholic cirrhosis, no previous decompensations. He was admitted to hospital with jaundice and ascites: severe alcoholic hepatitis (transjugular biopsy proven).

On admission the patient showed ascites, jaundice (bilirubin 34 mg/dl), grade I hepatic encephalopathy and renal failure (serum creatinine 2.03 mg/dl). No vascular, respiratory or coagulation failure (INR: 2.4)


Grade of ACLF? Grade 2

Tx: steroids+NAC
CLINICAL CASE 2

After 1 week of steroid treatment: ascites, bilirubin 44 mg/dl, grade I hepatic encephalopathy and renal dysfunction (serum creatinine 1.6 mg/dl). No vascular, respiratory or coagulation failure (INR: 2.37).

Lille score: 0.995

Tx: stop steroids

CLIF-C ACLF score? 63 points but just 1 OF

Tx: Plasma exchange therapy
### Score Formulae

<table>
<thead>
<tr>
<th>DATA</th>
<th>SCORES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Billirubin</strong> 44 mg/dl</td>
<td>Liver score 3</td>
</tr>
<tr>
<td><strong>Serum Creatinine</strong> 1.69 mg/dl</td>
<td>Liver failure Yes No</td>
</tr>
<tr>
<td><strong>Renal replacement therapy</strong></td>
<td>Kidney score 1</td>
</tr>
<tr>
<td><strong>Use of vasopressors</strong></td>
<td>Renal failure Yes No</td>
</tr>
<tr>
<td>(Hepatorenal syndrome indication)</td>
<td></td>
</tr>
<tr>
<td><strong>West-Haven grade for HE</strong></td>
<td>Brain score 2</td>
</tr>
<tr>
<td><strong>INR</strong> 2.37</td>
<td>Cerebral failure Yes No</td>
</tr>
<tr>
<td><strong>MAP</strong> 68 mm/Hg</td>
<td>Coagulation score 2</td>
</tr>
<tr>
<td><strong>Use of vasopressors</strong></td>
<td>Coagulation failure Yes No</td>
</tr>
<tr>
<td>(Circulatory failure indication)</td>
<td>Circulation score 2</td>
</tr>
<tr>
<td><strong>Select one</strong></td>
<td>Circulation failure Yes No</td>
</tr>
<tr>
<td><strong>PaO2 (preferred)</strong> 99</td>
<td>Lung score 2</td>
</tr>
<tr>
<td><strong>SpO2</strong> 35 %</td>
<td>Respiratory failure Yes No</td>
</tr>
<tr>
<td><strong>Mechanical Ventilation</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total Number Failures**: 1  
**CLIF Organ Failure Score**: 12  

**ACLF-Grade 1**: The patient has ACLF

### Probability of dying

| Probability of dying at 1 month | 68 %  |
| Probability of dying at 3 month | 84 %  |
| Probability of dying at 6 month | 87 %  |
| Probability of dying at 12 month | 90 %  |
CONCLUSIONS

- ACLF is not a “terminal event”. Its prognosis depends on the severity of systemic inflammation and on the number of organ failures (not on the precipitating event).

- It is especially severe in patients without prior decompensation.

- One-third of patients die within 28 days

- It is a highly dynamic and potentially reversible condition.
CONCLUSIONS

- Prognosis is better determined after initial intervention (3-7 days): evaluation of the number of OF and CLIF-C ACLF score.

- MARS improves HE in ACLF but has no impact on survival (as Prometheus)

- Liver transplantation is the only effective therapy

- Need for new treatments (MSC therapy, bioartificial liver support systems…) and for confirmatory studies (G-CSF, plasma exchange)