Acute liver failure - syndromes and management

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Acute Liver Failure

• Acute liver failure
  – Fulminant liver failure

• Acute liver failure with underlying cirrhosis
  – Acute on chronic liver failure (ACLF)
Cirrhosis progression

• Cirrhosis
  – Compensated
  – Decompensated
    • Ascites
    • Variceal bleeding
    • encephalopathy

• Decompensation associated with mortality (3-5 yrs)
Acute on Chronic Liver failure

- Decompensation associated with organ failures and poor survival
- 30d survival 25-40%

Moreau Gastroenterology 2013;144:1426–1
ACLF

- No agreed on definition
  - Western (US/Europe vs Asian)
  - Differing inclusion/exclusion criteria

- EASL-CLIF
  - Stratification by defined organ failures
  - SOFA
ACLF Grade and Outcome

Figure 4: Mortality in patients admitted to hospital with cirrhosis, by ACLF grade

Bernal Lancet 2015; 386: 1576
# ACLF - Precipitants

<table>
<thead>
<tr>
<th>Condition</th>
<th>CANONIC n=303, (9)</th>
<th>Shi et al n=405, (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation hepatitis B</td>
<td>--</td>
<td>145 (35.8)</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>98 (32.6)</td>
<td>113 (27.9)</td>
</tr>
<tr>
<td>GI haemorrhage</td>
<td>40 (13.2)</td>
<td>40 (9.8)</td>
</tr>
<tr>
<td>Active alcoholism within the past 3 months</td>
<td>69 (24.5)</td>
<td>25 (6.1)</td>
</tr>
<tr>
<td>Other (TIPSS, surgery, large volume paracentesis without albumin, hepatitis, alcoholic hepatitis)</td>
<td>25 (8.6)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Not identifiable</td>
<td>126 (43.6)</td>
<td>83 (20.4)</td>
</tr>
<tr>
<td>More than one</td>
<td>39 (13.5)</td>
<td>36 (8.9)</td>
</tr>
</tbody>
</table>
ACLF - pathophysiology

- Systemic inflammation
- Degree of inflammation related to outcome
ACLF - management

• Treat precipitating process
  – Infection
  – Alcoholic hepatitis - steroids
• Organ supportive therapy
  – Standard ICU management
  – If renal failure
    • CVVH
    • Use albumin/terlipressin
ACLF - management

- Liver support therapies (e.g. MARS)
  - Improved biochemistries
  - No evidence of outcome benefit
- Transplant
  - Yes, but controversial
    - Timing
    - Outcome, esp. with MOFS
- Immunotherapies
  - GCSF
  - Stem cells
Acute Liver Failure

- Severe acute liver injury
  - Encephalopathy
  - Synthetic dysfunction (INR > 1.5)
- No pre-existing cirrhosis
  - Encephalopathy within 26 wks of illness
- Alcoholic hepatitis excluded
  - ACLF
ALF - etiology

- Drugs
- Viral
- Autoimmune
- Vascular
- Toxins
- Shock liver
- HELLP
- Wilson disease
- Heat stroke
Etiology

• Geographic differences in most common causes

• Acetaminophen (paracetamol)
  – US, UK (approx 50%)

• Viral (Hep B)
  – France, Japan (45%)
Diagnosis

• Consider ALF if:
  – Mental status changes
  – Jaundice
  – RUQ pain

• LFTs

• If abnormal INR

• ABG, ammonia, lactate

• History important
  – Particularly for acetaminophen
Outcomes

• Dependent on etiology
• Improved outcomes in recent years
• Overall survival 75%
  – Transplant 96%
  – Without Tx 56%
• Acetaminophen more favorable outcomes
Management

• Specific treatment
  – n-acetyl cysteine
• Early referral to specialist center
• Medical support
  – Recovery
  – Transplant
  – Death
Specific Concerns
Cerebral Edema

- Glutamine production
- Oxidative stress
- hyponatremia
- Astrocyte swelling
- $\uparrow$ CBF

Specific Concerns
Cerebral Edema

• Uncommon in HE grade 1 & 2
• Grade 3 30%
• Grade 4 75%
• Higher risk
  – Higher ammonia (> 150)
  – Rapid rise in ammonia

Clemmesen  Hepatology 1999;29:648–653
Cerebral Edema Management

• As for other raised ICP
• Intubation, ventilation for grade 3 HE
• ICP monitoring
  – Controversial
  – No outcome benefit shown
Cerebral Edema Management

• Treat exacerbations (or high risk)
  – hyperventilation
  – Osmotic therapy (hypertonic saline vs mannitol)
  – Barbiturate coma

• Consider mild hypothermia (32-35°C)
  – Success in resistant ICP elevation
  – Or not

Jalan Gastroenterology. 2004;127(5):1338
Specific Concerns
Infection

• High risk for infection
• Prophylactic antimicrobials
• *or* treat at initial suspicion of infection
Specific Concerns
Coagulopathy

- PT/INR very high
- Normal thrombin generation
- No indication for prophylactic management
- Viscoelastic testing
ALF – prognostication
Transplant Benefit

• King’s College Criteria (1989)
• Still used
• May need revision in modern era

King’s College criteria

**ALF due to paracetamol**

- Arterial pH < 7.3 after resuscitation and > 24 h since ingestion
- Lactate > 3 mmol/L or
- The 3 following criteria:
  - Hepatic encephalopathy > grade 3
  - Serum creatinine > 300 μmol/L
  - INR > 6.5

**ALF not due to paracetamol**

- INR > 6.5 or
- 3 out of 5 following criteria:
  - Aetiology: indeterminate aetiology hepatitis, drug-induced hepatitis
  - Age < 10 years or > 40 years
  - Interval jaundice-encephalopathy > 7 days
  - Bilirubin > 300 μmol/L
  - INR > 3.5
Improved Outcomes
Acetaminophen OD

• 64 patients 2010 – 2016
• N-acetyl cysteine
• Prophylactic antimicrobials
• “4H” management
  – Mild hyperventilation
  – High-dose ultrafiltration
  – Hypothermia
  – Hypernatremia
• No ICP monitoring
• No transplantation

Porteous Liver Transplantation 2019;25: 35–44
Improved Outcomes
Acetaminophen

• 80% survival
• 70% meeting KC criteria
• UK Registration criteria for super-urgent transplant
  – More accurate than KC criteria

Porteous Liver Transplantation 2019;25: 35–44
# UK Registration Criteria for Super-Urgent Liver Transplantation

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiology</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>APAP</td>
<td>pH &lt; 7.25 more than 24 hours after overdose and after fluid resuscitation. Coexisting PT &gt; 100 seconds or INR &gt; 6.5 and serum creatinine &gt; 300 µmol/L or anuria, and grade 3-4 encephalopathy</td>
</tr>
<tr>
<td>2</td>
<td>APAP</td>
<td>Significant liver injury and coagulopathy following the exclusion of other causes of hyperlactatemia after adequate fluid resuscitation: arterial lactate &gt; 5 mmol/L on admission and &gt; 4 mmol/L 24 hours later in the presence of clinical HE</td>
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<tr>
<td>3</td>
<td>APAP</td>
<td>2 of the 3 criteria from category 2 with clinical evidence of deterioration (eg, increased ICP, FiO2 &gt; 50%, increasing inotrope requirements) in the absence of clinical sepsis</td>
</tr>
<tr>
<td>4</td>
<td>APAP</td>
<td>The presence of clinical HE is mandatory and PT &gt; 100 seconds or INR &gt; 6.5, or any 3 of the following: age &gt; 40 or &lt; 10 years; PT &gt; 50 seconds or INR &gt; 3.5; any grade of HE with jaundice to encephalopathy time &gt; 7 days; serum bilirubin &gt; 300 µmol/L</td>
</tr>
<tr>
<td>5</td>
<td>Favorable non-APAP (eg, viral hepatitis, cocaine)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Unfavorable non-APAP (eg, indeterminate ALF, DILI)</td>
<td></td>
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<tr>
<td>7</td>
<td>Acute Wilson’s disease or Budd-Chiari syndrome</td>
<td>A combination of coagulopathy and any grade of encephalopathy</td>
</tr>
</tbody>
</table>


James Findlay. 11-й Британо-Український Симпозіум. Київ, 2019
ALF – future directions

• Liver replacement devices
  – No evidence of benefit

• GCSF/Stem cells
  – Experimental
  – Small series in ACLF
Acute Liver Failure
Summary

• ACLF
  – Recent concept
  – Developing understanding

• ALF
  – Improving outcomes
  – Re-addressing outcome prediction
Thank you

https://youtu.be/Ydw2Mk-r2kw