Current Concepts in Diagnosis and Management of Acute Liver Failure

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Learning Objectives

• Define acute liver failure
• List the common etiologies of ALF
• Describe how to determine prognosis in ALF
• List the complications of ALF
• Identify basic management strategies in ALF
• Explain how to use the ALF Checklist
Clinical Case

- 50-year-old Japanese woman
- Chronic hepatitis B (sAg+)
- Diagnosed with breast cancer
- Chemotherapy with doxorubicin, cyclophosphamide, paclitaxel
- ALT: 23 → 42 → 103
Clinical Case

- Chemotherapy stopped

<table>
<thead>
<tr>
<th></th>
<th>0.5</th>
<th>0.9</th>
<th>1.7</th>
<th>3.0</th>
<th>17.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bili (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>92</td>
<td>1596</td>
<td>3542</td>
<td>3949</td>
<td>7319</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>103</td>
<td>2120</td>
<td>3758</td>
<td>4092</td>
<td>4583</td>
</tr>
<tr>
<td>INR</td>
<td>1.0</td>
<td>1.3</td>
<td>2.0</td>
<td>2.4</td>
<td>10.1</td>
</tr>
</tbody>
</table>

HBV DNA > 1 billion IU/mL
Initial Management

- HOB = 30°
- Sedation
- Neuro checks
- Finger sticks
- N-Acetylcysteine
- Mannitol

- Hypertonic (3%) saline
- Permissive hypothermia
- Permissive hypocapnea
- Diagnostic evaluation
- Liver transplant evaluation
Acute Liver Failure

Coagulopathy

Encephalopathy

No pre-existing liver disease
# Grades of Encephalopathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Changes in behavior, sleep cycle reversal</td>
</tr>
<tr>
<td>2</td>
<td>Disorientation, lethargy, asterixis</td>
</tr>
<tr>
<td>3</td>
<td>Marked confusion, obtundation</td>
</tr>
<tr>
<td>4</td>
<td>Comatose, unresponsive, loss of reflexes</td>
</tr>
</tbody>
</table>
Clinical Outcome

Necrosis

Regeneration
Clinical Outcome

- Died without transplant: 28%
- Transplanted: 24%
- Spontaneous survivors: 48%

Overall Survival 70%
Etiologies of ALF

- Acetaminophen: 46%
- Drug
- Viral
- Autoimmune
- Indeterminate: 15%
- Pregnancy-related
- Malignancy
- Wilson’s Disease
- Budd Chiari
- Ischemia
- Toxins/medications
Complications

- Hepatic encephalopathy & cerebral edema
- SIRS & multi-organ system failure
- Renal failure
- Infection & sepsis
- Hypoglycemia
- Bleeding?
Prognosis

Transplant-Free Survival

- Coma I-II
- Coma III-IV

Conditions:
- APAP
- HAV
- Ischemia
- AFLP
- HBV
- AIH
- Drug
- Indet
King’s College Criteria

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>Non-acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH &lt;7.30</td>
<td>INR &gt;6.5</td>
</tr>
<tr>
<td>Or all of the following:</td>
<td></td>
</tr>
<tr>
<td>INR &gt;6.5</td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt;3.4 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4 encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Or any 3 of the following:</td>
<td></td>
</tr>
<tr>
<td>Non-A, non-B, idiosyncratic</td>
<td></td>
</tr>
<tr>
<td>Jaundice to HE &gt;7 days</td>
<td></td>
</tr>
<tr>
<td>Age &lt;10 or &gt;40 years</td>
<td></td>
</tr>
<tr>
<td>INR &gt;3.5</td>
<td></td>
</tr>
<tr>
<td>Bilirubin &gt;17 mg/dL</td>
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</tbody>
</table>

O’Grady et al Gastroenterology 1989
Prognosis

- Etiology
- Coma grade
- King’s College Criteria
- Clichy Criteria
- Factor V
- MELD
- Phosphate
- ALFSG (Charleston) model

Koch et al Clin Gastroenterol Hepatol 2016
Ammonia and Prognosis

Clemmesen et al. Hepatology 1999
Initial Management of ALF

- Supportive
- Prevent complications
- Transfer to ICU/liver transplant center
- Assess severity of liver and other organ injury
- Determine etiology of liver injury

Cardoso et al J Crit Care 2017
Initial Management of ALF

- Correct factors contributing to encephalopathy
- Do not correct INR in absence of active bleeding or invasive procedure
- Surveillance for infection, low threshold for starting antibiotics
- Specific therapies for known or suspected etiologies
## Specific Therapies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine (NAC)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Delivery</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Entecavir</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Budd Chiari</td>
<td>Anticoagulation, TIPS</td>
</tr>
<tr>
<td>Amanita</td>
<td>Charcoal, NAC, PCN G, silibinin</td>
</tr>
</tbody>
</table>
N-Acetylcysteine (NAC)

- Increases glutathione stores
- Prevents formation of toxic metabolites of acetaminophen
- Effectively prevents or minimizes hepatotoxicity from acetaminophen overdose
NAC for Non-APAP ALF

Lee et al Gastroenterology 2009

NAC, HE grade I-II
Cerebral Edema and ICH
## Management of ICH

### Prevention

- Hypertonic saline
- Facilitate cerebral drainage
- Minimize stimulation
- Permissive hypothermia
- Permissive hypocapnea
- Continuous RRT

### Treatment

- Mannitol
- Pressors
- Sedation
- Therapeutic hypothermia
- Hyperventilation
- Barbiturate coma
Cerebral Edema and ICP Monitoring

• ICP monitored patients leads to more ICH-directed therapies:
  – Mannitol
  – Hypertonic saline
  – Hypothermia
• No difference in mortality

Karvellas, Fix et al Crit Care Med 2014
Acute Kidney Injury in ALF

• AKI in up to 70% of ALF, worse overall survival
• Indications for RRT:
  – Classic: acidosis, hyperkalemia, anuria/fluid overload
  – Removal of toxins (e.g., ammonia)
  – Increase serum sodium
  – Lower core temperature
• Only use continuous RRT in ALF
  – IHD can cause increased ICP, increased mortality

Slack et al Liver Int 2014
Cardoso et al J Crit Care 2017
Cardoso et al Hepatology 2018
Extracorporeal Liver Support

- High-volume plasmapheresis
  - Significantly improves transplant-free survival
- Artificial (e.g., MARS, Prometheus)
  - Improvement in jaundice, encephalopathy, MAP, ICP
  - No improvement in 6-month survival
- Bioartificial (e.g., ELAD)
  - No improvement in survival

Larsen et al J Hepatol 2016
Cardoso et al J Crit Care 2017
Improvement in ALF Outcomes

- Changes in etiologies
- Decrease in prevalence of cerebral edema/ICH
- Earlier illness recognition
- Improved ICU management
- Emergency liver transplantation

Bernal et al J Hepatol 2013
Fontana et al Liver Int 2015
Cardoso et al J Crit Care 2017
Liver Transplantation for ALF

Status IA criteria

• Encephalopathy <8 weeks after onset of first symptoms
• In the ICU
• One of the following:
  – INR >2
  – Mechanical ventilation
  – On CRRT

ALF Checklist

Acute Liver Failure Checklist
Developed by the Acute Liver Failure Study Group
NOW PUBLISHED IN PLoS ONE!

A checklist for experienced providers to help manage patients with acute liver failure in the ICU
Is this the day of admission to the ICU or a subsequent day?
- Day of admission
- Subsequent day

Check all the following that apply to your patient:
- Suspected acetaminophen overdose
- Abrupt deterioration in mental status
- Serum sodium <145 mMol/L
- Intubated
- Agitated or in pain
- Spontaneous hypothermia (34-37 °C)
- Encephalopathy grade III/IV
- Spontaneously hyperventilating
- Progression of encephalopathy
- SIRS
- Clinical deterioration
- Listed for transplant
- Mean arterial pressure (MAP) <75 mm Hg despite volume repletion
- Oliguria
- Rise in creatinine >0.3 mg/dL
- Ammonia >150 μM

alfchecklist.com
Development and Pilot of a Checklist for Management of Acute Liver Failure in the Intensive Care Unit

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1 Membership of the Acute Liver Failure Study Group is listed in the Acknowledgments.

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50-year-old woman with breast cancer and ALF from reactivation of HBV during chemotherapy.
Summary

• Etiology and encephalopathy grade are important determinants of prognosis in ALF
• Initial management is supportive, aimed at preventing complications and allowing the liver time to regenerate
• Consider NAC in almost all cases of ALF
• Aggressively prevent or treat suspected ICH
• Consider early use of CRRT
• Evaluate appropriate patients for liver transplantation
• Use the ALF Checklist for help
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