ADVANCED MANAGEMENT STRATEGIES IN APAP INDUCED FULMINANT HEPATIC FAILURE

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Disclosures: None
OUTLINE

• Definition
• Prognostic Indicators
• Diagnostic evaluation
• Management of Cerebral Edema and elevated Intra-cranial pressure
• Management of other organ systems
• Evaluation for liver transplantation (LT)
• Emerging non-transplant therapies
**Definition:**

**Acute (Fulminant) Liver Failure:** Onset of hepatic encephalopathy (HE) within 8 weeks of onset of symptoms of liver dysfunction in a patient without pre-existing liver disease

**Etiologies:**

- **Drugs and toxins** (e.g. acetaminophen, minocycline, lamotrigine)
- **Viral Hepatitis** (e.g. Hep A & B, HSV, EBV)
- **Autoimmune Hepatitis**
- **Metabolic:** Wilson’s Disease
- **Vascular:** Acute Budd-Chiari syndrome, Ischemic Hepatitis
- **Pregnancy related:** Acute Fatty Liver of Pregnancy
Worldwide Causes of ALF

Bernal WB, Wendon J. NEJM 2013; 369:2525-34
Assessment of Prognosis and Criteria for LT (1)

- The ability to predict the likelihood of spontaneous recovery, or death without LT is of paramount importance.

- Many criteria/models have been proposed, but none have been adequately sensitive or specific.

- Clinical judgment for LT candidacy based on team approach, with status of HE and coagulopathy guiding decision in particular.
Assessment of Prognosis (2): King’s College Criteria

- **King’s College Criteria** for LT in Acetaminophen induced ALF \(^1\):
  - Arterial ph < 7.3 OR
  - Grade III or IV Encephalopathy And
  - INR > 6.5 And
  - Serum Creatinine > 3.4 mg/ dl

- **Clinical judgment** for LT candidacy based on team approach, with **status of HE** and **coagulopathy** guiding decision in particular

HEPATIC ENCEPHALOPATHY (HE)

- Neurologic dysfunction in the presence of acute liver failure (ALF) or acute on chronic liver failure (ACLF)

- Potential Mechanism includes conversion of Ammonia to Glutamine that induces altered neuro-transmission and astrocyte swelling

- Chronicity of liver disease in ACLF allows the development of extrahepatic mechanisms of ammonia fixation (e.g. muscle), thereby limiting the degree of hyperammonemia in ACLF compared to ALF

- Clinically graded from Stage I to IV reflecting progression from mild confusion to coma; concern for elevated intracranial pressure in ALF (in contrast to ACLF) due to acute astrocyte swelling

- HE in ALF and ACLF differs in disease manifestation, therapy and prognosis
Grading of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mental Status</th>
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<tbody>
<tr>
<td>I</td>
<td>Mild confusion, slurred speech</td>
</tr>
<tr>
<td>II</td>
<td>Lethargy, moderate confusion</td>
</tr>
<tr>
<td>III</td>
<td>Marked confusion, Sleeping but arousable</td>
</tr>
<tr>
<td>IV</td>
<td>Coma</td>
</tr>
</tbody>
</table>
Diagnostic Evaluation

• **Assess mental status** and determine stage of HE, with serial neurologic exams

• Serial LFTs and PT/INR; Note: **INR** is the most sensitive and reliable biochemical indicator of hepatic synthetic function

• Serum workup to determine potential etiology: e.g. APAP level, EtOH level, Autoimmune hepatitis markers, Viral serologies, urine Cu
Diagnostic Evaluation: Imaging Studies

- Abdominal Ultrasound with Dopplers to assess hepatic parenchyma and assess vascular patency

- Non contrast Head CT as workup of decreased mental status to evaluate for bleed, and to confirm ICP monitor position (Note: CT insensitive for detecting early cerebral edema in ALF)

- Abdominal CT or MRI with contrast to rule out chronic liver disease (that would prevent emergent listing for LT), and assess vascular patency of portal vein, hepatic vein and IVC
Management of APAP Hepatoxicity

• **Pharmacologic:** IV or PO N-acetylcysteine (NAC)
  – IV regimen: 150 mg/kg LD, 12.5 mg/hr infusion x4h, then 6.25 mg/hr gtt (*no studies comparing efficacy of IV and PO NAC*)
  – Continue NAC till firm evidence of improved hepatic function (e.g. resolution of HE, INR < 1.5)

• **Liver Assist Devices:**
  – Artificial Liver Support (e.g. ‘MARS’ Albumin dialysis)
  – Bioartificial Liver Support (e.g. ELAD therapy)
Initial Management of Advanced HE

Grade 3/4 HE

Elective Endotracheal Intubation; IV Lidocaine to decrease DL induced ICP increase

Sedation and Analgesia with Propofol and Fentanyl drips to optimize patient-ventilator synchrony

Targets:

- **MAP** > 80 mm Hg (with goal to keep CPP > 60 mm Hg; CPP = MAP – ICP)
- **Na** 145-155 mmol/L
- **T** 33-35 °C

*(Role of ICP Monitoring controversial)*
Pharmacologic Management of Elevated ICP

**Mannitol** IV; 0.25-0.5g/kg boluses ; D/c if Serum Osm > 320mOsm/L or renal failure

**Hypertonic Saline:** 23.4% 30ml boluses Q2h with target serum Na of 145-155 mmol/L

**Hypothermia** with target of 33-35°C; external or internal cooling

**Barbiturate Coma:** thiopental 3-5mg/kg LD, 1-3 mg/kg/hr drip; EEG monitoring

*No established role yet for targeting hyperammonemia (> 150 –200 umol/ L)*
Organ System Specific Issues (1)

- **Cardiovascular:**
  - Norepinephrine 1\textsuperscript{st} vasoactive agent of choice for shock or CPP optimization
  - 2\textsuperscript{nd} line vasoactive agent: consider low dose vasopressin
  - Avoid Epinephrine due to potential side effect of mesenteric ischemia and decreased hepatic perfusion
  - IV access: If significantly ↑ICP, consider avoiding IJ site, which may impede CNS venous return
Organ System Specific Issues (2)

• Pulmonary:
  – No consensus regarding MV modes/strategies
  – Lung protective ventilation for ALI
  – Least PEEP to achieve adequate oxygenation (to decrease PEEP related ICP ↑)
  – Minimize ET suctioning and manipulation
  – HOB elevation to 30° to decrease ICP and for VAP prophylaxis
Organ System Specific Issues (3)

- Renal:
  - Acute Kidney Injury (AKI) in ALF likely not due to Hepatorenal Syndrome (HRS), which occurs in the setting of chronic portal hypertension.
  - If indication for Renal replacement therapy (RRT), initiate Continuous RRT (CRRT) even in hemodynamically stable patients for optimal hemodynamic and metabolic support.
  - No current recommendations to initiate CRRT for treatment of ↑ICP in the absence of AKI. (*Single center study suggests successful ammonia elimination with high volume, i.e. 90ml/kg/h, hemofiltration*)
  - During RRT, use bicarbonate buffer solutions, since both citrate and lactate require biotransformation to HCO₃ in the liver.

Organ System Specific Issues (4)

- **Hematologic: Coagulopathy**
  
  - Since the PT/INR is the best measure of hepatic synthetic function (and recovery), do not administer FFP if no active bleeding
  
  - Use **Recombinant F7a** (40ug/kg) for transient correction of INR for invasive procedures; therapeutic window of ~ 1hr; replete other factors of the coagulation cascade with FFP & cryoprecipitate (for fibrinogen < 100mg/dl) prior to RF7a dose
  
  - In the event of bleeding refractory to FFP and cryoprecipitate, optimize Plt to > 50, and consider antifibrinolytic agents and plasma exchange
  
  - GI bleed prophylaxis with IV PPI
Organ System Specific Issues (5)

- **Infectious Disease:**
  - Insufficient data to recommend routine use of prophylactic antibiotics
  - Consider empiric *antibacterial* and *antifungal* coverage in advanced HE, shock, and patients listed for LT
  - In the setting of ALF combined with AKI, consider empiric coverage with voriconazole for Aspergillus

- **Nutrition:**
  - *Enteral feeding* with high caloric density feeds to avoid excess free water and hypo-osmolality, which may worsen cerebral edema
  - *Glycemic control:* Since the ALF patient is at risk for hypoglycemia, consider liberal approach with target serum glucose < 150mg/dl
Evaluation for Liver Transplantation (LT)

• Early referral to LT center
  – consider transfer to LT/tertiary care center even if not LT candidate to facilitate neuro-intensive care /extracorporeal support

• Prior to Transport:
  – Consider elective ET intubation for airway protection
  – Large bore IV access given risk of worsening coagulopathy
  – Precise communication regarding HE grade and lab trends
  – Facilitate early hepatic imaging with CT or MRI, or bedside US, in particular to rule out chronic liver disease

• At LT center:
  – Confirmation of diagnosis of ALF, and emergent listing as \textbf{Status 1 (non MELD)} after standard serum and imaging workup, and absence of contraindications to LT
Liver Assist Devices

• Categories:
  – Artificial (e.g. MARS, Molecular Adsorbent Recirculating System)
  – Bio-artificial (e.g. ELAD) liver support systems.

• MARS is FDA approved for treatment of ALF due to drugs or toxins

• Multi-center ELAD trial examining its efficacy in alcoholic liver disease being initiated

• Further studies required to confirm efficacy of above devices
Principles of MARS® Therapy

- MARS® FLUX 2.1 membrane
  - PAES membrane
- Selective removal of solutes
  - Cut-off point ~50,000 Da
  - High adsorptive capacity
- Higher availability of toxin-binding sites in albumin dialysate
- Presence of free-floating toxins in the serum
MARS® FLUX 2.1 Toxin Removal

Table 1. Removal of Substances During Albumin Dialysis MARS

<table>
<thead>
<tr>
<th>Albumin-Bound Substances</th>
<th>Water-Soluble Substances</th>
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<tbody>
<tr>
<td>Benzodiazepines*†</td>
<td>Ammonia</td>
</tr>
<tr>
<td>Bilirubin, conjugated</td>
<td>Aromatic amino acids</td>
</tr>
<tr>
<td>Bilirubin, unconjugated</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Bile acids</td>
<td>Interleukin 6</td>
</tr>
<tr>
<td>Copper</td>
<td>Tryptophan</td>
</tr>
<tr>
<td>Furancarboxylic acid</td>
<td>Tumor necrosis factor alpha</td>
</tr>
<tr>
<td>Indoyxlsulfate</td>
<td>Urea</td>
</tr>
<tr>
<td>Middle- and short-chain fatty acids</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>Para-cresol†</td>
<td></td>
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<tr>
<td>Protoporphyrin</td>
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Renal Replacement Therapy
Treatment Regimen

- FDA approved for treatment of ALF due to drugs or toxins and for advanced HE in ACLF

- 8 hours of MARS therapy / day for 3 consecutive days. Albumin dialysate: 600 ml of 16% albumin

- Exchange of MARS cartridges after every treatment session

- May continue CRRT portion of circuit after completion of MARS therapy

- Heparin or citrate anticoagulation
Beneficial Effects of MARS *(Case reports/series)*

- Improvement of jaundice and pruritis
- Improvement of hemodynamic instability (NO removal?)
- Reduction in portal pressure
- Reduction in ICP in ALF, and hepatic encephalopathy in ACLF
- Improvement of renal function in HRS

*MARS effect on bioavailability of highly protein bound drugs (including NAC) awaits further study*
RCTS with MARS

<table>
<thead>
<tr>
<th>Study</th>
<th>Device</th>
<th>Study population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heemann (Ref. [34])</td>
<td>MARS</td>
<td>AoCLF ($n = 24$)</td>
<td>Improvement of 30-day survival</td>
</tr>
<tr>
<td>Hassanien (Ref. [32])</td>
<td>MARS</td>
<td>Hepatic encephalopathy ($n = 70$)</td>
<td>Improvement of encephalopathy</td>
</tr>
<tr>
<td>RELIEF (Ref. [35])</td>
<td>MARS</td>
<td>AoCLF ($n = 189$)</td>
<td>No effect on 28-day survival</td>
</tr>
<tr>
<td>HELIOS (Ref. [36])</td>
<td>Prometheus</td>
<td>AoCLF ($n = 145$)</td>
<td>No effect on 28-day survival</td>
</tr>
<tr>
<td>FULMAR (Ref. [31])</td>
<td>MARS</td>
<td>ALF ($n = 102$)</td>
<td>No effect on survival</td>
</tr>
</tbody>
</table>

Current Practice:

- Bridge to spontaneous recovery in ALF
- Bridge to transplant in ALF and ACLF
- Treatment of intractable pruritis and HE in ACLF
ELAD Synopsis

- Form of Bioartificial Liver Support involving treatment with hepatocytes (mimics both detoxifying and synthetic functions of the liver)

- Prior small studies demonstrate a non-statistical survival benefit in alcohol induced liver disease (AILD) and ALF

- Multi-center studies in progress to study the efficacy of ELAD in AILD and ALF
ELAD® C3A Cells

Allogeneic Cell Therapy

- C3A hepatocytes divide to fill available extra-capillary space in the cartridges
- Plasma flows through semipermeable hollow fibers
  - Bidirectional diffusion between UF and C3A cell
  - Toxins processed and metabolites secreted across membrane to UF
Summary

• Early referral to Liver Transplant Center

• Serial Neurologic exams

• Elective Intubation for G3/4 HE

• Aggressive management of ICP and CPP with pharmacologic therapy

• Avoid treatment with FFP in the absence of bleeding in order to use the INR as a prognostic indicator

• Use of recombinant F7A for transient reversal of coagulopathy for invasive procedures

• If RRT is indicated, initiate CRRT for optimal ICP management

• Empiric antibacterials and antifungals for worsening clinical status in anticipation of LT