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

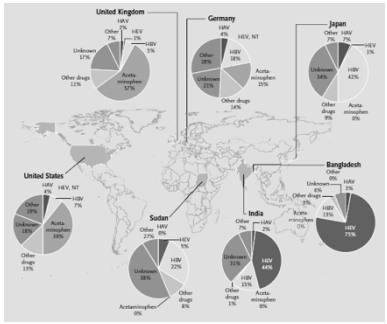
Definition:

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

1. O'Grady et al. Gastroenterology 1989; 97: 439

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

Grade	Mental Status
I	Mild confusion, slurred speech
II	Lethargy, moderate confusion
III	Marked confusion, Sleeping but arousable
IV	Coma

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 6.25mg/ 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

↓ (*Role of ICP Monitoring controversial*)

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

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 1st vasoactive agent of choice for shock or CPP optimization
  - 2nd 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* [1])
  - During RRT, use bicarbonate buffer solutions, since both citrate and lactate require biotransformation to HCO_3 in the liver

1.Slack et al. Liver International 2014; 34: 42-8

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

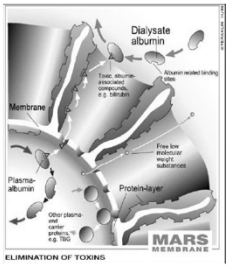
Evaluation for Liver Transplantation (LT)

- 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 **Status 1(non MELD)** after standard serum and imaging workup, and absence of contraindications to LT

Liver Assist Devices

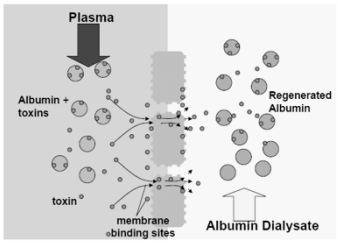
- Categories:
  - **Artificial** (e.g. MARS, Molecular Adsorbent Recirculating System)
  - **Bio-artificial** (e.g. ELAD) liver support systems.
- MARS is FDA approved for treatment of ALF due to drugs or toxins
- Multi-center ELAD trial examining its efficacy in alcoholic liver disease being initiated
- 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



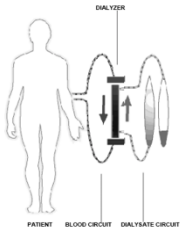
Stange J, Mitzner S. Int J Artif Organs. 1996 Nov;19(11):677-91

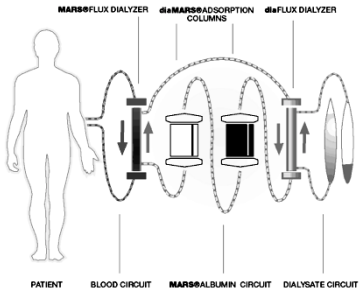
Table 1. Removal of Substances During Albumin Dialysis MARS

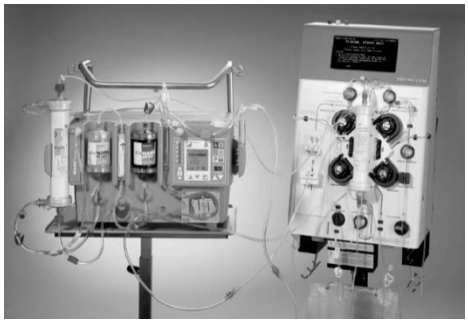
Albumin-Bound Substances	Water-Soluble Substances
Benzodiazepines*†	Ammonia
Bilirubin, conjugated	Aromatic amino acids
Bilirubin, unconjugated	Creatinine
Bile acids	Interleukin 6
Copper	Tryptophan
Furancarboxylic acid	Tumor necrosis factor alpha
Indoxylsulfate	Urea
Middle- and short-chain fatty acids	
Nitric oxide	
Para-cresol†	
Protoporphyrin	

Mitzner SR, Stange J,Klammt S, et al: Albumin Dialysis MARS:Knowledge from 10 years of clinical investigation. *ASAIO Journal* 2009: 498-502, 2009.

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

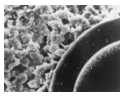
Study	Device	Study population	Outcome
Heemann (Ref. [34])	MARS	AoCLF ($n = 24$)	Improvement of 30-day survival
Hassanien (Ref. [32])	MARS	Hepatic encephalopathy ($n = 70$)	Improvement of encephalopathy
RELIEF (Ref. [35])	MARS	AoCLF ($n = 189$)	No effect on 28-day survival
HELIOS (Ref. [36])	Prometheus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

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

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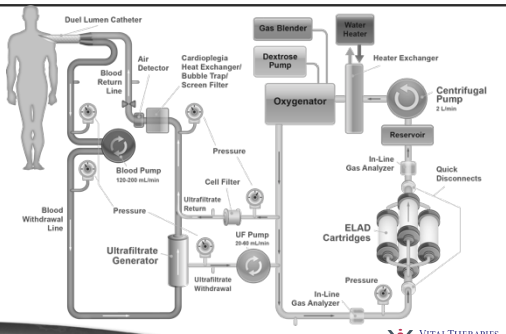
ELAD System Schematic



CONFIDENTIAL 32 VitalTherapies

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