Fulminant Hepatic Failure

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Definitions

• **Classic**: Development of hepatic encephalopathy within 8 weeks of initiation of symptoms in a patient without known chronic liver disease.

• **Practical**: Development of:
  – hepatic encephalopathy and coagulopathy (INR > 1.5)
  – within 26 weeks from the onset of jaundice,
  – in patient without known chronic liver disease.
Grades of Hepatic Encephalopathy
(Porto-Systemic Encephalopathy – PSE)

- **Grade I:**
  - Inverse sleep pattern, personality change, slight change in mental status. (GCS=14-15)
  - Normal EEG.

- **Grade II:**
  - Confusion, drowsiness, asterixis. (GCS=11-13)
  - Abnormal EEG with generalized slowing.

- **Grade III:**
  - Incoherence, stupor, agitation. (GCS=8-10)
  - Abnormal EEG.

- **Grade IV:**
  - Unresponsiveness, coma, decerebrate posturing, seizures, areflexia. (GCS<8)
  - Abnormal EEG.
Incidence

• *Incidence*:
  - 2300-2800/year in USA;
  - 6% of adult transplants;
  - 6% of liver-related deaths;
  - 0.1% of deaths in USA.
Factors Affecting Survival in FHF

- Acuteness of illness
- Etiology
- Brain Edema/ Intracranial Hypertension
- Acute Kidney Injury
- Superimposed Infection (bacterial or fungal)
Acuteness of Illness
Subtypes of (Fulminant) Hepatic Failure

- **Hyperacute:** encephalopathy in < 8 days from jaundice.
- **Acute:** encephalopathy 8 – 28 days from onset of jaundice.
- **Subacute:** encephalopathy from 29 days to 26 weeks after onset of jaundice
# Features of ALF by Type


<table>
<thead>
<tr>
<th>Feature</th>
<th>Hyper-Acute</th>
<th>Acute</th>
<th>Sub-Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of HE (days)</td>
<td>&lt;= 7</td>
<td>8d – 56</td>
<td>&gt; 56</td>
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<tr>
<td>Age (years)</td>
<td>25</td>
<td>25</td>
<td>45</td>
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<tr>
<td>Cerebral edema %</td>
<td>90</td>
<td>67</td>
<td>9</td>
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<tr>
<td>Ascites %</td>
<td>0</td>
<td>7</td>
<td>62</td>
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<tr>
<td>HRS %</td>
<td>20</td>
<td>35</td>
<td>62</td>
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<tr>
<td>Recovery %</td>
<td>75</td>
<td>40</td>
<td>&lt; 5</td>
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<tr>
<td>Common Etiology</td>
<td>APAP</td>
<td>Viral</td>
<td>DILI</td>
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<tr>
<td></td>
<td>Mushrooms</td>
<td>Pregnancy</td>
<td>Unknown</td>
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<tr>
<td></td>
<td>Vascular</td>
<td>Vascular</td>
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Etiology
Brain Edema/ Intracranial Hypertension
Acute Kidney Injury
FHF
Expected Survival by Etiology, Brain Edema & AKI

- Tylenol + Brain edema + AKI: 53%
- Tylenol + Brain edema: 71%
- Tylenol + NO Brain edema: 100%

% Survival
FHF
Expected Survival by Etiology, Brain Edema & AKI

- Hep A/B + Brain edema + AKI: 30%
- Hep A/B + Brain edema: 50%
- Hep A/B + NO Brain edema: 67%

% Survival
FHF
Expected Survival by Etiology

Wilson's
Cryptogenic
Idiosyncratic
Halothane

0 10 20 30 40 50 60 70 80 90 100

% Survival

0 18 18 20
Causes of Fulminant Hepatic Failure
Etiology of Acute Liver Failure
1998-2007

- Acetaminophen: 46.25%
- Indeterminate: 13.77%
- Drug: 11.46%
- HBV: 7.5%
- AIH: 5.77%
- Other: 4.86%
- Ischemia: 4.37%
- HAV: 2.72%
- Wilson's: 1.56%
- Pregnancy: 0.9%
- Budd-Chiari: 0.8%
Causes of FHF
Viral Infection

- Hepatitis A
- Hepatitis B +/- HDV
- Hepatitis E
- Hepatitis C (very rare)

- Herpes Simplex
- Cytomegalovirus
- Varicella-Zoster
- Epstein-Barr virus
- Paramyxovirus
- Adenovirus
- Hemorrhagic Fever
  - Yellow Fever,
  - Ebola,
  - Marburg,
  - Lassa,
  - Rift Valley
Causes of FHF
Drugs & Toxins

- **DOSE RELATED**
  - Acetaminophen
  - CCl₄
  - Amanita Poisoning
    (A. phalloides, A. ocreata, A. bisporigera, A. virosa, Galerinas, Lepiotas)
  - Yellow phosphorus
  - Bacillus cereus toxin

- **ISCHEMIA RELATED**
  - Long acting Niacin
  - Cocaine
  - Methamphetamine

- **IDIOSYNCRATIC**
Causes of FHF
Drugs - Idiosyncratic

- Amoxicillin-clavulanate
- Allopurinol
- Amiodarone
- Amphetamines
- Dapsone
- Diclofenac
- Didanoside
- Disulfiram
- Ecstasy
- Efavirenz
- Etoposide
- Flutamide
- Gemtuzumab
- Halothane
- Imipramine
- Isoflurane
- Isoniazid
- Ketoconazole
Causes of FHF

Drugs - Idiosyncratic

- Labetalol
- Lisinopril
- Metformin
- Methyldopa
- Nefazodone
- Nicotinic acid
- Ofloxacin
- Phenytoin
- Pirazinamide
- Propylthiouracil
- Quetiapine
- Rifampin-INH
- Statins
- Sulfonamides
- Tolcapone
- Trimethoprim-Sulfametox
- Troglitazone
- Valproic acid
Causes of FHF
Herbals & Supplements

- Bai-Fang herbs®
- Chaparral (Larrea tridentata)
- Comfrey (Symphytum officinale L)
- Germander (Teucrium chamaedrys)
- Greater celandine (Chelidonium majus)
- Green tea extract (Camellia sinensis)
- Gum Thistle (Atractylis gummifera L)
- He Shon Wu (Polygonum multiflorum)
- Heliotrope (Heliotropium popovii and H. lasiocarpum)
- Herbalife ®
- Huamanripa (Senecio tephrosioides)
- Hydroxycut ® (has green tea extract)
- Impila (Callilepis laureola)
- Jin Bu Huan®
- Kava kava (Piper metysticum)
- LipoKinetix®
- Ma Huang (Ephedra sinica)
- Pennyroyal (Mentha pulegium)
- Rattleweed (Crotalaria retusa)
- Senecio (Senecio vulgaris)
- Skullcap (Scutellaria lateriflora)
- Sunnhemp (Crotalaria juncea)
Causes of FHF
Metabolic & Pregnancy-related

- **METABOLIC**
  - Wilson’s Disease
  - Alpha-1-antitrypsin
  - Galactosemia
  - Tyrosinemia
  - Fructose Intolerance
  - Neonatal Fe storage dz

- **PREGNANCY-RELATED**
  - Acute fatty liver
  - HELLP Syndrome (Hemolysis, Elevated Liver function, Low Platelets)
Causes of FHF
Neoplastic & Miscellaneous

• **MISCELLANEOUS**
  - Autoimmune hepatitis
  - Budd-Chiari
  - Veno-occlusive/ SOS
  - Shock Liver & CHF
  - Heat Stroke
  - Adult onset Still’s dz
  - Reye’s syndrome

• **NEOPLASTIC**
  - Lymphoma
  - Liver Metastasis
    (breast, small cell lung cancer, melanoma)

• **CRYPTOGENIC**
Etiologic & Management Work-Up
FHF
Etiologic work-up

• Establish day of onset of jaundice.
• Travel History (exotic viruses)
• Medication (Rp & OTC), drug/alcohol, CAM therapies, environmental & food exposures.
• Sexual history, piercing, tattooing, …
• Family history (Wilson’s, alpha-1-antitrypsin,…)
• Stigmata of chronic liver disease.
• Mushroom poisoning with severe gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramping), which occur within hours to a day of ingestion
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Etiologic work-up

- **HAV** anti-HAIgM
- **HBV** anti-HBcIgM, HBV-DNA
- **HCV** HCV-RNA, anti-HCV
- **HDV** anti-HDIgG
- **HEV** anti-HEIgM
- **CMV** CMV-DNA, anti CMV IgG & IgM, buffy coat
- **HSV** Buffy coat, anti-HSV IgG & IgM, HSV PCR
- **EBV** acute serology, PCR
- **VZV** Serology, PCR
- **Drug/Toxin** History, toxicology drug screen

- **Wilson’s** 24h urine Cu > 100mg/dL, ceruloplasmin <20 mg/dL, K-F rings, [alk.phos/bili <4 (sn 94%,sp 96%) & AST/ALT >2.2] (sn 100%,sp 100% if both true; Hepatology. 2008 Oct;48(4):1167-74), low uric acid, (total & free Cu)
- **Autoimmune** ANA, anti-LKM, anti-SLA, ASMA, anti-LC, QIG’s
- **AFLP** Pregnancy +/- pre-eclampsia, ALT<500
- **Budd-Chiari** U/S+doppler, angio-CT
- **Ischemia** Hx.of shock or CHF; Echocardiogram
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Etiologic work-up in Recent Travel

• **West Africa, or South America’s Amazon region:**
  – Yellow Fever capture enzyme immunoassay.
• **Congo, Sudan, Uganda, Côte-d’Ivoire, Liberia:**
  – anti-Ebola virus by ELISA,
• **Uganda, Kenya, or Zimbabwe:**
  – anti-Marburg fever IgM-capture by ELISA,
• **Guinea (Conakry), Liberia, Sierra Leone, Nigeria, or other West African countries:**
  – anti-Lassa fever antibodies,
• **Senegal, Kenya, Saudi Arabia, Yemen, Egypt, Tanzania, Somalia, Jordan, and Mozambique:**
  – Rift Valley fever antibody (ELISA).
Management
Preventive Management

• Optimize likelihood of Transplant-free survival:
  – N-acetylcysteine IV

• Minimize Risk of Brain edema and Intracranial hypertension:
  – Keep serum Na of >/= 145 mEq/L (145-150-155)
  – Detect & treat Hepatic encephalopathy early
    • Recognize predictors of intracranial hypertension

• Minimize risk of infection:
  – Protect airway in grade III and IV hepatic encephalopathy
  – Enteric feeding to minimize bacterial translocation
  – Remove foreign bodies that facilitate infections (IUD, piercings)

• Treat infections early
  – Surveillance cultures
  – Recognize predictors of current infection
Preventive Management

- Protect Renal function:
  - Optimize intravascular volume
  - Avoid nephrotoxins
  - Treat Hepatorenal Syndrome early

- Minimize risk of bleeding
  - Correct coagulopathy for invasive procedures
  - Monitor & correct extreme coagulopathy
  - Proton pump inhibitors.

- Prevent hypoglycemia
  - Tube feeding or IV glucose
  - Close glucose monitoring
Optimizing Transplant-Free Survival
**IV NAC in Non-Acetaminophen ALF**

Lee WM et al. Gastroenterology. 2009 Sep;137(3):856-64

- **Patients:**
  - 848 adults screened,
  - 173 qualify and randomized.

- **Stratification:**
  - PSE I-II vs PSE III-IV

- **Intervention:**
  - IV NAC x 150 mg/kg/d x 72h (82 pts) vs Placebo (92 pts).

- **End point:**
  - 1: survival,
  - 2: OLTx free survival.

- **Etiology:**
  - Drug 26%,
  - Indeterminate 24%,
  - HBV 21%,
  - AIH 15%,
  - Other 14%.
CONCLUSION: In Early Non-Acetaminophen ALF, NAC improves Spontaneous Survival
Hepatic Encephalopathy
(Porto-Systemic Encephalopathy - PSE)
FHF
Hepatic Encephalopathy (PSE)

• Defines FHF.
  – Increases risk of brain edema, intracranial hypertension, and infection

• Caution: exclude other causes of altered mental status
  – sedatives, - encephalitis, or - meningitis

• Causative Factors:
  – ammonia, - mercaptans, - glutamate,
  – benzodiazepine-like substances, - aromatic aminoacids.

• Progression can be rapid:
  – Neurologic-check every hour,
  – Avoid sedatives/sedating anti-emetics.
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Hepatic Encephalopathy (PSE)

• Predictors of Severe PSE (III or IV):
  (Hepatology 2007;46:1844-1852)
  – Arterial ammonia > 100 mcM/L (N: < 54 mcM/L)
  – MELD > 32
  – All these patients should be treated for PSE

• Concerns in PSE Grades III & IV:
  – frequently associated with brain edema
  – may cause sub-clinical seizures
    • Prophylactic levetiracetam (Keppra) vs EEG monitoring
  – causes high risk for aspiration pneumonia.
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Management of Hepatic Encephalopathy
Airway Protection & Sedation
Crit Care Med 2007; 35:2498-2508

• In HE grade III or IV: **intubate, sedate & ventilate**;
  – **Intubate**: minimizing trauma (expert operator)
    • Cleanse mouth with chlorhexidine BID
  – **Sedate**: Propofol sedation not to exceed 80 mcg/kg/min (5 mg/kg/h)
    • in order to decrease risk of “Propofol infusion syndrome (PRIS)”: acute refractory bradycardia leading to asystole, in the presence of one or more of the following:
      – metabolic acidosis (base deficit > 10 mmol/L),
      – rhabdomyolysis,
      – hyperlipidaemia, and
      – enlarged or fatty liver.
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Hepatic Encephalopathy
Ventilation
Crit Care Med 2007; 35:2498-2508

• Ventilating to keep:
  • **Tidal Volume**: \( \leq 6 \text{ mL/kg of “predicted or ideal body weight” in Kg.} \)
    - [http://www.ardsnet.org/node/77460](http://www.ardsnet.org/node/77460)
    - Males: PBW (kg) = 50 + 2.3 (height (in) – 60);
    - Females: PBW (kg) = 45.5 + 2.3 (height (in) – 60)
  • **Plateau Pressure**: < 30 cm H\(_2\)O
    - (high “peak” increases ARDS risk)
  • **Respiratory Rate**: to keep PCO\(_2\) 30-40 mmHg;
  • **PEEP**: Avoid/minimize PEEP
    - (high PEEP increases Intracranial Pressure).
Brain Edema and Intracranial Hypertension
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Cerebral Edema Risk

• Brain Edema Risk:
  – HE grade IV: 65-80% have cerebral edema;
  – HE grade III: 25-35% have brain edema.
  – Arterial ammonia > 200 mcg/dl is associated to severe brain edema with herniation

• Repercussions of Brain Edema:
  – Permanent brain damage due to:
    • Intra Cranial Hypertension (ICP > 25 mm Hg)
    • Decreased Cerebral Perfusion (CPP < 50 mm Hg)
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Cerebral Edema & Intra-cranial Hypertension

• Intracranial HTN = ICP > 25 mmHg.
  – Is the main or the second cause of death.
  – May be silent or give:
    • *Cushing Reflex*: arterial hypertension + bradycardia + irregular respiration
    • Pupillary abnormalities: asymmetry, or dilation with sluggish response to light,
    • Decerebrate posturing, or epileptiform activity, or hypertonicity
  – Poor Dx tools: CT scan, fundoscopy, trans-cranial doppler, PET scan & MRI are not sensitive for IC HTN
  – **Best Dx Tool**: Epidural intra-cranial transducer
    • complication rate: epidural catheters (4%), subdural (20%), & parenchymal/intraventricular catheters (22%)
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Intra-cranial Hypertension Risk-Group

• Predictors of Intra-Cranial Hypertension
  (Hepatology 2007;46:1844-1852)
  – Arterial Ammonia > 150 mcM/L (sens: 40%, spec: 74%)
  – Arterial Ammonia > 100 but <= 150 mcM/L, not responding to therapy (sens: 73%, spec: 44%)
  – Grade IV Hepatic Encephalopathy
    • unresponsiveness, coma, decerebrate posturing, seizures, areflexia
  – Reverse jugular oximetry persistently < 60% or > 85%
  – All these patients are candidates for epidural ICP monitoring
Management of Brain Edema Complications
Brain Edema
Management Parameters
Clinics in Chest Medicine, 2009-03-01, Volume 30, Issue 1, Pages 71-87

- **Goal**: keep
  - CPP: 50 mmHg to 80 mm Hg (best 60-65) and
  - ICP < 20 mmHg

- Cerebral Perfusion Pressure (CPP) in mmHg =
  Mean Arterial Pressure (MAP) – Intra-Cranial Pressure (ICP)

- Clinical use:
  - CPP < 40 x 2 hours contraindicates Liver Tx.;
  - ICP > 50 x 2 h = poor neurological recovery
Intra-cranial Hypertension Management Options

- Decrease Brain Edema:
  - Induce hypernatremia or
  - Give Osmotic diuretics.
- Prevent brain accumulation of osmolar-active substances (ammonia, glutamate, etc):
  - Treat hepatic encephalopathy.
- Improve cerebral blood out-flow:
  - Head elevation of 30° (no if CPP < 50 mm Hg)
- Decrease Excessive Blood Flow without impairing cerebral perfusion:
  - Hypothermia (32-33°C),
  - Barbiturate coma,
  - Indomethacin
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Intra-cranial Hypertension Management

• Avoid brain overhydration;
  – Keep serum Na 145-\textbf{150}-155:
  – Water restriction and maintain IV fluid with D10-Normal Saline
  – Correct intravascular volume with 0.9% NaCl, or 5% albumin
  – Hypertonic saline (3%) when needed.
• Keep head $30^\circ$ elevated (unless CPP $< 50$ mmHg)
• Propofol sedation;
• Avoid sudden head movement;
• Treat Hepatic Encephalopathy:
FHF
Intra-cranial Hypertension Management

• Quiet room; do only indispensable interventions
• Endotracheal lidocaine for suction.
• Avoid “positive end-expiratory pressure” (PEEP)
• Avoid fever; keep temperature of 36.5 °C
• Treat arterial hypertension only if CPP > 110 mmHg & ICP > 20 mmHg.
  – Aggressive treatment of hypertension may decrease cerebral perfusion.
Risks of Inducing Hypernatremia

• In severe hyponatremia, the frequency of demyelinating lesions due to correction of plasma sodium concentration is:
  – Common if is raised more than 20 meq/L per day.
  – Rare at a rate below 10 to 12 meq/L per day.

• Late neurologic deterioration is rare if chronic hyponatremia is corrected at an average rate equal to or less than 0.5 meq/L per hour (12 mEq/L/day)

• To be safe is better to raise serum Na by only 8 mEq/L/day (0.33 mEq/L/h)
FHF

Intra-cranial Hypertension Management
Crit Care Med 2007; 35:2498-2508
Semin Liver Dis 2008; 28:188-200

• Hypertonic 3% NaCl:
  – Volume in mL to be given over 24 h =
    “Lean Body Weight (in Kg)” x “desired increase in Na (mEq/L)”
    (increase must be <= 8 mEq/L/day)
  – Lean Body Weight formula (in Kg)
    • http://www.medcalc.com/body.html
    • LBW men = (1.10 x Weight(kg)) - 128( Weight²/(100 x Height(m))²)
    • LBW women = (1.07 x Weight(kg)) - 148( Weight²/(100 x Height(m))²)

• Mannitol 20%
  – Initial dose: 0.5 g/kg over 30 min if urine output > 30ml/h or while in CVVHF/SLED;
  – Goal: Keep Osm > 310 & < 320;
  – Monitoring: serum Osm q 4h
  – Re-dosing: mannitol 0.5 g/kg when Osm < 305.
  – CVVHF/SLED management: remove 3-5X volume of mannitol given.
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Intra-cranial Hypertension Management

Crit Care Med 2007; 35:2498-2508
Semin Liver Dis 2008; 28:188-200

- **Hypothermia** (decreases cerebral blood flow)
  - **Candidates**: Mannitol or Hypernatremia non-responders.
  - **Goal**: Core temperature of 32-33 °C for up to 5 days. Slow rewarming of 1 °C per each 12 hours; try to rewarm every 24 h, and recool if ICP raises.
  - **Monitoring**: ICP, CPP.
    - Needs sedation & analgesia.
    - Cisatracurium is used for paralysis (shivering control).
    - Risk of infection and arrhythmia.

- **Thiopental** (decreases cerebral blood flow)
  - **Candidates**: Mannitol & Hypothermia contraindication/non-response.
  - **Dose**: 5 mg/kg IV over 15 min and followed by 3-5 mg/kg/h to keep ICP and CPP under control.
  - **Monitoring**: EEG (Neurologist), ICP, CPP.

- **Indomethacin** (decreases cerebral blood flow)
  - **Candidates**: Lack of response to all other measures.
  - **Dose**: 25 mg IV over 1 minute (or 25 mg Per Rectum).
  - **Monitoring**: ICP, CPP.
Metabolic & other Complications
FHF

Metabolic & other Complications

• **Hypoglycemia:**
  – Occurs in 45%.
  – Check glucose q 2 h and keep > 70 mg/dL and < 145 mg/dL;
  – Give D10, D20, or D50 (D10-NS to avoid overhydration)
  – **Naso-jejunal TEN > 60% of needs** (double-lumen N-G-J tube)
    (Hepatic-BCAA enriched formula)

• **Acute Pancreatitis:** due to tissue hypoxemia.

• **Acid-base disorders:** ABGs and lactic acid levels

• **Electrolyte disturbances:**
  – Follow BMP, phosphorus, Mg, Ca and correct abnormalities.
  – Hyperphosphatemia is a marker of poor outcome.

• **Prophylaxis for hemorrhagic gastritis:** PPI
Coagulopathy
Coagulopathy/Bleeding

- Prolongation of PT (after Vitamin K replacement) is a reliable indicator of prognosis and evolution;
  - repeat daily.
- Factor V activity has prognostic value (see later).
- Prophylactic platelets: only if
  - $\leq 10000$, or
  - $\leq 20000$ with petechiae or mucosal bleed.
  - **Dose:** 1 unit per 10 kilograms of body weight when using random pooled platelets, or one unit of single donor platelets per transfusion episode.
FHF
Coagulopathy/Bleeding

• Correct coagulopathy for invasive procedure or bleeding:
  – Platelets < 50K:
    • a) Random pooled platelets: 1 unit per each 10 kilograms of body weight, or
    • b) Single donor platelets: one unit
    • Platelet transfusion is more effective in improving thromboelastogram (and coagulation) than fibrinogen (cryoprecipitate) transfusion.
  – INR > 1.9 (> 1.7 for ICP monitor placement):
    • a) FFP: 15 mL/Kg (1 unit = 250 mL);
    • b) If after FFP, INR still > 1.9 (1.7 for ICP monitor), then give rVIIa: (40-60 mcg/kg IV) within 90 min before procedure.
  – Fibrinogen < 100 mg/dL, or < 150 mg/dL with bleed:
    • Cryoprecipitate: 1-1.5 units per each 10 kg of weight
Contraindications & Alternatives for rFVIIa

• Contraindicated in:
  – Active DVT
  – Budd-Chiari
  – ALF related to pregnancy or malignant infiltration.

• Contraindicated if in last 2 weeks patient had:
  – Myocardial Infarction
  – Unstable Angina
  – Stroke

• Alternative to treat persistent coagulopathy:
  – Plasma exchange
Thromboelastography guiding Prophylactic Management of Coagulopathy
Hemodynamic Compromise
Hypotension occurs in 20% of FHF patients. Defined as:

- BPs < 85 or MAP < 60 in normotensive, or
- MAP ≤ 80 mmHg in patients who suffer from hypertension.

Initial Basic Management:

- Resuscitate with colloids & crystalloids
- Keep CVP 8-10 cmH₂O
- Keep serum Na high normal (145-155)
FHF

Hemodynamic Management

• **Alfa-agonists & dopaminergic-agonists as needed**
  
  – **Alfa-agonists**: Norepinephrine (0.01-**0.1**-0.3 mcg/kg/min) +/- Phenylephrine (0.4-1.4-9.1 mcg/kg/min) +/- Vasopressin (0.6-1-4 IU/hour) or Terlipressin for “volume unresponsive” hypotension, if
    
    • MAP < 60 mmHg in “previously normotensive” *(goal > 75)* (Hepatology 2012; 55:965-967)
    
    • MAP < 80 mmHg in “previously hypertensive” *(goal = 85)*
  
    
    • Vasopressin 0.6-1-4 IU/h
  
  – **Inotropics**: Dopamine >/= 5 – 130 mcg/kg/min added if
    
    • not responding to “volume” + alfa-agonists, or
    
    • ScvO$_2$ or SvO$_2$ < 70% with Hct >/= 30, or
    
    • cardiac index < 3.5 L/min/m$^2$ + low perfusion

INITIAL STARTING DOSE IS IN YELLOW
Renal Failure
FHF
Renal Failure Management

- Renal failure occurs in 40-85% of FHF.
- Prevention, Evaluation & Management:
  - Avoid aminoglycosides, NSAID’s, IV contrast.
  - Protect kidney with NAC.
  - Obtain urine analysis + microscopic exam + Eos; Ultrasound of kidneys for renal dz/obstruction.
  - Correct volume depletion and hypotension
  - In ATN, consider early bicarbonate –buffered SLED/CVVH.
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Renal Failure Management

• Hepatorenal syndrome (HRS):
  – Low GFR (Cr > 1.5 mg/dL or CrCl < 40 ml/min)
  – Absence of: shock, nephrotoxin, volume depletion.
  – No Response to: diuretic withdrawal + 1g/kg 5% albumin infusion.
  – Proteinuria < 500 mg/dL &
  – U/S without obstruction or parenchymal renal disease.

• In HRS after normalization of CVP with albumin & NS:
  – Midodrine 7.5-20 mg po TID + Octreotide 100-200 mcg SQ TID + albumin for CVP 8-10, to keep MAP =/> 85 mmHg or
  – Norepinephrine to increase MAP to 85 mmHg + albumin for CVP 8-10

• Consider Misoprostol
Infection
FHF
Infection

• Predisposing Factors:
  – Low opsonins & complement,
  – Gut-bacteria translocation,
  – WBC dysfunction,
  – Lines & catheters,
  – Immunosuppressive cytokines, …

• Bacterial infection in 60-80%;
  – Gram(+) in 80%: mostly Staphylococcus.
  – Gram(−) in 20%: E.coli, Pseudomonas., Klebsiella
  – Pneumonia 50%, bacteremia 26%, UTI 22%.

• Fungemia in 30%;
  – Usually late and with bacteremia.
  – Poor prognosis.
FHF Infections

• **Early Diagnosis:**
  – Daily blood, sputum, urine & line cultures.
  – Daily fungal cultures

• **Risk Minimization:**
  – Remove intrauterine devices (IUDs), body piercing, unnecessary lines/catheters.
  – TEN to decrease gut-bacteria translocation

• **Early Intervention:**
  – Neutropenia: filgrastim (Neupogen), or GM-CSF
  – Guided broad-spectrum antibiotics and anti-fungals by criteria (see later)

• **Bacterial, or Fungal Infection contraindicates Liver Transplant.**
**FHF**

**Infections**

- Empiric broad spectrum antibiotic and antifungal for:
  - Rapid progression to stage IV encephalopathy.
  - Refractory hypotension,
  - SIRS by two of the following
    - 1) Temperature $> 38^\circ$C or $< 35^\circ$C,
    - 2) Heart rate $> 90$ beats/min,
    - 3) Respiratory rate $> 20$ breaths/min or PaCO2 $< 32$ mmHg,
    - 4) WBC $> 12,000$ cells/mm$^3$, $< 4000$ cells/mm$^3$, or $> 10$ percent immature (band) forms.
FHF
Specific Therapies

• **Acute Fatty Liver of Pregnancy**: Delivery
• **Acetaminophen**:  
  – Activated charcoal 1 gm/kg + N-acetyl-cysteine,  
  – Molecular Absorbent Recirculating System (MARS)
• **Mushroom (Amanita)**:  
  – PNC 7 million q 4 hour IV (toxin binding?),  
  – Silibinin 30-40 mg/kg/day x 4 days (milk thistle is 70% sylimarin)  
  – Silymarin 300 mg BID PO or by NGT  
  – Legalon-SIL: 5 mg/kg/day IV (given in 4 divided doses) or 5 mg/kg IV loading dose followed by 20 mg/kg/day via continuous infusion. Blocks hepatocyte uptake of amatoxin. (request toll free # 866-520-4412)
• **Autoimmune hepatitis**: Prednisone +/- Imuran
FHF
Specific Therapies

- **Wilson’s:**
  - Zn 50-60 mg TID to decrease hemolysis;
  - NAC;
  - MARS or continuous hemofiltration;
  - Liver Transplantation.

- **HSV or EBV:** Acyclovir 10 mg/kg (by IBW) IV q 8h adjusted by kidney function.

- **CMV:** Ganciclovir 5 mg/kg IV every 12 hours (using IBW) adjusted for kidney function.

- **Chronic HBV flare-up with ALF presentation** (anti-HBcIgM s/n ratio < 5.08 in 79%, & HBV-DNA in millions IU/mL):
  - Tenofovir improves survival
    - in acute HBV with ALF, therapy may worsen outcome
Liver Transplant in Fulminant Hepatic Failure
Liver Transplant in Fulminant Hepatic Failure

• Mean waiting time = 3.3 days (2000-2003)
• Receive ABO incompatible liver = 11%
  (1.9% in chronic ESLD)
• Patient survival: 1 year = 82% (2000-2003)
  (78-85% in chronic ESLD); 91% in ALFSG
• Graft survival: 1 year = 75% (2000-2003)
  (70% in chronic ESLD)
Predictors of Outcome
A 3-fold increase of AFP from day 1 to 3,

or

$\text{AFP} > 3.9 \text{ mcg/L or ng/mL one day after peak ALT,}$

suggests survival without transplantation.
Predictors of Poor Outcome Without Transplantation
FHF
Predictors of Poor Outcome Without Transplantation

Kings College Predictors of Mortality

- **Acetaminophen** (PPV = 0.95   NPV = 0.78)
  
  • Arterial pH < 7.3
  
  • PT with INR > 6.5 + creatinine > 3.4 mg/dL
Predictors of Poor Outcome Without Transplantation

Kings College Predictors of Mortality

- **Non-Acetaminophen** (PPV=1.0; NPV=0.3)
  - Patient with INR > 6.5, or
  - Three of the following:
    - Age < 10 or > 40
    - Drug reaction or FHF of indeterminate cause
    - Jaundice > 7 days before encephalopathy
    - PT with INR > 3.5
    - Bilirubin > 17.6 mg/dL
FHF
Predictors of Poor Outcome Without Transplantation

- **Acute Viral Hepatitis** (PPV=0.89, NPV=0.36)
  - Age < 30 & Factor V < 20 mg/dL, or
  - Age > 30 & Factor V < 30 mg/dL
### Wilson’s Disease

- **Modified Nazer’s score** for WD & OLTx
- **Score =/> 11, or INR =/> 7** needs OLTx; all other can receive chelation therapy.

<table>
<thead>
<tr>
<th>Points</th>
<th>Bili</th>
<th>AST</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;5.84</td>
<td>&lt;100</td>
<td>&lt;1.3</td>
</tr>
<tr>
<td>1</td>
<td>5.85-8.7</td>
<td>100-150</td>
<td>1.3-1.6</td>
</tr>
<tr>
<td>2</td>
<td>8.8-11.6</td>
<td>151-200</td>
<td>1.6-1.9</td>
</tr>
<tr>
<td>3</td>
<td>11.7-17.5</td>
<td>201-300</td>
<td>1.9-2.4</td>
</tr>
<tr>
<td>4</td>
<td>&gt;17.5</td>
<td>&gt;300</td>
<td>&gt;2.4</td>
</tr>
</tbody>
</table>
If patient is Transplant candidate

Transfer to Transplant Center
Keeping Na 145-150 mEq/L
Volume of 3% NaCl Needed to raise Na by 8 mEq/L

- Sodium Deficit = Total Body Water x (desired Na - actual Na)
- TBW = lean body weight (kg) times 0.5 for women, or 0.6 for men.
- To raise Na by 8 mEq (desired Na – actual Na = 8), replace the
  - Na Deficit = [Lean body weight (kg) x 0.5] x 8 mEq = mEq
    to be given over 24h
- 3% NaCl (hypertonic saline) has 513 mEq/L of Na = 0.51 mEq/mL
- Total volume of 3% NaCl (mL) to be given over 24 h =
  - Na Deficit / 0.51 mEq/mL =
    [Lean body weight (kg) x 0.5 L/kg] x 8 mEq/L / 0.51 mEq/mL =
Sodium Deficit = Total Body Water x (desired Na - actual Na)

TBW = lean body weight (kg) times 0.5 for women, or 0.6 for men.

To raise Na by 8 mEq (desired Na – actual Na = 8), replace the

Na Deficit = [Lean body weight (kg) x 0.5] x 8 mEq = mEq to be given over 24h

3% NaCl (hypertonic saline) has 513 mEq/L of Na = 0.51 mEq/mL

Total volume of 3% NaCl (mL) to be given over 24h =

Na Deficit / 0.51 mEq/mL =

[Lean body weight (kg) x 0.5 L/kg] x 8 mEq/L / 0.51 mEq/mL =

Lean Body Weight (in kg) x 8
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Expected Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson’s dz</td>
<td>0%</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>Idiosyncratic</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>Halothane</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>Hep A/B+brain edema+ARF</td>
<td>30%</td>
</tr>
<tr>
<td>Hep A/B+brain edema</td>
<td>50%</td>
</tr>
<tr>
<td>Hep A/B+ HE 3/4 (no brain edema)</td>
<td>67%</td>
</tr>
<tr>
<td>Tylenol+brain edema+ARF</td>
<td>53%</td>
</tr>
<tr>
<td>Tylenol+brain edema</td>
<td>71%</td>
</tr>
<tr>
<td>Tylenol+ HE 3/4 (no brain edema)</td>
<td>100%</td>
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</table>