Acute Liver Failure

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Financial Disclosures

- No disclosures

Objectives

- To identify medications that commonly cause acute liver failure (ALF)
- To describe the role of N-acetylcysteine (NAC) for the management of drug-induced ALF and to review the data for other potential pharmacological options
- To list various complications of ALF with a focus on the management of cerebral edema and bleeding
- To analyze the optimal supportive care options for hemodynamics and those who require intubation and sedation
- To explain drug dosing considerations for patients with ALF who are critically ill
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**Introduction**

- Rare condition resulting in rapid deterioration of liver function
- Altered mentation and coagulopathy
- Approximately 2000 cases yearly in U.S.
- Accounts for 6% of liver transplants in adults
- Common causes including drug induced, viral hepatitis, autoimmune, shock, unknown (20%)
- High mortality and mortality
  - 15% versus > 65% survival pre and post transplant

Source: D.A. Sass et al., Liver Transplantation 2008;11:594-605

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**Definition**

- Onset of hepatic encephalopathy and coagulopathy
  - Mental alteration
  - INR ≥ 1.5
- Within 26 weeks (jaundice to encephalopathy interval)
  - Hyperacute < 7 days
  - Acute 7-21 days
  - Subacute >21 days - 26 weeks
- Without pre-existing liver disease


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**Etiologies**

- >1100 drugs are implicated

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Study</th>
<th>Patients</th>
<th>Cause</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (APAP)</td>
<td>308</td>
<td>73% women, Age 39</td>
<td>13% idiosyncratic drug reactions</td>
<td>67% survival at 3 weeks, 29% had liver transplant, 43% survived without transplant, 68% survival for APAP causes vs. 25% vs. 17%</td>
</tr>
<tr>
<td>Drug induced liver injury (DILI)</td>
<td>1198</td>
<td>71% women, Age 44</td>
<td>11% drug induced liver injury</td>
<td>27% transplant free survival at 3 weeks, 42% successful transplantation (66% survival)</td>
</tr>
</tbody>
</table>

Reuben A et al. Hepatology 2010;52:2065-76
Common Drug Induced ALF

Reuben A et al. Hepatology 2010;52:2065-76

Idiosyncratic Drug Induced Liver Injury

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Statins</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Medication</td>
<td>Known drug</td>
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<tr>
<td>Imipramine</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Gemtuzumab</td>
<td>Medication</td>
<td>Known drug</td>
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<tr>
<td>Nitrofurantoin</td>
<td>Medication</td>
<td>Known drug</td>
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<tr>
<td>Terbinafine</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>MDMA (Ecstasy)</td>
<td>Medication</td>
<td>Known drug</td>
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<tr>
<td>Valproic acid</td>
<td>Medication</td>
<td>Known drug</td>
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<tr>
<td>Labetalol</td>
<td>Medication</td>
<td>Known drug</td>
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<tr>
<td>Amiodarone</td>
<td>Medication</td>
<td>Known drug</td>
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<tr>
<td>Tolcapone</td>
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<tr>
<td>Dapsone</td>
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<td>Known drug</td>
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<tr>
<td>Allopurinol</td>
<td>Medication</td>
<td>Known drug</td>
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<tr>
<td>Etodolac</td>
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<tr>
<td>Ketoconazole</td>
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<td>Known drug</td>
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<tr>
<td>Didanosine</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Medication</td>
<td>Known drug</td>
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<tr>
<td>Carbamazepine</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Combination Products</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Trimethoprim - Sulfamethoxazole</td>
<td></td>
<td>Combination of two drugs</td>
</tr>
<tr>
<td>Rifampin - Isoniazid</td>
<td>Medication</td>
<td>Known drug</td>
</tr>
<tr>
<td>Amoxicillin - clavulanate</td>
<td>Medication</td>
<td>Combination of two drugs</td>
</tr>
</tbody>
</table>

Herbals:
- Kava
- Herbalife
- Hydroxycut
- Comfrey
- Senecio
- Greater celandine
- He Shon Wu
- LipoKinetix
- Ma Huang

Focus on Drug Induced Etiologies

- Details of all medications
  - Prescription and non-prescription drugs, herbs and dietary
  - Taken within the last year
- Rarely cause dose-related toxicity except acetaminophen
- Idiosyncratic reaction
  - Immunologic mediated injury caused by drug or metabolite
  - Commonly onset 4-6 weeks up to 6 months
- No antidotes
  - Steroids indicated unless drug hypersensitivity

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Acetaminophen induced ALF

- Leading cause in U.S. and Europe
- Leads to ALF with doses > 10 gm/day
- High aminotransferases seen > 3,500 IU/L
  - Highly correlated with ingestion, prompt consideration even when evidence lacking

Lee WM et al. Hepatology 2011;55:1

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Acetaminophen induced ALF

- Level should be drawn in all patients
  - Low or absent levels do not rule out use
- Activated charcoal within 3-4 hours after ingestion (I)
- NAC effective and safe, should be given in all patients (II-1)

Lee WM et al. Hepatology 2011;55:1

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Viral Etiologies

- Infrequent cause in U.S. (hepatitis B 8%; hepatitis A 4%) 
  - Supportive care
  - Nucleoside analog (lamivudine, adefovir) in acute HBV (III)
- Herpes virus infection
  - Rare but can occur in immunosuppressed or pregnant patients
  - Liver biopsy to confirm
  - Acyclovir for suspected or documented (5-10 mg/kg IV Q8h)
- Other
  - CMV, EBV, Varicella zoster virus, adenovirus, paramyxoma virus

Tillmann HL et al. J Viral Hepat 2006;13:256
Kumar M et al. Hepatology 2007;45:97
Other Etiologies
- Mushroom poisoning
- Pregnancy
- Shock liver
- Wilson's disease
- Budd-Chiari syndrome
- Autoimmune hepatitis
  - Recent small retrospective study
  - No improvement in outcomes with use of corticosteroids
  - Increase in septic complications


Pathogenesis
- Cytotoxic injury
  - Direct injury to hepatocytes by toxic viruses (HAV), drugs, toxins
- Cytopathic injury
  - Immune-mediated response to hepatocytes
    - Express abnormal cell surface antigens (HAV / idiosyncratic drug reactions)
- Histologic patterns
  - Most common: hepatocellular necrosis


Comparison of Different Acute Liver Failure Etiology Groups

Lee WM. Semin Respir Crit Care Med. 2012;33:36-45.

ALT, alanine aminotransferase; TX, transplantation
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Question 1

- What is the most common cause of ALF in the United States?
  a. Acetaminophen
  b. Viral hepatitis
  c. Autoimmune diseases
  d. Idiosyncratic drug reactions

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Question 1

- What is the most common cause of ALF in the United States?
  a. Acetaminophen
  b. Viral hepatitis
  c. Autoimmune diseases
  d. Idiosyncratic drug reactions

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Studied Treatment Modalities

- NAC for Non-APAP etiologies
- Corticosteroids
- Liver Assisting devices
**Slide 19: NAC for Non-APAP ALF**

- **Mechanism**
  - Replenishes glutathione stores, radical scavenger
  - Reduces TNF-alpha, IL-8, IL-17
  - ↑ nitric oxide production → vasodilation → ↑ tissue oxygen delivery
- May be beneficial for acute liver failure due to drug-induced liver injury (I)

  *Bass S et al. Am J Health Syst Pharm 2013;70:1496-1501*

**Slide 20: NAC for Non-APAP ALF**

- **IV in all patients with**
  - > grade 1 encephalopathy
  - Hypotension
  - Other reasons (vomiting, airway is compromised, ileus, postoperative state)
- **Duration generally determined by clinical improvement**
  - Generally beyond 72-96 hours

  *Stravitz RT et al. Crit Care Med 2007;35:2498-2508*

**Slide 21: NAC for Non-APAP ALF**

- **Prospective, double blind trial**
- **Acute liver failure without clinical or historical evidence of acetaminophen overdose**
- **Assigned to**
  - NAC or placebo (dextrose) for 72 hours
- **Outcomes**
  - Primary: Survival at 3 weeks
  - Secondary: Transplant free survival

  *Lee WM et al. Gastroenterology 2009;137:856-64*
NAC for Non-APAP ALF

- Baseline demographics (placebo vs. NAC)
  - Sex (female) 68% vs. 47%, Age ~41 years
  - Bilirubin ~21 mg/dL, creatinine ~1.1 mg/dL, INR 2.9 vs. 2.4, MELD ~32, ALT 765 vs. 999 IU/L
- Etiologies
  - Drug induced 25%, HBV 21%, autoimmune hepatitis 15%, 24% indeterminate

Lee WM et al. Gastroenterology 2009;137:856-64

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NAC for Non-APAP ALF

- Graph showing outcomes

Lee WM et al. Gastroenterology 2009;137:856-64

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NAC for Non-APAP ALF

- Graph showing outcomes

Lee WM et al. Gastroenterology 2009;137:856-64

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Corticosteroids for ALF

- Retrospective analysis
- Patients in the Liver Failure Group from 1998-2007
- Primary endpoint
  - Overall and spontaneous survival (without transplant)
- 361 patients
  - 56 with autoimmune, 164 indeterminate, 131 drug induced


Results

- No difference in survival with or without steroids
  - 61% versus 66% (p=0.41)
- No difference in outcome based on diagnosis category
- Diminished survival in a subgroup of patients
  - MELD > 40 (survival 30% versus 57%, p<0.03)
- Marginal benefit in spontaneous survival
  - 30% versus 23%, p=0.047
  - Not seen in multivariate analysis


Liver Assist Devices

- Potential support until regain in liver function or transplant
- Difficult to develop an ideal device
  - Liver performs diverse and vital synthetic functions
- Results have been disappointing or inconclusive
- Not widely available

<table>
<thead>
<tr>
<th>Function</th>
<th>Artificial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma or human liver cells maintained in a cartridge that patient's blood flows through</td>
<td>Albumin dialysis, charcoal hemoperfusion, photopheresis, pyrogenic filtration or sorbent adsorption</td>
</tr>
<tr>
<td>Example</td>
<td>Bio-artificial</td>
</tr>
<tr>
<td>CLAD, HepatAssist, MARS, and Prometheus</td>
<td></td>
</tr>
</tbody>
</table>
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Liver Support Devices with Studies

<table>
<thead>
<tr>
<th>Device</th>
<th>Main Characteristics</th>
<th>Clinical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Adsorbent Recirculating System (MARS)</td>
<td>Molecularly detoxifying 20% albumin solution</td>
<td>• Improvement in biochemical parameters in ALF and acute on chronic liver failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Benefits in pruritus, encephalopathy, hemodynamics</td>
</tr>
<tr>
<td>High-volume plasmapheresis</td>
<td>Removal of patient plasma and replacement with fresh frozen plasma</td>
<td>• Improvement in encephalopathy, hepatic and cerebral blood flow</td>
</tr>
<tr>
<td>HepatAssist</td>
<td>Remove hepatic necrosis</td>
<td>• Survival benefit in subgroup of patients with fulminant/subfulminant hepatic failure</td>
</tr>
<tr>
<td>Extracorporeal/Liver Assist Device (ELAD)</td>
<td>CSA cells, four hollow fiber cartridges</td>
<td>• Survival benefit in acute-on-chronic liver failure</td>
</tr>
</tbody>
</table>

Tritto G et al. Semin Respir Crit Care Med 2012;33:70-79

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Liver Devices

Tritto G et al. Semin Respir Crit Care Med 2012;33:54-79

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General Considerations

- Managed in centers with liver transplant programs
  - Only 40% recover spontaneously
  - Deteriorate rapidly
- Unit of care
  - General medical floor
  - Grade I encephalopathy
  - Frequent neurological checks
  - ICU
  - Grade II or higher

Complications of ALF

- Metabolic abnormalities
  - Hypokalemia, hyponatremia, hypoglycemia, hypophosphatemia
- Acute renal failure
  - 30-50% of patients; poor prognosis, consider CRRT
- Pulmonary complications
  - 30% develop: pulmonary edema and pulmonary infections

Saas DA et al. Liver Transplantation 2005; 11:594-605

Complications of ALF-Infections

- Most common cause of death
- Immunosuppressed, lack of signs of infections frequently
- Pneumonia (50%), sepsis (22%), catheter bacteremia (12%), spontaneous bacteremia (15%)
  - Pneumonia and sepsis (37%) develop in 80% of patients
- Gram negative enteric bacilli, gram positive cocci, Candida species
- Treat empirically when SIRS criteria met, refractory hypotension, progression or advanced HE, listed for transplant

Saas DA et al. Liver Transplantation 2005; 11:594-605
Saas DA et al. Liver Transplantation 2005; 11:594-605
Stravitz RT. Chest 2008; 134:1092-1102

Complications of ALF-Seizures

- 32% have subclinical seizures seen by EEG
- No role for prophylaxis
- Treat promptly to avoid increases in ICP and cerebral hypoxia
- Phenytoin first line and most studied
- Minimize use of sedatives to avoid delaying the evaluation of mental status

Saas DA et al. Liver Transplantation 2005; 11:594-605
Complications of ALF

- Hepatic Encephalopathy
- Cerebral Edema and Intracranial Hypertension
- Bleeding

Hepatic Encephalopathy

Frederick RT. Gastroenterol Hepatol. 2011;7:222-233

Ach=acetylcholine; AChE=acetylcholinesterase; BBB=blood brain barrier; Gln Synth=glutamine synthetase; NMDA=N-methyl-D-aspartic acid; NT=neurotransmitter; RNS=reactive nitrogen species; ROS=reactive oxygen species.
### Hepatic Encephalopathy

**West Haven Criteria Grade**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Neurological Status</th>
<th>Treatment</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Euphoria; occasional depression; fluctuating level of attention; excessive sleep; profound sleep; altered speech; disorientation; good responders to painful stimulation.</td>
<td>Night</td>
<td>Usually normal</td>
</tr>
<tr>
<td>II</td>
<td>Accentuation of stage I; drowsiness, but easily arousable; inappropriate behavior; able to maintain sphincter control.</td>
<td>presents</td>
<td>Abnormal; Generalized slowing</td>
</tr>
<tr>
<td>III</td>
<td>Sleeps most of the time but is arousable; speech is incoherent; confusion is marked.</td>
<td>Usually present if patient can cooperate</td>
<td>Always abnormal</td>
</tr>
<tr>
<td>IV</td>
<td>Not arousable; may or may not respond to painful stimuli.</td>
<td>Usually absent</td>
<td>Always abnormal</td>
</tr>
</tbody>
</table>

### Hepatic Encephalopathy Treatment

- Grade II progression should be managed in the ICU
- Avoid sedation (if necessary short acting benzodiazepines)
- Lactulose and non-absorbable oral antibiotics (lack of data)
  - Small retrospective study showed increased survival time in lactulose group compared to no treatment but no difference in overall survival in lactulose group
  - Risk of abdominal distention with lactulose, oral administration in late stage HE concerning due to risk of aspiration

### Complications of ALF

- Hepatic Encephalopathy
- Cerebral Edema and Intracranial Hypertension
- Bleeding
Cerebral Edema and Intracranial Hypertension

- Cerebral edema
  - 25-35% with Grade III and 75% with Grade IV HE
  - Transplant free survival: 52% Grade I and II, 33% Grade II and up

- Intracranial Hypertension
  - Accounts for 25-35% of deaths

Mohsenin V. Journal of Crit Care 2013;28:783-91

Cerebral Edema and Intracranial Hypertension

- Pathogenesis
  - Osmotic disturbances in the brain
    - Due to accumulation of ammonia and glutamine
    - Astrocyte swelling
  - Heightened cerebral blood flow
    - Loss of cerebral autoregulation
  - Inflammation (TNF alpha, IL1 beta, IL-6) and infection

Cerebral Edema and Intracranial Hypertension-Diagnosis

- Clinical findings of intracranial hypertension
  - New systemic hypertension, progression of HE, alterations in capillary refilling, signs of decerebration
  - CT done to assess for cerebral edema, mass effect, midline shift
  - Transcranial Doppler
    - Measurement of blood flow velocity of intracranial vessels
    - CTA variability versus CTA with CT showed intracranial hypertension
  - Intracranial pressure monitoring
    - Most accurate method and allows for rapid and specific treatment
      - Risk for infection and hemorrhage (10-20%, proportional to depth of insertion)

Mohsenin V. Journal of Crit Care 2013;28:783-91
Cerebral Edema and Intracranial Hypertension - Management

- Goal to maintain ICP < 20-25 mm Hg and CPP > 50-70
- Blood pressure support to maintain CPP
  - Volume challenge, vasopressors
- Osmotic therapy (mannitol, hypertonic saline)
- Hyperventilation to PaCO₂ of 25-30 mm Hg
  - Only acutely if osmotic therapy fails and herniation
- Short term barbiturates
- Induction of hypothermia to 34-35 C in refractory cases

CPP, cerebral perfusion pressures

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Osmotic Therapy

<table>
<thead>
<tr>
<th>Mannitol</th>
<th>Hypertonic Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Draws water from the extracellular space into the intravascular space</td>
</tr>
<tr>
<td>Dose</td>
<td>0.25-1 g/kg/day, 0.25-0.5 g/kg/day</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Serum osmolality every 6 hours to target 300-320 mOsm/L, repeat doses if ICP &gt; 20-25 mm Hg and serum Osm &lt; 320 mOsm/L</td>
</tr>
<tr>
<td>Concerns</td>
<td>Dehydration, hyperosmolality, renal toxicity, osmotic demyelination, requires central line with &gt;3% NaCl</td>
</tr>
</tbody>
</table>

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Slide 45

Acute Fulminant Liver Failure and Osmotic Therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canalese et al.</td>
<td>N=44</td>
<td>HE Grade IV</td>
<td>1- Mannitol 1 g/kg + dexamethasone (32 mg x1, 8 mg daily) 2- Dexamethasone (Dex) 3- Mannitol - Dex given prophylaxis, - Mannitol when ICP &gt; 30 for &gt; 5 mins</td>
</tr>
<tr>
<td>Rocha Filho et al.</td>
<td>N=10</td>
<td>HE Grade IV, previous ICH, Orthotopic liver transplant</td>
<td>1- NaCl 7.5%, 4 mL/kg over 10 minutes 2- Control</td>
</tr>
<tr>
<td>Murphy et al.</td>
<td>N=30</td>
<td>HE Grade III-IV RCT</td>
<td>1- 15 pts standard of care 2- 15 pts standard of care and 30% NaCl titrated 5-20 mL/hr to maintain sodium 145-155, ICP monitors</td>
</tr>
</tbody>
</table>

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Prospective Studies with Mannitol vs. Hypertonic Saline

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Agent</th>
<th>Conditions</th>
<th>Total N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ichai et al. 2009</td>
<td>RCT</td>
<td>3% sodium lactate vs. 20% mannitol</td>
<td>TBI, 34</td>
<td></td>
<td>HS &gt; Mannitol for ↓ ICP, ↑ GOS at 1 year</td>
</tr>
<tr>
<td>Francony et al. 2008</td>
<td>RCT</td>
<td>7.5% HS vs. 20% mannitol</td>
<td>TBI, Stroke</td>
<td>20</td>
<td>Both ↓ ICP</td>
</tr>
<tr>
<td>Haldenby et al. 2006</td>
<td>RCT</td>
<td>20 mL, 20% mannitol vs. 7.5% HS dextran</td>
<td>TBI, SAH</td>
<td>9</td>
<td>HS &gt; mannitol for ↓ ICP</td>
</tr>
<tr>
<td>Harutjunyan et al. 2005</td>
<td>RCT</td>
<td>7.2% HS + 6% HES vs. 15% mannitol</td>
<td>Neurosurgical pts</td>
<td>40</td>
<td>HS &gt; mannitol for ↓ ICP</td>
</tr>
<tr>
<td>Qadri et al. 2018</td>
<td>RCT</td>
<td>7.5% HS vs. 20% mannitol</td>
<td>TBI</td>
<td>20</td>
<td>HS &gt; mannitol for reducing elevated ICP episodes</td>
</tr>
</tbody>
</table>

RCT, randomized controlled studies; HES, hetastarch; HS, hypertonic saline; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage; ICP, intracranial pressure; GOS, Glascow Outcome Scores

Meta-Analysis of Randomized Controlled Studies

- Included 5 studies, 112 patients with TBI, stroke, tumors

Barbiturates

- Thiopental or pentobarbital
  - Pentobarbital 3.5 mg/kg IV loading dose followed by 1-3 mg/kg/hr
  - Thiopental 5-10 mg/kg IV loading dose followed by 3-5 mg/kg/hr
- Use in severe cases not responsive to other measures
- Limitations
  - Systemic hypotension, hypothermia, immunosuppression, hypokalemia, ileus, prolonged coma
Hypothermia

- Shown in animal models to prevent cerebral edema
- Mechanism: preventing hyperemia, altering brain ammonia, glucose metabolism, reduces cerebral blood flow, cytokine production, and oxidative stress
- Limited data in humans
  - Bridge to liver transplant or during transplant surgery
- No data to improve transplant free survival
- Concerns
  - Infection, coagulation disturbances, arrhythmias, hepatic regeneration?
  - Shivering may increase ICP

Jalan R et al. Gastroenterology 2004;127:1338-46
Jalan R et al. Transplantation 2003;75:2034-9

Indomethacin

- May be considered as salvage therapy
- Refractory to all measure
- 25 mg intravenous bolus for ALF
  - Not available in the U.S.
  - Shown to acutely decrease ICP and improve CPP in 12 patients
- Data in traumatic brain injury and spontaneous intracerebral hemorrhage patients
  - Loading dose 0.5 mg/kg followed by a 2 hr. infusion (0.5 mg/kg/h)
  - Decreased ICP and improved CPP

Godoy DA et al. Neurocrit Care 2014;20:230-9

Question 2

- In which incident(s) would hypertonic saline be preferred over mannitol for the management of cerebral edema or elevated ICP in an ALF patient?
  a. Hypovolemia
  b. Acute kidney injury with anuria
  c. Sodium value of 135 mEq/L
  d. All of the above
Question 2

- In what incidents would hypertonic saline be preferred over mannitol for the management of cerebral edema or elevated ICP in an ALF patient?
  - a. Hypovolemia
  - b. Acute kidney injury with anuria
  - c. Sodium value 138 mEq/L
  - d. All of the above

Complications of ALF

- Hepatic Encephalopathy
- Cerebral Edema and Intracranial Hypertension
- Bleeding

Bleeding and Prevention

- Multifactorial mechanism
  - Impaired anticoagulants and fibrinolytic system
  - Platelet dysfunction, ↓ synthesis of procoagulant factors, ↑ von willebrand factor and factor VIII
- Significant spontaneous bleeding is uncommon
  - Recent study using thromboelastography showed hemostasis preserved in ALF patients (↑ factor VIII, normal fibrinogen/platelets)
  - Usually mucosal sites: genitourinary, stomach, lungs
- Levels of factor V + VII shown to be predictors of outcomes

Lee W et al. J Hepatol. 2007;47:1283-1290
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**Bleeding and Prevention**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Frozen Plasma</td>
<td>Indication: Only when bleeding or invasive procedures and INR &gt; 1.5.</td>
</tr>
<tr>
<td>Platelets</td>
<td>Bleeding or invasive procedures: platelets &gt; 50,000/mm³. No bleeding: 10,000-20,000/mm³ (no data).</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Recommended when significant hypofibrinogenemia (fibrinogen &lt; 100 mg/dL).</td>
</tr>
<tr>
<td>Anti-Fibrinolytic agents</td>
<td>Consider with evidence of mucosal and puncture wound bleeding.</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>IV 1-2 mg for at least 3 days.</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Rarely used in U.S., potential role when bleeding not responding to conventional.</td>
</tr>
<tr>
<td>Recombinant Factor VIIa</td>
<td>Consider when FFP has failed or patient volume overloaded before invasive procedures or bleeding.</td>
</tr>
</tbody>
</table>


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**Recombinant Factor VIIa**

- 40 mcg/kg immediately before procedure or when bleeding
- Concerns:
  - Serious thromboembolism in ALF
  - Portal vein thrombosis, myocardial infarction (MI) at doses of 90 mcg/kg
  - Arterial thrombosis (MI, cerebral infarction) doses > 80 mcg/kg
  - Cost ~$1,000-1,500 per mg
- Avoid in the following:
  - History of MI, stroke, unstable angina within 2 weeks, active deep venous thrombosis, Budd-Chiari syndrome, suspected malignant infiltration of liver


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**Recombinant Factor VIIa**

- Study: Shami et al.
  - Patients: 15 ALF
  - Intervention: 8 pts. FFP 2 - 7 pts. FFP + rFVIIa 40 units/kg
  - Outcomes:
    - INR < 1.6 and PT < 4 sec above normal (1 vs. 2): 0% vs. 100% (p=0.002) at 30 min
    - ICP placed in 38% vs. 100% (p=0.03)
    - Death 75% versus 14% (p=0.04)
    - FFP volume 19 units vs. 13 units
    - Anasarca 88% versus 29%
  - Adverse Effects: None noted


- Study: Le TV et al.
  - Patients: 12 ALF with grade III/IV HE
  - Intervention: 8 pts. FFP + rFVIIa 3 mg (average 36.7 mcg/kg) and ICP monitor placed within 15 mins - 2 hours
  - Outcomes: No hemorrhagic complications, death, stroke, major surgical complication, coagulopathy
  - Adverse Effects: None noted

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Recombinant Factor VIIa

**Study Design**

<table>
<thead>
<tr>
<th>Dose (mcg/kg)</th>
<th>Duration of PT normalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2 hours</td>
</tr>
<tr>
<td>20</td>
<td>6 hours</td>
</tr>
<tr>
<td>80</td>
<td>12 hours</td>
</tr>
</tbody>
</table>

Results

13 Patients
- Vitamin K 10 mg if no response
- rFVIIa 5, 20, 80 mcg/kg during 3 weeks

Duration of PT normalization:
- 5: 2 hours
- 20: 6 hours
- 80: 12 hours

p = 0.0001

17 patients
- Child Pugh B/C
- Liver biopsy
- PT > 3 sec ULN
- rFVIIa 5, 20, 80, 120 mcg/kg
- 74% achieved hemostasis within 10 minutes, duration longest with 80 - 120 mcg/kg doses (83 - 280 mins)

Bernstein DE et al. Gastroenterology 1997;113:1930-7
Jeffers I et al. Gastroenterology 2002;123:118-26

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**Question 3**

- FD is a 65 y/o F with a PMH of RA, STEMI (DES 08/2014), HTN, and HLD, who has been hospitalized for ALF due to HSV infection with Grade III HE. FD's INR is 2, aPTT/PT of 40/20 sec, platelets of 80, and the team wants to reverse her coagulopathy in order to place an ICP monitor. What would be your recommendation?

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**Question 3**

- a. Administer platelets to a goal of >100
- b. Recommend FVIIa dosed at 90 units/kg
- c. Recommend FVIIa dosed at 40 units/kg
- d. Avoid FVIIa since the patient had a recent MI and consider FFP at 10-15 mL/kg
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Question 3

a. Administer platelets to a goal of >100
b. Recommend FVIIa dosed at 90 units/kg
c. Recommend FVIIa dosed at 40 units/kg
d. Avoid FVIIa since patient had a recent MI and consider FFP at 10-15 mL/kg

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Supportive Care Considerations

- Cerebral edema
  - Quiet environment with limited stimulation
  - Minimize chest physiotherapy and ET suctioning
  - Bed elevated to 30 degrees and head in a neutral position
  - Avoid fever
    - Associated with worse outcomes and intracranial hypertension
    - Treat aggressively with cooling blankets, fans, non-invasive devices


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Supportive Care Considerations

- Acute renal failure
  - Continuous renal replacement therapy to improve cardiovascular and intracranial parameters (I)
  - Avoid nephrotoxic agents
- Hypoglycemia
  - Continuous glucose infusate since symptoms might be masked
- Frequent phosphate, magnesium, and potassium respletion
- Early feeding initiated early
  - Caloric goals 25-30 kcal/kg/day or minimum trophic feeds
  - Avoid protein restriction (60 g/day)

**Vasopressor Support**

- Goal to maintain adequate renal and brain perfusion
- MAP goal > 65-75 mm Hg and CPP 50-80 mm Hg
  - Administer normal saline first line in hypotensive patients
  - Norepinephrine first line vasopressor
    - Preserves splanchnic blood flow, less tachycardia, and augments peripheral organ perfusion
  - Vasopressin can be added
    - Potentiates effect of norepinephrine, increases CPP, reduces ICP

Stravitz RT et al. *Crit Care Med* 2007;35;2498-2508

**Adrenal Insufficiency**

- Adrenal insufficiency can occur in up to 62% of with acute hepatic dysfunction
  - Shown to correlate with severity of illness and mortality
  - Consider steroids, however lack of data in ALF

Harry R et al. *Hepatology* 2002;36:395-402
Tsai MH et al. *Hepatology* 2006;43:673-81
Harry et al. *Liver International* 2003;23:71-7

**Intubation**

- Indications
  - Respiratory failure, airway protection in setting of HE stage III/IV, agitation, ICP monitor placement
  - Transient ↑ ICP
  - High positive end-expiratory pressure may ↑ ICP
    - Clinical relevance?: maintain lowest level for adequate $O_2$
  - Low tidal volumes for ARDS result in hypercarbia → ↑ ICP

Stravitz RT et al. *Crit Care Med* 2007;35;2498-2508
Pharmacological Considerations in Intubation

- Non-depolarizing neuromuscular blocking agents preferred
  - Do not cause muscle contraction or increases in ICP
  - Cisatracurium
- Prophylactic IV lidocaine before endotracheal suctioning
- Sedation and analgesia
  - Agitation and pain can ↑ ICP
  - Adequate sedation and analgesia is required

Sedation and Analgesia Options

- Short acting agents preferred
- Sedation
  - Propofol preferred for sedation
    - May reduce cerebral blood flow and ICP
    - Small doses due to increased half-life
  - Benzodiazepines should be avoided since they can worsen HE
  - Dexmedetomidine lack of data and effect on CPP
- Analgesia
  - Fentanyl preferred for analgesia as bolus doses for pain
  - Avoid morphine and meperidine due to active metabolites

Question 4

- All of the following interventions are appropriate for patients with ALF except?
  a. Using propofol and fentanyl for sedation/analgesia
  b. Using succinylcholine for intubation since it has a short duration
  c. Administering prophylactic lidocaine during intubation
  d. Consider norepinephrine as first line for MAP < 65
Question 4

- All of the following interventions are appropriate for patients with ALF except?
- a. Using propofol and fentanyl for sedation/analgesia
- b. Using succinylcholine for intubation since it has a short duration
- c. Administering prophylactic lidocaine during intubation
- d. Considering norepinephrine as first line for MAP < 65

---

Prognosis and Liver Transplant

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Prediction of Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Idiosyncratic drug injury, acute hepatitis B and other non-hepatitis A viral infections, autoimmune hepatitis, mushroom poisoning, Wilson disease, Staph/Chlamydia, idiopathic cause</td>
</tr>
<tr>
<td>Coma Grade on Admission</td>
<td>III or IV</td>
</tr>
<tr>
<td>King's College Criteria (APAP induced)</td>
<td></td>
</tr>
<tr>
<td>Strongly consider OLT listing if:</td>
<td></td>
</tr>
<tr>
<td>- Arterial lactate &gt; 3.5 mmol/L after early fluid resuscitation</td>
<td></td>
</tr>
<tr>
<td>- pH &lt; 7.3 or lactate &gt; 10 mmol/L, after fluid resuscitation lactate 0 or 0 to 9 mmol/L within 2 hours</td>
<td></td>
</tr>
<tr>
<td>- INR &gt; 6.5 and encephalopathy</td>
<td></td>
</tr>
<tr>
<td>- OR any of the 3: Age &lt; 10 or &gt; 40, jaundice for &gt; 7 days</td>
<td></td>
</tr>
<tr>
<td>- OR any of the 3: Age &lt; 10 or &gt; 40, jaundice for &gt; 7 days, creatinine &gt; 3.4 mg/dL</td>
<td></td>
</tr>
<tr>
<td>King's College Criteria (non-APAP induced)</td>
<td></td>
</tr>
<tr>
<td>List for OLT if:</td>
<td></td>
</tr>
<tr>
<td>- INR &gt; 6.5 and encephalopathy</td>
<td></td>
</tr>
<tr>
<td>- OR any of the 3: Age &lt; 10 or &gt; 40, jaundice for &gt; 7 days</td>
<td></td>
</tr>
<tr>
<td>- OR any of the 3: Age &lt; 10 or &gt; 40, jaundice for &gt; 7 days, creatinine &gt; 3.4 mg/dL, unfavorable etiology (Wilson Disease, seronegative hepatitis)</td>
<td></td>
</tr>
<tr>
<td>Lee WM. Semin Respir Crit Care Med 2012;33:36-45</td>
<td></td>
</tr>
</tbody>
</table>

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Prognosis by Etiology

[Graph showing transplant-free survival by etiology and coma grade]
Prognosis and Liver Transplant

- Transplantation survival ~67%, only 24% ALF transplanted
  - Worse survival at 1 year compared to chronic liver failure
  - Improved long-term survival
- Living donor liver transplantation (right lobe)
  - 1 year survival ~75%
- Auxiliary liver transplant (partial left or right lobe)
  - Recipient liver in place, donor partial lobe temporary support
  - Survival 60-65%, withdrawal of immunosuppression at 1 year

Lee WM. Semin Respir Crit Care Med 2012;33:36-45

DRUG DOSING CONSIDERATIONS

- Pharmacokinetics
  - Phase I metabolism affected early (oxidation, reduction, hydrolysis)
  - Phase II metabolism affected later (conjugation) in advanced cirrhosis
  - ↓ Albumin and α1-acid glycoprotein
  - ↑ Bilirubin and other endogenous compounds, inhibition of plasma binding of certain drugs
  - ↓ Protein binding of highly bound drugs
  - ↑ In hydrophilic drugs in volume-overloaded patients, ascites

ALF and Drugs Pharmacokinetics
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**Extraction Ratio of Drugs**

- Categorized by the efficiency of the liver in removing the substance from circulation
  - High extraction ratio > 0.7, limited to blood flow (cirrhosis)
  - Low < 0.3, affected by change in blood plasma binding and hepatic intrinsic clearance
  - Intermediate (0.3-0.7), can be affected by change in all 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Extraction Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.8</td>
</tr>
<tr>
<td>B</td>
<td>0.6</td>
</tr>
<tr>
<td>C</td>
<td>0.4</td>
</tr>
</tbody>
</table>


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**Hepatic Function and Cytochrome Activity**

- Common CYP 2C19 Substrates
  - Cilostazol, citalopram, clobazam, diazepam, fosphenytoin, omeprazole, esomeprazole, pantoprazole, phenobarbital, phenytoin, sertraline, voriconazole


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**Child Pugh Score**

- Recommended for assessing severity of liver impairment
- Provides guidance for dosage adjustments
- Lacks sensitivity to individual drugs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Class A (5-6) (least severe)</th>
<th>Class B (7-9) (moderate)</th>
<th>Class C (10-15) (most severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Mild or moderate (grade 1 or 2)</td>
<td>Severe (grade 3 or 4)</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Mild or moderate (diuretic responsive)</td>
<td>Severe (diuretic refractory)</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>INR &lt;4</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
</tr>
</tbody>
</table>

Applicability to ALF

<table>
<thead>
<tr>
<th>Phase I Algorithm</th>
<th>Phase II Algorithm</th>
<th>Phase III Algorithm</th>
<th>Phase IV Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase Vd, Phase I metabolism</td>
<td>Biliary Elimination, Phase II metabolism</td>
<td>PD Changes (e.g., CYP2C19 &gt; CYP1A2 &gt; CYP2D6 &gt; CYP2E1)</td>
<td>Cholestasis, (intrahepatic or extrahepatic) leads to ↓ clearance through biliary pathway, can impair activity of CYP2C and CYP2E1</td>
</tr>
</tbody>
</table>

- Reduced protein binding; higher unbound concentrations
- Larger loading doses for hydrophilic drugs
- Affected earlier (CYP2C19 > CYP1A2 > CYP2D6 > CYP2E1)
- Altered sensitivity
  - Phenytoin, valproic acid, methadone, benzodiazepines
  - Beta-lactams, vancomycin, aminoglycosides
  - Therapeutic drug monitoring or more vigilant titration to affect, lower dose considerations, consider phase II drugs

- Increased: benzodiazepines, opioids
- Decreased: diuretics, beta-blockers


---

Question 5

- Hepatic dosing concerns should be considered when ALF patients have:
  - a. Developed ARDS and need to be started on a midazolam drip (with low albumin) for heavy sedation not controlled on propofol
  - b. Developed a STEMI and are receiving clopidogrel
  - c. Developed HIT with cholestasis and will be started on an argatroban drip
  - d. All of the above
Conclusion

- APAP is the most common cause of drug-induced liver disease (DILD)
  - Followed by antimicrobials, antituberculos, and sulfur-containing medications
- NAC can be used for the management of non-APAP DILD with a potential transplant-free survival benefit in patients with Grade I-II HE
- Common serious complications in patients with ALF:
  - Cerebral edema should be closely monitored with HE grade III-IV and managed with osmotic therapy
  - Bleeding and prevention of bleeding prior to invasive procedures should be managed according to guidelines with a potential role for Factor VIIa
- Supportive care should be provided to adequately manage hemodynamics and to prevent ICP increases
- Drug dosing adjustments should be evaluated in all patients with ALF

Questions?

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PGY-1 Pharmacy Residency Program Coordinator
NYU Langone Medical Center
Email: Diana.Esaian@nyumc.org
October 24th, 2014

Mushroom Poisoning

- Mushroom poisoning (amanita phalloides), 2-5% of ALF cases
  - Suspected based on patient history of recent ingestion
  - Severe gastrointestinal symptoms
  - Nausea, vomiting, diarrhea, abdominal cramping within hours to a day
  - Gastric lavage and activated charcoal with early ingestion
  - Supportive care
    - Penicillin G: 300,000-1,000,000 units/day in 4 divided doses as needed (III)
    - Sildenafil (glycinin or milk thistle) 20-40 mg/kg/day for 3-4 days
    - NAC (III)
    - Transplantation
