Acute Liver Failure

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Disclosure

• I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Pharmacist Objectives

• Upon completion of this activity, the participant should be able to:
  – Define acute liver failure (ALF) and recognize signs and symptoms
  – Identify common causes and medications implicated in acute liver failure
  – Describe the non-pharmacological treatment measures for acute liver failure
  – Recommend pharmacologic therapies for the management of acute liver failure and its complications

Technician Objectives

• Upon completion of this activity, the participant should be able to:
  – List the causes of acute liver failure
  – Describe the signs and symptoms of acute liver failure
  – Identify drugs used in the management of acute liver failure

Patient Case

• 50 year old woman in Florida on vacation
• Chief complaint: Transferred to JMH for liver transplant evaluation secondary fulminant liver failure
• HPI: Fever spikes to 103°F, chills, rash
• Self medicated with 2gm of acetaminophen prior to presenting to OSH where she began to complain of arthralgia.
• PMH: Nonsignificant

Definition of ALF

“A potentially reversible condition, the consequence of severe liver injury, in which encephalopathy developed within 8 weeks of the appearance of first symptoms, in the absence of preexisting liver disease”

• Patients without preexisting cirrhosis with
  – Evidence of coagulation abnormality (INR ≥ 1.5)
  – Any degree of mental alteration (encephalopathy)
  – Duration < 26 weeks

Mortality and Prognosis

- Mortality
  - Prior to transplantation, studies suggested a survival rate less than 15%
  - One year survival of all patients is greater than 65%

- Prognosis
  - Etiology serves as an indicator of prognosis
  - May use evaluation systems for prognosis
    - Example: King’s College Criteria

Etiology

- Viruses*
  - Hepatitis A, B, and E
  - HSV, CMV, EBV, paroviruses

- Drug-induced*
  - Intrinsic
  - Idiosyncratic

- Autoimmune*
  - Indicates most common causes of ALF

- Acute ischemic hepatocellular injury*

- Metabolic diseases
  - Wilson disease
  - Budd-Chiari syndrome

- Acute fatty liver of pregnancy

- Neoplastic infiltration

Common Drug Causes of ALF

- APAP
- NSAIDs
- Antibiotics
  - Amoxicillin
  - Clavulanate
  - Isoniazid
  - Macrolides
  - Nitrofurantoin
  - Minocycline
- Antiepileptics
  - Phenobarbital
  - Carbamazepine
  - Lamotrigine
  - Valproate
- Immune Modulators
  - Interferon-β
  - Interferon-α
  - Anti-TNF agents
  - Azathoprine
- Herbas
  - Green Tea Extract
  - Andrographis
- Miscellaneous
  - Methotrexate
  - Alopurinol
  - Aminoglutethimide
  - Prophythiouracil
  - Androgen-containing steroids
  - Inhaled anesthetics
  - Sulfasalazine
  - Proton pump inhibitors

Back to the Patient

- Per OSH records, patient was + HepBSAg
- Within 24 hours of presenting she was in fulminant liver failure with
  - Elevated LFTs
  - Pulmonary edema and respiratory failure on mechanical ventilator
  - Elevated creatinine on CVVHD
  - Ammonia of 273 with hepatic encephalopathy Grade II
  - Elevated INR
  - Afib and PVCs with no prior cardiac history

Patient Laboratory Values

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<thead>
<tr>
<th>Date</th>
<th>SCR</th>
<th>Total Bilirubin</th>
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<td>5,517</td>
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<td>4/19</td>
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Medications Started On Arrival

- Albuterol/Ipratropium nebulizations q4h
- Entecavir 0.5mg PO q48h
- Nexium 40mg IV q24h
- Lasix 40mg IV push x 1
- Mannitol 35gm IV x 1 followed by Sodium Chloride 3% at 20mL/hr
- Sodium bicarbonate 100mEq IV push x 3
- Sodium bicarbonate IV infusion 150 mEq in 1 L D5W
- Dextrose 10% in Water at 20mL/hr
- Propofol infusion at 30mg/kg/min
- Acetylcysteine 11gm in 200mL D5W over 1 hour followed by 7gm in 1000mL D5W at 62.5mL/h x 48h
Clinical Features

• Depends on severity of liver injury
  – Nonspecific
    • Nausea
    • Vomiting
    • Right upper quadrant tenderness
  – Confusion
  – Agitation
  – Coma
  – Jaundice (+/-)

• Diagnosis based on liver and coagulation studies

Laboratory Analysis

• Prothrombin time/INR
• Basic Metabolic Panel
  – LFTs
• ABG
• Arterial lactate
• Complete blood count
• Blood type and screen
• Acetaminophen level
• Toxicology screen
• Amylase and lipase
• Pregnancy test
• Autoimmune markers
  – ANA, ASMA, immunoglobulin levels
• Viral hepatitis serologies
  – Anti-HAV IgM, HBSAg, anti-HBc IgM, anti-HEV, anti-HVC
• Ammonia (arterial)
• HIV status

ALF General Management

• Patients should be hospitalized, likely require ICU monitoring
• Contact with a transplant center early
  – Transfer appropriate patients
  – Progression of disease state can preclude transfer
• Attempt to identify etiology
• Discontinue all non-essential medications

Acetaminophen Toxicity

Pathophysiology

- Dose-related toxin
  - Typically doses > 10gm/day (~150mg/kg)
  - Can be seen with 3-4gm/day
- Draw serum level in all patients with ALF
  - Correlated with levels ≥ 3,500 IU/L
  - Low/absent levels do not rule out acetaminophen poisoning
- Patient characteristics
  - Very high aminotransferases + low bilirubin levels
  - Absence of apparent hypotension/CV collapse
Guidelines Recommendations for N-Acetylcysteine

- Known or suspected acetaminophen toxicity within 4 hours of presentation
  - Give activated charcoal 1gm/kg prior to N-Acetylcysteine (NAC)
  - Possible benefit at 48 hours or more from ingestion
- May also be considered in
  - When acetaminophen ingestion is possible
  - Known or suspected mushroom poisoning
  - Drug-induced liver injury

NAC for Acetaminophen Overdose

- Oral administration (more common)
  - Loading dose: 140mg/kg
  - Followed by: 70mg/kg q4h maintenance
- Intravenous administration
  - Loading dose: 150mg/kg
  - Followed by: 50mg/kg/hr x 4h
  - Continuous infusion: 100mg/kg/hr x 16h
  - Use with encephalopathy > Grade I, hypotension, or if unable to tolerate oral administration
- Controversial endpoint of NAC therapy: Discontinue at 72hr or when LFTs have improved

Intravenous N-Acetylcysteine Improves Transplant-Free Survival in Early Stage Non-Acetaminophen Acute Liver Failure

Gastroenterol. 2009; 137: 856-864.

Lee WM, et al.

- Study Population – 173 patients
  - 18 years of age and older with evidence of ALF caused by an illness of less than 24 weeks’ duration
  - Any degree of coagulopathy or encephalopathy
- Exclusion Criteria
  - Known or suspected acetaminophen overdose, previously received NAC, determined to have shock liver, liver failure caused by pregnancy or cancer
  - Refractory hypotension, sepsis, age > 70 yo, expected liver transplant within 8 hr

Lee WM, et al.

- Objective
  - Determine if patients with non-acetaminophen ALF benefit from IV N-acetylcysteine
- Study Design
  - Prospective, randomized, double-blind trial
  - 5% dextrose with N-acetylcysteine vs. dextrose 5%
    - Loading dose: 150mg/kg/hr over 1 hr
    - Followed by: 12.5mg/kg/hr over 4 hr
    - Continuous infusion: 6.25mg/kg for remaining 67 hours

Lee WM, et al.

- Primary outcome – overall survival at 3 weeks
  - 70% for NAC vs. 66% for placebo (P = 0.283)
- Secondary outcomes
  - Transplant free survival
    - 40% for NAC vs 27% for placebo (P<0.43)
    - Greatest benefit was seen in patients coma grade I-II
      - OR 2.46 (95% CI 1.14-5.30) for NAC in coma grade I-II
      - OR 0.33 (95% CI 0.06-1.74) for NAC in coma grade III-IV
  - Overall transplant rates
    - 32% for NAC vs. 45% for placebo (P=0.93)
### NAC for Non-Acetaminophen ALF

- Based on Lee WM, et al., NAC may improve outcomes in non-acetaminophen ALF
  - Improved transplant free survival among patients presenting with encephalopathy Grade I or II
  - Must be initiated early within the disease to affect outcome
  - Trend towards improved outcomes with
    - Hepatitis B virus
    - Drug-induced liver injury

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### Etiology-Specific Management

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ischemic hepatitis</td>
<td>Cardiovascular support, manage underlying cause</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Supportive Care</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>Activated charcoal recommended early</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>NAC (as for APAP overdose) + Penicillin G 300-1 million units/kg/day IV</td>
</tr>
<tr>
<td>Herpes Simplex Virus</td>
<td>Acyclovir 5-10mg/kg every 8 hours x 7 days of until herpes simplex virus</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>Prednisone 40-60mg/day in patients without multiorgan failure</td>
</tr>
<tr>
<td>AFLP/HELLP</td>
<td>Delivery of the fetus; may require transplant if liver failure does not</td>
</tr>
<tr>
<td></td>
<td>resolve quickly after delivery</td>
</tr>
</tbody>
</table>

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### Management of ALF

- Patients who progress to high-grade hepatic encephalopathy (grade III or IV) should undergo endotracheal intubation
  - Pain and agitation contribute to intracranial hypertension
    - Propofol or short-acting benzodiazapine infusion
    - Short-acting opiate infusions
      - Avoid morphine and meperidine due to accumulation of active metabolites and lowering of the seizure threshold with meperidine

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### Management of Coagulopathy

- Provide replacement therapy for prolonged prothrombin time and/or thrombocytopenia only in the setting of
  - Hemorrhage
  - Prior to invasive procedures
- Hypofibrinogenemia <100mg/dL
  - Administer cryoprecipitate
- INR > 1.5 and platelets < 50,000/mm³
  - Administer fresh frozen plasma and platelets

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### Management of Coagulopathy

- Transfuse platelets when
  - Significant bleed with platelets < 50,000/mm³
  - Prior to invasive procedures to reach platelet counts of 50-70,000/mm³
  - For platelet counts < 10,000/mm³
- Vitamin K deficiency has been reported in patients with ALF
  - Administer 5-10mg routinely
Management of Circulatory Support

- Maintain adequate intravascular volume
  - Initial treatment of hypotension with normal saline
- Systemic vasopressor support for
  - Volume-refractory hypotension
  - Maintain adequate cerebral perfusion pressure (CPP)

Norepinephrine

- Preferred agent but may compromise hepatic blood flow

Dopamine

- Low-dose dopamine is not recommended as it has not been shown to decrease the risk of renal failure

Vasopressin

- Use with caution; increases cerebral vasodilation and potentially exacerbate intracranial hypertension

Levothyroxine in ALF

- A cross-sectional study found that acute hepatitis (AH), chronic liver disease (CLD) and liver transplant (LT) patients are associated with endocrine disturbances
  - AH and LT patients had significantly lower T3 levels than healthy controls
  - Patients with CLD Child-Pugh stage B or C had significantly lower levels of all thyroid hormones compared to controls and CLD Child-Pugh stage A

Levothyroxine in ALF

- Prospective study in potential organ donors hemodynamically unstable patients were given
  - A bolus of 25gm IV 50% dextrose, 2gm methylprednisolone IV, and 20mcg levothyroxine IV
  - Followed by a continuous levothyroxine infusion at 10 mcg/hr
- Results: Significant ↓ in vasopressor requirement
  - 11.1±0.9mcg/kg/min vs 6.4±1.4mcg/kg/min (P=.02)
  - Ten patients had complete discontinuation of vasopressors

Levothyroxine in ALF

- May be considered for patients requiring high doses of vasopressors by increasing cardiac output
  - Concentration
    - Levothyroxine 500mcg in 250mL NS
  - Dosing
    - 30-50mcg/hr for short duration based on patient response

Management of Fluids and Electrolytes

- Maintain metabolic homeostasis carefully
- Monitor nutritional status and electrolytes frequently with expeditious correction of derangements
  - Hypoglycemia
  - Hypokalemia
  - Hyponatremia
  - Hypophosphatemia
  - Hypomagnesemia
Acute Renal Failure

- Common complication in ALF
  - Greater frequency with ALF due to direct nephrotoxins
  - May indicate a worse prognosis
- Make every effort to protect renal function
  - Maintain adequate hemodynamics
  - Avoid nephrotoxic agents
  - Prompt treatment of infections

Management of Acute Renal Failure

- If dialysis is required for acute renal failure a continuous mode is recommended over intermittent hemodialysis (IHD)
  - Patients tolerate IHD poorly due to hemodynamic instability and fluid shifts
  - IHD may increase intracranial pressure (ICP)
  - Citrate is preferred over heparin
  - Bicarbonate buffer solution preferred

Management of ALF – Supportive Care

- Seizures may develop in up to 30% of patients
  - Use sedatives with antiepileptic activity
  - Monitor with EEGs in patients without sedation
  - Treat seizures promptly to reduce hypoxia
    - Phenytoin
    - Short-acting benzodiazepines
  - Recommend against prophylactic use of phenytoin
- Stress ulcer prophylaxis
  - Histamine-2 blocking agents
  - Proton pump inhibitors

Encephalopathy Grading

I. Slow mental function
II. Inappropriate behavior
III. Permanent somnolence
IV. Coma

Grading indicates prognosis but is specific for the type of acute hepatic failure

Management of Encephalopathy

- Lactulose in ALF
  - May use oral or rectal routes of administration
    - Should not be administered to the point of diarrhea according to guidelines, but likely want to be more aggressive in acute patients than chronic
    - May interfere with surgical field by increasing bowel distention during liver transplantation
  - Assess for abdominal distention regularly
  - Do not administer prior to intubation in late stages
  - Avoid intravascular depletion

Mechanism of Encephalopathy

- Increased ammonia levels in the brain
- Lactate accumulation in the brain
- Increased levels of proinflammatory cytokines and neuropathology

Adapted from: http://www.nature.com/nrgastro/journal/v10/n9/images/nrgastro.2013.99-f1.jpg
Management of Encephalopathy

- Elevation of some opioid peptides have been found in acute and chronic liver failure
  - May modulate various neurotransmitters
  - Opioid receptor antagonist naloxone has shown efficacy
    - Significant improvement in HE (relative risk 1.45; 95% CI 1.27-1.67; \( P = 0.0005 \))
  - Consider in patients not responding to standard therapies

Naloxone in ALF

- Concentrations
  - Fluid restricted: Naloxone 4mg in 250mL of NS
  - Standard: Naloxone 2mg in 500mL of NS
- Dose
  - 0.4mg/hr
- Duration
  - Administer for 3 days or until patient awakes

Management of Cerebral Edema

- Indications for ICP monitor (controversial)
  - Patients with stage III/IV encephalopathy listed for liver transplantation
  - Non-transplant patients who have a reasonable likelihood of spontaneous survival
- Head CT before monitor placement
  - Stage III or IV encephalopathy
  - Acute change in mental status

Intracranial Hypertension

- General Management
  - Minimize stimulation that cause increases in ICP
  - Elevate the head of the bed to 30 degrees
  - Maintain MAP ≥ 75 mmHg and CPP at 60-80 mmHg
  - Maintain a Pco₂ between 30 and 40 mmHg
  - Maintain euthermia (36.5-37.5°C)

Mannitol Therapy

- ICP ≥ 25 mmHg for > 10 minutes
  - Mannitol 0.5-1 g/kg/body weight
  - Prophylactic doses of mannitol not recommended
- Controlled trial of 34 liver failure patients with cerebral edema
  - 17 patients received mannitol, 17 did not
  - Episodes of cerebral edema resolved more quickly in the mannitol group
  - Significantly improved survival (47.1% vs. 5.9%, \( P = 0.008 \))

Mannitol Administration

- Administer over 30 minutes
- May repeat doses of 0.25-1gm/kg every 6-8h
- Hold for
  - Serum osmolality > 320 mOsm/kg with a osmol gap > 20 mOsm/kg
  - Serum Na > 155 mEq/L
  - Hypotension
  - Severe dehydration
  - Renal dysfunction
Hypertonic Saline (HTS) Administration

- Bolus dosing may be given prophylactically or in place of mannitol
  - Sodium chloride 23.4% - 30mL
  - Sodium chloride 3% - 250mL
- Patients should receive a central line
- Check serum sodium levels every 4-6h
- Hold for serum
  - Na > 155 mEq/L
  - Serum osmolality > 320mOsm/kg

Prophylactic Hypertonic Saline

- Study of 30 ALF patients with Grade III or IV encephalopathy were randomized to
  - Standard of care (n = 15)
  - Hypertonic saline (30%) infusion (n = 15)
- ICP was monitoring via subdural catheter for 72h
  - Significant ↓ in HTS group (P = 0.003, 13 patients)
  - Significantly lower incidence of intracranial hypertension in HTS group (P = 0.04)
  - Patients in CG required norepinephrine ↑ compared to HTS (P = 0.001, 13 patients)

Prophylactic Hypertonic Saline

- Reduces the incidence and severity of intracranial hypertension in ALF patients
- Maintain a sodium level of 145-155mEq/L in patients at highest risk for cerebral edema
  - Serum ammonia >150 mcg/dL
  - Grade III/IV hepatic encephalopathy
  - Acute renal failure
  - Requiring vasopressors to maintain MAP

Refractory Intracranial Hypertension

- In patients with intracranial hypertension refractory to osmotic agents may consider
  - Short-acting barbiturates
  - Induction of hypothermia to a core body temperature of 34-35°C
  - Target temperatures in literature suggest lower goals of 32-34°C
- Provide treatment as a bridge to liver transplantation

Ref refractory Intracranial Hypertension

- Barbiturate coma
  - Loading dose: Pentobarbital 3-5mg/kg IV
  - Followed by: 1-3mg/kg/hr continuous infusion
  - Potential severe AE: Hypotension, hypothermia, paralytic ileus, immunosuppression, hypokalemia, and prolonged coma
  - Should be done in experienced institutions
  - Use vasopressors to maintain MAP > 50mmHg

Liver Support Systems

- Purpose
  - Provide support to native liver for recovery
  - Bridge to transplant
- Artificial support
  - Detoxifies only
- Bioartificial support
  - Uses hepatocytes in extracorporeal circuits
- Currently not recommended outside of clinical trials
**Patient Summary**

- Orthotopic liver transplant on 4/19
- Prolonged hospitalization due to severity of illness on presentation
  - Required extensive rehabilitation and physical therapy
- Etiology of ALF was never determined
  - Discharged on entecavir due to +HepBSAg
- Discharged home and is doing well

**Summary**

- Seek etiology and discontinue potential offenders
  - Consider NAC for acetaminophen and non-acetaminophen ALF
- Provide supportive care
  - Fluid resuscitation and vasopressor support
  - Manage complications
    - Bleeding
    - Renal failure
    - Hepatic encephalopathy
    - Intracranial hypertension

**Assessment Questions**

- NAC is used only for acute hepatic failure secondary to acetaminophen toxicity. **False**
- Renal failure is a common complication of acute hepatic failure. **True**
- Management of hepatic encephalopathy is similar between acute and chronic hepatic failure. **False**

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