End Stage Liver Disease and Liver Transplantation

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Objectives

• Gain an Understanding of...
  • Acute Liver Failure
  • End Stage Liver Disease
  • Encephalopathy in ALF and ESLD
  • Indications/contraindications for transplantation in ALF/ESLD
Chronic Liver Failure (Decompensated cirrhosis)
- Protracted course
- Complications of advancing portal hypertension
- Rarely reversible when advanced

Acute Liver Failure (Fulminant hepatitis)
- Short course < 8 weeks
- Acute portal hypertension
- Spontaneously reversible

ESLD and ALF = need for liver transplantation
Etiologies of Liver Failure

**CHRONIC**
- Cirrhosis
  - hepatitis C, B
  - alcohol
  - metabolic
  - cholestatic
  - autoimmune

**ACUTE**
- Drug-induced
- Viral
- Idiopathic
- Toxic
- Cardiovascular
- Autoimmune
## Types of Hepatic Encephalopathy

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<thead>
<tr>
<th>Type</th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
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<tbody>
<tr>
<td>Definition</td>
<td>Associated with <strong>Acute Liver Failure</strong></td>
<td>Associated with portosystemic bypass without hepatocellular disease</td>
<td>Associated with cirrhosis, portal HTN, or portosystemic shunts</td>
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<td>Episodic</td>
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Part 1: Focus on Acute Liver Failure
Acute Liver Failure

- Rapid onset of synthetic dysfunction (jaundice, coagulopathy)
- Encephalopathy
- No prior liver disease (except Wilson Disease/acute HBV)
- Interval between jaundice and encephalopathy may determine the course of disease
  - < 1 week - hyperacute
  - 8-28 days - acute
  - 29 days - 12 weeks - subacute
Acute Liver Failure

• High mortality rate
  • Hemodynamic instability
  • Coagulopathy
  • Profound metabolic disturbances
  • Susceptibility to infection
  • Multiorgan failure
  • Cerebral edema
Etiologies of acute liver failure in the U.S. 1998-2007

- Acetaminophen: 46%
- Indeterminate: 14%
- Other: 7%
- Wilson Disease: 2%
- Ischemia: 4%
- Autoimmune: 5%
- HAV: 7%
- HBV: 11%
- Drug:
Management of ALF

- Close monitoring in ICU
- Volume resuscitation and cardiac monitoring
- Intubation for encephalopathy and clinical neurologic monitoring
- Resist temptation to correct coagulopathy
The Big Picture

- Identify/remove the cause of hepatic injury
- Optimize conditions for hepatic regeneration
- Anticipate and prevent complications
- Early recognition of those who need transplant!
Improving Outcomes

Survival rates for patients with ALF (grade 3-4 encephalopathy) at Kings College – N=2017

Encephalopathy of acute liver failure

- Rapid deterioration in the level of consciousness
- Increased intracranial pressure (ICP)
- Reduced cerebral perfusion pressure
- Neuropathologically, there is brain edema
- Pathogenesis is multifactorial with ammonia playing a major role
Putative Mechanisms Underlying Hepatic Encephalopathy and Brain Edema

**A Normal Ammonia Metabolism**
- Mucosal enzymes
- Protein metabolism
- Ammonia release
- Ammonia enters portal circulation
- Ammonia enters portal circulation
- Ammonia enters portal circulation
- Ammonia enters portal circulation
- Urea cycle
- Urea

**B Hyperammonemia**
- Hepatic failure and ammonia accumulation
- Ammonia enters systemic circulation
- Normal neuron

Anticipatory Management of Cerebral Edema in ALF

- **General measures**
  - raised head
  - maintain blood pressure (cerebral perfusion pressure 50-65 mmHg)

- **Reduction of brain edema**
  - Mannitol/Hypertonic saline

- **Reduction in cerebral blood flow**
  - Hypothermia

- **Reduction of inflammatory response**
  - Antibiotics
Liver Transplant for ALF

- Overall survival is 65%
- Must be “fulminant” to achieve UNOS Status I
- Contraindications
  - Extrahepatic malignancy
  - Uncontrolled extrahepatic sepsis
  - MOF
  - Irreversible brain damage
  - Unresponsive cerebral edema with a sustained ICP elevation >50mmHg and a decrease in CPP < 40 mmHg
Part 2: Focus on Chronic Liver Failure/ESLD
Complications of Cirrhosis Result from Portal Hypertension and/or Liver Insufficiency

Cirrhosis

Portal hypertension

Liver insufficiency

Variceal hemorrhage

Ascites

Encephalopathy

Jaundice
Hepatic Encephalopathy in Cirrhosis

• Neuropsychiatric complication of cirrhosis
• Results from spontaneous or surgical / radiological portal-systemic shunt + chronic liver failure
• Failure to metabolize neurotoxic substances
• Alterations of astrocyte morphology and function (Alzheimer type II astrocytosis)
A Clinical Diagnosis

- Clinical findings and history important
- Ammonia levels are unreliable
- Ammonia has poor correlation with diagnosis
- Measurement of ammonia **not** necessary
- Trails test, stroop test, serial 7s
- Slow dominant rhythm on EEG
## Stages of Hepatic Encephalopathy

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<tr>
<th>Stage</th>
<th>Mental state</th>
<th>Neurologic signs</th>
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<tbody>
<tr>
<td>1</td>
<td>Mild confusion: limited attention span, irritability, inverted sleep pattern</td>
<td>Incoordination, tremor, impaired handwriting</td>
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<tr>
<td>2</td>
<td>Drowsiness, personality changes, intermittent disorientation</td>
<td>Asterixis, ataxia, dysarthria</td>
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<td>3</td>
<td>Somnolent, gross disorientation, marked confusion, slurred speech</td>
<td>Hyperreflexia, muscle rigidity, Babinski sign</td>
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<td>4</td>
<td>Coma</td>
<td>No response to pain, decerebrate posture</td>
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Minimal Hepatic Encephalopathy

- Occurs in 30-70% of cirrhotic patients without overt hepatic encephalopathy
- Detected by psychometric and neuropsychological testing
- May improve with lactulose or synbiotics (probiotics and fermentable fiber)
- Predicts overt encephalopathy
Management of Encephalopathy

- Identify and treat precipitating factor
  - Infection
  - GI hemorrhage
  - Prerenal azotemia
  - Sedatives
  - Constipation
- Lactulose (adjust to 2-3 BM/day) p.o. or tap water enemas
- Rifaximin for recurrent HE
Management of Encephalopathy

- Take a careful history
  - Medication adherence
  - Dietary indiscretion
- Identify and treat precipitating factor
  - Infection
  - GI hemorrhage
  - Prerenal azotemia
  - Sedatives
  - Constipation
Management of Encephalopathy

- Discontinue diuretics
- Discontinue sedatives
- Lactulose (adjust to 2-3 BM/day) p.o. or tap water enemas
- Rifaximin for recurrent HE
Actions of Lactulose

- Lactic acid
- Decreased pH
- NH₃
- NH₄⁺
- Urease-producing bacteria
- Increase cathartic effect
Part 3: Focus on Liver Transplantation
Liver Transplant

**Indications**
- Decompensated cirrhosis - all causes
  (hepatitis C most common indication, NASH a close second)
- Intrahepatic malignancy (mainly HCC)
- Acute liver failure
- Metabolic disease

**Contraindications**
- Extrahepatic malignancy
- Active infection
- Active substance abuse
- Advanced cardio-pulmonary disease
- Extensive thrombosis (PV → SMV extension)
MELD (Model for End-Stage Liver Disease) + Na

- Predicts 3-month mortality among patients with chronic liver disease on the liver waiting list
- Now incorporates serum sodium
- Minimum score = 6 (risk of death on WL 20%)
- Maximum score = 40 (risk of death on WL 100%)

MELD and Survival on Transplant Waiting List

Probability of survival %

Months from listing

- 92.3%
- 90.7%
- 66.0%
- 33.8%
- <15
- 15 - 20
- 20 - 29
- 30+
Organ Allocation for Liver Transplant

- Fulminant hepatic failure has highest priority

- MELD score determines priority in cirrhosis
  - Amongst patients with same blood type, highest MELD score determines priority
  - Waiting time used only to break ties with identical MELD scores

- MELD scores are updated at regular intervals

- Exceptions for complications such as HCC, hepatopulmonary syndrome, portopulmonary HTN
Liver Transplantation in the U.S.

- Current 1- and 3-year survival rates are 90% and 80%, respectively
- During 2016, **7,841** liver transplantations were performed
- There are **14,198** patients on the waiting list
- In 2016, **2,623** patients either died on the list or were removed because they became too sick to be transplanted
- Main problem is the shortage of donors
- Expansion of donor pool: marginal livers, split-livers, live donors, advances in organ preservation