Liver Failure and ESLD

Management of the patient with ESLD and portal hypertension requires a thorough understanding of the systemic manifestations of end stage liver disease and appreciation of the increased risk of perioperative morbidity and mortality.

ANESTHETIC CONSIDERATIONS:

- Systemic illness
  - Complications:
    - **Encephalopathy**
    - **Hypoglycemia**
    - **Hypovolemia**
    - **Shock**: High output shock, cardiogenic shock (cardiomyopathy of EtOH)
    - **Hypoxemia**: Hepatopulmonary syndrome, restrictive LD with ascites
    - Hepatorenal syndrome
    - **Coagulopathy**
    - **Altered drug metabolism**
    - Increased risk of **aspiration**
    - Increased risk of infection
- Risk of **transmission** in viral forms
- Increased perioperative mortality risk
- Underlying cause of liver failure
  - Toxicity (alcohol, acetaminophen etc.)
  - Autoimmune (autoimmune hepatitis, primary biliary cirrhosis)
  - Viral (hepatitis A, B, C
  - Metabolic (Wilson's disease, Hemochromatosis, NASH)

ANESTHETIC GOALS:

- Anticipate & prevent post-induction circulatory collapse in patients on diuretics and with hypoalbuminemia (true & relative depletion of intravascular volume)
- Minimize perioperative liver dysfunction by avoiding reduction in hepatic blood flow:
  - Minimize catecholamine release
  - Avoid decreased MAP
  - Avoid hypoxemia, hypocarbia
  - Avoid PEEP (controversial)
- Prevent elective or non-emergent surgery in acute liver dysfunction
- Universal precautions to prevent transmission when viral cause

HISTORY

- AMPLE
- Cause (viral, autoimmune, drug toxicity including alcohol) and duration (acute vs. chronic) of liver failure
- Delineate extrahepatic manifestations
  - **Hematologic** – anemia, thrombocytopenia, coagulopathy, fibrinolysis
  - **Respiratory** – ascites (rapid change in abdominal girth causing restrictive pattern with decreased FRC) / pleural effusions, hypoxemia d/t hepatopulmonary syndrome, pHTN d/t portopulmonary syndrome
  - **Cardiovascular** – high CO / low SVR +/- cardiomyopathy (esp. with EtOH) → failure in late disease, sudden death, arrhythmias (hyperbilirubinemia associated with complete heart block on induction)
  - **CNS** – encephalopathy (acute hepatic dysfunction or end-stage chronic liver disease) +/- increased ICP
  - **Renal**
    - Water overload & hyponatremia (secondary hyperaldosteronism, made worse by hypoalbuminemia & portal HTN / ascites formation)
    - Electrolyte & metabolic abnormalities (chronic diuretic use)
      - Hyperkalemia (spironolactone)
      - Hypokalemia (loop diuretics)
    - Hepatorenal syndrome (renal hypoperfusion associated with peripheral vasodilation → RAAS activation → ADH release resulting in renal vasoconstriction → Na & H_2O retention resulting in dilutional hyponatremia)
  - **Gastrointestinal** – portal HTN & portosystemic shunting → formation of varices (can lead to catastrophic GI bleeding → patients can be on beta-blockers for this; high incidence of GERD secondary to portal hypertensive gastropathy
  - **Infectious** – Increased risk of spontaneous bacterial peritonitis

Table 1 Grades of hepatic encephalopathy

Grade	Status
0	Alert and orientated
1	Drowsy but orientated
2	Drowsy and disorientated
3	Agitated and aggressive
4	Unrousable to deep pain

- **Child-Pugh-Turcotte classification**

Parameter	1	2	3
Albumin	>35	28-35	<28
INR	<1.7	1.7-2.2	>2.2
Bilirubin	<34	34-50	>50
Ascites	None	Mild	severe
Encephalopathy	None	Gr I-II	Gr III-IV

  - Used to assess severity
  - Correlate with 1- and 2-year survival:
    - A (5-6)– 100 & 80%
    - B (7-9) – 80 & 60%
    - C (10-15) – 45 & 35%
  - Also most commonly used predictor of **perioperative mortality and morbidity**:
    - Class A – Approximately 10%

        - Class B – Approximately 30%
        - Class C – Approximately 75-80%
- MELD score:
    - MELD uses the patient's serum Cr, Bilirubin and INR to predict survival; UNOS modification uses a value of 4 for Cr if patient has been dialyzed within the last week, and a value of 1 for any value less than 1
        - 0.95(Cr) + 0.38(Bil) + 1.12(INR)+0.643 x 10
        - In hospitalized patients – 3 month mortality:
            - >40 – 71.3% mortality
            - 30-39 – 52.6% mortality
            - 20-29 – 19.6% mortality
            - 10-19 – 6% mortality
            - <9 – 1.9% mortality

PHYSICAL

- **VITALS** – Including O_2 saturation (hypoxia with hepatopulmonary syndrome), BP (high output state, low SVR)
- **CVS** – **Hyperdynamic cardiac exam** (high CO, low SVR – progresses to low CO state in advanced disease) → CV depression / failure (pulmonary edema, hypotension) → can progress to sudden cardiac death (encephalopathy usually present as well), arrhythmias, hypovolemia (tachycardia / hypotension)
- **RESP** – **Hypocapnia** (central hyperventilation with encephalopathy), restrictive pattern with **ascites**, **pleural effusions**, **hypoxia** (hepatopulmonary syndrome – pulmonary vascular dilation and intrapulmonary shunting leading to V/Q mismatch)
- **GI** – Stigmata of liver disease → jaundice, ascites, collateral portal circulation (spider angiomas, history of GI bleed), hepatic encephalopathy (asterixis), clubbing
- **CNS** – Hepatic encephalopathy (asterixis, level of consciousness), signs of **increased ICP** from cerebral edema
- **HEME** – Coagulation defects (easy bleeding / bruising → petechiae)
- **RENAL** – Hepatorenal syndrome (ascites – Mg / PO_4 wasting & free H_2O retention, oliguria)
- **METAB** – Hypoglycemia (insulin resistance), hyper- / hyponatremia

INVESTIGATIONS

- **Labs**
    - CBC (**anemia**, **thrombocytopenia**, immunosuppression), PTT / INR / fibrinogen (**coagulopathy**)
    - Serum Na / K & urinary Na (hyper- / hyponatremia d/t hepatorenal syndrome), , BUN / Cr, glucose (hypoglycemia / insulin resistance in alcoholics), Mg / PO_4 (wasting)
    - AST / ALT (hepatitis), bilirubin (hyperbilirubinemia), albumin (hypoalbuminemia), LDH
    - ABG (central hyperventilation, hypoxemia)
- **Imaging**
    - ECG
    - CXR (pleural effusions)
- **Special**
    - PFTs (decreased FRC with effusions)
    - ECHO (pulmonary artery pressures, valvular lesions / cardiomyopathy)
    - Exercise stress test or dobutamine stress echocardiography

OPTIMIZATION

- Consultation with hepatic specialist / program
- Aspiration prophylaxis
- Thiamine and B_{12} replacement in alcoholics
- Optimize nutritional status
- Coagulopathy correction (need for FFP?)
    - Vitamin K (10 mg SC / IM and can give again in 12 hours)
- May need preoperative pRBCs or PLTs
- ICP (elevated in end stage liver failure)
    - Mannitol
    - Mild hyperventilation
    - Head elevated
- Paracentesis / drainage of effusions if marked respiratory dysfunction
- Volume resuscitation prior to induction (avoid too quick correction of hyponatremia d/t risk of central pontine myelinoslysis) – 25% albumin if large amounts of ascites – guided by CVP / PAC ideally
    - Consider preoperative fluid restriction, hyperosmolar solutions, dialysis to correct hyponatremia

ANESTHETIC OPTIONS

- Local
- GA
    - GA decreases hepatic blood flow by decreasing cardiac output
    - Inhaled anesthetics undergo hepatic metabolism; risk of 'halothane hepatitis':
        - Halothane>>enflurane>isoflurane>desflurane
        - Desflurane undergoes the least degree of hepatic metabolism
        - Sevoflurane does not get metabolized into aceylated compound responsible for halothane hepatitis
- Regional
    - Risk of coagulopathy & epidural varices increase risk of epidural hematoma
    - Spinal / epidural also poses problems in face of major hemorrhage as circulatory collapse can occur and hemodynamic responses blunted
    - Infection risk is great with immunocompromised
    - Regional anesthesia decreases hepatic blood flow primarily by decreased afterload and hepatic artery flow even in patients with adequate preload

ANESTHETIC SETUP

- **Drugs**
  - Resuscitative, blood products (pRBCs, FFP, PLTs)
  - Short acting drugs which do not rely on hepatic metabolism
    - Propofol, fentanyl or remifentanil
  - Octreotide infusion if GI bleed
    - Octreotide 25-50 mcg/h IV infusion
- **Equipment**
  - CAS monitors +/- 5 Lead ECG
  - A-line (hemodynamic and frequent blood sampling), PNS (altered metabolism of NMBAs)
  - Consider CVP (jugular route d/t risk of coagulopathy) or TEE
  - Large bore IV access and rapid infuser if necessary or high risk surgery

MANAGEMENT OF ANESTHESIA

- **Induction**
  - Aspiration prophylaxis
  - Colloid resuscitation prior to induction if intravascularly volume deplete
  - Art line prior to induction if ssx vasodilatory shock
  - RSI with cricoid (full stomach / aspiration risk) or awake intubation
    - SCh may be prolonged
    - Propofol okay but cardiac depression
    - Thiopental less cardiac depression but needs reduced dose and question of necrosis in zone 3
  - Predict and prevent hypotension
  - Decrease dose of induction agents
- **Maintenance**
  - Remifentanil (not affected by liver failure)
  - Volatile agents:
    - desflurane (minimal metabolism and quickly cleared, some evidence that it influences hepatic artery buffer response less than other volatile agents and preserves hepatic blood flow)
    - Isoflurane recommended by some as it decreases hepatic blood flow the least
    - Large experience in Japan with sevoflurane in liver failure
  - Rocuronium – caution! primarily hepatically metabolized
  - Cis-atracurium (or atracurium) for maintenance neuromuscular blockade
    - Metabolized via hoffman elimination and ester hydrolysis
    - Laudanosine can accumulate in both hepatic and renal failure and theoretically cause seizures though clinically relevant neurotoxicity has not been reported in this patient population
  - Frequent glucose checks
  - Colloid for fluid
    - Some recommend dextrose containing solution with NAC 6 g in 1000 mL to provide glutathione for the impaired liver
  - Avoid hypoxemia / hypercarbia / acidosis (worsens pHTN associated with portopulmonary syndrome)
  - If hypotensive in spite of adequate cardiac filling pressures:
    - Phenylephrine (may require large doses)
    - Can consider non-adrenergic vasoconstrictor (vasopressin)
    - norepinephrine
  - Maintain good urine output
    - Can use loop diuretics or spironolactone to maintain
- **Emergence**
  - Predict postoperative ventilation in these patients (based on cardiorespiratory involvement)

DISPOSITION & MONITORING

- ICU if requiring postoperative ventilation

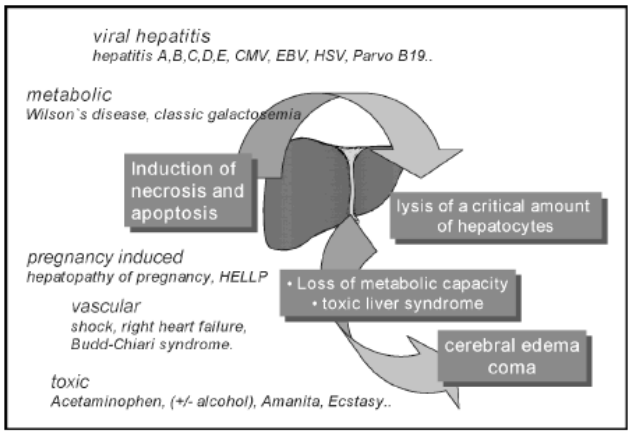
COMPLICATIONS

- Bleeding
- Prolonged drug effects
- Cardiovascular collapse
- Hypoxia
- Sepsis
- Worsening of hepatic function
- Renal dysfunction
- Hypoglycemia
- Acute alcohol withdrawal

PATHOPHYSIOLOGY

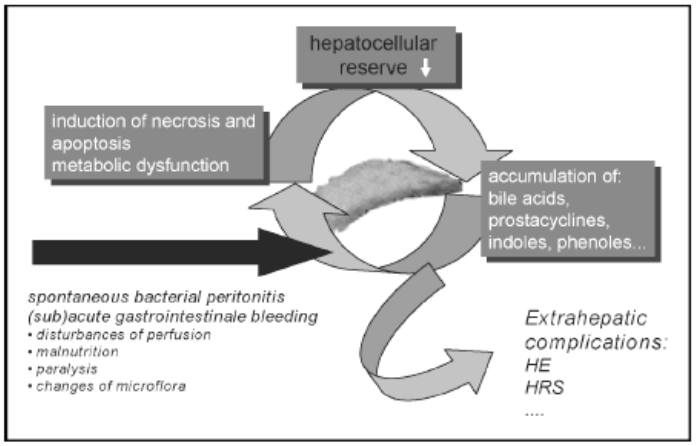
- Functions of the liver
  - Carbohydrate metabolism
  - Lipid metabolism
  - Protein metabolism
  - Drug, toxin and hormone metabolism
  - Modulation of formed elements of blood
  - Bile synthesis and excretion

Figure 1. Pathogenesis of acute liver failure



CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; Parvo B19, parvovirus B19.

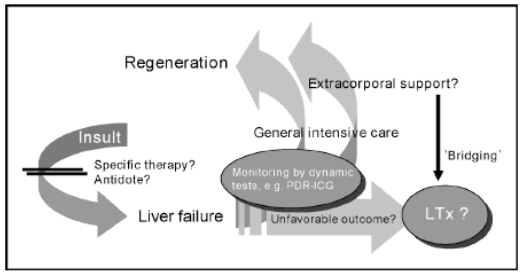
Figure 2. Pathogenesis of 'acute-on-chronic' liver failure



HE, hepatic encephalopathy; HRS, hepatorenal syndrome.

- Hepatic blood flow is approximately 29% of cardiac output
  - Portal system provides 75 % of the blood flow but only 50% of the oxygen
  - Hepatic artery provides 25% of the blood flow and 50% of the oxygen supply
  - Decreased by:
    - PEEP, PPV
    - Hypoxemia, hypocarbia, β, α_1, H_2-blockers and vasopressin
    - Up to 60% reduction in hepatic blood flow with upper abdominal surgery
    - Regional anesthesia decreases hepatic blood flow primarily by decreased afterload and hepatic artery flow even in patients with adequate preload
    - GA decreases hepatic blood flow by decreasing cardiac output
  - Increased by:
    - Low dose dopamine
- **Causes of liver dysfunction**
  - Acute hepatocellular damage
    - Viral Hepatitis
    - Drug Inducted
      - Therapeutic
        - Acetaminophen: single dose 10-15 g, fatal dose > 25 g, in chronic alcoholics the dose may be as low as 2 g
          - Treat with N-acetylcysteine
        - Halothane: not a direct hepatotoxin, genetic predisposition to idiosyncratic reaction, risks include: adults, obese women
          - Treatment is supportive, mortality ~ 20-40%
        - Isoniazid, rifampin, valproic acid, phenytoin, methyldopa, ASA, NSAIDs
      - Carbon tetrachloride, vinyl chloride, toxic mushrooms (Amanita phalloides)
  - Chronic
    - Autoimmune hepatitis
    - Primary biliary cirrhosis
    - Metabolic – Wilson's (copper), hemochromatosis (iron), α_1-antitrypsin deficiency etc.
    - Alcoholic

Figure 3. Treatment algorithm



LTx, liver transplantation.

- **Anesthetic drugs**
  - Induction agents
    - Thiopental – prolonged half life due to reduced cytochrome P450 activity & altered redistribution (reduced plasma proteins) – concern about causing zone 3 necrosis
    - Propofol – thought to have extrahepatic sites of metabolism since clearance exceeds liver blood flow
  - Opioids
    - Morphine-6-glucuronide formation from morphine may be reduced
    - Fentanyl has inactive metabolites excreted in urine and has normal half-life when used in small doses (accumulation with repeated doses)
    - Remifentanil unchanged
  - NSAIDs
    - Ill advised (d/t effects on GI system, platelets & renal function)
  - Acetaminophen
    - Not contraindicated in liver failure but great care must be taken in its use
    - Alcoholics with depleted glutathione reserves may be susceptible to acetaminophen toxicity at therapeutic levels
  - Inhalational
    - Isoflurane decreases hepatic blood flow the least
    - Desflurane and isoflurane metabolized the least
    - Sevoflurane least likely to cause immune mediated hepatocellular injury ('halothane hepatitis')
  - Neuromuscular Blockers
    - Succinylcholine & mivacurium prolonged due to reduced plasma pseudocholinesterase concentrations
    - Liver failure significantly prolongs pancuronium and rocuronium blockade
      - Pancuronium & vecuronium are significantly metabolized by liver
      - Rocuronium and vecuronium are significantly excreted in the bile
    - Cis-atracurium and atracurium depend on Hoffman elimination (to lesser extent in atracurium) and since Vd is increased in liver failure these drugs may actually have a small decrease in duration of action

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