Anesthetic Management of the Patient with Severe Liver Disease

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- No financial disclosures related to this presentation

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Objectives

1. Review normal hepatic physiology and the pathophysiology of end-stage liver disease (ESLD)
2. Identify the major comorbidities of patients with ESLD that impact anesthetic management
3. Describe pre-operative evaluation/optimization and considerations for intraoperative management and post-operative care for patients with ESLD

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A lot of this material is refresher/background...

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Liver Anatomy/Physiology

- Anatomy – right and left anatomic lobes are separated
- by the falciform ligament
  - Right lobe
    - Caudate lobe
    - Quadrate lobe
  - Left lobe
- Surgical Anatomy – right and left surgical lobes based on blood supply (point of bifurcation of the hepatic artery and the portal vein)
  - Eight surgical segments

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Liver Anatomy/Physiology

- Lobules – discrete anatomic functional units
  - Hepatocytes arranged around a centrilobular vein
- Sinusoidal channels
  - Contains blood from hepatic arterioles and portal venules
  - Lined by endothelial cells
  - Kupffer cells (macrophages) that remove bacteria endotoxins, viruses, proteins and particulate matter
- Venous drainage from the central veins form the hepatic veins that empty into the IVC

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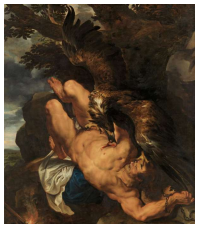
Bonus: Trivia

- Zeus
  - Stole fire from mankind out of anger
- Prometheus
  - Returned fire to man
- Punishment
  - Chained to a rock in in the mountains of Scythia where an eagle would eat part of his liver each day.
  - The liver would regenerate overnight while the eagle was asleep



Prometheus Bound. Peter Paul Rubens, 1612. Displayed at the Philadelphia Museum of Art

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Liver Anatomy/Physiology

- Blood flow: ~25% of cardiac output
  - Hepatic artery
    - ~25% of blood flow
    - 45-50% of the livers O_2 supply
    - Autoregulated based on metabolic demand
  - Portal vein
    - ~75% of blood flow
    - 50-55% of the livers O_2 supply
    - Dependent on blood flow
    - Normal pressure: 7-10mmHg with low resistance
- Buffer Response: A decrease in flow through either will result in a compensatory increase in the other
- Blood reservoir - can shift blood from the hepatic veins and sinusoids into the central circulation
  - Lowering CVP will reduce hepatic venous pressure and hepatic blood volume and can reduce blood loss during hepatic surgery

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Bonus: Trivia

- Liver Augury (aka hepatoscopy)
  - Animal sacrifice
  - Performed to learn the intention of the Gods
  - Limited to visually inspecting the exterior of the liver
  - No anatomical dissection
- No actual evidence that the Greeks knew of the regenerative power of the liver.
  - Viewed as the most vital organ and associated with the Gods
  - Gods are immortal

Reading of a liver (Vatican: Gregorian Museum, Rome, cat #12240)

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Liver Anatomy/Physiology

- Metabolic Function (simplified)
  - Bile production
  - Synthesis
    - Clotting factors (except factor VIII and vWF)
      - Vitamin K required cofactor for synthesis of factors II, VII, IX and X
    - Plasma cholinesterase (pseudocholinesterase)
  - Immune System
  - Nutrient metabolism
  - Hepatic biotransformation

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Laboratory Tests

- Cellular injury:
  - Aspartate aminotransferase (AST)
  - Alanine aminotransferase (ALT)
- Biliary obstruction
  - Alkaline Phosphatase
  - γ-glutamyl transferase (GGT)
  - Bilirubin
    - Indirect (unconjugated): excess production of bilirubin (hemolysis) or decrease in uptake
    - Direct (conjugated): impaired intrahepatic excretion or extrahepatic obstruction
      - Renally excreted
- Synthetic Function:
  - Albumin (3 week half life)
  - PT/INR (short half life of factor VII)
    - Dependent on adequate intake of vitamin K which requires adequate bile salt secretion (i.e. can be elevated in biliary obstruction despite no issue with hepatic function)

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MELD 3.0

- MELD 3.0 is now the standard (replaced MELD-Na)
  - More accurate mortality prediction
  - Takes more variables into account
  - Recommended by OPTN in 2022
- Sex
- Creatinine
- Total Bilirubin
- INR
- Sodium
- Albumin
- HD/CVVHD use

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Hepatic Pathology*

- Acute
  - Drug Toxicity
    - Acetaminophen
    - Non-acetaminophen
  - Infection
  - Acute alcoholic hepatitis
  - Pregnancy-related
- Chronic
  - Chronic viral hepatitis
  - Alcoholic liver disease
  - Non-alcoholic steatohepatitis (NASH)/Metabolic Dysfunction-Associated Steatohepatitis (MASH)

**There are obviously a lot more pathologies, we will focus on the most common*

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ESLD/Cirrhosis

- Cirrhosis → Portal Hypertension
  - Jaundice
  - Ascites
  - Spider angiomas, palmar erythema, caput medusae
  - Pruritis
  - Esophageal Varices
  - Hepatic Encephalopathy
    - Grade I: Changes in behavior with minimal change in consciousness
    - Grade II: Gross disorientation, drowsiness, possible asterixis
    - Grade III: Marked confusion, incoherent speech, sleeping most of the time but arousable
    - Grade IV: Comatose, unresponsive to pain

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Chronic Liver Disease

- Cardiovascular
  - Hyperdynamic circulation
  - Relative hypervolemia
  - Cirrhotic cardiomyopathy
- Pulmonary
  - Hepatic hydrothorax
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension
- GI
  - Portal hypertension
  - Spontaneous bacterial peritonitis
- Renal
  - Acute or chronic kidney disease
  - Hepatorenal syndrome
- CNS
  - Hepatic Encephalopathy
- Endocrine
  - Adrenal insufficiency
- Hematologic
  - Coagulopathy
  - Anemia
  - Thrombocytopenia
  - Hypofibrinogenemia
- Malnutrition
- Muscle wasting
- Impaired wound healing

Adapted from Gilbert-Kawai N, Hogan B, Milan Z. Perioperative management of patients with liver disease. BJA Education. 2022, 22(3):111-117

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Acute Liver Failure

- Definition:
  - Coagulopathy
  - < 26 weeks duration with no prior evidence of liver disease
  - Encephalopathy
- Causes:
  - Acetaminophen toxicity
  - Unknown?
  - Drug induced liver injury (DILI)
  - Autoimmune hepatitis
  - HBV
  - Ischemia

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Acute Liver Failure

- Early recognition is key, survival can be as low as 50% without transplantation
  - Liver transplantation is used in select patients
- Progression to cerebral edema is biggest risk (can cause herniation and death)
  - Can occur in up to 80% of patients with Grade VI hepatic encephalopathy
- ALF is a contraindication to any elective surgery
- These patients may present to the OR for ICP monitor placement, ICP monitoring and maintenance of CPP become exceedingly important

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Guiding the future of patient care

These are some of the comorbidities that can really make it difficult to anesthetize someone with ESLD

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Cirrhotic Cardiomyopathy

- Patients with ESLD normally have a hyperdynamic circulation
  - High cardiac output ("normal" EF can actually be quite concerning)
  - Low SVR
- Cirrhotic Cardiomyopathy (CCM) - criteria proposed at 2005 WCG
  - Systolic and diastolic dysfunction
  - Resistance to ß-adrenergic stimulation
    - Downregulation of beta receptors from relative intravascular hypovolemia
  - Electrophysiologic abnormalities
    - Prolonged QT

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Portopulmonary Hypertension

- WHO Group 1 Pulmonary Arterial Hypertension
  - PAH that exists in a patient with portal hypertension and no alternative cause of PAH
- Mechanism
  - True cause is unknown....
  - Best theory: Disparity between vasoconstrictive and vasodilatory mediators
- Diagnosis
  - mPAP > 20mmHg
  - PCWP ≤ 15mmHg
  - PVR ≥ 3 WU (240 dynes/sec/cm^{-5})

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Portopulmonary Hypertension

- Treatment follows the same algorithms as those for other causes of PAH
  - Phosphodiesterase-5 Inhibitors (sildenafil, tadalafil)
  - Endothelin receptor antagonists (can be associated with liver toxicity)
  - Prostacyclin agonists (epoprostenol, etc)
  - Endothelin receptor antagonists (macitentan, etc)
- Beta blockers and calcium channel blockers are generally avoided
- TIPS may worsen PVR
- Liver transplantation is not a treatment

- These patients need extensive pre-operative optimization, risk/benefit discussions of surgical intervention, coordinated surgical planning and extensive hemodynamic monitoring (TEE, PAC)

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Hepatopulmonary Syndrome

- Abnormal oxygenation due to the presence of intrapulmonary vascular dilations and shunts in patients with portal hypertension
  - Platypnea - increase in dyspnea when upright and relieved when supine
  - Orthodeoxia - decrease in arterial oxygenation when the patient moves from supine to upright
- TTE: intrapulmonary shunts seen on bubble study
  - "late" bubbles (usually more than 3 cardiac cycles)
- Hypoxemia develops from VQ mismatch

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Hepatopulmonary Syndrome

- Severity
  - Mild: PaO2 ≥ 80 mmHg (on RA)
  - Moderate: PaO2 ≥ 60mmHg and < 80 mmHg (on RA)
  - Severe: PaO2 ≥ 50 mmHg and < 60mmHg (on RA)
  - Very Severe: PaO2 < 50mmHg (on RA) or PaO2 < 300mmHgon 100% O2
- Liver Transplantation is the only definitive therapy

- These patients should be counseled on the likelihood of post-operative mechanical ventilation and have a thorough risk/benefit discussion regarding surgical intervention

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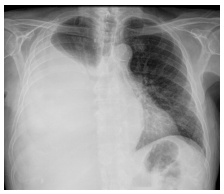
Hepatic Hydrothorax

- Right sided pleural effusion
  - Can occur on the left or bilaterally
  - Transudative
  - Thought to be related to ascites passing from the peritoneal cavity into the pleural space from small defects in the diaphragm
- Dyspnea
- Pleuritic chest pain
- Non-productive cough



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Coagulopathy

- Reduction of pro-coagulant and anti-coagulants
  - Increased risk of both bleeding and thrombosis
  - Protein C, protein S, antithrombin reduction
  - Increased vWF
- Coagulation factor deficiencies
- Thrombocytopenia (and platelet dysfunction)
  - Impaired platelet production
  - Increased platelet sequestration
  - Reduced function
- Hyperfibrinolysis
- Hypofibrinogenemia

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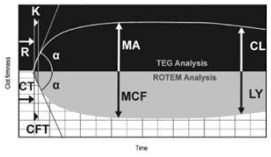
Coagulopathy

- Viscoelastic Testing (TEG and ROTEM)
  - Typically show relatively preserved hemostasis
  - Preserved clot initiation and propagation
  - Reduced clot strength
    - Reduced MA or MCF



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Hepatorenal Syndrome

- Splanchnic vasodilation → decrease in effective circulating blood volume → renal vasoconstriction (RAAS activation)
  - Serum sodium increase by ≥ 0.3mg/dl within 48 hours or increase to ≥ 1.5x baseline creatinine within the prior 7 days
  - No other cause of AKI (diagnosis of exclusion)
  - No improvement with volume challenge (Albumin)
- Treatment
  - Vasoconstrictors
    - Norepinephrine
    - Midodrine, octreotide
    - Terlipressin
  - Albumin
  - RRT as a bridge to liver transplant

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Hepatic Encephalopathy

- Systemic inflammation and elevated ammonia are involved in the pathogenesis
- Can vary widely from subtle deficits to hepatic coma
- Severity:
  - Grade I - Changes in behavior, mild confusion, disordered sleep, slow speech
  - Grade II - Lethargy, moderate confusion, asterixis
  - Grade III - Marked confusion, incoherent speech, sleeping but arousable
  - Grade IV - Unresponsive to pain, coma

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Bonus: Trivia

- "Canine recipient of an orthotopic liver homograft, 5 years later. The operation was on March 23, 1964. The dog was treated for only 120 days with azathioprine and died of old age after 13 years."
- They did not provide the name of the dog in the paper.... 🎃

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Colorado Review of Anesthesia for Subscribers And Hospitals
Guiding the future of patient care

What should we do when someone shows up to pre-op clinic...

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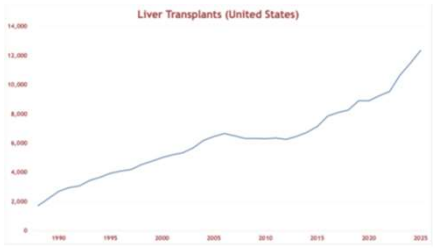
ESLD is becoming more common



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Pre-operative Evaluation

- Cardiac
  - CCM
  - POPH
- Pulmonary
  - HPS
- CNS
  - Encephalopathy
- Renal
  - HRS
- Hematology
  - Coagulopathy
- GI
  - Degree of liver disease

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Morbidity & Mortality

- Risks of bleeding
- Risks of infection
- Poor wound healing
- Decompensation of liver disease
- Acute kidney injury

- Is it emergent or elective?
- Can the patient be further optimized?
- Have they been evaluated for transplant/referred to transplant center?

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What surgery/procedure?

- Liver

  Hepatic resection
- Non-liver
  - Everything else....

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What surgery/procedure?

- Liver
  - Planned resection
  - Volume goals
  - Coagulopathy
    - Blood product requirements
    - Large volume IV access
  - Clamping
    - Inflow limitations
      - Pringle Maneuver
    - IVC manipulation/clamping
  - Plus - you'll want to know everything else that you'd want to know for any surgical procedure

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Anesthesia and the Liver

- Decreased hepatic blood flow
  - Sympathetic activation
    - Vasoconstriction of both arterial and venous splanchnic vasculature
  - Positive pressure ventilation
    - Reduces venous return → decreases preload and decreases CO
    - Increased hepatic venous pressure
- IV anesthetics have no real effect (when used for short periods)

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Volatile Anesthetics

- Reduction in hepatic blood flow
  - Isoflurane and sevoflurane cause very little reduction in hepatic blood flow (at 1 MAC)
  - Desflurane can decrease blood flow up to 30% at 1MAC
  - Don't use halothane....
- Hepatotoxicity
  - Once again....don't use halothane
  - Sevoflurane → fluoride and hexafluoroisopropanol (HFIP)
    - Conjugated in the liver and excreted by the kidney
    - No evidence that these metabolites cause hepatic injury
    - No evidence that compound A (metabolite) produce hepatic injury
  - Isoflurane and desflurane undergo metabolism to trifluoroacetyl chloride (TFA) - which is involved in hepatic toxicity from halothane but these are produced in much lower amounts

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Bonus: Trivia

- First Liver Transplant: 1963
  - Dr. Thomas Starzl at the University of Colorado
- First "successful" liver transplant: 1967
  - Dr. Thomas Starzl at the University of Colorado

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What should we do when someone shows up to the OR...

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Coagulopathy Correction

- Vitamin K
  - Can be used pre-operative in patients with Vitamin K deficiency
  - Poor nutrition, EtOH, cholestatic disease
- Platelets
  - If moderate or higher risk surgery, can correct up to a value of 50,000/μL
- Fibrinogen
  - Goal fibrinogen level is 150-200mg/dL for surgery
  - Minimally invasive procedures may be done with fibrinogen levels > 100mg/dL
- INR
  - Should not be used to guide therapy
  - FFP administration to correct INR is not generally recommended
- TEG/ROTEM should be used to guide coagulation correction

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Intra-operative Management

- Induction
  - POPH
    - May require pre-induction arterial line
  - Ascites
    - May inhibit the ability to lay flat and may necessitate RSI
  - HPS
    - May desaturate very quickly
- MAC/Sedation may be contraindicated in the setting of significant ascites and gastroparesis

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Intra-operative Management

- Monitors
  - Arterial catheter
    - May be indicated for both hemodynamic monitoring and to obtain arterial blood sampling
  - Central venous catheter
    - Not routinely used for CVP monitoring
    - Often indicated for venous access and vasopressor administration
  - Transesophageal echocardiography (TEE)
    - Can be used to monitor volume status and cardiac function
    - Risks related to esophageal varices and increased bleeding risk
    - Can avoid transgastric views to reduce risk

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Intra-operative Management

- Laboratory
  - Acid/base status
    - Prolonged Pringle maneuver may lead to acidosis
  - Coagulopathy
    - Conventional laboratory values: PT/INR, PTT, fibrinogen, platelet count
    - Viscoelastic testing: TEG or ROTEM
  - Hemoglobin goals should remain the same as for patients without ESLD
- Medications
  - Propofol, etomidate, ketamine clearance is similar to healthy patients
    - Prolonged propofol infusions may result in prolonged recovery
  - Benzodiazepines can result in enhanced sedation and prolonged duration
  - Dexmedetomidine may also have prolonged duration

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Pain Control

- Neuraxial anesthesia
  - Neuraxial often contraindicated due to coagulopathy and/or thrombocytopenia
  - New coagulopathy may be present post-operatively after hepatic resection (may impact ability to remove catheter)
- Opioids
  - Reduced metabolism
  - Increased dosing intervals recommended
  - Bolus dose elimination less affected
  - Hydromorphone should be administered in reduced doses and at increased dosing intervals
  - Meperidine should be avoided (reduced clearance)
- Acetaminophen
  - Doses up to 2g/day generally safe
- NSAIDs usually avoided

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Postoperative Management

- High risk of postoperative morbidity
- May require ICU care post-operatively depending on intraoperative course
- Cautious with opioids and sedatives
- Monitor fluid status carefully

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Questions?

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