LIVER DISEASES AND ITS ANESTHETIC IMPLICATIONS
MICROSTRUCTURE AND HISTOLOGY
HEPATIC BLOOD SUPPLY

- 25% to 30% of CO

Dual supply

Portal V (75%) - 50-60% of oxygen supply

Hepatic A (25%) - 40-55% of oxygen supply
HEPATIC BLOOD FLOW

Central vein system
Hepatic vein
Portal vein
Portal triad of structures
Right and left hepatic ducts (bile ducts)
Right and left hepatic arteries
1) HEPATIC ARTERIAL BUFFER RESPONSE

- most important intrinsic mechanism
- changes in portal venous flow cause reciprocal changes in hepatic arterial flow
- mechanism involves the synthesis and washout of adenosine (i.e., a vasodilator) from periportal regions
2) AUTOREGULATION

- Mechanism involves myogenic responses of vascular smooth muscle to stretch
- Only in postprandial state

3) METABOLIC CONTROL

- Decrease oxygen tension or pH of portal venous blood increase hepatic arterial flow whereas postprandial hyperosmolarity increase both hepatic and portal flow
• **B. EXTRINSIC REGULATION**

• 1. NEURAL CONTROL
  - Fibers of the vagus, phrenic, and splanchnic nerves (postganglionic sympathetic fibers from T6 through T11)
    - *Vagal stimulation*: alters the tone of the presinusoidal sphincters
    - the net effect is a redistribution of intrahepatic blood flow without changing total hepatic blood flow.

• 2. HUMORAL CONTROL
  - hepatic arterial bed has $\alpha_1$, $\alpha_2$, and $\beta_2$-adrenergic receptors
  - portal vein has only $\alpha$-receptors
  - **Glucagon** induces relaxation of hepatic arterial smooth muscle.
  - **angiotensin II** constricts the hepatic arterial and portal venous beds.
  - **Vasopressin** elevates splanchnic arterial resistance, but it lowers portal venous resistance.
SPECTRUM OF LIVER DISEASE

PARENCHYMAL

- Acute – infectious or non infectious
- Chronic Hepatitis – alcohol, autoimmune, drugs, inherited (Wilson, alpha 1 antitrypsin), NASH, viral
- Hepatic Cirrhosis (+ portal hypertension)

CHOLESTATIC

- Intrahepatic
  - viral hepatitis
  - drug induced
- Extrahepatic (Obstructive jaundice)
  - Calculi, stricture, growth.
CIRRHOSIS OF LIVER

• A chronic progressive disease
• Extensive degeneration & destruction to the liver parenchymal cells
• Cell necrosis → scar tissue → nodular structure → impedes blood flow → hypoxia
Causes

• Chronic viral hepatitis
• Metabolic: hemochromatosis, Wilson dis, alfa-1-antitrypsin, NASH
• Prolonged cholestasis (primary biliary cirrhosis, primary sclerosing cholangitis)
• Autoimmune diseases (autoimmune hepatitis)
• Drugs and toxins
• Alcohol
Pathophysiology

• **Alcoholic cirrhosis** – accumulation of fat and scar formation in the liver cells

• **Postnecrotic cirrhosis** – broad bands of scar tissue resulted from viral, toxic, or autoimmune hepatitis

• **Biliary cirrhosis** – diffuse fibrosis with jaundice from chronic biliary obstruction

• **Cardiac cirrhosis** – from long-standing right sided heart failure
Clinical Manifestations

• Early
  – GI disturbances, dull pain in RUQ/epigastrium, fever, malaise, enlargement of liver & spleen

• Late
  – Jaundice, skin lesions (spider angiomas, palmar erythema), hematologic problems, endocrine disturbances, peripheral neuropathy
Complications

1. Portal Htn
2. Oesophagogastric varices
3. Ascites
4. Anemia & coagulopathy
5. SBP (spontaneous bacterial peritonitis)
6. Cardiomyopathy
7. Arterial hypoxemia & Hepatopulmonary syndrome
8. Hepatorenal syndrome
9. Hypoglycemia
10. Duodenal ulcer
11. Gallstones
12. Hepatic encephalopathy
13. Primary HCC
Pathophysiology of End Stage Liver Disease

• Predominant pathophysiological manifestation of liver disease is portal hypertension.

• Normal portal pressures are usually in the range of 5-12 mmHg.

• Portal hypertension is generally defined when any 2 of the following 3 criteria are met: splenomegaly, ascites or bleeding esophageal varices.

• Portal pressures at this time are usually > 20 mmHg
Varices

- Due to ↑portal hypertension
- Varicosities develop where collateral & systemic circulations communicate → esophageal & gastric varices, caput medusae, & hemorrhoids
- most common - gastroesophageal varices
- Painless massive haematemesis with or without melena & other features of PH.
- Endoscopy- best for evaluation
Collaterals

SITES:
1. Oesophagus
2. Gastric
3. Colo-rectal
4. Portal hypertensive gastropathy
STANDARD TREATMENT OF PORTAL HYPERTENSION

1. Pre-primary prophylaxis – EGD, no treatment for PH, treat cause of cirrhosis.

2. Primary prophylaxis - non-selective b-blockers (propranolol, nadolol) are as effective as Endoscopic variceal ligation(EVL) depending upon risk

3. Controlling acute variceal hemorrhage - Safe vasoactive drugs are started as soon as possible, prior to diagnostic endoscopy. EVL is the procedure of choice if source confirmed, Sclerotherapy second line. TIPS recommended when everything fails

4. Secondary prophylaxis- if TIPS performed consider for transplant. If TIPS not performed combination of pharmacological (NSBB alone or NSBB + ISMN) plus EVL is associated with lower rebleeding rates than either therapy alone
Ascites

• Accumulation of serous fluid in peritoneum

**OVERFLOW MODEL** excessive renal retention of sodium $\rightarrow$ intravascular volume to expand, causing

(1) plasma oncotic pressure decreases, with the liver unable to produce sufficient
(2) portal hydrostatic pressure increases

• The combination of low oncotic pressure and portal hypertension accelerates the formation of edema and ascites.

**UNDERFILL MODEL** cirrhosis causes the effective plasma volume to decrease, which activates homeostatic mechanisms to retain sodium and water.
• Tense ascites may decrease functional residual capacity (FRC), adversely affect pulmonary gas exchange and increase risk of aspiration.
• Hydrothorax or pleural effusions may produce atelectasis.
• Secondary hyperaldosteronism may manifest as hypokalemic metabolic alkalosis.
• There is intra and extra-pulmonary shunting, elevated mixed venous oxygen saturation (SvO2), altered lactate metabolism.
• Treatment: diagnostic paracentesis, salt restriction to 2000mg/day, diuretics (furosemide or spironolactone), Large-volume paracentesis, TIPS
COAGULOPATHY

• All coagulation factors except for VIII are markedly reduced in patients with liver disease
• CLD patients have thrombocytopenia due to splenomegaly and decreased thrombopoietin
• Antithrombin-III (AT-III) levels fall due to reduced synthesis and/or increased consumption due to fibrinolysis
• Hemostatic changes associated with surgical bleeding are
  1. thrombocytopenia,
  2. platelet function defects,
  3. inhibition of platelet aggregation and adhesion by nitric oxide and prostacyclin,
  4. decreased levels of coagulation factors: II, V, VII, IX, X, XI, quantitative and qualitative abnormalities of fibrinogen,
  5. low levels of α2-antiplasmin, Factor XIII and thrombin activatable fibrinolysis inhibitor, and elevated tPA.
Hemostatic changes associated with thrombosis:

1. Elevated vWF, decreased levels of ADAMTS-13 (a vWF cleaving protease),
2. Decreased levels of anti-coagulants: ATIII, Protein C and S, α2 macroglobulin, elevated levels of heparin cofactor II, elevated VIII, decreased levels of plasminogen, normal or increased PAI-1.
3. Hypercoagulability can occur in patients with liver disease, especially those with cholestatic disease.
Portopulmonary hypertension (POPH)

- Pulmonary hypertension syndrome with vascular obstruction and increased resistance to pulmonary arterial flow.
- It occurs due to pulmonary endothelial/smooth muscle proliferation, vasoconstriction and in-situ thrombosis.
- The development of POPH has not been demonstrated to correlate with the severity of liver disease.
- The diagnostic criteria for POPH include a mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest and a pulmonary vascular resistance (PVR) of > 240 dynes.s.cm.
- A better measure is a transpulmonary gradient > 12 mmHg (mPAP-PAOP) as this reflects the obstruction to flow (PVR).
• Female gender and autoimmune hepatitis have been reported to be risk factors.
• In cases confirmed by right-sided heart catheterization, treatment with epoprostenol or bosentan may reduce pulmonary hypertension and thereby facilitate liver transplantation;
• Liver transplantation is contraindicated in patients with moderate to severe pulmonary hypertension (mean pulmonary pressure > 35 mm Hg).
Hepatopulmonary syndrome (HPS)

• Characterized by arterial hypoxemia caused by intrapulmonary vascular dilatations.

• The clinical triad of

• 1) portal hypertension; 2) hypoxemia; and 3) pulmonary vascular dilatations
European Respiratory Society (ERS)/European Association for Study of the Liver (EASL) Task Force have certain set diagnostic criteria for hepatopulmonary syndrome (HPS).

These include:

• Diagnosis of liver disease,
• An A-a oxygen gradient > 15 mmHg,
• Pulmonary vascular dilatation documented by “positive” delayed, contrast-enhanced echocardiography with left heart,
• Detection of microbubbles for > 4 cardiac cycles after right heart opacification of microbubbles
• Brain uptake > 6% following 99mTc macroaggregated albumin (MAA) lung perfusion scanning
TREATMENT

• Medical therapy has been disappointing
• Experimentally, iv methylene blue, oral garlic powder, and oral norfloxacin may improve oxygenation by inhibiting nitric oxide-induced vasodilation
• Pentoxifylline may prevent hepatopulmonary syndrome by inhibiting production of tumor necrosis factor.
• Long-term oxygen therapy is recommended for severely hypoxemic patients
• The syndrome may reverse with liver transplantation, although postoperative mortality is increased in patients with a preoperative arterial oxygen tension < 50 mm Hg or with substantial intrapulmonary shunting.
• TIPS may provide palliation in patients with hepatopulmonary syndrome awaiting transplantation.
Hepatorenal syndrome

- Pre-renal acute kidney injury that occurs in decompensated cirrhosis.
- The syndrome is classified into two types:
  - Type 1 is characterized by a doubling of the serum creatinine level to greater than 2.5 mg/dl in less than 2 weeks
  - Type 2 is characterized by a stable or slower progressive course of renal failure
• The International Ascites Club has suggested FIVE major criteria to confirm the diagnosis of HRS:
(1) chronic or acute liver disease with advanced hepatic failure and portal hypertension;
(2) a low GFR as assessed by serum creatinine >1.5 mg/dL or creatinine clearance below 40 mL/min;
(3) absence of shock, ongoing bacterial infection, fluid losses, or treatment with nephrotoxic drugs;
(4) no sustained improvement in renal function after oral diuretic withdrawal and plasma volume expansion; and
(5) less than 500 mg/day proteinuria with no ultrasonographic evidence of parenchymal renal disease or urinary obstruction
MANAGEMENT

• IV infusion of albumin + vasoconstrictor regimens for 7–14 days:
  1. IV vasopressin or ornipressin (ischemic s/e);
  2. IV ornipressin plus dopamine;
  3. IV terlipressin (preferred agent);
  4. IV norepinephrine;
  5. oral midodrine, an -adrenergic drug, plus the somatostatin analog octreotide, s/c or iv.

• MARS (molecular adsorbents recirculating system), a modified dialysis method that selectively removes albumin-bound substances.

• TIPS

• Liver transplantation is the treatment of choice.
Spontaneous bacterial peritonitis

- Consists of fever, leukocytosis, abdominal pain, and decreased bowel sounds
- ↑ gut wall permeability → growth of bacteria in peritoneal fluid
- Associated ↓ macrophage function
- Risk factors - low protein in ascitic fluid, variceal bleeding
- Antibiotic prophylaxis in Pts with GI haemorrhage is recommended.
- High mortality (20-50%)
Hepatic Encephalopathy

- Pathophysiologic phenomena that contribute to the syndrome include:
  1. hepatobiliary dysfunction,
  2. decreased hepatic blood flow, and
  3. extrahepatic diversion of portal venous flow through collateral vessels

- Euphoria, irritability, confusion, slurred speech, slow & deep respiration, hyperactive reflexes, positive Babinski’s reflex

- Asterixis, fetor hepaticus, deep coma
Factors That May Precipitate Hepatic Encephalopathy

- Excessive dietary protein
- Constipation
- Gastrointestinal bleeding
- Infection
- Azotemia

- Diarrhea and vomiting
- Diuretic therapy
- Paracentesis

- Hypoxia
- Hypotension
- Anemia
- Hypoglycemia

- Sedatives/hypnotics -- Action at the GABA<sub>A</sub>/benzodiazepine receptor complex
- Creation of portal-systemic shunt -- Reduced hepatic metabolism

- Increased ammonia production
- Dehydration with electrolyte and acid-base imbalance, increased ammonia generation, and decreased hepatic perfusion

- Adverse effect on liver and brain function
MANAGEMENT

- Dietary protein withheld or limited to 60–80 g/d; vegetable protein better
- Control GI bleed and purge blood out. 120 mL of magnesium citrate orally or NG tube 3-4hrly until the stool is free of gross blood, or by administration of lactulose (two or three soft stools per day)
- Oral antibiotic; nonabsorbable agent rifaximin, 400 mg orally three times daily, is preferred. Other agents metronidazole or neomycin
- Flumazenil is effective in about 30% of patients with severe hepatic encephalopathy, but the drug is short-acting requiring iv administration.
- Branched-chain amino acids unnecessary except patients who are intolerant of standard protein supplements.
- Treatment with acarbose (an alpha glucosidase inhibitor) and L-carnitine (an essential factor in the mitochondrial transport of long-chain fatty acids) is under study
Figure 41-6 Clinical effects of cirrhosis of the liver. (From Bullock BL: Pathophysiology: Adaptations and Alterations in Function [4th Ed]. Philadelphia, Lippincott-Raven, 1996.)
PREOPERATIVE ASSESSMENT

OBJECTIVES
1. Assess the type and degree of liver dysfunction.
2. Type of surgery
3. Assess effect on other system.
4. To ensure – post operative facilities (High risk patient).
PREOPERATIVE ASSESSMENT

HISTORY
- Dyspnoea, syncope, bleeding, delerium, effort tolerance

CLINICAL EXAMINATION
- Blood pressure, pulse, oxygenation, bruising, ascites, orientation, jaundice

INVESTIGATIONS
PREOPERATIVE INVESTIGATIONS

A) TO ASSESS GENERAL CONDITION OF PATIENT

1) Haematological
   Hb
   TLC, DLC
   Platelet Count
   Clotting factors
      (PT, PTTk)

2) Cardiorespiratory
   Chest X-ray
   ECG
   Pulmonary.fn.tests
   Blood gases
   Echocardiography

3) Metabolic
   Serum proteins
   Serum glucose
   Electrolyte
   Urea / Creatinine
B) TO KNOW THE PATTERN OF DISEASE

- S. Bilirubin
- SGOT, SGPT 90% predictive
- Alk. phosphatase

**Single Marker**

- Glutathione S transferase – drug induced
- Glutamyl transpeptidase – alcohol/drug induced
C) TO JUDGE THE SYNTHETIC ABILITY OF LIVER
   Serum albumin– < 2.5 gm% - severe damage
   Albumin/globulin ratio– reversed.
   Prothrombin time– > 1.5 sec. Over control
       – INR - > 1.3

C) OTHER TESTS (DONE ONLY FOR MAJOR SURGERY)
   - liver biopsy
   - screening for hepatitis
   - α fetoprotein – Hepatocellular Carcinoma
   -↓ Antinuclear antibodies – prim. biliary cirrhosis
   -↑ Copper & Ceruloplasmin level – Wilson's disease
   ferritin and transferritin – Haemochromatosis
Cardiac assessment of End Stage Liver Disease (ESLD) patients

• May develop cirrhotic cardiomyopathy
• Increased CO and compromised ventricular response to stress leads to cardiac depression and repolarization abnormalities
• Low systemic vascular resistance and bradycardia
• Increase QT interval, electrical and mechanical dysynchrony, chronotropic incompetence
• Can develop CAD if cardiac risk factors present
• Left ventricular outflow tract obstruction (LVOTO)
ROLE OF ECHO

• Preop echo
  1. Ventricular function, size
  2. Valvular function
  3. Pulmonary artery pressure
  4. Exclude any LVOTO or pericardial effusion
  5. Pulmonary artery systolic pressure calculation
• TEE and/or pulmonary artery catheterization may be used intraoperatively to allow for real-time hemodynamic monitoring and volume management.
• Stress testing of ESLD patients can be done to detect CAD.
• Coronary angiography is the gold standard for detecting CAD
• Rt heart catheterization role to measure PAP,PCWP and TPG
GRADING OF SEVERITY OF DISEASE

Mild Hepatic dysfunction
- Cl. History + evidence of liver pathology
- normal plasma albumin, but enzymes

Moderate Hepatic dysfunction
- Limited impairment of synthetic function
  PT not $> 2.5$ sec. above normal
  Plasma albumin at least 3 gm%.

Severe hepatic dysfunction
- More impairment of synthetic function.
Surgical Risk

• Elective surgery is contraindicated when the patient has acute viral hepatitis, alcoholic hepatitis, fulminant hepatic failure, severe chronic hepatitis, is a Child Pugh C patient or has other manifestations of end stage liver disease.

• Two risk stratification schemes developed to assess the perioperative risk of patients with cirrhosis:
  1. Modified Child- Turcotte -Pugh Scoring System
  2. The Model of End-Stage Liver Disease (MELD) score
# Modified Child- Turcotte –Pugh Scoring System

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Bilirubin</td>
<td>&lt; 2 gm%</td>
<td>2 – 3 gm%</td>
<td>&gt; 3 gm%</td>
</tr>
<tr>
<td>S. albumin</td>
<td>&gt; 3.5 gm%</td>
<td>2.8 –3.5 g%</td>
<td>&lt; 2.8 gm%</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>slight-moderate</td>
<td>tense</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade I &amp; II</td>
<td>Grade III &amp; IV</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sec prolonged</td>
<td>&lt; 4</td>
<td>4 - 6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7 - 2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>
### Modified Child- Turcotte –Pugh Scoring System

<table>
<thead>
<tr>
<th>CLASSES</th>
<th>SCORE</th>
<th>MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5-6</td>
<td>10%</td>
</tr>
<tr>
<td>B</td>
<td>7-9</td>
<td>31%</td>
</tr>
<tr>
<td>C</td>
<td>10-15</td>
<td>76%</td>
</tr>
</tbody>
</table>
MELD

• Objective assessment in predicting 3-month mortality

0.38 \times \ln(\text{bilirubin mg/dl}) + 1.12 \times \ln(\text{INR}) + 0.96 \\
\ln(\text{creatinine mg/dl}) + 0.64

**Best outcomes : MELD score < 14.**

• For patients with a MELD score of 15-24 
  • Clinical judgment 
  • Further discussion with the family and the patient
Asymptomatic Patient with Abnormal Liver Test Results

↑ALT/↑AST

< 2x NL → Normal Alkaline phosphatase Bilirubin INR → Proceed with surgery

> 2x NL → HX – (e.g., R/O drug/ETOH use) → Repeat test

< 2x NL → Proceed with surgery

ALT > AST → Viral hepatitis screening

AST > ALT → Formal assessment (e.g., ultrasonography, computed tomography, liver biopsy) prior to surgery

 ↑ALT/↑AST and abnormal INR → Hepatobiliary dysfunction → Formal assessment prior to surgery

↑Alkaline phosphatase

< 2x NL → Normal GGT Bilirubin → Proceed with surgery

> 2x NL and Abnormal GGT/bilirubin → Biliary disease → Formal assessment prior to surgery
Preoperative approach: Patient with Known/Suspected liver disease
PERIOPERATIVE MANAGEMENT

PREOPERATIVE PREPARATION

(1) Childs Group
   A – Elective Surgery recommended
   B – acceptable after correction
   C – only for emergency

(2) Assess hydration status.

(3) Correct Anemia / Coagulation / hypoalbuminemia

(4) Arrange appropriate blood / blood products.

(5) Inform – postoperative complications
PREMEDICATION

- If neuro. status normal – anxiolytic (oral)
- oral H2 antagonist
- Vit. K (Obst. J) – 10 mg B D X 3 day
- If Bilirubin > 8 mg% –
  Mannitol - 100 ml of 20% 2 hrs preop
ANAESTHETIC MANAGEMENT

GENERAL CONSIDERATIONS

Minimize physiological insult to liver & kidney

- Maintain O2 supply – demand relationship in liver.
  Adequate pulmonary ventilation and cvs fn.
- Maintain renal perfusion
  Avoid Hypotension, hypoproteinemina & hypoxia

Meticulous fluid balance

Choose appropriate anaesthetic agent

Metabolism of drugs + Effect on HBF
General anaesthesia

Induction agent

Thiopentone / propofol
Given in slow titrated dose
Avoid hypotension
Avoid sympathetic stimulation

Propofol:
Highly lipid soluble
High extraction ratio
However kinetic profile similar to normal patients

Thiopentone:
Low extraction ratio
Elimination half life *unaltered* secondary to increased Vd
Muscle relaxants

Decreased S. Alb – Increased free drug concentration
Drugs with hepatic clearance avoided

- Vecuronium
- Rocuronium
- Pancuronium
- Mivacurium (infusion avoided)

Atracurium/Cis atracurium – Non specific ester hydrolysis

- Succinylcholine – For RSI
  - After screening for the usual contraindications
    - Prolonged immobility
    - Critical illness
    - Hyperkalemia

- Severe liver dysfunction - decrease cholinesterase activity
- May prolong the effect of succinylcholine somewhat
- Rarely causes a clinical problem.
Morphine
- Reduced metabolism
- Prolonged elimination half life
- Inc. Bioavailability
- Inc. Sedative and Respiratory depressant effects
- Administration interval should be increased 1.5- to 2-fold in these patients

Meperidine
- 50% reduction in clearance
- Doubling of the half-life
- In addition, clearance of normeperidine is reduced
- Patients with severe liver disease may experience neurotoxicity
Fentanyl and Sufentanil

No significant change in pharmacokinetics

Repeated administration or continuous infusions, accumulation may occur and lead to prolonged effects

Alfentanil

Shows decrease in plasma clearance

Half-life is almost doubled in patients with cirrhosis

Remifentanil

Elimination is unaltered in patients with severe liver disease
Spasm Of Sphincter Of Oddi

- Opioids can cause spasm of sphincter of oddi
  Increase common bile duct pressures
- More with morphine, fentanyl, meperidine
- Avoided if intraoperative cholangiogram to be done

- Treatment - Opioid antagonists (naloxone)
  - Smooth ms.relaxant(nitroglycerine)
  - Glucagon
Sedatives

• Midazolam:
  • Reduced protein binding and increased free fractions
  • Reduced clearance in patients with end-stage liver disease
  • Produces prolonged elimination half-lives
  • Enhanced sedative effect especially after multiple doses or prolonged infusions

• Dexmedetomidine
  • Primarily metabolized in the liver with minimal renal clearance.
  • Patients with hepatic failure of varying severity have
    • Decreased clearance
    • Prolonged half-lives
    • Lower bispectral index values

  Hence dose adjustments indicated
**Voltaile Anesthetics**

- Useful & well tolerated
- Can be entirely eliminated

**Sevoflurane:** Most effective in maintaining
  - HBF
  - Hepatic O2 delivery

**Isoflurane /:** Very good maintenance of
**Desflurane**
  - HBF
  - Hepatic O2 delivery
  - O2 delivery to consumption ratio
Halothane

Halothane (avoided)

Detrimental reductions in

• Hepatic oxygen delivery

• HBF by alterations in

  Cardiac output

  MAP

• Halothane hepatitis (rare)
TFA-S100 + Adjuvants

Spleen
↑ Cellularity
↑ TNF-α
↑ IL-1β
↑ IL-6
↑ IL-10
↑ IL-13
↑ IFN-γ
↑ Serum IL-4
↑ Serum TFA IgG1 Ab

Liver
↑ Mast Cells
↑ Neutrophils
↑ Eosinophils
↓ Kupffer cells
↓ Hepatoprotective
IL-6 and IL-10

Hapten-induced Hepatitis
## Clinical Features of Halothane Hepatitis

<table>
<thead>
<tr>
<th>Mild Form</th>
<th>Fulminant Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence, 1 : 5</td>
<td>Incidence, 1 : 10,000</td>
</tr>
<tr>
<td>Repeat exposure</td>
<td>Multiple exposures</td>
</tr>
<tr>
<td>Mild elevation of ALT, AST</td>
<td>Marked elevation of ALT, AST, bilirubin,</td>
</tr>
<tr>
<td>Focal necrosis</td>
<td>Massive necrosis</td>
</tr>
<tr>
<td>Self-limited</td>
<td>Mortality rate, 50%</td>
</tr>
<tr>
<td></td>
<td>Antibodies present</td>
</tr>
</tbody>
</table>
Xenon:

- Considered to be an ideal inhaled anesthetic
  - Nonexplosive and nonflammable
  - Rapid induction and recovery profiles
  - Cardiac stability
- It does not alter HABF
- Does not alter the results of liver function tests
- Animals exposed to xenon: Higher hepatic venous oxygen content levels
  - Secondary to a possible reduction of plasma catecholamine levels
  - Subsequent reduced hepatic metabolism

*Xenon may prove to be an ideal anesthetic relative to hepatic perfusion.*
**Intraoperative considerations**

- IV access using large bore peripheral catheters as well as central venous access catheters.
- RSI in tense ascites pt – risk of aspiration
- Preventing circulatory collapse by administration of IV colloid solutions because intravascular volume re-equilibrium occurs 6 to 8 hrs after removal of larger volumes of ascitic fluid.
- Large volumes of colloids/crystalloids maybe given within a few minutes with the assistance of commercially available rapid infusion devices.
- Red cell salvage should be facilitated with use of Cell savers with/without leukocyte filters.
- Blood administration may be associated with hyperkalemia and hypocalcemia.
• Bleeding during liver surgery could be either surgical, due to previous or acquired coagulation disturbances, or both.
• The preoperative INR has no predictive value
• FFP role debatable
• Intraoperative hemostasis panels consisting of INR, fibrinogen and platelet count, and platelet function assays for both platelet count and function.
ROLE OF THROMBOELASTOGRAPH

- Thromboelastograph (TEG)- useful intraoperative test for coagulation
- Net effect of pro and anti-coagulant and pro and anti-fibrinolytic factors and the resulting clot tensile strength.
- Rate, strength of clot formation and clot stability/fibrinolysis.
- For detecting intraoperative hypercoagubility.
- TEG facilitate specific goal directed therapy.
- Fibrinolysis - diagnosed on the TEG causing clinically significant microvascular ooze, small doses of epsilon aminocaproic acid (EACA) or tranexamic acid (TA) are suitable antifibrinolytics.
- Factor VII has been used to control massive bleeding during liver surgery;
Intra Operative Monitoring

Routine

NIBP  ECG
Et CO2  SPO2
Urine output  N/ms monitoring

Longer and extensive surgeries

CVP
ABG
Invasive blood pressure monitoring
S. Electrolyte, Blood sugars
TEG
POSTOPERATIVE MANAGEMENT

1) Minor Surgery or mild-mod. liver dysfn.
   N/ms block reversed → Extubate

2) Major surgery / severe liver dysfn.
   - Continue IPPV in P.op. period
   - Fluid & Electrolyte imbalance corrected
   - CVS stability achieved
   - Hypothermia corrected
   - Urine Output 1 ml/kg/hr

3) Adequate analgesia (Small doses)

4) Blood / blood product replaced.
Postoperative pain relief

• Thoracic epidural analgesia provides excellent analgesia for liver resections but restricted due to coagulation defects
• The catheter is usually inserted at the T6-T9 space. Ropivacaine or bupivacaine are common local anesthetics used with or without the addition of small amounts of opioids such as fentanyl, sufentanil, hydromorphone or morphine.
• It also reduces the gastrointestinal paralysis compared with systemic opioids
• NSAIDS - risk of GI bleeding, platelet dysfunction and nephrotoxicity; avoided.
• Paracetamol is sometimes used
• Fentanyl PCA is generally well tolerated
• Morphine PCA can also be used but a lower bolus dose may be needed, again to avoid accumulation.
POSTOPERATIVE JAUNDICE

- Incidence < 1%
- Cause - Overproduction or under excretion of bilirubin
  - direct hepatocellular injury
  - extrahepatic obstruction
- Mild < 4mg/dl
  - Severe > 4mg/dl
Causes Of Postoperative Liver Dysfunction

Immediate Postoperative Jaundice (<3 wk)

- Hemolysis
- Anesthesia
- Hypotension/hypovolemia
- Drugs
- Infection/sepsis
- Bleeding/resorption of hematoma
- Bile duct ligation/stricture/surgical injury
- Hepatic artery ligation
- Retained common duct stone
- Postoperative pancreatitis/cholecystitis
- Acute viral hepatitis
- Gilbert’s syndrome/Dubin-Johnson syndrome
- Inflammatory bowel syndrome
- Heart failure
- Pulmonary postoperative jaundice
- Blood transfusion

Delayed Postoperative Jaundice (>3 wk)

- Drugs
- Blood transfusion
- Post–intestinal bypass status
- Total parenteral nutrition
<table>
<thead>
<tr>
<th>Agent</th>
<th>Hepatocellular</th>
<th>Steatosis</th>
<th>Cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Aspirin</td>
<td>*</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Amoxi-clav</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>*</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCP</td>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>TPN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>
Transjugular Intrahepatic Portosystemic Shunt

Percutaneously created intrahepatic connection of the portal and systemic circulations

1. Stent is passed through the IJV over a wire into the hepatic vein

2. Dilated EV are apparent. The wire and stent are then advanced into the portal vein

3. Blood can pass through the PV into the HV and bypass and decompress dilated esophageal veins
Typically used in patients with end-stage liver disease

- To decrease portal pressure
- Attenuate the complications
  - Variceal bleeding
  - Refractory ascites

Complications

- Encephalopathy
- Stent stenosis and occlusion
Hepatic resection

• Preoperative considerations
  • Involve risk assessment: MELD classification.
  • Severe thrombocytopenia or large varices: Major perioperative risk

• Fluid management: Controversial.
  • Liberal use: Goal of increasing intravascular volume as a buffer.
  • Low central venous pressure: Minimize blood loss from Major veins

• Intravenous fluids
  • Supplemented sodium or potassium phosphate
Hepatic cryotherapy

- Treat nonresectable malignant hepatic tumors
- Involves usage of subzero temperature
- Multiple-lumen probes positioned under USG guidance
- Heat conservation instituted during the procedure
- With continual monitoring of core temperature.
- “Cryoshock syndrome”:
  - Postoperative
    - Pulmonary
    - Renal
    - Coagulation problems
Liver transplantation: Advances and perioperative care
# LIVER TRANSPLANT

<table>
<thead>
<tr>
<th>INDICATIONS</th>
<th>CONTRAINDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEPATITIS</td>
<td>SEPSIS</td>
</tr>
<tr>
<td>ALD</td>
<td>CARDIOPULMONARY DISEASE</td>
</tr>
<tr>
<td>HEMOCHROMATOSIS</td>
<td>EXTRA HEPATIC MALIGNANCY</td>
</tr>
<tr>
<td>PBC</td>
<td>AIDS</td>
</tr>
<tr>
<td>PSC</td>
<td>ANY SUBSTANCE ABUSE</td>
</tr>
<tr>
<td>CF</td>
<td>UNFAV PSYCHOSOCIAL</td>
</tr>
<tr>
<td>WILSON</td>
<td>CIRCUMSTANCE</td>
</tr>
<tr>
<td>AMYLOIDOSIS</td>
<td></td>
</tr>
<tr>
<td>MALIGNANCY</td>
<td></td>
</tr>
<tr>
<td>BUDD CHIARI</td>
<td></td>
</tr>
</tbody>
</table>
STAGES

• Preanhepatic - from start of surgery to clamping of hepatic artery
• Anhepatic – from clamping to reperfusion of new liver
• Postanhepatic - from reperfusion to end of case
Order of reconstruction

• Standard method – suprahepatic ivc followed by infrahepatic ivc anastomosis – PV anastomosis - arterial reconstruction – biliary drainage

• Piggy back method – only one ivc anastomosis

Test clamp maneuver

• Used in standard method to assess resilience of circulatory system

• Suprahepatic ivc clamped – arterial pressure , CO decrease

• If excessive circulatory depression proceedings delayed , reassess volume status , cardiac performance , metabolic state.

• Venovenous bypass – if still circulatory depression
Intraoperative Monitoring and Management

- **Haemodynamic monitoring** - standard cardiovascular monitors (electrocardiogram, pulseoximetry, invasive and non-invasive blood pressure)
- Additionally requires CO monitoring
- Pulmonary artery catheter (PAC) is the gold standard used in haemodynamic monitoring
- Monitoring of central venous oxygen saturation and mixed venous oxygen saturation during liver transplantation is of little value
Hemodynamic management

• During the different stages of liver transplantation, i.e. pre-anhepatic phase, anhepatic phase and neohepatic phase, there are rapid fluid shifts due to blood loss, inferior vena cava clamping and reperfusion.

• Decreasing central venous pressure (CVP) either by phlebotomy or avoiding plasma transfusion during the pre-anhepatic phase have shown to reduce red cell transfusions
• Vasopressin is often added intraoperatively to maintain the systemic vascular resistance.
• Vasopressin reduces portal blood flow by selective splanchnic vasoconstriction and hence may be useful in reducing the intraoperative blood loss.
• Methylene blue at a dose of 0.5 mg/kg body weight over 10 min rescue to treat hypotension due to vasopressor-resistant vasoplegic shock.
• Phenylephrine is often used to tide over acute hypotensive episodes
Fluid management

• Liver transplant surgery - massive fluid shifts both from intravascular volume depletion and large surgical blood loss.

• Albumin can be used as pts are hypoalbuminaemic and hypovolaemic; cost factor limits its use.

• Crystalloids use depends on their pH, electrolyte composition, osmolarity and metabolism.
• No ideal crystalloid solution
• 0.9% NS causes hyperchloremic acidosis while the lactate in Ringers Lactate (RL) requires liver metabolism for its elimination.
• RL is a hypotonic solution and may increase the intracellular fluid.
• Plasmalyte has a pH near normal, electrolyte and osmolarity similar to plasma and acetate, which is metabolised extrahepatically to bicarbonate, but it is proinflammatory and potentially cardiotoxic.
Coagulation monitors

- PT and APTT limited role
- Thromboelastogram (TEG), rotational thromboelastometry (ROTEM) and Sonoclot provide a detailed assessment

Blood component management

- Pre-anhepatic phase is associated with blood loss
- The aim at this stage is to avoid large volume of transfusion and dilutional coagulopathy
- Antifibrinolytics are used in the liver transplantation to prevent the hyperfibrinolytic state during the anhepatic and neohepatic phases
- The neohepatic phase is associated with a multifactorial coagulopathy of hyperfibrinolysis, dilutional coagulopathy, heparin-like effect, platelet dysfunction, hypothermia and hypocalcaemia
Ischemia reperfusion injury

- Ischemia reperfusion injury (IRI) is associated with primary graft dysfunction and delayed graft function.
- N-acetyl cysteine (NAC) is being used in liver transplantation patients to prevent renal failure and IRI of the new liver. NAC, in addition to its direct antioxidant property, replenishes glutathione and acts as a free radical scavenger.
- Inhalational anaesthetics, especially sevoflurane, have been shown to offer protection against IRI in the myocardium in cardiac patients.
• Early extubation in selected patients improves early graft function and reduce duration of stay in the Intensive Care Unit and nosocomial infections

• Selection of patients for early extubation depends on duration of the surgery, amount of blood and products transfused, patients' pre-operative status (MELD score), ischaemia time and status of the graft.

• A safe operating room extubation after liver transplantation (SORELT) prediction rule may be used to select patients for early extubation, but requires validation
CONCLUSION

• Patients with liver disease are at increased risk for both perioperative morbidity and mortality.

• The multi-system impact of liver failure means assessment and management of these patients often requires multi-disciplinary discussion and critical care admission to optimise outcome.
THANK YOU
# ROLE OF THROMBOELASTOGRAPH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Interpretation</th>
<th>Preferred therapy for abnormal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>R is the time of latency placed in the TEG® analyzer until initial fibrin formation</td>
<td>FFP</td>
</tr>
<tr>
<td>α</td>
<td>The α-value measures rapidity of fibrin build up and cross linking</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>K</td>
<td>K time is a measure of the rapidity to reach certain level of clot strength.</td>
<td>FFP</td>
</tr>
<tr>
<td>MA</td>
<td>MA, or Maximum Amplitude, direct function of the maximum dynamic properties of fibrin and platelet bonding and represents the ultimate strength of fibrin clot.</td>
<td>Platelets</td>
</tr>
</tbody>
</table>