PBLD - Table # 24

A three week old neonate with hemochromatosis presenting for liver transplantation.

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Objectives:

Understand the differences in indications for liver transplantation between neonates and other age groups.

Understand the implications of hemochromatosis.

Understand the ranking on the pediatric transplant waiting list.

Understand surgical techniques used in pediatric liver transplantation.

Understand the specific neonatal issues for anesthesia for liver transplantation in neonates.

Case History:

A neonate develops signs of liver failure soon after birth with coagulopathy and encephalopathy. He is diagnosed with hemochromatosis and is transferred to the Children's Hospital.

What are etiologies for neonatal liver failure?
What is hemochromatosis?
What are the natural history, work-up, and management of neonatal liver failure?

The transplant group puts the patient on the transplant list emergently with the transplant meeting to follow.

What is the process of putting a patient on the transplant list?
What is the role of the anesthesiologist?
How are patients ranked on the pediatric transplant list?
What should preoperative workup include?
What should consent include?

An uncle says he heard he could donate part of his liver and offers to do so. An organ of an older patient becomes available after seven days on the waiting list and the patient is scheduled for liver transplant. He weighs 3kg.

What are surgical options for liver transplantation in children?

The patient is induced. The oxygen saturation rapidly declines. Intubation is easy, but the saturation is slow to recover.

What drugs and techniques should be used for induction?
What would be possible mechanisms for this desaturation?
What lines and tubes will be necessary or useful during the procedure?
What anesthetic maintenance would be suitable?
Your resident wants to start TXA. Any thoughts?
What about fenoldopam? Dopamine?
Will you need a heparin infusion?
Alprostadil?

Following your local protocol, the nurse calls for six units PRBCs, six units FFP, six units platelets, six bottles of albumin. The anesthesia technician has set up two burretrols with lactated Ringer's solution and a rapid infuser with saline. There are many episodes of hypotension during induction, during hepatectomy, during reperfusion, and during completion of the transplantation. The platelet count is 80k at the completion of the surgery and the surgeon asks you not to transfuse platelets.

What fluids and products will you use and do you want available in the OR?
What are typical times and reasons for intraoperative hypotension?
What are the classical stages of liver transplantation? j
How do you prepare for reperfusion?
What are the hematologic goals?

The surgery is coming to completion and the surgeon asks you to extubate the patient. However, the neonatologist calls you from the NICU and asks you to leave the patient intubated.

> *What should be the postoperative disposition for this patient? (NICU vs MSICU, PICU, extubation vs postop ventilation, pain management)*

Discussion:

Liver failure and liver transplantation

Definition of acute liver failure:

Adult: Severe liver injury in a patient without a previous history of liver disease who develops hepatic encephalopathy within 8 weeks of the initial symptoms.

This definition is not practical in neonates and infants:
Neonatal: Acute liver failure occurring within the first 28 days of birth.

Criteria:

- Hepatic based coagulopathy (PT >/= 15 sec, INR >/= 1.5 not corrected by Vit K in the presence of clinical hepatic encephalopathy or a PT>/=20sec or INR>/=2.0 regardless of presence or absence of hepatic encephalopathy
  (Note: isolated elevated PTT is not due to liver disease)
- Biochemical evidence of acute liver injury
- No known evidence of chronic liver disease

Etiologies of liver failure and indications for liver transplant

Typical indications for liver transplantation in adults:

- Fulminant liver failure (acetaminophen, other drugs, indeterminate, viral)
- Complications of cirrhosis
- Hepatocellular carcinoma
- Pulmonary syndromes (hepatopulmonary syndrome, portopulmonary hypertension)
- Polycystic liver disease
- Liver based metabolic disease with systemic complications

Most common indications for liver transplantation in the adult:

- Hepatitis C - cirrhosis
- Cholestatic cirrhosis

Alcoholic cirrhosis
Cryptogenic cirrhosis
Hepatocellular carcinoma

Typical indications for liver transplantation in pediatrics:
Biliary atresia (>41%)
Acute liver failure (14.5%)
Metabolic (14.5%)
Other cholestatic liver disease
Cirrhosis
Tumor

Most common causes of acute liver failure in pediatrics:
1. Indeterminate (50%)
2. Autoimmune
3. Infectious (viral)
4. Toxic (drugs)
5. Metabolic

Typical metabolic disorders treated with liver transplantation in pediatrics:
Crigler-Najjar
Tyrosinemia
Organic acidemias
Urea cycle defects (ornithine transcarbamylase deficiency [OTC deficiency])
Oxalosis

Etiologies of chronic liver disease in children:
Cholestatic disease
Biliary atresia
Progressive familial intrahepatic cholestasis PFIC
Alagille syndrome
TPN associated liver disease
Metabolic liver disease resulting in cirrhosis
Alpha-1 antitrypsine deficiency
Tyrosinemia type 1
Wilson's disease
Cystic fibrosis
Glycogen storage disease type 3 or 4
Chronic hepatitis
Autoimmune
Sclerosing cholangitis
Viral hepatitis
Others
Budd Chiari

Liver Tumors in children:

- Hepatoblastoma
- HCC
- Vascular tumors
- Sarcoma
- Hamartoma
- Focal nodular hyperplasia
- Adenoma

Causes of neonatal liver failure:

1. Neonatal hemochromatosis
2. Viral infection (herpes simplex virus most common, herpes family, enterovirus, adenovirus, parvovirus); high dose acyclovir to be started until HSV ruled out
3. Hematologic malignancies (hemophagocytic lymphohistiocytosis HLH: liver transplant contraindicated in HLH)
4. Metabolic (galactosemia: lactose free diet until ruled out, tyrosinemia, hereditary fructose intolerance, ornithine transcarbamylase deficiency, mitochondrial disorders, deficiencies of complex I, III, IV, multiple and mitochondrial DNA depletion syndrome)
5. Others (hypoxic/ischemic, toxic)

Neonatal hemochromatosis: rare condition of unknown etiology unrelated to hemochromatosis of the adult

Etiology: Etiology is unknown. May be related to a fetal hepatic insult with a common pathway of iron deposition. Based on association with renal disease, insult may occur around or before 24th week. Prenatal disease process as there is cirrhosis present at birth. Alloimmune mechanism may be involved as there are maternal antibodies against fetal liver antigen resulting in risk to subsequent pregnancies. No paternal risk but high maternal risk (80%) for affected subsequent pregnancy.

Presentation: Decompensated cirrhosis at birth resulting in small liver, normal transaminases, mildly raised bilirubin, markedly reduced albumin, coagulopathy and possibly features of portal hypertension.

Pathophysiology: fetal onset liver injury associated with massive iron deposition (diagnosed by MRI) in liver and extrahepatic tissues including oral mucosa (biopsy), heart and pancreas/endocrine and exocrine glands, but with sparing of the reticulo-endothelial system (spleen); fetal liver insult leads to siderosis (hepatocyte siderosis on biopsy), iron induced oxidant injury causes liver damage (hence antioxidant and chelation therapy)

Diagnosis: prenatal oligohydramnios (intra-uterine hepatorenal syndrome), acute liver failure; two or more of following: family or prenatal history; high serum ferritin; decreased transferrin and increased transferrin saturation; histologic confirmation of iron deposition by lip biopsy or autopsy; extrahepatic (heart, pancreas) iron overload by MRI (also prenatally) in liver and extrahepatic tissue but with sparing of the spleen

Prognosis: poor, 10% survival without transplantation; 50% with liver transplantation

Treatment: desferroxime/deferoxamine (chelates iron: contraindicated in MOF) and N-acetylcysteine (antioxidant cocktail with vitamin E and PGE1, ursodeoxycholic acid, selenium)
Prevention: IVIG antenatal every week after week18
Indication for liver transplant: INR > 4; (10% die on waiting list, 10% removed due to spontaneous recovery, 80% transplanted)
Other criteria: bilirubin > 235 mmol/l; age < 2 years; WBC > 9000/ml; fibrinogen < 1 g/l; hyperammonemia > 150 mmol/l; worsening lactic acidosis; deterioration within 48 hours of admission; seizures, hepatorenal syndrome

Presentation of neonatal liver failure/complications:

1. Non-specific symptoms: irritability, lethargy, poor feeding, vomiting, failure to thrive, fever; hepatomegaly, splenomegaly, ascites, peripheral edema
2. Encephalopathy (difficult to assess in neonates, excessive crying, poor feeding, sleepiness, lethargy, coma; increased ICP - normoventilation, mannitol, inotropes, N-acetylcysteine; DD intracranial bleed)
3. Infection (54-80% sepsis in adult liver failure; hemodynamic changes similar to SIRS, requiring fluid and possibly inotropes (preferred norepinephrine), if refractory: hydrocortisone
4. Abnormal liver function tests (increased aminotransferases, increased bilirubin: in viral more than in metabolic diseases), hypoalbuminemia, coagulopathy (factor V and VII levels prognostic, due to short half life they represent synthetic dysfunction well; FVII levels lower than 10-15% of age appropriate predicted level in NH sign of poor prognosis), hypoglycemia (decreased neoglycogenesis, increased insulin), hyperammonemia,

Pathophysiology of acute liver failure:

1. Loss of liver function
Impaired glucose homeostasis (risk of hypoglycemia from impaired glycogen storage, impaired gluconeogenesis)
Synthetic deficiency (coagulopathy from decreased pro- and anticoagulant proteins, decreased albumin with changed drug binding and oncotic pressure)
Metabolic activity (drug metabolism, encephalopathy)

2. Encephalopathy
Hyperammonemia, metabolic disturbances, increased cerebral blood flow, increased ICP
Seizures from encephalopathy or hypoglycemia
(Acute management: mannitol, hypertonic saline, moderate hypothermia 32-34)

3. Renal failure
Prerenal failure

Nephrotoxic medications
Hepatorenal syndrome (vasoconstrictor response to severe arterial underfilling and portal hypertension)

4. Bacterial infections and sepsis
Impaired immune and complement function

5. Cardiovascular changes
Hypovolemia
Cardiac hyperkinesia with elevated cardiac indices and low systemic vascular resistance
Risk of pulmonary edema, central neurogenic pulmonary edema
Vasoplegia with hypotension, need for alpha-adrenergic agents (norepinephrine)
Adrenal insufficiency (give hydrocortisone)

6. Pulmonary changes
Respiratory failure
Atelectasis
Hepatopulmonary syndrome

Contraindications to liver transplantation:
10-20% of cases: permanently fixed/dilated pupils; uncontrolled sepsis; severe respiratory failure; uncontrolled intracranial hypertension; uncontrolled multiorgan failure; diseases not cured with liver transplantation (malignant disease, Reye syndrome, mitochondrial respiratory chain disorder with neurologic involvement)

Outcome of acute liver failure:
148 infants under 90 days:
60% spontaneous survival
16% liver transplantation
24% death without liver transplantation

Outcome of liver transplantation (UNOS data):
Patient (graft) survival 1 and 5 years post transplant
Neonates: not listed separately on UNOS website

Children under 1 year:	89/76 (81/63)%
Children 1-5 years:	85/76 (78/66)%
Children 6-10 years:	90/85 (84/75)%
Adults 50-64 years:	86/70 (82/65)%

Listing for pediatric liver transplantation:
Local transplant committee which includes the director of transplant anesthesia discusses indications and contraindications for liver transplant candidates and lists patients with the local Organ Procurement Organization (OPO).

MELD/PELD scores reflect the risk or probability of death within the next 3 months without transplant:

PELD score (Pediatric End Stage Liver Disease score) for children under 12 years:
10 x [-0.687 x log e (albumin g/dL) + 0.480 x log e (bilirubin mg/dL) + 1.857 x log e (INR) + 0.436 (if child < 1 year old) + 0.667 (if growth failure present < -2 standard deviations)]
Range (rounded) 6 - 40

MELD score (Model for End Stage Liver Disease) for patients over 12 years of age:
10 x [0.957 x log e (creatinine mg/dL) + 0.378 x log e (bilirubin mg/dL) + 1.120 x log e (INR)] + 6.43
Range (rounded) 6 - 40

Exemptions:

Status 1a: fulminant liver failure
Status 1b: exemption for severely ill pediatric patients (MELD/PELD > 25 plus mechanical ventilation/GI bleed/renal failure/GCS < 10 within 48 hours), no 1b for adults
Hepatoblastoma: 30 points for 30 days then 1b
Urea cycle defects or organic acidemias: 30 points for 30 days then 1b
Status 1a, 1b: geographic prioritization (local, regional, national)

Surgical options for neonatal and pediatric liver transplantation:

living related donation
whole organ (neonatal vs non-neonatal)
split graft
reduced size graft
staged closure (temporary PTFE mesh to temporarily enlarge recipient's abdominal cavity)
piggy-back technique with donor IVC to recipient hepatic vein confluence instead of IVC clamping for IVC interposition
aorto-hepatic arterial graft instead of end-to-end anastomosis of the hepatic artery
biliary drainage via Roux-en-Y instead of end-to-end anastomosis of bile duct
veno-venous bypass (rare in children)

Anesthesia for neonatal liver transplantation

Anesthetic concerns for neonates in general:

Immaturity of all organ systems
- immature CNS
- immature respiratory system
- immature cardiovascular system
- immature hepatic function
- immature hematologic system
- immature renal function
- immature pharmacokinetics and pharmacodynamics
- immature metabolic function
- immature immune function
- immature endocrine function

Neonatal anatomy:
- neonatal airway

Some implications:
- Concern about neurotoxicity of anesthetics
- Risk for hypoglycemia
- Different therapeutic window and drug dosing
- Risk of postanesthetic apnea
- Intubation
- Difficult line placement

Stages of liver transplantation and anesthetic considerations and concerns:

Preoperative

Anesthetic history and family history
Assessment of clinical status in particular encephalopathy, cardiorespiratory status, abdomen
Labs: CBC, coags, LFTs, BUN/creat, electrolytes, blood sugar
Imaging studies: CXR, echo, head ultrasound, MRI/CT

Room setup

Fluids: dextrose 5-10% with electrolytes, Plasmalyte, albumin, PRBCs (washed or less than one week old), fresh thawed plasma, platelets available depending on count, cryo available, not thawed; factor VIIa available
Infusion pumps
Rapid transfusion devices likely less useful in neonates and infants due to iv size limitation

Fluid warmer
Patient warmer
Multiple transducers
Cell saver
All anesthetic drugs drawn up in neonatal aliquots and dilutions if indicated
Resuscitation drugs in appropriate dilution and quantity
Antibiotics and immunosuppressants per surgical protocols

Induction

Sedation if necessary and feasible to allow for preoxygenation
Ketamine or etomidate vs propofol, rapid sequence (NPO, ascites) with sux vs roc, ventilation vs true rapid sequence
Reasons for desaturation: ascites, mainstem intubation with high diaphragms, poor compliance, hepatopulmonary syndrome, aspiration

Line placement and monitoring

standard monitoring
multiple peripheral ivs (for maintenance, for meds, for volume, backup iv), large bore volume lines in neonates may be 22G, volume line preferred above the diaphragm due to potential IVC clamping or bleeding
NIBP plus two invasive arterial monitoring sites (at least one upper extremity)
central venous access and pressure monitoring
dual pulse oximetry monitoring (at least one on upper extremity)
dual temperature monitoring rectal/esophageal
NIRS in neonates
BIS in older patients
TEE
labs intraop: ABG for oxygenation, ventilation, acid-base-monitoring, electrolytes, lactate, blood glucose, hematocrit (goal around 30% for viscosity), platelet count (goal above 60k), coagulation studies, TEG

Waiting periods

Due to difficult line placement, we tend to induce early, but there may be a waiting period after induction and line placement before incision until the procurement team has sent their message, similarly, there may be a waiting period after laparotomy and mobilisation of the recipient liver before removal of the liver until the donor organ has been optimized on the back table

Pre-anhepatic stage (dissection/hepatectomy)

The preanhepatic stage is the time from incision to hepatectomy. Antibiotics are typically administered before incision. The course of this time very much depends on the underlying liver disease. Patients in liver failure will be coagulopathic, patients with

cirrhosis will have bleeding from collaterals, patients with metabolic or oncologic diseases may have normal coagulation, patients with previous surgeries (Kasai procedure for biliary atresia) will have adhesions with potential bleeding; blood transfusions and calcium administration are typically required during this stage in neonates undergoing liver transplantation for acute liver failure, glucose administration may be necessary in liver failure, dopamine may be started in renal dose for diuresis and anticipating increased requirements during reperfusion; there is often pronounced hemodynamic instability related to surgical manipulation of the venous return

Anhepatic stage

During the anhepatic stage, venous return is surgically impaired; depending on the surgical technique, the entire IVC blood flow may be interrupted or only the hepatic venous return; veno-venous bypass is not feasible in neonates; volume administration must be judicious to avoid overfilling after reperfusion; increase in dopamine rate may be initiated; blood sugar must be checked to avoid hypoglycemia during the anhepatic phase; ABG and electrolytes should be checked to correct hypocalcemia and acidosis or address hyperkalemia prior to reperfusion; drop in patient temperature may be noted during this time; immunosuppressant and steroids are often administered during this time

Reperfusion

Prior to reperfusion, a blood flush may be used to wash out cold, acidotic, hyperkalemic presvative fluid from the donor organ; in neonates this may constitute a large portion of their circulating blood volume and should be accompanied by blood transfusion, calcium administration and increased dopamine infusion; even in spite of the blood flush, repefusion may be followed by hyperkalemia, profound acidosis, acute hypothermia, air or particulate embolisation, acute cardiac failure and arhythmias, and hypovolemia, all resulting in profound hypotension and possibly cardiac arrest; hyperkalemia, acidosis and hypovolemia must be treated aggressively and use of higher doses of dopamine or small bolus doses or continuous infusion of epinephrine may become necessary

Post-anhepatic

During the post-anhepatic phase following reperfusion, the hapatic artery anastomosis and the biliary drainage are completed, the abdomen is closed and typically ultrasound studies are performed at various stages to monitor vascular patency; due to the high concern regarding hepatic artery thrombosis, the surgeon may ask for heparin or alprostadil drips to be started; there may be less but continuing blood loss and blood product management should be cautious and in discussion with the surgeon; hematocrit not over 30 and platelet count down to 60 are our local surgeon's preference; following the immunosuppressive steroid dose, blood transfusions and liver reperfusion, the blood sugar may be very high and require intervention; liver function may be noticeable with decreasing lactate levels, increasing alkalosis (from citrate metabolism) and improving clotting studies without further plasma transfusion

Postoperative disposition

All patients following liver transplantation will be recovered in an ICU. Neonates may be coming from the NICU, but the surgical ICU may be more used to management protocols following liver transplantation; generally following liver transplantation, extubation should be considered unless contraindications to extubation exist; neonates may be at increased risk for postoperative apnea and the need for reintubation due to their immaturity and their response to opioid analgesics, and postoperative ventilation may be indicated; postoperative analgesia typically is by intravenous opioids.

Return to OR

Hepatic artery thrombosis is a high risk in pediatric liver transplant and requires urgent re-exploration for possible thrombectomy; patients may also return to the OR for management of bleeding, completion of biliary drainage or abdominal closure.

Complications

Intraop and postop complications including anesthetic neurotoxicity, hypoglycemia, metabolic stroke (with certain metabolic disorders such as aromatic acidemias), intraventricular hemorrhage or ischemia; hypotension (multiple etiologies including bleeding, impaired venous return from surgical retraction, clamping, abdominal compartment syndrome, pulmonary hypertension, ventricular insufficiency, peripheral vascular dilation, hypocalcemia), hypothermia, hyperkalemia (from reperfusion flush, transfusion and acidosis), acute arrhythmias from cold, electrolyte (potassium, calcium, magnesium) or acidosis related changes; intractable bleeding (surgical, coagulopathy, hypothermia); surgical and postoperative complications include bleeding; hepatic artery thrombosis, portal vein thrombosis, biliary leak; rejection, infection; abdominal compartment syndrome; renal failure.

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