Immediate Post-Liver Transplant Complications

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SPLIT Society of Pediatric Liver Transplantation

OHSU DOERNBECHER CHILDREN'S Hospital

Introduction

- Pediatric solid organ transplant began in the mid-1960s
- Outcomes have dramatically improved over the past few decades in part due to advances in:
  - Surgical technique
  - Technology
  - Improvements in patient care and donor selection
  - Development of potent immunosuppressive agents
- With the advent of new drugs, most children can be expected to survive into adolescents and adulthood

Transplant Table of Contents

Is life worth living? It all depends on the liver.

– *William James (Philosopher)*

- It's your first night on call as a fellow

- The PICU calls to inform you that a new liver transplant patient who just came out of the OR

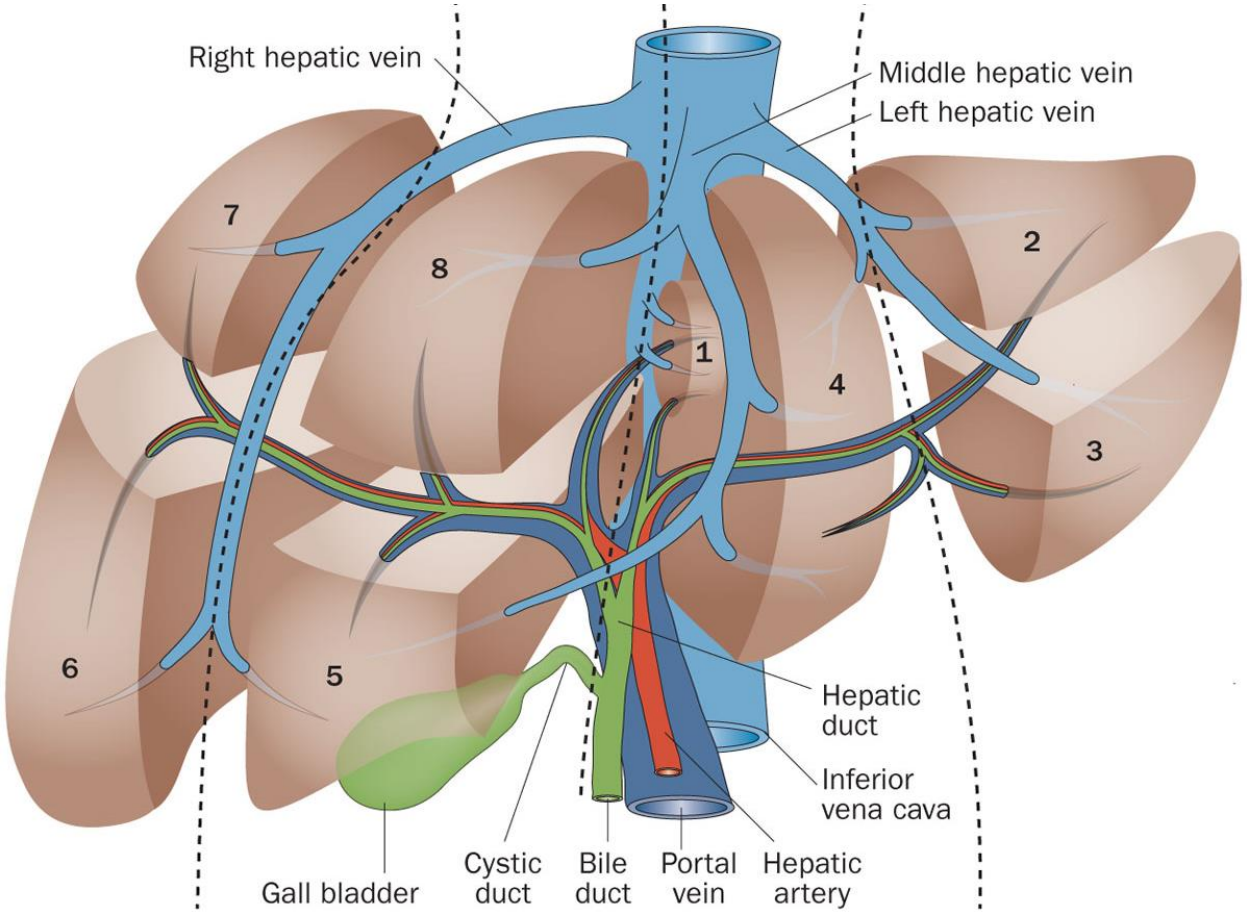
- What do you want to know?
- What do you want to do next?

Key information of the transplant

- Graft Type
  - Whole or split
- Donor type
  - Deceased donor or living donor
- Ischemia time
- Anastomoses
- Donor and recipient blood type
- CMV status

Surgical Sections

- Left Lateral Segment
  - 2 + 3
- Left Segment
  - 2, 3, 4
- Right Segment
  - 5, 6, 7, 8



Siriwardena, A. K. *et al.* (2014) Management of colorectal cancer presenting with synchronous liver metastases. *Nat. Rev. Clin. Oncol.*

Ischemia Time

- Warm Ischemia Time
  - Time that an organ remains at body temperature after its blood supply has been stopped
- Cold Ischemia Time
  - Time that an organ is cold and not receiving blood supply
  - Time varies widely by organ
  - Sooner an organ can be transplanted, the better

Cold Ischemia Times

Heart	Lungs	Liver	Pancreas	Intestines	Kidneys
4 hours	4-6 hours	6-10 hours	12-18 hours	6-12 hours	24 hours

Potential Donor Organ Options

- Brain Death
  - Majority of donors, but <1% of hospital deaths

- Donation after Cardiac Death (DCD)
  - High risk because of longer ischemia time

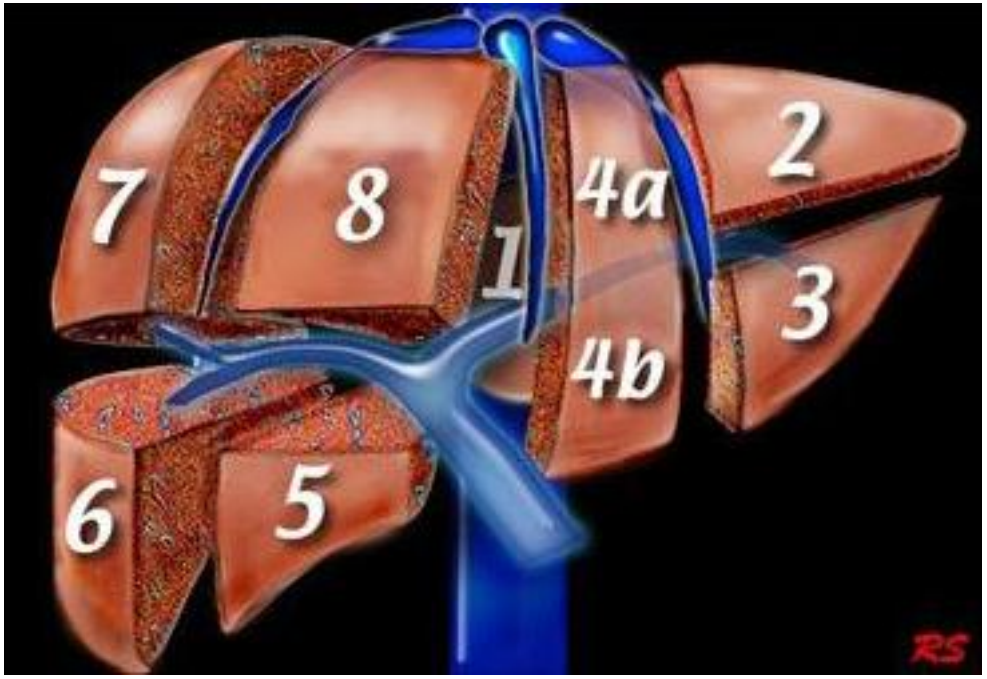
  Steps:

  1. Withdraw support
  2. Declare cardiac death
     - No blood pressure, pulse or cardiac sounds
     - No spontaneous respiration
  3. Wait 5 minutes to ensure no auto resuscitation

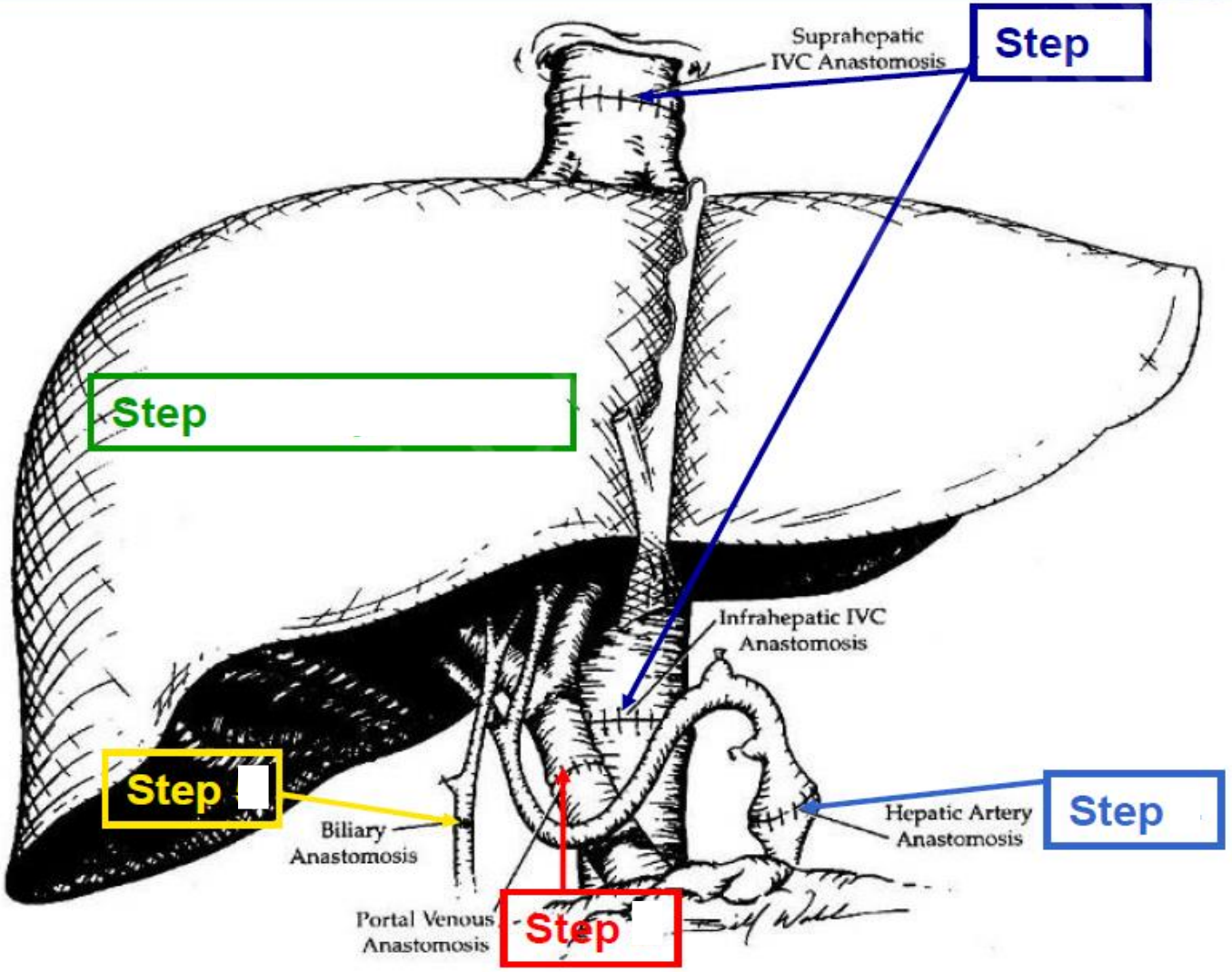
- Living Donor (Split Liver)
  - Requires careful donor and recipient selection process
  - Associated with excellent results in the child and generally safe for the donor (20% morbidity, 0.01% mortality).

Anastamosis

1. IVC / Hepatic Vein
2. Portal Vein
3. Hepatic Artery
4. Bile Duct

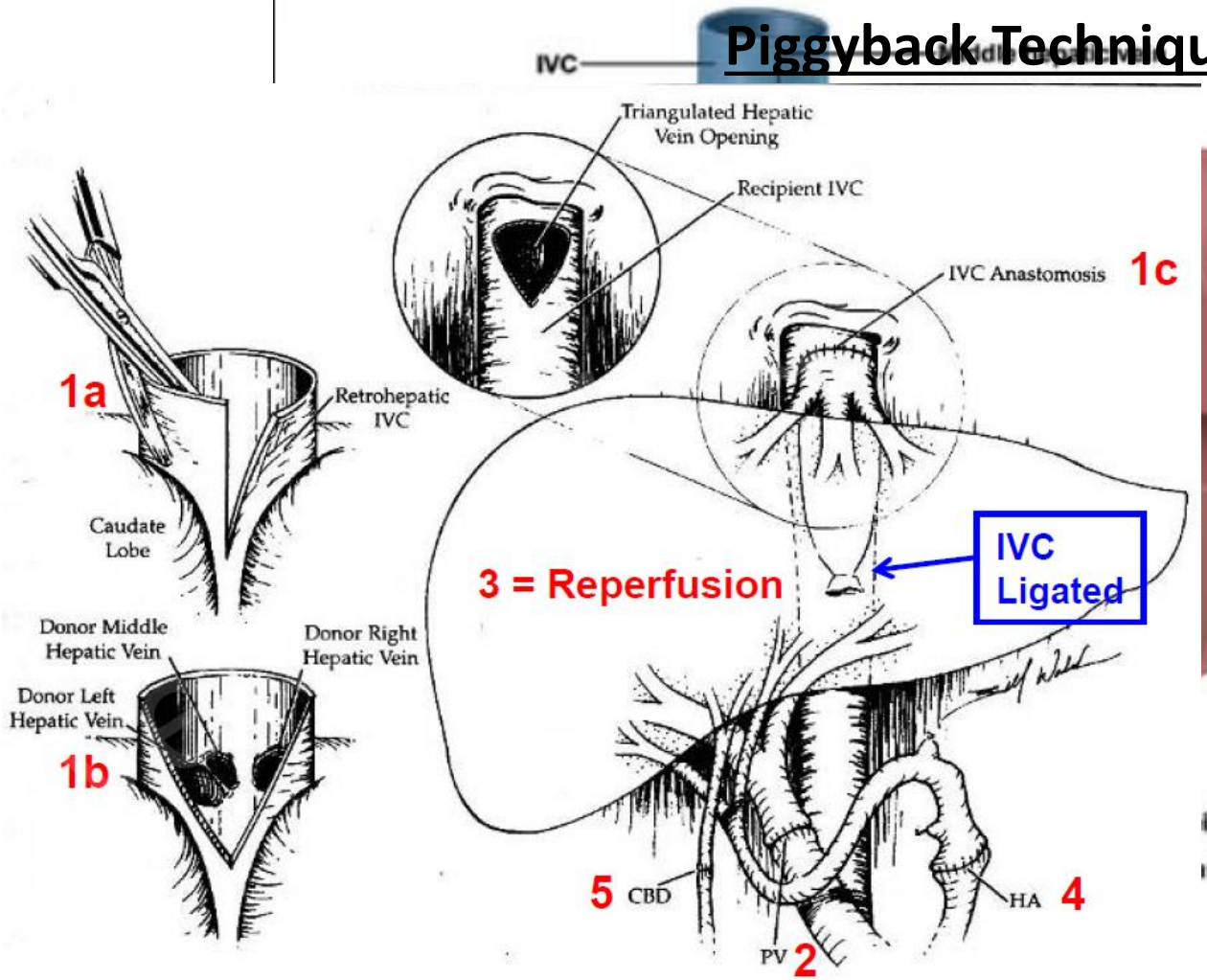


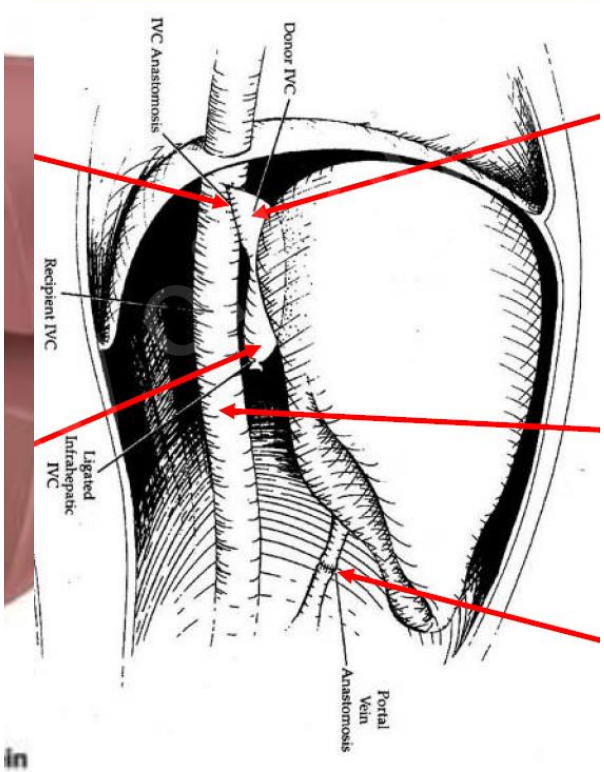
Steps in OLT


Suprahepatic
IVC Anastomosis
Step
Step
Infrahepatic IVC
Anastomosis
Step
Biliary
Anastomosis
Hepatic Artery
Anastomosis
Step
Portal Venous
Anastomosis
Step

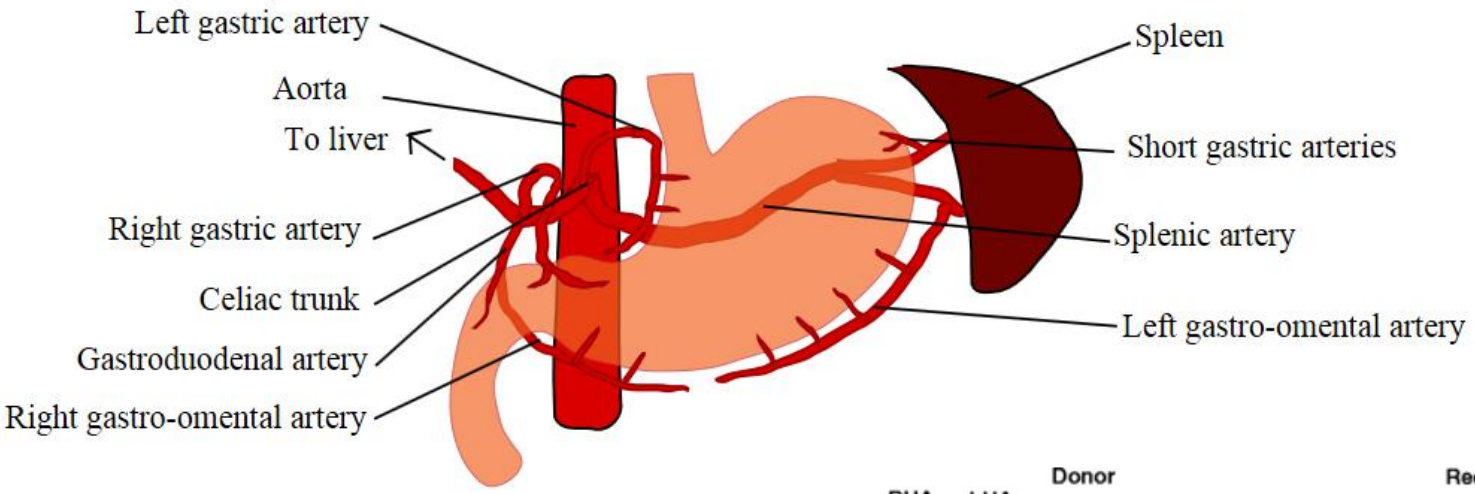
IVC / Hepatic Vein Anastomosis

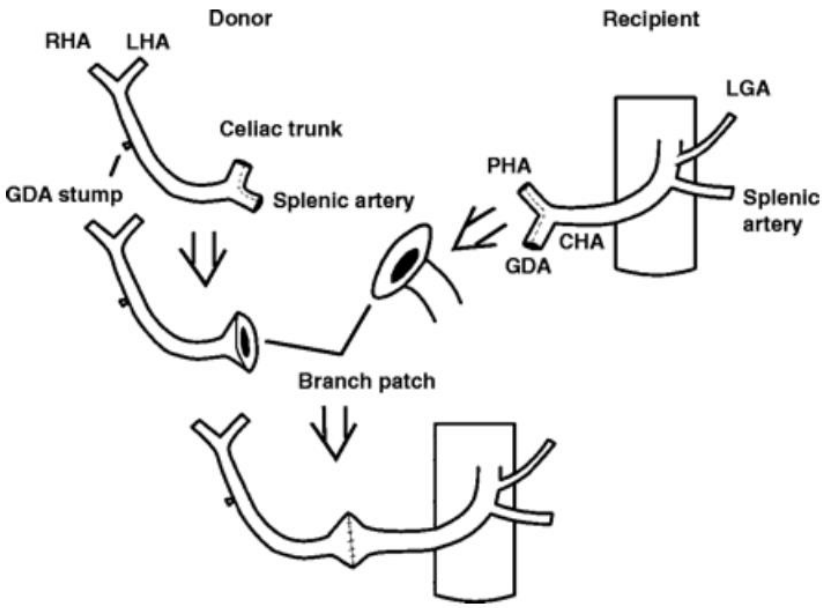
Piggyback Technique





Arterial Anastomosis





What are potential technical complications associated with liver transplantation?

Table I. Technical complications after liver transplantation: type and onset.

Complication	Type (onset)
Abdominal bleeding	Anastomoses (immediate)
	Site of implantation (immediate)
Vascular complications	Hepatic artery thrombosis (early)
	Hepatic artery stenosis (late)
	Portal vein thrombosis (early)
	Portal vein stenosis (immediate)
	Suprahepatic/infrahepatic vena caval obstruction (immediate)
Biliary complications	Biliary leakage (early)
	Biliary strictures (late)
	Stenosis of papilla vateri (early)
Non-specific surgical complications	Infections (early/late)
	Small bowel obstruction (early/late)
	Injury of intra-abdominal organs (immediate)
	Previous operations (immediate)

Meuller et al 2004

Review of Surgical Phases in OLT

1. Hepatectomy
2. Anhepatic
   - Clamp IVC and PV
   - Can do veno-veno bypass (IVC and PV to SVC) to avoid cardiovascular instability and protects renal function
3. Anastomosis
   - Suprahepatic vena cava / Infrahepatic vena cava
   - Portal Vein
   - Hepatic Artery
4. Recirculation
5. Hepatic phase
   - Biliary anastomosis

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If someone's liver doesn't work, we blame it on the genes; if someone's brain doesn't work properly, we blame the school. It's actually more humane to think of the condition as genetic. For instance, you don't want to say that someone is born unpleasant, but sometimes that might be true.

- James D. Watson

If someone's liver doesn't work, we blame it on…

- You are called by the PICU about a recent liver transplant recipient patient who they would like to transfer to the floor…

- By the way, the child has a temperature to 39.0 ^{o}C

- What do you want to know?
- What do you want to do next?

Additional Information

- 15 month old girl with BA
  - s/p deceased donor OLT 36 hours ago
- Anastomoses
  - Bile duct to roux
  - Portal Vein to portal vein
  - Hepatic artery to branch patch
  - Hepatic vein/IVC piggyback
- Labs
  - ALT 305, AST 477, T. bilirubin 4.1, C. bilirubin 1.8, GGT 596
  - Albumin 2.8, Ammonia 49, LDH 1309, lactate 2.1
  - WBC 12.7, Hgb 10.9, Platelets 316, INR 1.71
  - Blood & urine culture pending
- What would like to do next?

Fever immediate post-transplant

- What is considered a fever?
  - >38.5°C or associated with chills
- What are potential etiologies of a fever in the immediate post-transplant period?
  - Infection
  - Rejection
  - Thrombosis
- Is this primary non-function?

Primary Non-function

- Characterized by post-transplant encephalopathy, coagulopathy, minimal bile output, progressive renal and multisystem failure
  - Rising serum lactate, LFTs
  - Hepatocyte necrosis in the absence of any vascular compromise

- Risk factors → Donor liver status
  - Ischemic injury
  - Macrovesicular steatosis
    - Microvascular steatosis is not related to PNF

- How much steatosis is too much?
  - >40-50% fatty infiltration are not candidates to be donors

- Complete non-function requires <u>immediate</u> re-transplantation

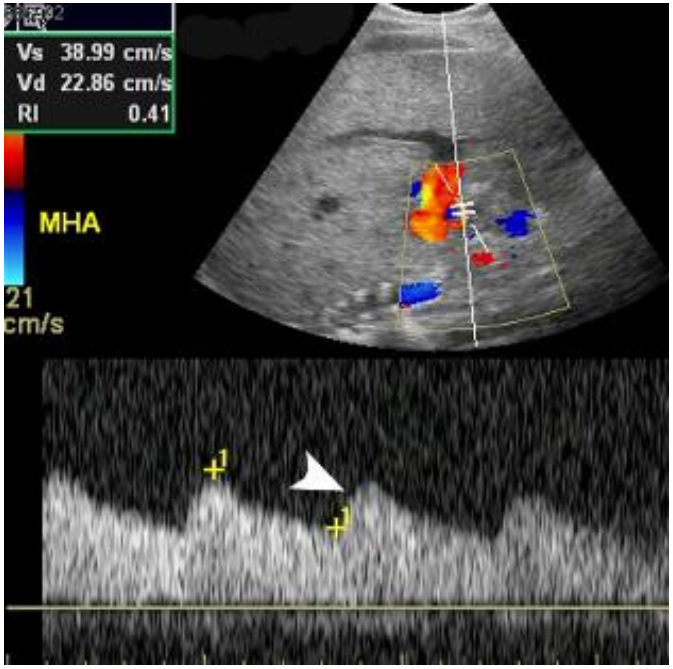
Causes of Allograft Failure

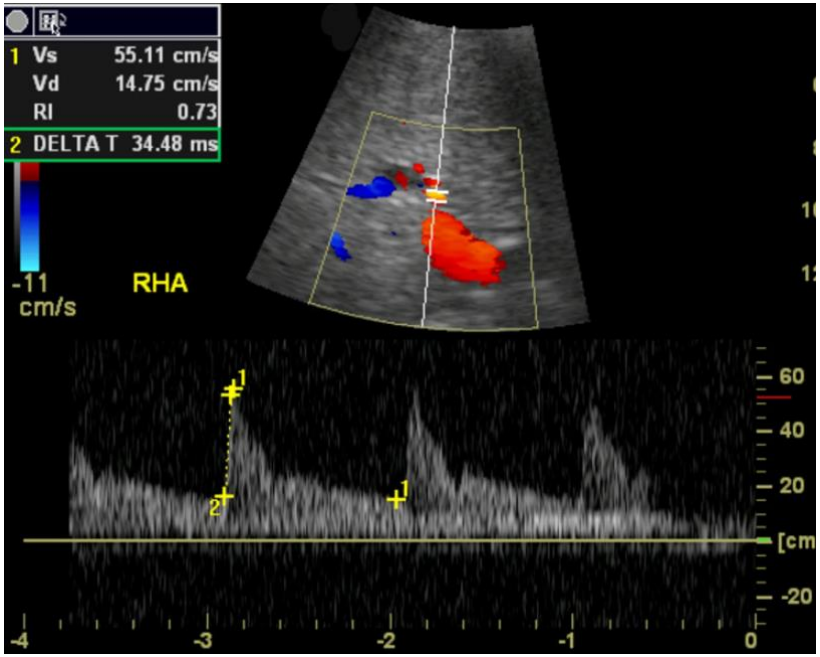
- Primary Non-function
  - Slightly more common in Living Donors
- Vascular Complications
  - Hepatic Artery Thrombosis/Stricture
  - Portal Vein Thrombosis/Stricture
  - Hepatic Vein Thrombosis/Stricture
- Biliary Complications
  - Donors after Cardiac Death, Living Donors
- Rejection
- Recurrence of disease

Recurrent Diseases

- What are the recurrent diseases that can cause allograft failure?
  - AIH, PBC, PSC
  - EtOH → 20% with recurrent use
  - HCC (within Milan Criteria) → 10% risk of recurrence
- What percentage of autoimmune hepatitis recurs?
  - 10-20%
- What is de novo autoimmune hepatitis?
  - Newly arising autoimmune liver disease after liver transplant
  - Histopathology identical to AIH

Back to our patient: Ultrasound with Doppler



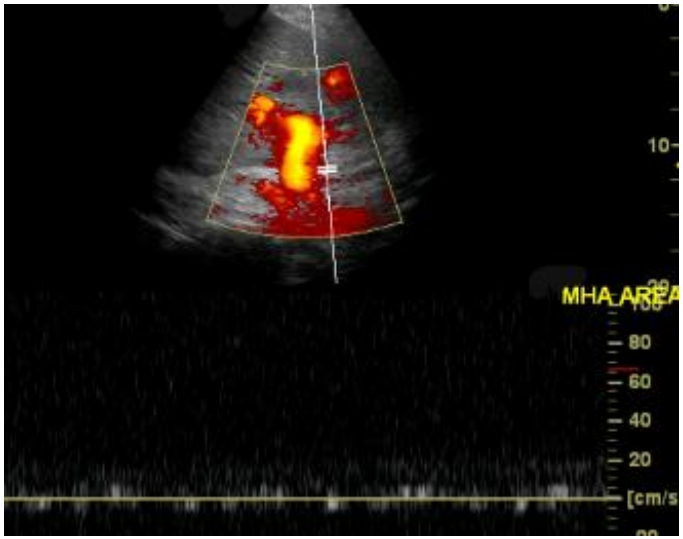


Hepatic artery stenosis

- Delayed systolic upstroke
- Rounding of systolic peak

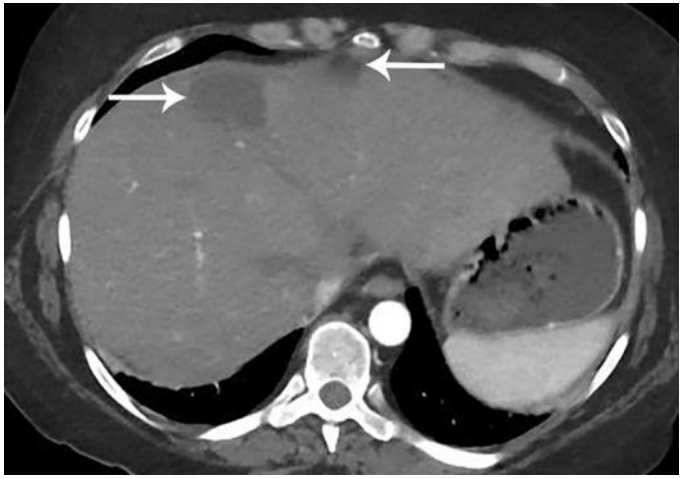
Patent Hepatic Artery

Repeat ultrasound the next day…



Hepatic artery thrombosis

Figure 4c: Hepatic artery thrombosis with secondary biliary necrosis. Images from c) digital subtraction angiography show occlusion of the hepatic artery near the anastomotic site (arrow in



What is concerning about this CT?

- Biloma

https://www.iame.com/course/980/take

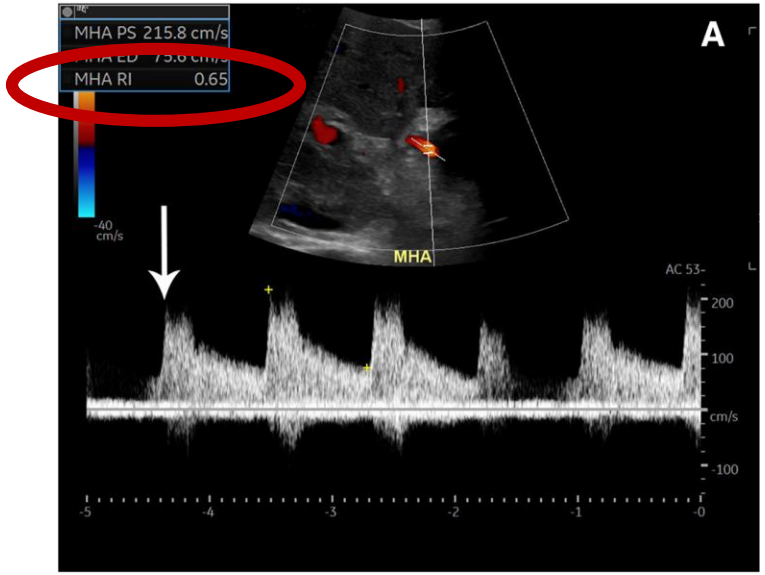
Hepatic Artery Thrombosis (HAT)

- What is the incidence of hepatic artery thrombosis?
  - 5-10%
- Is HAT more common in adults or children?
  - Occurs 3-4 times more frequent in children (but incidence is decreasing)
- Is there a difference in incidence of HAT with use of whole liver vs. split liver vs living donor?
  - Not really

More Facts about HAT

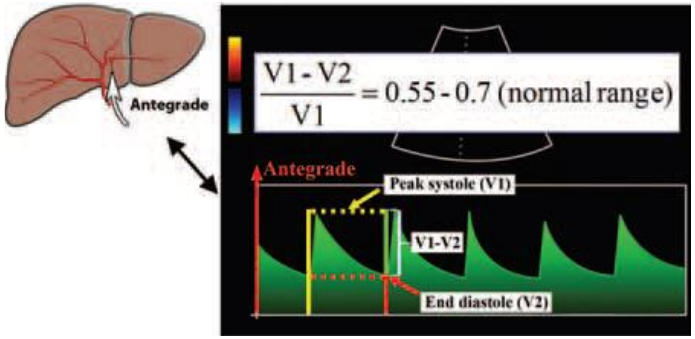
- What is the median time to detection of HAT?
  - ~1 week (6.9 days per Craig & Heller 2019)
- What are risk factors for HAT?
  - ABO incompatibility, prolonged cold ischemia time, rejection, size of blood vessel/anastomosis
- What is a main complication that can arise post-HAT?
  - Biliary complications

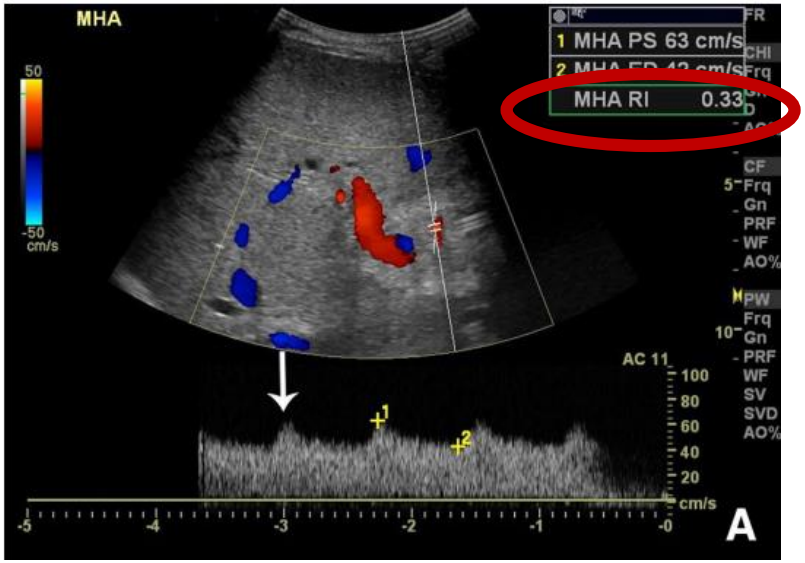
Doppler Review



Normal hepatic artery

- Brisk systolic upstroke with flow throughout diastole



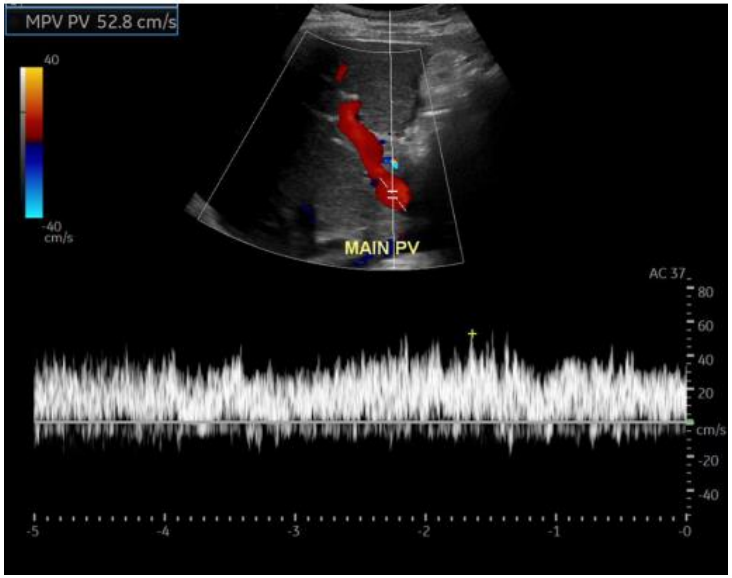


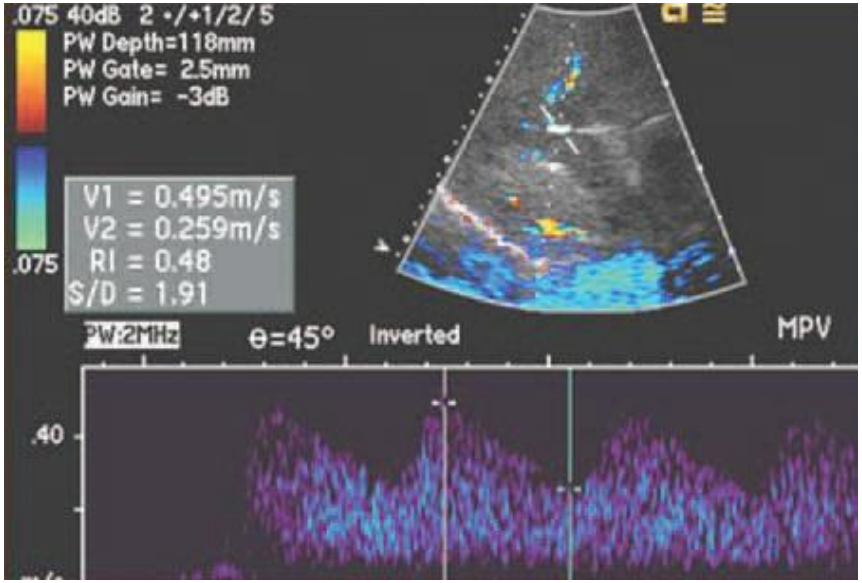
Hepatic Artery Stenosis

- Rounding of systolic peak
- Decreased resistive indices

Craig & Heller 2019

Doppler Review





Normal portal vein

- Hepatopedal flow with mild undulation

Craig & Heller 2019

Portal Vein Thrombosis

- Distended main portal vein without color flow
- Spectral waveform is pulsatile (arterialization)

Craig & Heller 2019

Portal Vein Thrombosis

- What are types of post-transplant portal vein complications?
  - Anomalies of portal flow
  - Stenosis
  - Thrombosis
- What is the incidence of portal flow anomalies?
  - ~10%
- What is the management of portal flow anomalies?
  - Rarely need a specific intervention, but persistent stenosis or signs of portal hypertension need to be corrected → balloon dilatation +/- stent
- What is the incidence of portal vein thrombosis?
  - ~5%

Alvarez. Curr Gastroenterol Rep 2012

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A bad liver is to a Frenchman what a nervous breakdown is to an American. Everyone has had one and everyone wants to talk about it.

- Art Buchwald

A bad liver is to a Frenchman…

- An 11 y/o girl who is s/p OLT 3 months ago secondary to autoimmune hepatitis is seeing you in clinic
  - Whole liver from a deceased donor
- She has been doing well and is back in school.
  - No complaints of bruising or bleeding, abdominal pain, vomiting, or fatigue
- She is on tacrolimus and prednisone.
- Would you like any additional information?
- How would you proceed with management during this visit?

Initial Screening Labs

- ALT 30, AST 31, bilirubin 1, GGT 56
  - Are you concerned?

- What if ALT 50, AST 57, bilirubin 1.2, GGT 55?

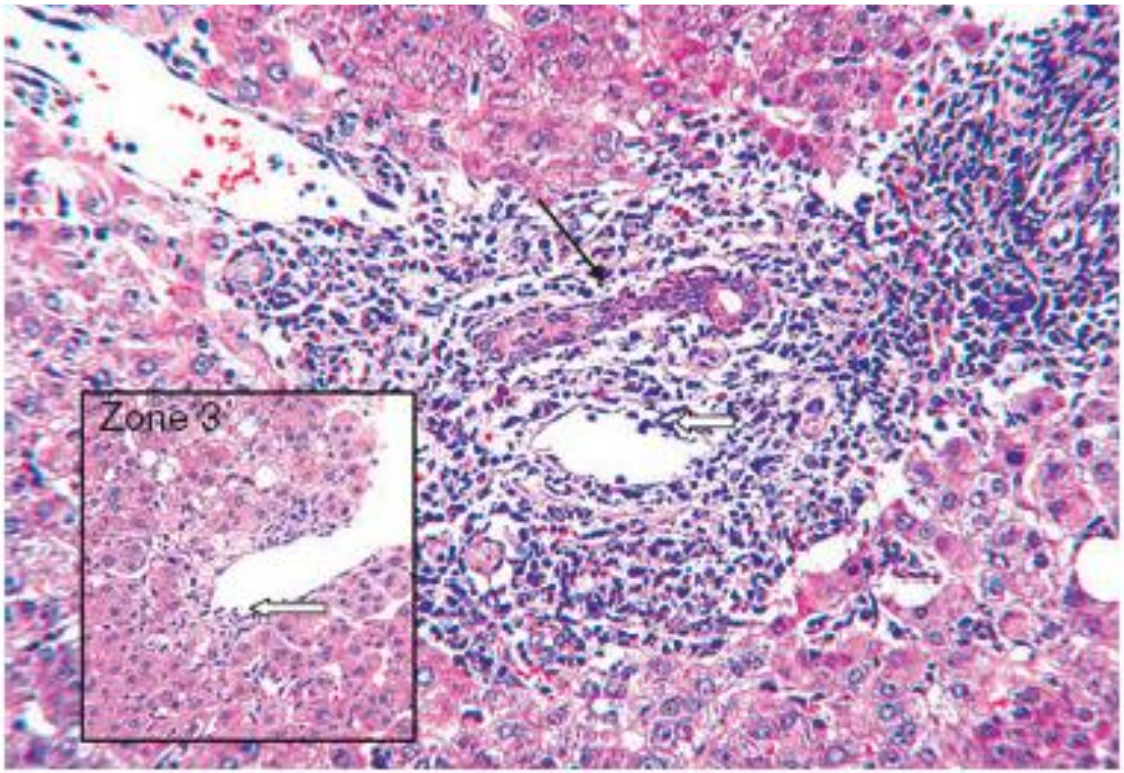
- What would you like to do?
  - Repeat labs in 1 day
  - Repeat labs in 3 days
  - Repeat labs in 1 week
  - Repeat labs in 1 month
  - None of the above

Next Steps

- Medications
  - Tacrolimus 2.5mg BID
  - Prednisone 3mg daily, recently weaned from 6mg daily
- Tacrolimus level → 9.7
  - What do you want to do?
- You increased tacrolimus to 3mg BID and repeat labs one week later show
  - ALT 120, AST 117, Bilirubin 1.2, GGT 113
- What would you like to do now?
- What are you concerned about?

Would you like to…

- Increase prednisone
- Increase tacrolimus
- Add mycophenolate mofetil
- No med changes for now, monitor liver labs
- Check autoimmune hepatitis panel
- Check EBV
- Abdominal ultrasound
- Liver biopsy

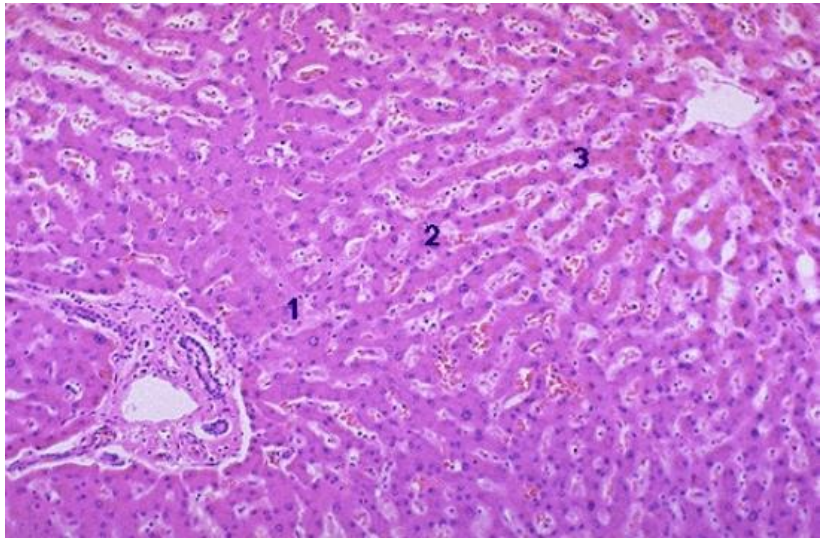


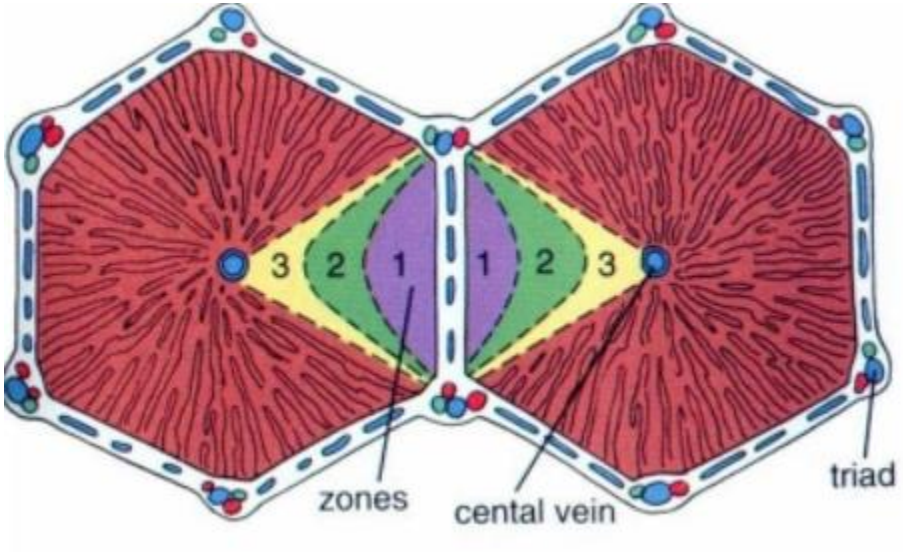
- Banff Grading System → score of 1-3 for each factor
  - Portal Inflammation
  - Bile Duct Inflammation/damage
  - Venous Endothelial Inflammation

- What is common among these types of cells?
  - Rejection targets endothelial cells

Wyatt (2010) Histopathology 57, 333–341

Zones of the Liver





- Which zone is most susceptible to ischemic injury?
  - Zone 3
- Which zone do you typically see infectious injury?
  - Zone 1
- Which zone is usually affected in toxin mediated damage?
  - It depends on the drug
  - Zone 3 - hepatic necrosis, Zone 1 - coagulative necrosis

Acute Cellular Rejection

- What are some signs and symptoms of rejection?
  - Fever
  - Jaundice
  - Light Stools/Dark Urine
  - Increase in Liver Enzymes → may be only indicator
    - Bilirubin or GGT may rise first as rejection targets endothelial cells

- What is the treatment of acute cellular rejection?
  - Pulse doses of Methylprednisolone (10mg/kg x 3 days) and then add prednisone
  - Mycophenolate Mofetil (Cellcept/MMF)
  - Increase tacrolimus goal levels

All About Rejection

- Is rejection antibody or T-cell mediated?
  - T-cell
- How early can rejection occur?
  - 7 to 10 days after OLT
- What is the frequency of acute cellular rejection?
  - High → 60% in the first 6 months post-transplant
  - Risk 1st 3 months > 1st year > subsequent years
- How successful is treatment of acute cellular rejection?
  - High → 75-80% respond to short course of high dose steroids followed by rapid taper

More About Rejection

- What are medical options for rejection refractory to treatment?
  - Rituximab, Anti-lymphocyte therapy (thymoglobulin, OKT3), Transplantation
- Is chronic rejection related to acute cellular rejection?
  - Possibly, as some studies suggest that prior episodes of acute cellular rejection is a primary risk factor
- What is the incidence of chronic rejection?
  - 5-10%
- What do you see in chronic rejection?
  - Ductopenia
- Two clinical forms of chronic rejection
  1. Injury to biliary epithelium with development of ductopenia → spontaneous resolution in half of patients
  2. Early development of progressive ischemic injury to bile ducts and hepatocytes that leads to ductopenia and ischemic necrosis with fibrosis

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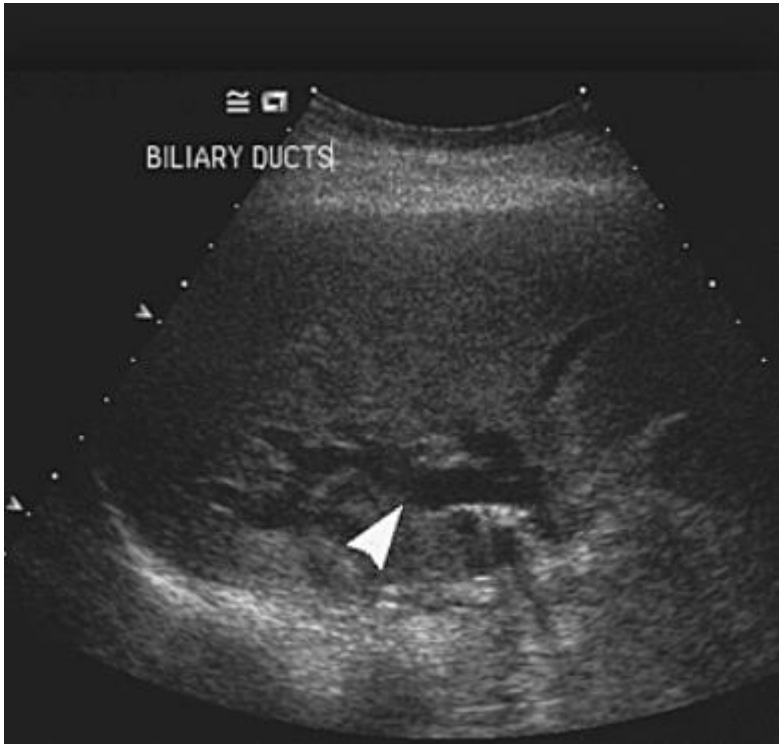
"Other than your gallbladder photobombing your liver, your CT scan looks normal."

- A 6 y/o girl who is s/p OLT 9 months ago for MMA presents for routine follow-up in clinic.

- Routine labs
  - AST 60, ALT 51, T. bilirubin 4.5, GGT 90
  - Tacrolimus level 9.1

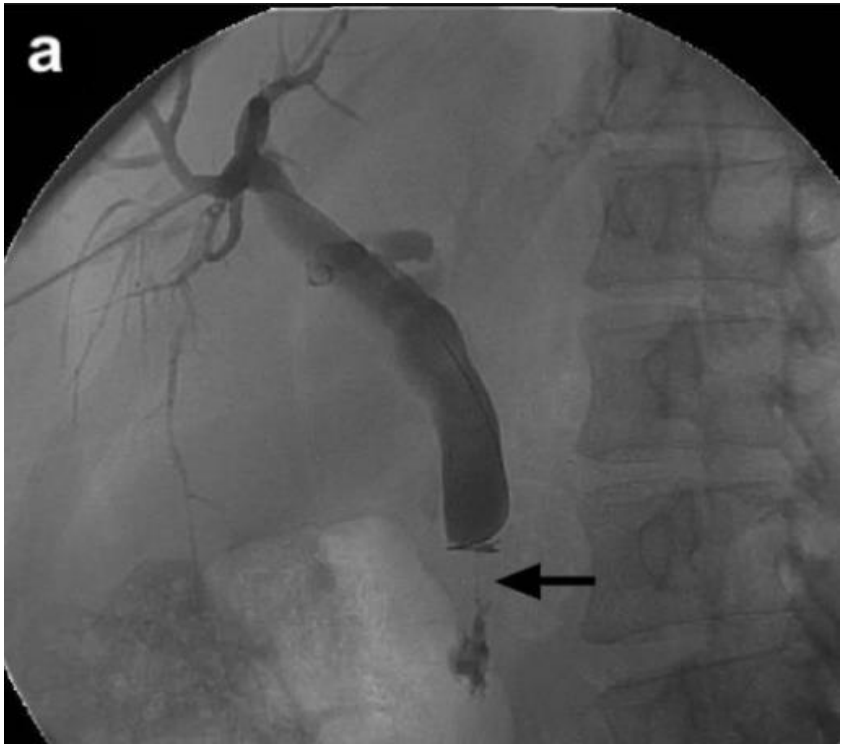
- What would you like to do next?

Imaging Studies



Ultrasound

- Intrahepatic bile duct dilation



PTC

- Distal biliary stricture

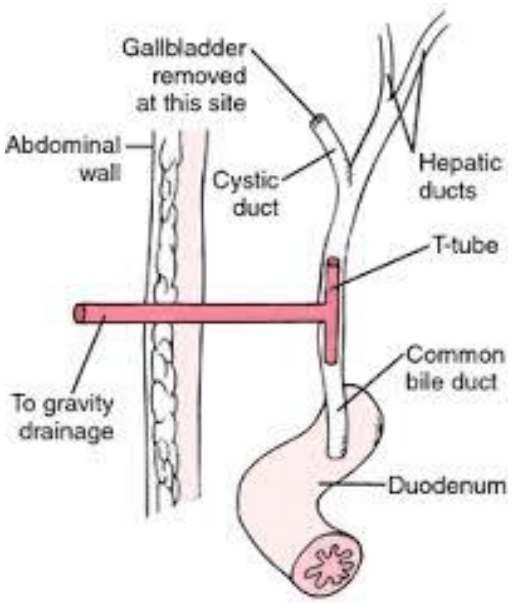
Biliary Complications

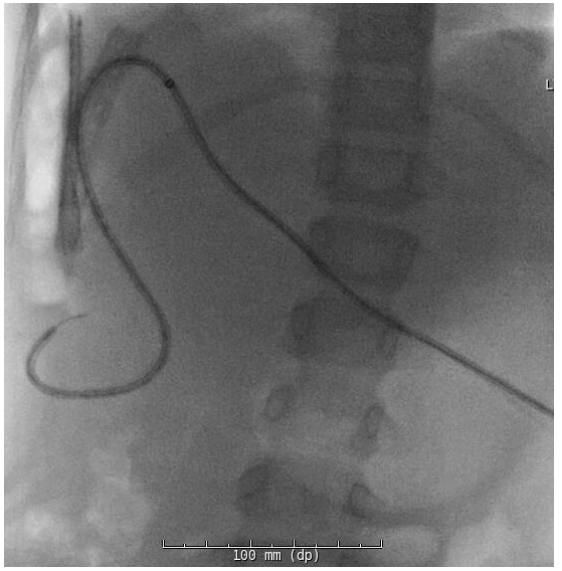
- What is the frequency of biliary complications in pediatric liver transplant?
  - 10%
- What are common biliary complications?
  - Biliary stricture, biloma, bile leak, recurrent cholangitis
- What is the most common risk factor for biliary complications?
  - Poor hepatic artery flow
- Are biliary complications more common in whole or surgically reduced allografts?
  - Equivalent risk of biliary complications
  - However, bile leaks slightly more common in split liver, while anastomotic strictures are more common in living donor

Back to the patient…

- What is the management for a biliary stricture?
  - Biliary stent and/or biliary drain
- When would you consider a biliary drain?
  - Bile leak
- When do you consider a IR versus ERCP?
  - Biliary stent – ERCP
  - External/internal biliary drain – IR

Anatomy of a Biliary Drain





- What are some routine biliary drain care instructions?
  - Flush catheter with 5-10 mL of sterile water or NS every 24 hours to prevent debris collection and catheter blockage

One month later…

- You receive a call that the patient has a fever to 38.5°C.

- What would you like to do?
  - Assessment by pediatrician and draw labs
  - Come to CHOP ED for labs → If well appearing, give dose of ceftriaxone and discharge with close follow-up
  - Obtain ultrasound to look for biliary obstruction and then call IR
  - Automatic admission for 48 hour rule out

Fever Follow-up

- What management advice would you give over the phone to the family prior to arriving to the ER?
  - Uncap the biliary drain
- Parents uncap the drain, but nothing comes out. Would you advise flushing the biliary drain to clear possible debris that may be obstructing the catheter?
  - No
- What is the treatment for recurrent stenosis or persistent postoperative leak?
  - Roux-en-Y choledochojejunostomy

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