# Pediatric Liver Transplantation

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## Objectives:

- Review indications for pediatric liver transplant
- Disease-specific indications and contraindications
  - Biliary atresia
  - Hepatoblastoma
  - PFIC
  - Metabolic – urea cycle defect
- Pediatric listing/PELD

- Liver transplant can be indicated for children with:
  - End stage liver disease
  - Acute liver failure
  - Variety of metabolic disorders and malignancies
- Advances in surgical techniques and organ preservation
  - Expanded the donor pool for children
  - Reduced waiting list mortality
- Improvements in immunosuppression management and post transplant care have resulted in 1-year survival rate of >90%.




## Indication for Pediatric Liver Transplant

1. Primary liver disease that is expected to progress to death
2. Secondary liver disease, such as cystic fibrosis with biliary cirrhosis but few pulmonary complications
3. Primary unresectable hepatic tumor with limited disease
4. Liver disease with morbidity that outweighs the risk of transplantation (i.e. linear growth failure, intractable pruritus, complications from portal hypertension)
5. Metabolic disease

## "Disease" Indications for Liver Transplant

- Obstructive cholestasis
  - **Biliary atresia, Alagille syndrome**
- Hepatocellular Disease
  - Autoimmune hepatits, viral hepatitis
- Metabolic / Genetic
  - **Alpha-1 antitrypsin deficiency**, tyrosinemia, glycogen storage diseases, **Progressive familial intrahepatic cholestasis** , Wilson disease, gestational alloimmune liver disease, cystic fibrosis, **urea cycle defects**, maple syrup urine disease, familial hypercholesterolemia, Crigler-Najjar
- Tumors
  - **Hepatoblastoma**, HCC
- Acute Liver Failure




## Metabolic Diseases

Diseases that lead to structural liver damage with liver failure or cirrhosis, +/- injury to other tissues

Examples:

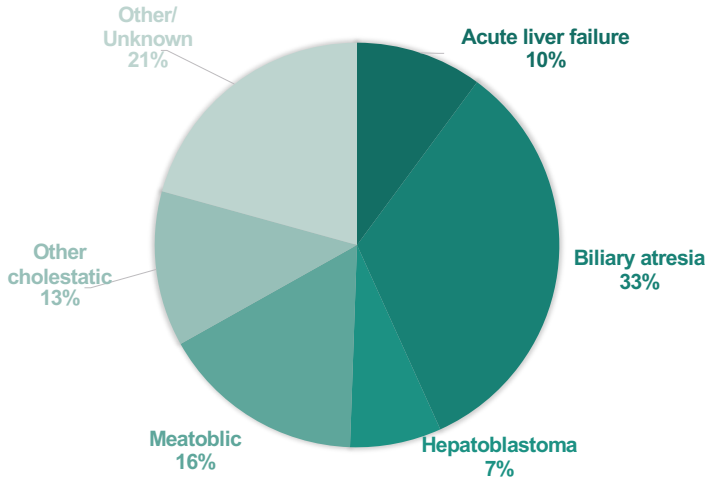
- **A1ATD**, cystic fibrosis, **tyrosinemia**, Wilson disease, **PFIC**, GALD, **GSD**, bile acid synthesis disorders, mitochondrial hepatopathies

Diseases due to metabolic defect expressed solely or predominantly in the liver but leading to injury to other organ systems

Examples:

**Urea cycle disorders**, familial hypercholesterolemia, Criggler–Najjar syndrome, **organic acidemias**, primary hyperoxaluria, disorders of branched-chain amino acids, generalized mitochondrial disease

# Indications for Pediatric Liver Transplant (2018)



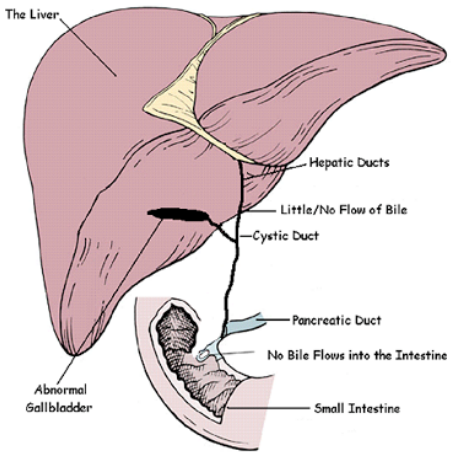

*Data from* Organ Procurement and Transplantation Network (OPTN)





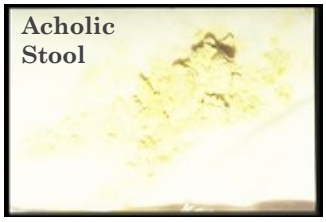
## Biliary Atresia

- Progressive extrahepatic biliary obstruction due to inflammatory fibrosing cholangiopathy
- Affects 1:8,000 – 1:15,000 live births
- Early identification is critical
  - Primary therapy is surgical (Kasai hepatoportoenteorstomy) before 60 days of age
- Leading indication for pediatric liver transplant
  - ~50% transplanted by age 2
  - ~85% by 20 years old

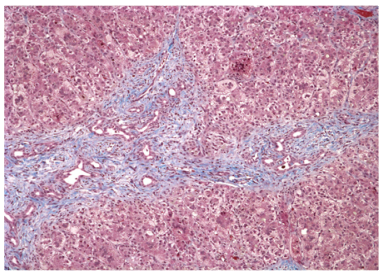



http://www.barcnetwork.org/families/diseases.html

## Presentation of Biliary Atresia




- Well appearing infant
  - Acholic stools, dark urine
  - Jaundice, icterus
  - Hepatosplenomegaly
- 20-30% have associated anomalies
  - Splenic malformations (asplenia, polysplenia)
- Liver histology characterized by:
  - Bile duct proliferation
  - Portal tract expansion
  - Canalicular plugging

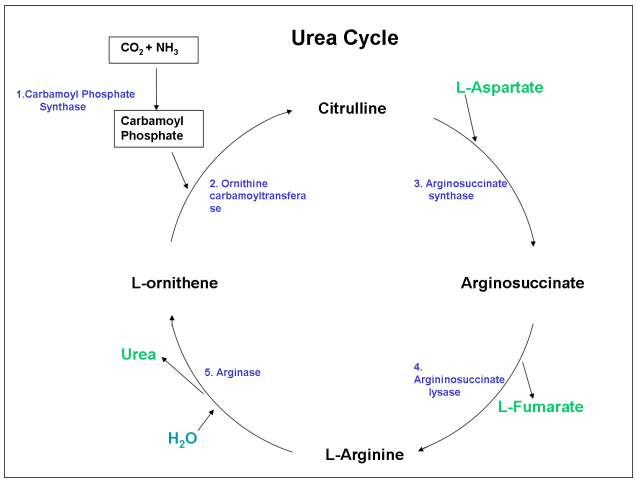





## Alagille Syndrome

- Multisystem, autosomal dominant disorder due to mutation sin JAG1 or NOTCH2
  - Can affect the liver, heart, skeleton, eyes, and face
- Liver involvement is variable and some can develop severe chronic cholestasis
  - Cholestasis complications includes severe pruritus, xanthomas, poor growth, deficiency of fat soluble vitamins
  - Minority of patients may require liver transplant

## Liver transplant can cure or *improve* metabolic disease burden




https://edu.apnafort.com/

- Urea cycle defects
  - 6 enzymes plus several mitochondrial transporters)
- Transplant eliminates the risk of hyperammonemia
  - Risk of other neurometabolic complications remains
  - May still require supplements of urea cycle intermediates




## Urea Cycle Defects

- NAGS, OTC, and CPS1 deficiencies
  - Most severe metabolic derangements with worst outcomes
  - Neonatal onset of hyperammonemia and death within 1st year of life if untreated
  - Medical management used as a bridge to transplant
- ASS and ASL deficiencies
  - More likely to survive infancy with medical management
  - High risk of long term intellectual deficit (67% and 60%), and increased risk for HCC
  - Primary medical management, but growing consideration for earlier transplantation

## Organic Acidemias

- Includes propionic academia, primary methylmalonic academia
- Transplant improves hyperammonia
  - Can lead to improved cardiac disease, quality of life, less strict dietary restrictions
  - May not prevent CNS complications such as metabolic stroke and progressive renal failure




## Alpha-1 Antitrypsin Deficiency

- Affects 1:1500 individuals
  - Estimated that <10% have been diagnosed
- Autosomal recessive disorder that may cause cirrhosis
  - ZZ is the most common Pi type associated with liver disease
- Liver disease due to intracellular accumulation of abnormal alpha-1 antitrypsin protein
  - Characterized by accumulation of PAS-positive, diastase resistant cytoplasmic globules in hepatocytes on H&E
  - Increased risk of HCC in patients with A1AT associated cirrhosis

## Glycogen Storage Disease

- Type I
  - Most common GSD but does not typically develop into cirrhosis
  - Risk of developing multiple hepatic adenomas, although malignant transformation is rare
  - Transplant can be indicated because of growing or changing adenomas
- Types III, IV, VI, and IX can also be associated with severe liver disease
  - Typically managed medically, though patients are at risk for malignancies (HCC) and cirrhosis
  - Transplant will not cure extrahepatic manifestations such as renal disease, cytopenias




## Hereditary tyrosinemia Type 1

- Autosomal recessive disorder characterized by loss of fumarlacetoacetate hydrolase (FAH) activity
  - Accumulation of toxic metabolites leading to liver and kidney toxicity
- Hepatic injury leading to cirrhosis in first few months of life
  - High risk of HCC starting around 3 years of age
  - Can also see renal and neurologic manifestations (neurologic crises due to accumulation of porphyrin)
- Early treatment prevents or ameliorates most of manifestations but unclear how risk of HCC changes
  - Liver transplant should be considered
  - NTBC (Nitisinone) → competitive inhibitor of 4-hydroxyphenyl pyruvate dioxygenase, an enzyme upstream of FAH, which can prevent accumulation of fumarylacetoacetate

# Progressive Familial Intrahepatic Cholestasis (PFIC)

- Group of cholestatic conditions due to defects in biliary epithelial transporters
  - Type 1 (Byler Disease)
    - Mutation in ATP8B1 gene which is responsible phospholipid translocation and involved in normal secretion of bile
  - Type 2 (BSEP Deficiency)
    - Mutation in ABCB11 gene, leads to retention of bile salts within hepatocytes
- Characterized by a low GGT cholestasis
  - In contrast to other neonatal cholestatic disorders such as biliary atresia and Alagille syndrome which have an elevated GGT
  - Symptoms include pruritus from peripheral accumulation of bile salts and diarrhea as the protein is also expressed in intestine
- Management
  - Medications target symptoms (pruritus), ursodiol can help with bile flow
  - Often surgery is needed: liver transplant or partial external biliary diversion




# Hepatoblastoma

- Most common primarily hepatic tumor in children
  - More common in males
  - Associated with other syndromes such as Beckwith Weidemann, hemihypertrophy, and familial polyposis.
  - Prematurity is also a risk factor
- Presents in the first few years of life
  - Alpha-fetoprotein level are usually elevated
- Management is with surgical resection
  - If tumor is unresectable and if there are no distant metastases (Stage 3), liver transplant is indicated
  - Chemotherapy is given before and after transplant

## Pediatric Acute Liver Failure

- Account for 10-15% of pediatric liver transplants
  - Transplant has reduced 21-day mortality rate to 11%
- Clinical manifestation for a heterogenous group of injuries
  - Causes differ by age
  - Includes infectious, genetic, metabolic, and immune-mediated disease as well as medications, toxins, and trauma
  - Acetaminophen toxicity account for ~13% of cases
- Specific diagnosis is not established in up to 50% of cases
  - Indeterminate ALF associated with aplastic anemia (25-30%)




## PELD

- Components of PELD
  - Albumin, bilirubin, INR, age, and growth
- Status 1B (unique to pediatrics)
  - Biopsy-proven hepatoblastoma without evidence of metastatic disease
  - Organic acidemia or urea cycle defect and an approved MELD or PELD exception meeting standard criteria for metabolic disease for at least 30 days
  - PELD or MELD >25 and one of the following
    - Mechanical ventilation
    - GI bleeding requiring at least 30mL/kg of PRBC within 24 hours
    - Renal insufficiency requiring dialysis, CVVH, or CVVD
    - GCS < 10 within 48 hours

## PELD Scoring System

**PELD** = (0.436 x **age***)-(0.687 x log(**albumin**))+(0.480 x log(**bilirubin**))+(1.857 x log(**INR**))+(0.667 X **growth failure**†) x 1

* Age < 1 year gets 1, Age >1 year gets 0

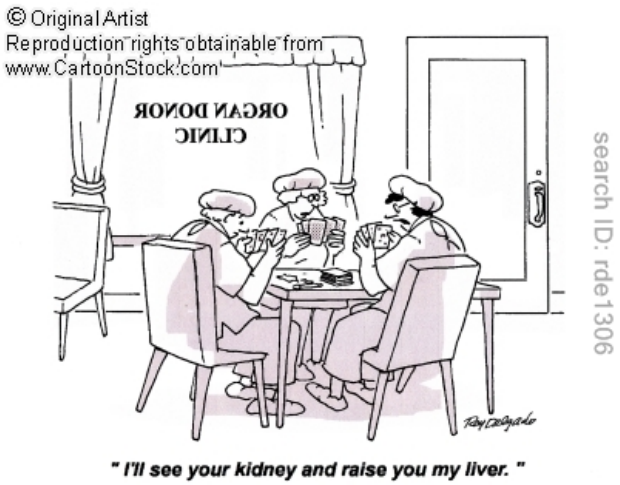
† growth failure =1, no growth failure =0

- Growth failure = height or weight < 2 SD below the mean values for that age





## Questions



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