Hyperbilirubinemia in Infancy

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Disclosures

The speaker has no conflicts of interest and nothing to disclose.

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Objectives

- Explain the basics of bilirubin metabolism, differentiate conjugated versus unconjugated hyperbilirubinemia
- Provide an overview of common causes of cholestasis, clues to diagnosis, available investigative tests/ procedures
- In-depth discussion on presentation, diagnosis and management of biliary atresia
- Discuss complications of cholestasis, available and future therapies
- Provide real-life case examples and general recommendations

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Patient Case

- 6-week-old, jaundice since birth, presents to PCP on a Tuesday morning
- **PMH:** Term infant, no complications to pregnancy or delivery, NSVD. Uneventful nursery course, total bilirubin at 24 hrs old was 4.1. Discharge home DOL# 2.
  - First visit 2 weeks old- BF infant, gaining weight, mildly jaundiced, TC bili 8.0, presumed BM jaundice, recommend follow-up 4 weeks old.
- **FH:** Unremarkable; **Soc Hx:** Lives with mom + dad (healthy), first child.
- **Meds:** None.
- **HPI:** Some reflux/ vomiting, persistent jaundice. No other complaints. Asked about stool color- mom thinks they have been yellow.
- **Exam:** Normal VS. Weight-for-age decreased 40→20%.
  - Scleral icterus. Smiling/ playful.
  - Round, distended abdomen. Liver 2-3 cm below right CM, firm. Spleen 1-2 cm below left CM.
  - Thin extremities.
  - No stool available to examine.

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Patient Case

- Work-up completed that day:
  - CBC-diff: unremarkable
  - CMP: AST 75, ALT 56 IU/L, alk phos 750 IU/L, total bilirubin 5.1 mg/dL
  - Direct bilirubin: 3.9 mg/dL
  - GGT: 950 IU/L
  - INR: 1.2
- **US- Report:** Hepatomegaly, homogeneous appearance to liver, difficulty in visualizing GB or CBD. No comment on spleen as was limited to RUQ.
- Called hepatology team on call, scheduled for urgent new patient visit. Asked family to save stool to bring to clinic with them.
- **Hep clinic** (3 days later, Friday AM, now 7 weeks old):
  - Exam confirmed
  - Labs repeated: Tbili 5.2, Dbili 3.7, GGT 965, INR 1.3
  - Mother brought stool sample with her:

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Patient Case

- Patient admitted to hospital under hepatology on Sunday
- Pediatric Surgeons consulted, Monday morning taken to OR
- Exploratory laparotomy, intraoperative cholangiogram- no excretion of contrast into common bile duct/ duodenum, confirming diagnosis of biliary atresia (BA)
- Perform Kasai portoenterostomy
- Obtain wedge liver biopsy
  - Biopsy reviewed- overall consistent with BA
- Remained in the hospital 5 days post-op, discharged home with hepatology and surgery follow-up.
- 3 months post-Kasai, total bilirubin 1.8, direct 1.2. Clinically doing well, followed closely in outpatient hepatology clinic.

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What is Bilirubin?

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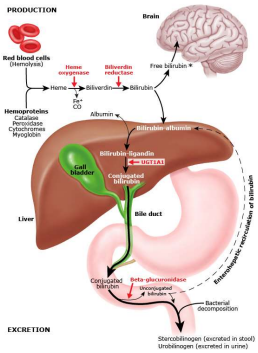
What is Bilirubin?



Risk of bilirubin-induced neurologic dysfunction/ kernicterus

-Bilirubin has a yellow/orange pigment
-Conjugated measured as direct bilirubin
-Unconjugated/ indirect estimated as total minus direct

Hansen et al. *Care of the Jaundiced Neonate*, 2012.

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Indirect or Direct (or both): That is the (first) Question

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Indirect or Direct (or both): That is the (first) Question

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Indirect hyperbilirubinemia In Infancy: Potential Causes

TABLE 1
Causes of unconjugated hyperbilirubinemia in neonates[4-6]

Increased bilirubin production	Increased enterohepatic circulation	Decreased clearance of unconjugated bilirubin	Metabolic conditions	Inborn errors of metabolism
Hemolysis (immune-mediated, heritable)	Insufficient breast milk/ feeding	Prematurity	Hypothyroidism	Gilbert syndrome
Extravasation (cephalohematoma)	Pyloric stenosis	G6PD deficiency	Hypopituitarism	Crigler-Najjar syndrome (I and II)
Polycythemia	Bowel obstruction			Breast milk jaundice due to other bilirubin UGT1A1 mutations
Sepsis	Ileus			
Disseminated intravascular coagulation				
Macrosomic infants of diabetic mothers				

G6PD, glucose-6-phosphate dehydrogenase; UGT1A1, uridine diphosphate-glucuronosyltransferase, family 1, polypeptide A1.

Pace et al. *J Fam Pract*, 2019.

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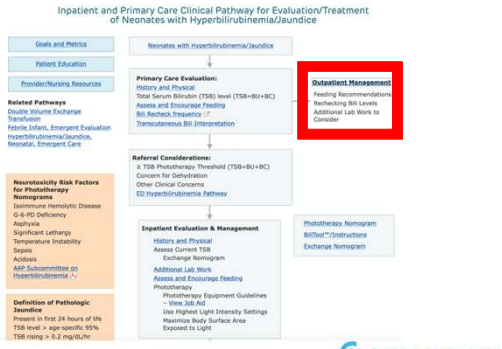
Management of Indirect Hyperbilirubinemia



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Management of Indirect Hyperbilirubinemia

Outpatient Management

Feeding Recommendations	Consider nursing consult for lactation Encourage frequent feedings Avoid formula in breastfeeding infants
Rechecking Bili Levels	Consult BiliTool™ for recheck guidance Once level is out of phototherapy range, recheck is not needed
Consider Additional Lab Work	Check birth history for maternal/infant blood types If blood type unknown or no DAT result, draw a DAT If DAT positive, draw CBC and retic Consider sending direct bilirubin

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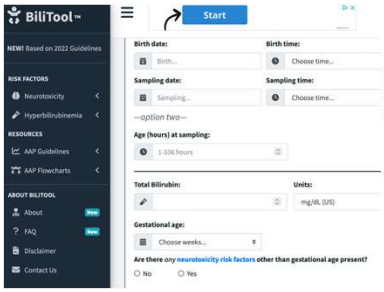
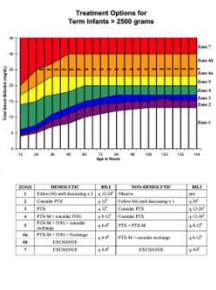
Risk Assessment Tools

BiliTool



Emory Nomogram



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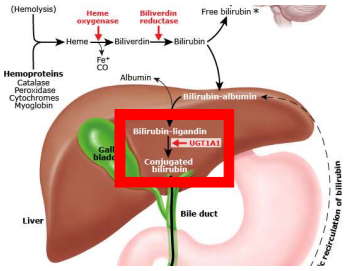
Crigler-Najjar and Gilbert Syndrome



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Crigler-Najjar Syndrome

- Autosomal recessive, rare- 0.6 to 1 case per million
- Mutations in UGT1A1 gene, encoding protein to conjugate bilirubin
- **Type 1: No enzyme activity**
  - Severe, persistent elevation in UNCONJUGATED bilirubin within first few days after birth
  - Requires chronic phototherapy
  - Phototherapy→ lumirubin, excreted without conjugation
  - Liver transplantation is curative
- **Type 2: Partial activity (<10%)**
  - Can present as unconjugated hyperbilirubinemia during neonatal period or later. Lower risk of neurotoxicity. Risk increases with illness.
  - Responsive to phenobarbital- two weeks trial should decrease bilirubin by >25%, then can use long-term.

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Gilbert Syndrome

- Autosomal recessive
- Common (4-16%), higher in African Americans (up to 25%, one allele seen in >40%)
- Benign
- Mutations of same gene that causes Crigler-Najjar Syndrome (UGT1A1) but maintain appx 1/3 normal activity.
- Increased risk for more severe/ prolonged neonatal jaundice.
- Intermittent jaundice (UNCONJUGATED), may not present until adolescence, or with acute illness.
- No treatment needed, genetic testing typically not warranted, only useful if provides reassurance/ information to family.

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Direct Hyperbilirubinemia/ Neonatal Cholestasis

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Cholestasis

- Chole= bile, Stasis= stoppage/ slowing of flow
- Bile= fluid secreted by liver, helps digest lipids, fat-soluble vitamins.
- Mostly water (up to 98%), as well as bile acids, conjugated bilirubin, phospholipids, cholesterol, fatty acids, electrolytes, etc.
- Poor bile flow can be reflected by elevation in serum direct/ conjugated bilirubin and/or serum bile acids.
- Direct bilirubin >1 mg/dL.
- If total bilirubin is very high, then more concerning for cholestasis if direct is >20% of total
  - I.e. Tbili 18, Dbili 1.2 less concerning

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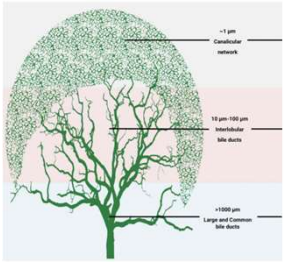
Cholestasis

- 1 in 2500 term infants
- Two broad origins of cholestasis:
  - Bile ducts (intrahepatic small bile ducts or large, extrahepatic, obstructive)



Jansen et al. *Hepatology*, 2017.

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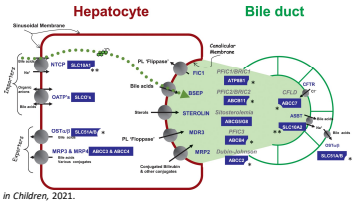
Cholestasis

- 1 in 2500 term infants
- Two broad origins of cholestasis:
  - Bile ducts (intrahepatic small bile ducts or large, extrahepatic, obstructive)
  - Hepatocytes (defect in membrane transport, embryogenesis, metabolic dysfunction).



Karpen et al. *Liver Disease in Children*, 2021.

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Causes of Neonatal Cholestasis

Box 1 | Causes of neonatal cholestasis

Infectious
Viruses, bacteria, spirochaetes and parasites

Toxins
Drugs, endotoxins, total parenteral nutrition-associated cholestasis and herbal products

Endocrine
Hypothyroidism and panhypopituitarism

Immune
Gestational alloimmune liver disease

Anatomic obstruction
Biliary atresia, choledochal cyst, cholelithiasis, biliary sludge, inspissated bile, spontaneous perforation of common bile duct and tumour

Other
Idiopathic neonatal hepatitis (transient neonatal cholestasis), cardiovascular and circulatory disorders, haemophagocytic lymphohistiocytosis, malignancy and congenital lupus

Genetic and metabolic[a]
- α1-Antitrypsin deficiency (SERPINA1)
- Alagille syndrome (*JAG1* and *NOTCH2*)
- Arthrogryposis–renal dysfunction–cholestasis syndrome (*VPS33B* and *VIPAR*)
- Caroli disease and congenital hepatic fibrosis (*PKHD1*)
- Chromosomal (trisomy 21, Turner syndrome)
- Citrin deficiency (*SLC25A13*)
- Cystic fibrosis (*CFTR*)
- Disorders of bile acid synthesis (*AKR1D1*, *AMACR*, *CYP7B1*, *HSD3B7*, *CYP7A1* and *CYP27A1*)
- Disorders of bile acid conjugation (*BAAT* and *SLC27A5*)
- Fatty acid oxidation defects (*SCAD* and *LCAD*)
- Galactosaemia (*GALT*)
- Glycogen storage disease type IV (*GBE1*)
- Hereditary fructose intolerance (*ALDOB*)
- Mitochondrial respiratory chain disorders (*DGUOK*, *MPV17* and *POLG*)
- Neonatal ichthyosis–sclerosing cholangitis syndrome (*CLDN1*)
- Neonatal sclerosing cholangitis (*DCDC2*)
- Niemann–Pick disease type C (*NPC1* and *NPC2*)
- Peroxisomal disorders (*PEX1*, *PEX6*, *PEX10*, *PEX11B*, *PEX12*, *PEX13*, *PEX14*, *PEX16*, *PEX19*, *PEX2*, *PEX26*, *PEX3*, *PEX5* and *PEX7*)
- Progressive familial intrahepatic cholestasis (*ATP8B1*, *ABCB11*, *ABCB4*, *TJP2*, *NR1H4*, *MYO5B* and *UNC45*)
- Lipid storage diseases (*SCP2*)
- Tyrosinaemia (*FAH*)
- Urea cycle defects

[a]For genetic and metabolic causes, the affected gene or genes are listed in parenthesis when known.

In premature, sick children with prolonged NICU courses, need for TPN, cholestasis is **often multifactorial**

Feldman et al. *Nat Rev Gastroenterol Hepatol*, 2019.

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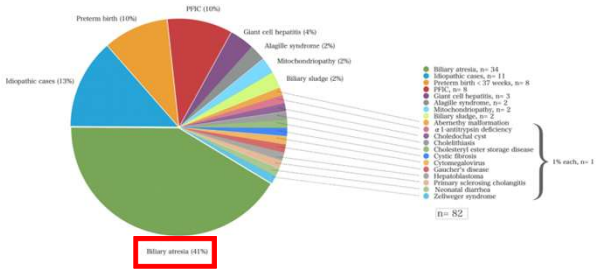
Causes of Neonatal Cholestasis



Hoerning et al. *Front Pediatr*, 2014.

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Biliary Atresia (BA)

- Atresia= absence/ closure.
- Congenital, progressive, obstructive cholestasis, extrahepatic (+ intrahepatic) bile ducts do not form/function properly.
- 1 in 10-15K children, etiology unknown
  - Possible prenatal insult due to viral infections, toxins, inflammation, or underlying genetic causes?
  - 15% have other malformations (cardiac, GI, spleen). 10% syndromic with laterality defects (heterotaxy).
  - Cystic BA- associated cyst of extrahepatic bile duct (need to differentiate from isolated choledochal cyst).

Most common reason for pediatric liver transplantation

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BA- Presentation and Diagnosis

- Jaundice
- Acholic/ clay-colored stools, dark urine
- Abdominal distention- hepatosplenomegaly, firm liver, ascites
- Feeding difficulties/ vomiting, can have thin extremities (weight not always a good marker of nutritional status)
- **Labs:**
  - ⇧ Direct bilirubin early, elevated GGT (cell membrane of hepatocytes and cholangiocytes), AST, ALT
- **US: non-specific**, may have difficulty visualizing GB, small/ abnormal shape, difficulty seeing CBD, cystic CBD, triangular cord sign (fibrous tissue near portal vein- ductal remnant of extrahepatic bile duct), can see polysplenia.
  - Can also appear relatively normal. Sonographer/ radiologist dependent.

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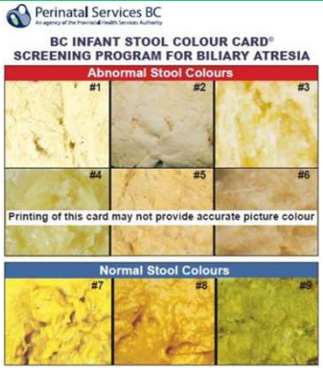
Stool Pigment Charts



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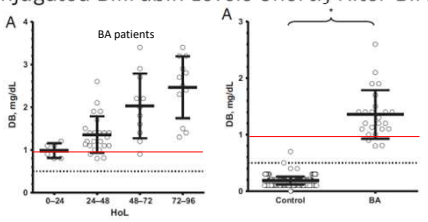
Direct bilirubin at Birth

Patients With Biliary Atresia Have Elevated Direct/ Conjugated Bilirubin Levels Shortly After Birth



- 34 patients with BA, assessing direct/conjugated bilirubin versus controls
- Statistically higher direct bilirubin by 24 hrs of life, increasing over time
- SENSITIVE screening tool
- **Argument to screen ALL babies with a direct bilirubin for earlier detection**

Harpavat et al. *Pediatrics*, 2011.

PEDIATRICS

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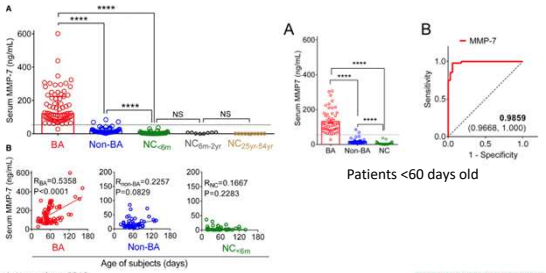
MMP-7

- Endopeptidase, remodel extracellular matrix, liver regeneration, antifibrotic/ profibrotic
- Evidence of serum marker- elevation is sensitive and specific for BA
- Unclear role in the newborn period, timing and ideal cutoffs



Patients <60 days old

Yang et al. *Hepatology*, 2018.

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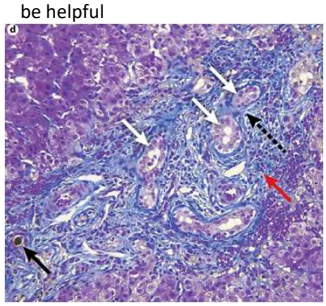
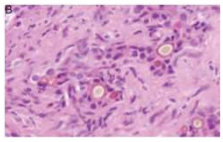
BA- Liver Biopsy

- If picture is unclear and patient presents early, liver biopsy can be helpful





-bile plugging
-bile duct proliferation
-inflammation
-portal fibrosis

Fawaz et al. *JPGN*, 2017. Feldman et al. *Nat Rev Gastroenterol Hepatol*, 2019.

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Biliary Atresia- Diagnostic Fallacies

- The parents said the stool was pigmented so it's not BA-
  - **FALSE**: Parent report of stool color, especially when mixed with urine, is often unreliable
- Patient had documented dark meconium so it's not BA-
  - **FALSE:** Does not rule out BA
- The patient had a normal abdominal US so it's not BA
  - **FALSE:** US can not reliably diagnose or exclude BA
- I ordered a HIDA (hepatobiliary iminodiacetic acid) scan and it did not excrete, so the patient has BA
  - **FALSE:** A non-excreting HIDA scan is not diagnostic for BA, though an excreting HIDA provides evidence against BA
- Liver biopsy likewise provides evidence for or against BA but is not perfect and findings are dependent on patient age

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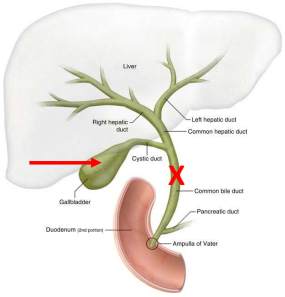
BA- Definitive Diagnosis and Management

- If suspicious for BA, definitive diagnosis is via intraoperative cholangiogram



https://radiologykey.com/the-biliary-tree/

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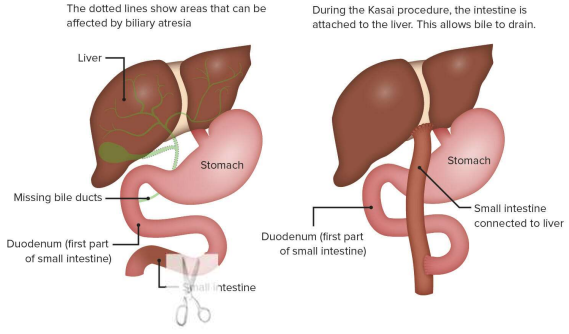
Kasai Portoenterostomy



Oiseth, S et al. *Lecturio.com*. 2022.

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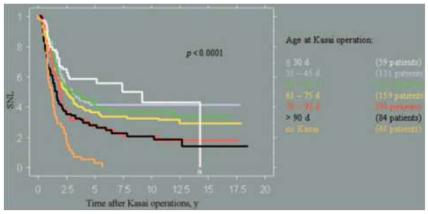
Kasai- Timing is Key

- French study, 743 patients with BA (later French study >1400, same results)
- Best long-term results (survival without transplant) if Kasai completed <30 days. BUT median around 60 days.
- Patients with Kasai >90 days had only 13% chance of surviving with native liver until adolescence



Serinet et al. *Pediatrics*, 2009.

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Cholestasis Etiology- Clues and Testing

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Clues to Underlying Causes of Cholestasis

Red flag	Disease
Prenatal history	
Ultrasonography abnormality	Choledochal cyst, cystic biliary atresia or gallstone
Cholestasis of pregnancy	PFIC or mitochondrial disease
Acute fatty liver of pregnancy	LCHAD
Maternal infection during pregnancy	Congenital infection
Physical finding	
Alcoholic stool	Biliary atresia, choledochal cyst, gallstone or biliary sludge
Palpable mass in the right upper quadrant	Choledochal cyst
Heart murmur	Alagille syndrome or biliary atresia
Butterfly vertebrae	Alagille syndrome
Ascites	Spontaneous perforation of the bile duct
Dysmorphic facies	Alagille syndrome, Zellweger syndrome or chromosomal abnormality
Microcephaly	Congenital infection
Posterior embryotoxon	Alagille syndrome
Chorioretinitis	Congenital infection
Cataracts	Congenital infection or galactosaemia
Vision or eye movement abnormalities	Septo-optic dysplasia with panhypopituitarism
Splenomegaly	Niemann–Pick disease type C
Lax skin	Arthrogryposis
Limb or long bone abnormalities	Arthrogryposis or congenital syphilis
Purpura	Congenital infection
Hypotonia	Mitochondrial disorder or peroxisomal disorder
Neurological abnormalities (irritability, lethargy, poor feeding, hypotonia or seizures)	Sepsis, intracranial haemorrhage, metabolic and mitochondrial disorders or panhypopituitarism
Petechiae or thrombocytopenia	Congenital infection or congenital Lupus
Family history	
Early emphysema	α1-Antitrypsin deficiency
Liver disease in siblings or stillbirths	Genetic or metabolic liver disease
Consanguinity	Autosomal recessive genetic liver disease

LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; PFIC, progressive familial intrahepatic cholestasis.

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Feldman et al. *Nat Rev Gastroenterol Hepatol*, 2019.

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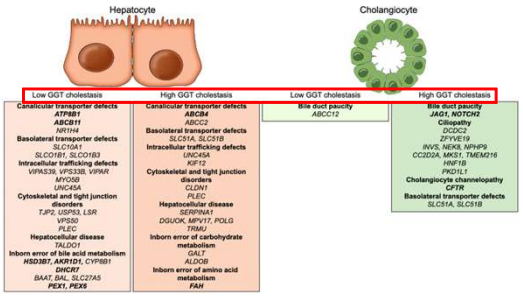
Genetic Causes and Testing



Ibrahim et al, Hepatology, 2022.

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Genetic Testing

- Evolving role of whole exome sequencing in patients with unclear genetic diagnosis

Testcholestasis.com 38

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Complications of Cholestasis

- Liver:
  - Fibrosis→ Cirrhosis
  - Portal HTN, ascites, development of varices, other complications
  - Risk of malignancy
- Nutritional:
  - Increased metabolic demand
  - Feeding difficulties- oral→ NG→ TPN
  - Fat malabsorption- high-MCT formula
  - Fat-soluble vitamin deficiencies (D,E, K, A, supplement in absorbable micelle)
  - Altered gut microbiome
- Systemic:
  - Pruritis, fatigue, cardiac or renal dysfunction, etc.

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Treatments- Ursodeoxycholic acid

- Ursodiol or UDCA
- Naturally occurring bile acid. Benign.
- Prescribed to promote bile flow
- Also used to help dissolve cholesterol gallstones
- Used frequently, though NOT a magic bullet for cholestatic diseases or associated symptoms
- Norursodeoxycholic acid (norUDCA), a derivative of UDCA, is promising alternative in clinical trials.

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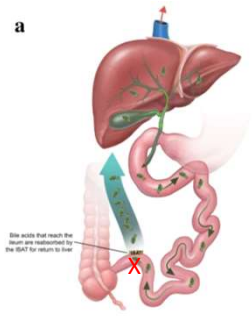
IBAT inhibitors



- Pruritis/itching in cholestasis can be unremitting.
- Limited efficacy of older medications (Rifampin, Ursodiol, antihistamines)
- Blockage of ileal bile acid transporters (IBAT's) prevents bile acids from returning to liver via enterohepatic circulation
- Multiple drugs have been created, FDA approval for treatment of pruritis in PFIC, Alagille
- Potential role in decreasing/ delaying hepatotoxicity and cholangiopathy in chronic liver diseases, still under investigation

Karpen et al, *Hepatology International*, 2020.

Children's Healthcare of Atlanta 41

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Outpatient Calls

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NICU Cholestasis Follow-up #1

- 4-week-old, ex-36 weeker, presenting to clinic for follow-up
- 3-week NICU course for feeding difficulties, mild cholestasis presumed to be due to prematurity and brief TPN use
  - DOL #2: Tbili 4.5, Dbili 0.4
  - DOL #21 (NICU discharge): Tbili 5.3, Dbili 3.6, AST 110, ALT 175
  - DOL #28 (today): Tbili 4.7, Dbili 3.7, AST 125, ALT 210, GGT 125, INR 1.0
- Stools pigmented by history, not visualized.
- **Question**: Is this Normal? What do I do?

  Answer: No. Call/ referral to hepatology for further work-up.
- **Question:** Is this BA?

  Answer: Unlikely, but not clear (normal direct bilirubin at birth, pigmented stools by history).
- **Investigation:** Admitted, undergoes liver biopsy- not concerning for BA.
  - Liver enzymes persistently elevated, no evidence of improvement.
  - A1AT phenotype sent- normal (MM). Urine CMV sent- returned positive. No other signs of CMV infection. Patient treated with valganciclovir, and labs improve over time.

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NICU Cholestasis Follow-up #2

- 3-month-old, ex-30 weeker, history of NEC requiring prolonged TPN use, mild neonatal cholestasis in NICU, resolving by time of discharge
- Seen for first follow-up at PCP since leaving NICU
- Patient now doing well clinically, fully PO fed, gaining weight
- Last inpatient labs: Tbili 4.2, Dbili 0.8, GGT 90, AST 30, ALT 27
- Today's labs: Tbili 1.9, Dbili 0.5, GGT 80, AST 27, ALT 26
- **Question**: The portion of bilirubin that's direct (Dbili/Tbili) increased from 19% to 26%. Should I be concerned?

  Answer: No. Everything is improving, can take several weeks for labs to fully normalize.

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Toddler with a White Stool

- 2-year-old, previously healthy, with prior normal stools.
- Recovering from rhinovirus infection, otherwise at baseline. Yesterday, his stools turned white (and mom has pictures).
- **Question:** Is this BA? What should I do?

  -Answer: No, this is not BA. BA is congenital, does not newly present in a toddler/ older child.

  -An intermittent pale stool can occur in childhood, especially in the setting of illness.

  -If persisting, this warrants at least a basic investigation (CBC-diff, CMP, Dbili, GGT at minimum) but can be normal and resolve within a few days.

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The Jaundiced Teenager

- 15-year-old Black male, previously healthy
- Developed gastroenteritis this week. Mom noticed his eyes started turning yellow. Feels fine now.
- Labs sent PCP:
  - Tbili 3.2, Dbili 0.3, GGT 20, AST 21, ALT 30
  - Hgb 13.2, MCV 85. Platelets 315.
  - INR 1.0
- **Question**: What is going on? What should I do?

  Answer: Most likely diagnosis is Gilbert's. Highly prevalent in AA. Rest of labs are reassuring. No evidence of cholestasis (normal Dbili, normal GGT). No evidence of hemolysis. Benign, genetic diagnosis is not needed unless to provide reassurance to family.

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Summary and General Recommendations

- In a persistently jaundiced infant, send a CBC-diff, CMP, direct bilirubin, and GGT at minimum
  - At 2 weeks if formula fed, by 3 weeks if Breast fed
- Direct bilirubin >1.0 mg/dL is considered pathologic, should be discussed with hepatology/ GI
- Thorough physical exam is vital, assessing for HSM, ascites, cardiac abnormalities, nutritional status, ill-appearance.
- Important to visualize stool directly if able (or have parents take picture)- don't their word that it looks normal!
- Confirm patient's NBS is normal (CF, thyroid, Hgb SS, etc.)

When in doubt, call us! We are always happy to talk through things.

Fawaz et al, *JPGN*, 2017.

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