APPROACH TO ELEVATED LIVER ENZYMES IN CHILDREN

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LIVER FUNCTION

- Excretory
- Synthetic
- Metabolic

- Liver function test → misnomer
- True liver function test → prothrombin time, albumin

TESTS OF LIVER FUNCTION

- Liver injury: liver enzymes ALT, AST
- Impaired bile flow or cholestasis: Alk phos, GGT, Bilirubin
- Impaired synthetic function: Albumin, PT, PTT, INR, Factor VII and V
- Metabolic functions: Ammonia

LIMITATIONS OF LIVER TESTS

1) Normal test ≠ patient is free of liver disease (e.g. compensated cirrhosis)

2) Not specific for liver dysfunction

3) Only indicates a liver disorder, not a specific etiology

AMINOTRANSFERASES: AST & ALT

- Indicate liver injury
- AST
  - Enzyme present in both cytosol and mitochondria
  - Found in liver, heart & skeletal muscles, kidney, brain, pancreas, lungs, leukocytes and RBCs
- ALT
  - Enzyme found in cytosol and present at highest concentrations in the liver
  - More specific to liver

IF AST DISPROPORTIONATELY HIGH

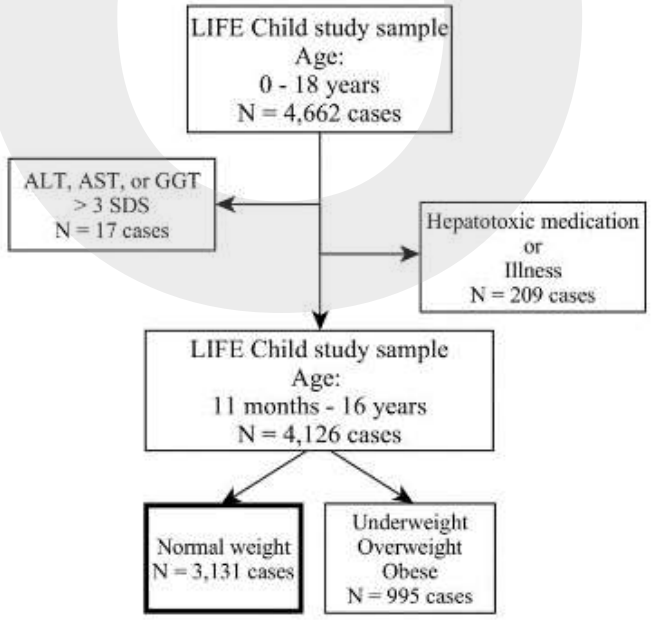
Consider:

- Hemolysis
- Rhabdomyolysis
- Myopathy
- Myocardial disease
- Recent rigorous exercise
- Macro-AST up to 30% of children with isolated high AST

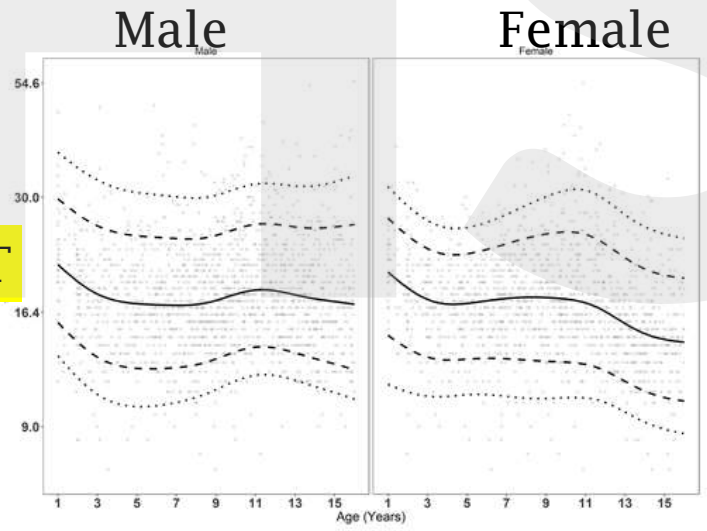
If elevated AST, consider checking haptoglobin, LDH, creatine kinase, and aldolase

NORMAL TRANSAMINASE LEVELS

Bussler et al.
- New pediatric percentiles of liver enzyme serum levels (ALT, AST, GGT) + effects of age, sex, BMI, and pubertal stage

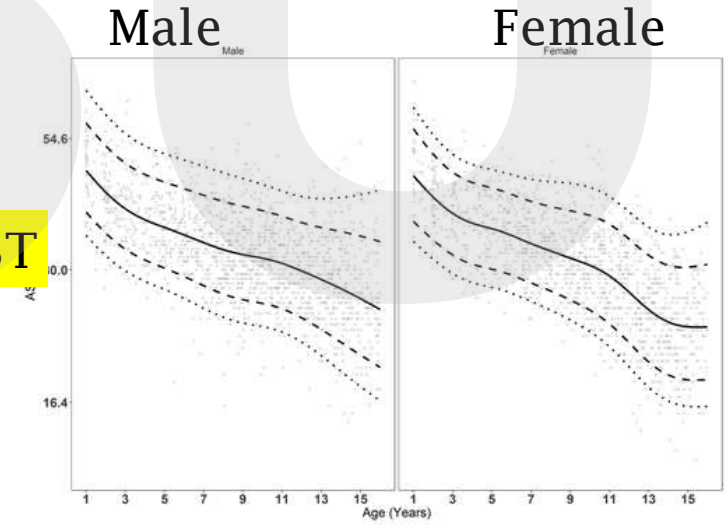


ALT

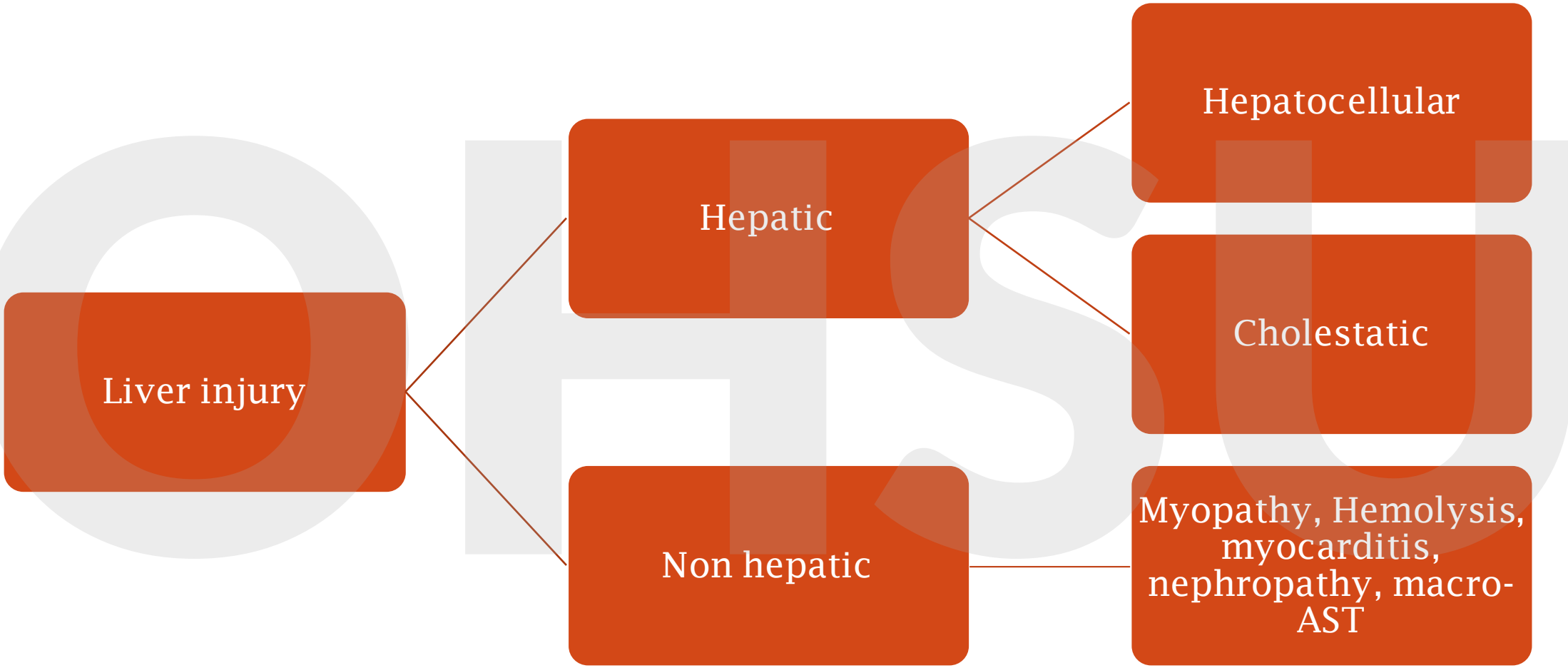


Age

AST



Age


Liver injury
Hepatic
Non hepatic
Hepatocellular
Cholestatic
Myopathy, Hemolysis, myocarditis, nephropathy, macro-AST

HEPATOCELLULAR INJURY

- Disproportionate elevation of AST/ALT compared to Alkaline phosphatase (opposite is true with biliary injury)
  - AST 120 IU/mL (normal ≤40 IU/mL)
  - Alkaline phosphatase of 130 IU/mL (normal ≤120 IU/mL)

- Viral hepatitis, Autoimmune hepatitis, NAFLD, Wilson's disease, Alpha 1 antitrypsin deficiency, metabolic disease, drugs, Celiac, IBD

ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries

Paul Y. Kwo, MD, FACG, FAASLD[1], Stanley M. Cohen, MD, FACG, FAASLD[2] and Joseph K. Lim, MD, FACG, FAASLD[3]

- Mild AST and/or ALT elevation: 2–5X ULN
- Moderate AST and/or ALT elevation 5–15X ULN
- Severe AST and/or ALT elevation >15X ULN
- Massive AST and/or ALT >10,000 IU/l

If liver enzymes >500, repeat within 24 hours and get an INR

Test	Reason
Creatine kinase (CK)	Muscle injury, muscular dystrophy, other disorders
Serum albumin	Liver function
Serum bilirubin (total and direct)	
Prothrombin time (INR)	
Alkaline phosphatase (ALP)	Cholestasis, disease of the biliary system
Gamma-glutamyl transpeptidase (GGT)	
Ultrasound (ideally with Doppler) of abdomen or right upper quadrant	Assess for liver size, appearance (echogenicity, surface texture) of liver parenchyma, gallbladder wall, gallbladder or bile duct stones, obstruction/ narrowing of hepatic vessels, abdominal masses, ascites, etc.

WHEN TO ADMIT OR REFER

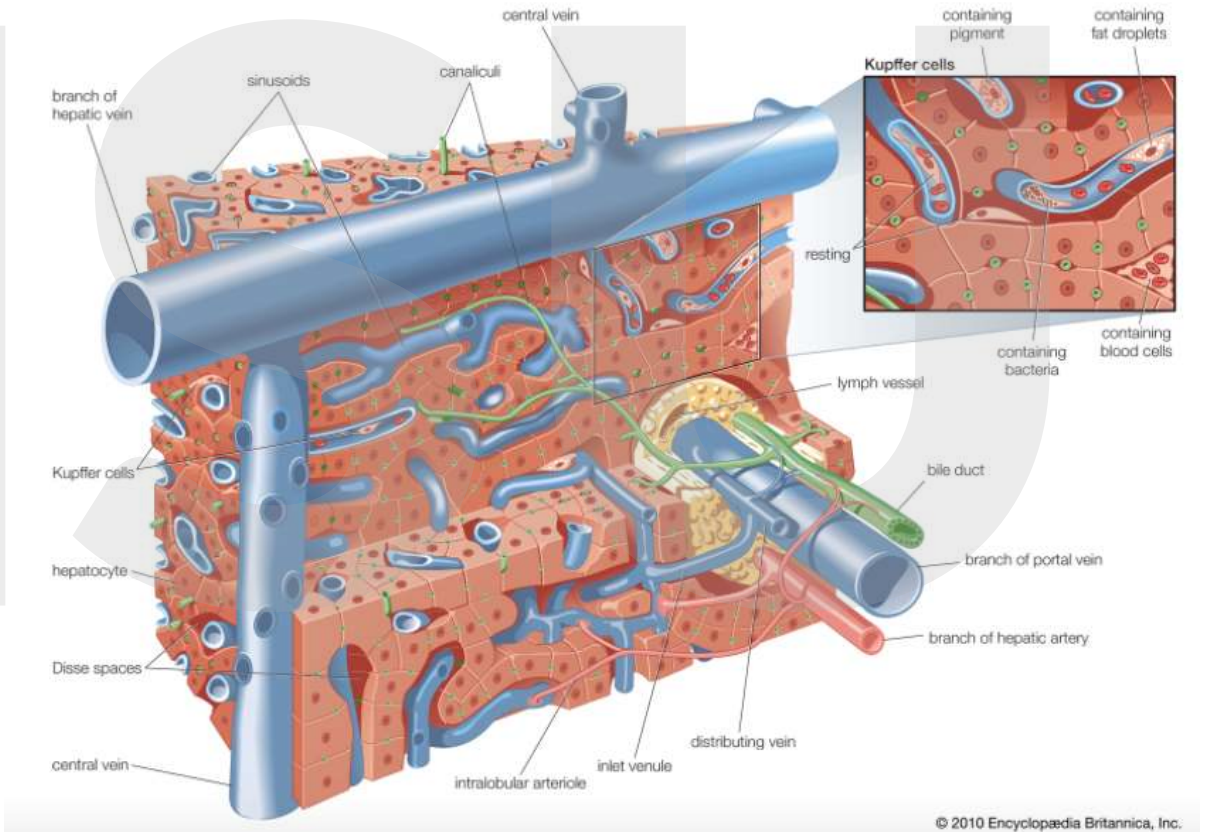
- Acute Hepatitis
  - Hepatic injury or inflammation of the liver
  - Reflected by an elevated AST and ALT level
  - Does not always indicate liver failure

- Acute liver failure
  - No evidence of prior or chronic liver disease
  - Coagulopathy unresponsive to Vitamin K
    - INR $\geq$ 1.5 with encephalopathy
    - INR $\geq$ 2
  - Admit for observation at a liver transplant center if possible

CHOLESTASIS/IMPAIRED BILE FLOW

Alkaline phosphatase

- Found in canalicular membrane of hepatocytes, osteoblasts, small intestine, kidneys, placenta, WBC
- Level varies with age – high in normal growing children or rapidly growing teens
- Differential for high ALP
  - pregnancy, familial inheritance, chronic kidney failure, Blood groups B & O, transient hyperphophatasemia
- Low ALP
  - zinc deficiency and Wilson's disease

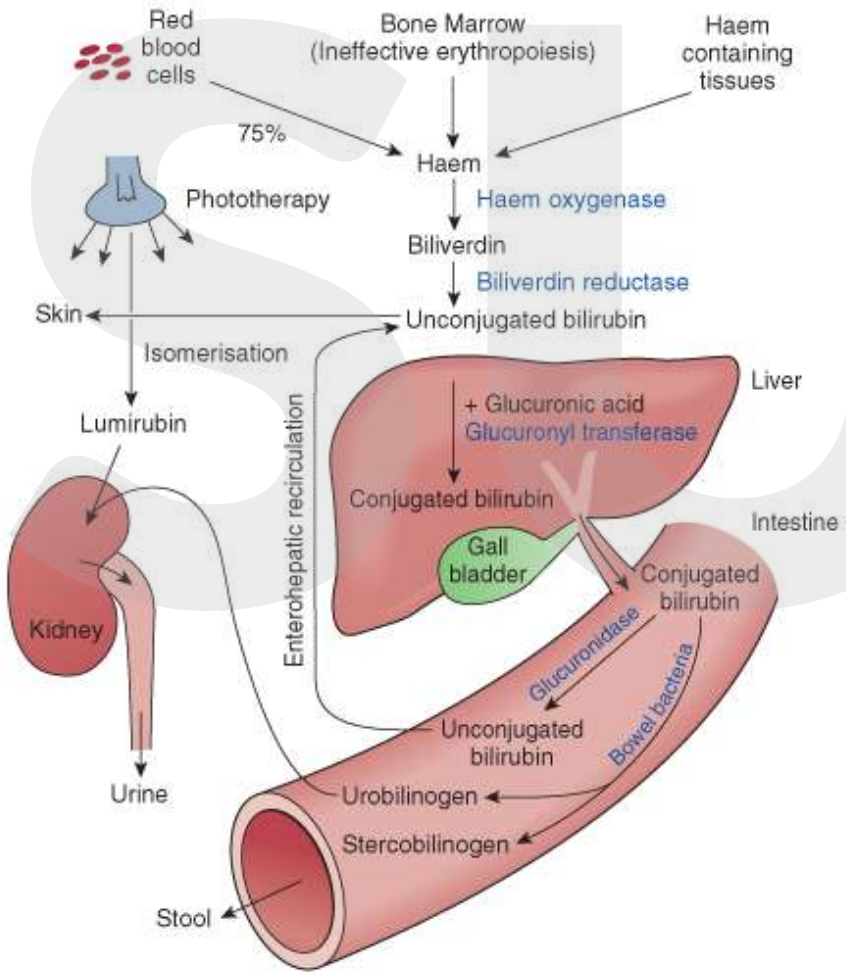


CHOLESTASIS/IMPAIRED BILE FLOW

Bilirubin

- Produced by normal breakdown of pigment-containing proteins
  - Hgb from senescent RBC
  - Myoglobin from muscle breakdown

- Unconjugated bilirubin → conjugation in liver → excreted through gut. Some reabsorbed through enterohepatic circulation → Some then excreted through kidney



BILIRUBIN DEFINITIONS

- Unconjugated bilirubin: Water-insoluble, transported by albumin, a/w toxic effects
- Conjugated bilirubin: Conjugated to glucuronic acid in the liver = bilirubin glucuronides
- Delta bilirubin: bilirubin glucuronides bound to albumin

BILIRUBIN DEFINITIONS

- Direct & conjugated often used interchangeably → not accurate
  - Direct bilirubin may include both the conjugated fraction and bilirubin bound to albumin (delta bilirubin)
- Total bilirubin = unconjugated + conjugated + delta
- Delta bilirubin can prolong direct hyperbilirubinemia while other liver tests are normalizing
  - Half life ~21 days, similar to albumin

NEONATAL CHOLESTASIS

- Evaluate for cholestasis in:
  - Any jaundiced infant at 2 weeks of age
  - Measure total and direct bilirubin

- However, breast-fed infants…
  - Who can be reliably monitored
  - Who have an otherwise normal history (no dark urine or light stools) and physical exam
  - **May return at 3 weeks of age and if jaundice persists, measure total and direct bilirubin**

DIRECT BILIRUBIN IN NEONATES

- If the Total Bilirubin is <5 mg/dL
  - Abnormal direct bilirubin is defined as >1mg/dL

- If the Total Bilirubin is >5 mg/dL
  - An abnormal direct bilirubin is defined as a value that is >20% of the total

Jaundice facts

- ~15% of neonates develop jaundice
  - 9% of breast-fed infants are jaundiced at 4 weeks
  - <0.1% of bottle-fed infants are jaundiced at 4 weeks

- Incidence of cholestatic jaundice is 1 in 2,500 infants

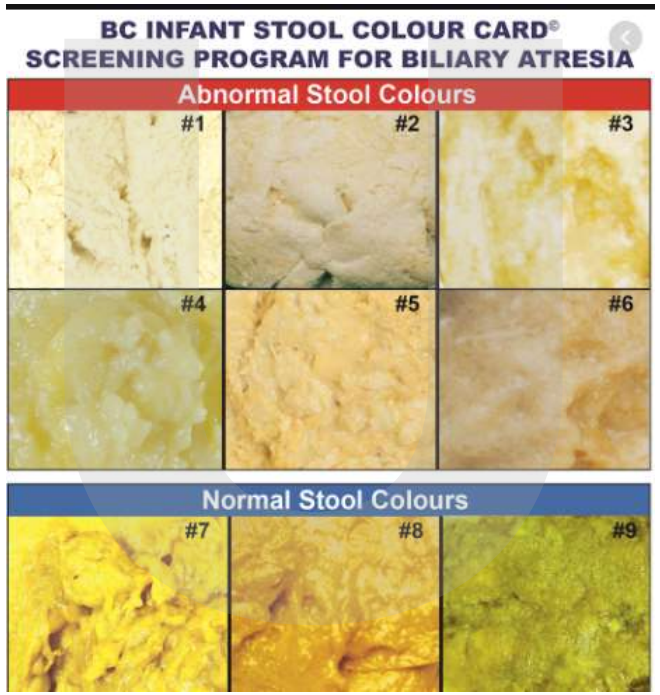
ETIOLOGIES

Most common causes of neonatal cholestasis

Diagnosis	Proportion of young infants with conjugated hyperbilirubinemia
Extrahepatic biliary atresia	25% (range 2 to 55%)
Idiopathic neonatal hepatitis	25% (range 4 to 45%)
Infectious hepatitis (eg, cytomegalovirus)	11% (range 3 to 38%)
Parenteral nutrition-associated	6% (range 7 to 30%)
Metabolic disease (eg, galactosemia, tyrosinemia)	4%
Alpha-1 antitrypsin deficiency	4%
Alagille syndrome	1%
Progressive familial intrahepatic cholestasis	1%

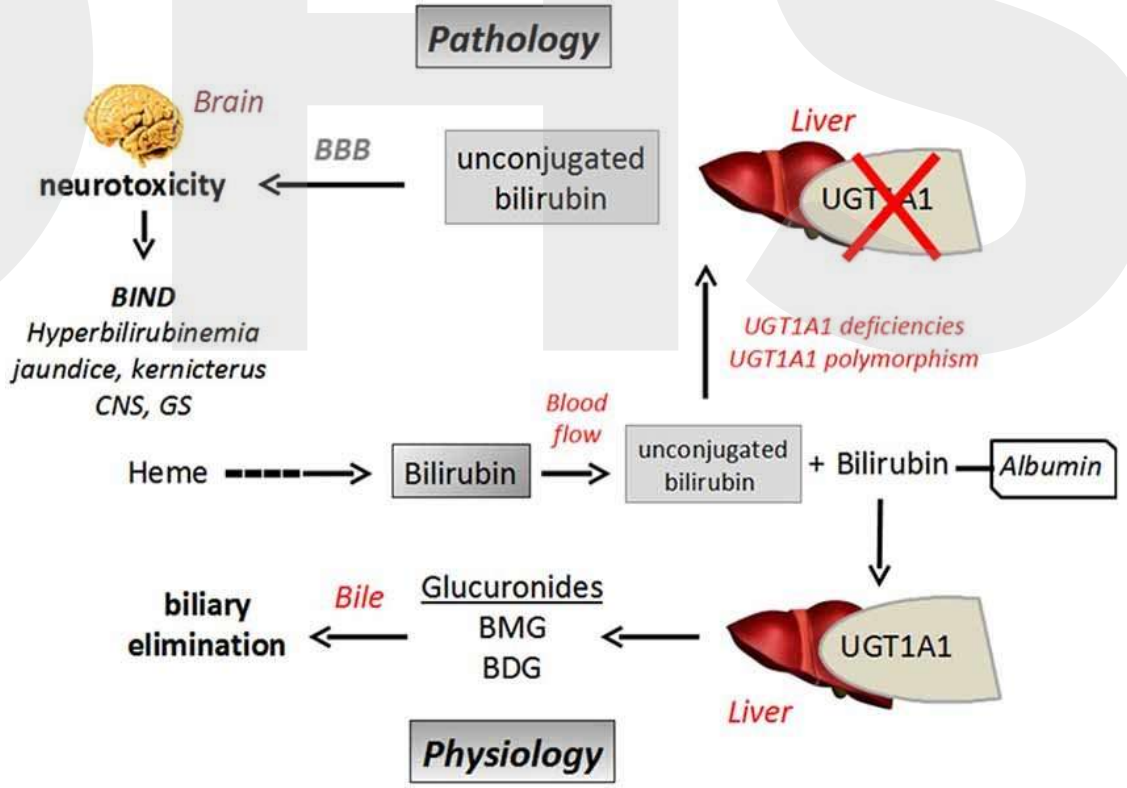
BILIARY ATRESIA

- Progressive, fibro-obliterative disorder of intra and extrahepatic bile ducts, onset within first 3 months of life → obstructive pathology (reduced bile flow)
- ***VISUALIZE stool color**
- Need to evaluate for BA if high direct bili, high GGT and pale colored stools
- Contact on-call GI physician
- Ultimately, need intra-operative cholangiogram to confirm, then proceed with Kasai hepatoportoenterostomy
- Time-sensitive → delay in Kasai = worse outcomes
  - Kasai within the first 60 days of life → 70% of patients will establish bile flow; after 90 days of life → 25% will achieve bile flow



LIVER CAUSES OF INDIRECT HYPERBILIRUBINEMIA

	UGT1A1 Activity	Serum Bilirubin
Crigler-Najjar Type 1	None	>15mg/dL
Crigler-Najjar Type 2	<10%	8-18mg/dL
Gilbert	~30%	<5mg/dL



GGT

- Found in many tissues
  - Bile ducts/gallbladder, kidney, brain
  - Heart, pancreas, spleen, seminal vesicles
- GGT levels change with age
  - Highest in premature infants
  - Declines in infancy to the normal adult GGT sometime between 6 to 9 months

NORMAL GGT

Table 8.2: Reference Normal Values for Serum γ-Glutamyltransferase by Patient Age

Patient Age	*Sex*	*U/L*
<1 mo	M, F	<385
1–2 mo	M, F	<225
2–4 mo	M, F	<135
4–7 mo	M, F	<75
7 mo–15 yr	M, F	<45
>15 yr	M	<75
>15 yr	F	<55

From the Hospital for Sick Children [37]; used with permission.

GGT INTERPRETATION

- Sensitive for detecting hepatobiliary disease, but limited by lack of specificity
  - If normal bilirubin, look for other sources of elevated GGT
- High GGT also seen with medications
  - Phenytoin and barbiturates
- GGT may increase with recovery from bile duct injury
  - Decrease in GGT may lag behind bilirubin decrease

MARKERS OF SYNTHETIC FUNCTION

- PT/INR
- Albumin
- Ammonia

PT/INR

- Clotting factors primarily made in the liver
  - Exception is Factor VIII
- Vitamin K dependent factors → II, VII, IX, X
- Short half life of clotting factors makes it a sensitive indicator for hepatic dysfunction
  - Factor VII with shortest half life of 3-5 hours
- Not all coagulopathy is indicative of hepatic dysfunction

MECHANISMS OF LIVER DISEASE THAT CAUSE ABNORMAL HEMOSTASIS

- Diminished hepatic synthesis of coagulation factors
  - V, VII, IX, X, and XI, prothrombin, and fibrinogen
- Dietary vitamin K deficiency due to inadequate intake or malabsorption
- Dysfibrinogenemia
- Enhanced fibrinolysis due to decreased synthesis of α_2-plasmin inhibitor
- Disseminated intravascular coagulation
- Thrombocytopenia due to hypersplenism

ALBUMIN

- Synthesized in liver
  - Half life around 20 days
- Decrease in albumin could indicate hepatic dysfunction
- Other etiologies of hypoalbuminemia include:
  - Malnutrition or inadequate protein intake
  - Protein loss → nephrotic syndrome, malabsorption, protein losing enteropathy
  - Chronic inflammation

AMMONIA

- Ammonia - waste product from protein catabolism
  - Produced predominantly by colonic bacterial urease
  - 80% NH_3 removed in first hepatic pass of portal blood
  - Processed in the liver and converted to urea

- Elevated ammonia levels can indicate:
  - Increased colonic production
  - Porto-systemic shunting (extrahepatic or intrahepatic)
  - Generalized liver failure
  - Isolated defects of urea cycle enzymes
  - Reye syndrome, valproate, fatty acid oxidation, etc

AMMONIA LIMITATIONS

- Human factors can cause falsely elevated ammonia levels
  - Deamination generates ammonia in freshly collected blood samples
  - Traumatic collection or hemolysis
  - Excessive fist clenching

- Obtain ammonia from free flowing lab draw
  - Store immediately on ice

SUMMARY

- ALT, AST → liver injury
- Alk phos, GGT, Bilirubin → impaired bile flow
- Albumin, INR → impaired synthetic function

- If very high liver enzymes → should also obtain CBC, GGT, fractionatde bilirubin (if high total bili), INR + repeat labs within 24h
- If >INR 2 (or >1.5 with encephalopathy) → admit for observation, ideally at a liver transplant center
- Neonatal cholestasis – evaluate for pigmented stools! BA is urgent and time sensitive
- When in doubt, call your friendly, neighborhood GI colleague :)

THANK YOU!