When to Worry about Elevated AST/ALT?

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Disclosures

- Mirum – Advisory board
- Albireo – Advisory board

Objectives

- Review of interpretation of liver function tests
- Overview of diagnostic approach to elevated liver enzymes
- Discuss management of select etiologies of elevated liver enzymes

Test of Liver Function

- Releases from damaged hepatocytes
  - AST, ALT
  - LDH
- Impaired bile flow or transport
  - Bilirubin
  - GGT
  - Alkaline phosphatase
- Synthetic Function
  - INR
  - Albumin
  - Cholesterol
  - Ammonia

Liver Biochemical Test Limitations

- Screening laboratory tests may lack sensitivity
  - Normal test does not ensure that the patient is free of liver disease
- Tests are not specific for liver dysfunction
- Liver chemistry tests rarely provide a specific diagnosis

Aminotransferases (AST & ALT)

- Most sensitive marker for acute liver injury
- AST
  - Enzyme is located in cytosol and mitochondria
  - Found in hepatocytes as well as cardiac & skeletal muscle, kidney, brain, erythrocytes
- ALT
  - Cytoplasmic enzyme
  - Found primarily in hepatocytes

Why we should worry about elevated AST/ALT

- 2005 study of 425 children with isolated elevated aminotransferases without typical symptoms
  - 12% found to have underlying genetic disease

Table 1. Genetic disorders identified in 51 children with hypertransaminasemia

Genetic disorders	No. of patients (males)	Median age, in years, at diagnosis (range)
Wilson disease	18 (13)	7.5 (4.4–14.6)
Muscular dystrophy	14 (12)	2.2 (1.3–5)
Alpha-1-antitrypsin deficiency	4 (2)	4.6 (2.5–7)
Alagille syndrome	4 (0)	4.1 (1–8.5)
Hereditary fructose intolerance	4 (2)	2.4 (1.8–3.5)
Glycogen storage disease[a]	3 (2)	5 (4–8)
Ornithine transcarbamylase deficiency	2 (0)	2.5 (2–3)
Shwachman's syndrome	2 (2)	2.5 (2–3)

[a] Glycogenosis IX

Iorio et al. 2005

What is a Normal AST and ALT?

Table 1. Serum analytes of 4326 subjects in different age groups*

	3–6 yr (n=2029)	9–12 yr (n=1624)	13–15 yr (n=325)	≥20 yr (n=348)	$p^{\dagger}$
Analytes					
ALT (IU/L)	12.66±11.32	15.88±13.68	15.94±13.77	25.33±23.73	<0.01
Glucose (mg/dL)	76.15±12.13	81.52±11.0	81.59±10.64	85.33±20.48	<0.01
BUN (mg/dL)	13.19±2.91	12.15±2.57	11.48±2.42	13.88±3.48	<0.01
Creatinine (mg/dL)	0.55±0.12	0.81±0.16	0.91±0.14	0.98±0.24	<0.01
B/C ratio	24.74±6.97	15.52±4.52	13.83±2.96	13.49±4.70	<0.01

*Data presented as mean±standard deviation; †children (3–15 years) versus adults (≥20 years), analysed by one-way analysis of variance. ALT=alanine aminotransferase; BUN=blood urea nitrogen; B/C=BUN/creatinine.

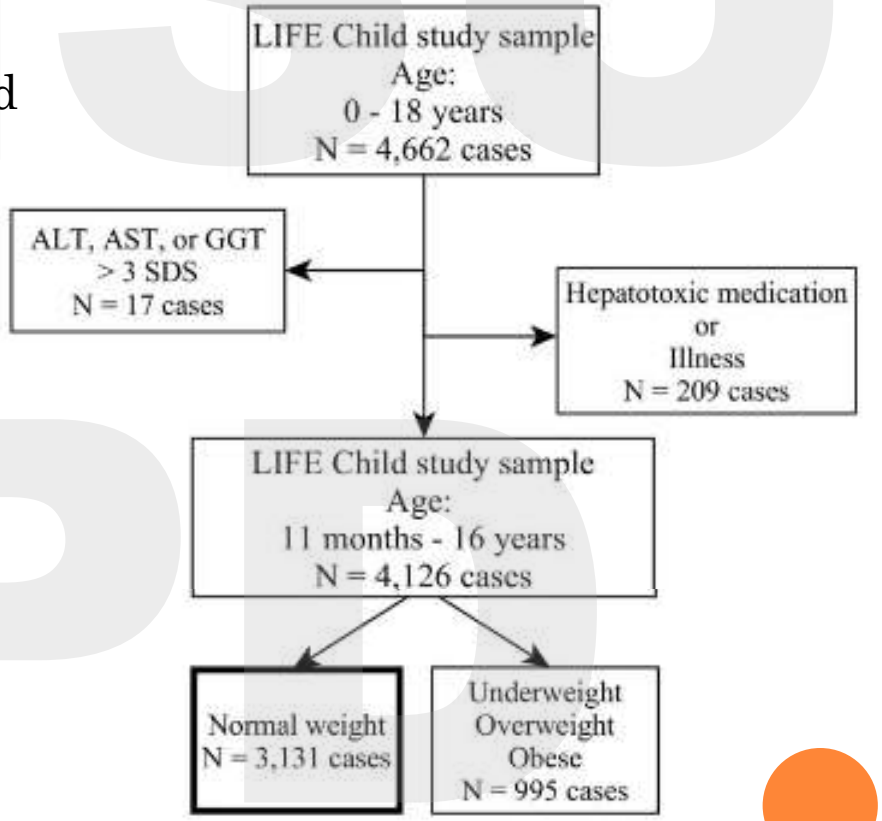
Lai DS et al. JFMA 2009

Gender	Age Range (Years)	ALT (U/L)
Female	0–11	<29
	12–17	<25
	≥18	<33
Male	0–11	<30
	12–17	<31
	≥18	<45

LabCorp 2013

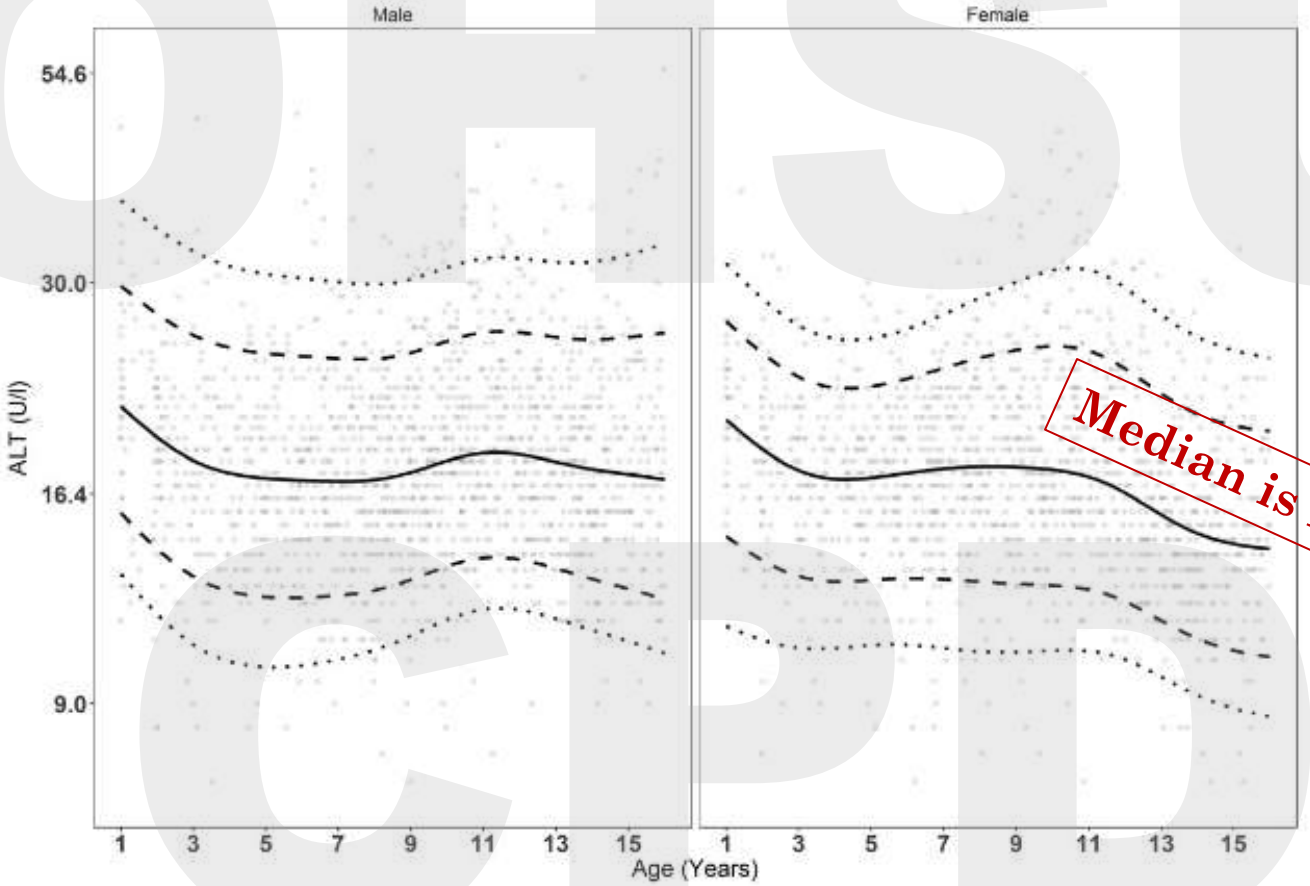
'New' Normal AST and ALT Values

- Previous normal values of AST/ALT thought to be high
  - Due to prevalence of obesity and nonalcoholic fatty liver disease
- Bussler et al 2018
  - Clarified the effects of sex, age, BMI, and puberty on transaminases



Bussler et al 2018

Age & Sex-Related %-tiles of **ALT**



Median is in the 20s

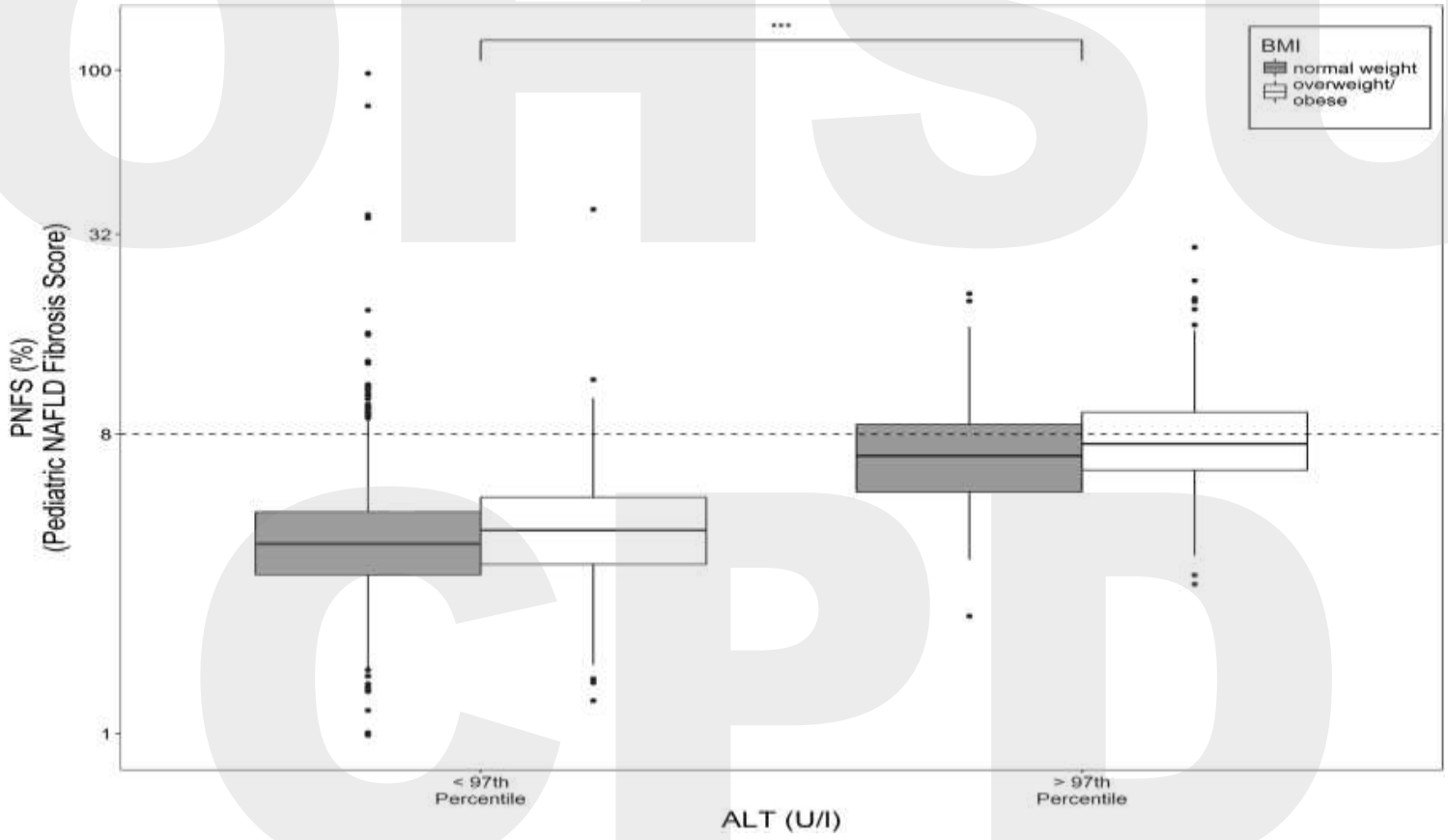
FIG. 2. Age- and sex-related percentiles of alanine aminotransferase (ALT). Smoothed percentile curves for alanine aminotransferase (ALT) (U/l, y-axis: log scale) in males/females over the age (11 months to 16.0 years) based on a normal weight reference population from a LIFE Child study sample: (N = 3,131, N_{Male} = 1,664, N_{Female} = 1,467. The 3rd (P3), 10th (P10), 50th (P50, median), 90th (P90) and 97th (P97) percentiles are shown.

Bussler et al 2018

Factors Influencing AST, ALT, and GGT

- Sex
  - Boys with higher mean levels of ALT, AST, and GGT
  - Effect is strongest for AST
- Puberty
  - Significantly higher ALT and GGT during puberty
  - AST negatively associated with puberty
- BMI
  - Positive correlation with ALT and GGT
  - Weak negative association AST

Positive Correlation Between BMI and ALT



- Elevated ALT and obesity influence the risk for liver fibrosis

Bussler et al 2018

What AST and ALT Should Prompt Additional Work-Up?

- Anything above the reference range?
- >40 for either AST and ALT
- >50 for either AST and ALT
- >2 times the upper limit of normal
- Something else?

Etiologies of Transaminitis

Hepatic

- Infectious (Viral)
- Autoimmune liver disease
  - AIH, PSC
- Metabolic
  - Non-alcoholic fatty liver disease
  - Alpha-1 antitrypsin deficiency
  - Wilson Disease
- Toxic
  - Drugs and alcohol
- Other
  - Celiac disease
  - Inflammatory bowel disease
  - Cystic fibrosis

Non-Hepatic

- Myopathies
  - Duchenne/Becker muscular dystrophy
- Hemolytic disorders
- Macro - AST
- Myocardiopathies
- Nephropathies

Differential diagnosis of mildly and moderately elevated serum aminotransferases (<15 times upper limit of normal)

Hepatic disease		Nonhepatic disease
ALT predominant (AST/ALT <1)	**AST predominant (AST/ALT ≥1)**	
Drug-induced liver injury	Alcohol-associated hepatitis	Muscle injury (strenuous exercise, myopathy)
Chronic viral hepatitis (HBV, HCV)	Cirrhosis due to viral hepatitis or NAFLD	Adrenal insufficiency
Occupational, toxin-related hepatocellular damage	Wilson disease	Myocardial infarction, heart failure
Autoimmune hepatitis		Anorexia nervosa
NAFLD		Thyroid disease
Genetic disorders ▪ Wilson disease ▪ Hemochromatosis ▪ Alpha-1 antitrypsin deficiency		Celiac disease
Congestive hepatopathy		Macro-AST
Malignant infiltration of the liver		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic fatty liver disease.

Evaluation of Isolated **Mild Chronic** Elevation of Aminotransferases

Mild = <2x ULN,
Chronic =< 4 weeks

	Initial Evaluation	2nd Line	3rd Line
Neonate			
Toddler			
Adolescent			

- Alpha-1 antitrypsin level
- Autoimmune hepatitis labs
- BMP
- CBC
- Celiac serologies
- Ceruloplasmin
- CMV
- Creatinine Kinase
- EBV serologies
- Echocardiogram
- Haptoglobin
- Hepatitis A serologies
- Hepatitis B serologies
- Hepatitis C serologies
- HFE mutation analysis
- INR
- Lactate Dehydrogenase
- Lactate / Pyruvate
- Liver Biopsy
- Neonatal Cholestasis Panel
- Pi typing
- TSH
- Ultrasound
- Ultrasound elastography
- Other ?

Evaluation of Isolated **Mild Chronic** Elevation of Aminotransferases

	Initial Evaluation	2nd Line	3rd Line
Neonate	A1AT / Pi typing Viral by hx CBC, INR, BMP U/S	LDH Lactate/Pyruvate AIH HFE by hx	CK Liver bx if persistent
Toddler	A1AT / Pi typing Viral by hx U/S	AIH BMP, LDH Lactate/Pyruvate HFE by hx	CK ?Celiac Liver bx if persistent
Adolescent	A1AT / Pi typing Ceruloplasmin Viral by hx AIH, U/S	Celiac HFE by hx	Liver bx if persistent

What would you do if you got an ultrasound first in an adolescent and it shows steatosis?

Suggested Approach for Hepatic Steatosis with elevated AST/ALT

- Depends on degree of transaminase elevation & patient factors
- Assess for common causes of transaminitis
- Empiric trail of dietary modifications and exercise
  - Repeat LFT in 3 months
  - Additional work-up for other etiologies
  - Potential role of liver biopsy

Patterns of AST and ALT Elevation

- Acute viral hepatitis or toxin-related hepatitis with jaundice
  - AST and ALT >25x ULN
- Ischemic hepatitis
  - AST and ALT >50x ULN (LDH also markedly elevated)
- Chronic hepatitis C
  - Variable, typically < 2x ULN, rarely >10x ULN
- Chronic hepatitis B
  - Variable, may be normal in inactive carriers
  - Typically <2x ULN, rarely >10x ULN
- Alcoholic fatty liver disease
  - AST < 8x ULN; ALT <5x ULN
- Nonalcoholic fatty liver disease
  - AST and ALT <4x ULN

Etiologies to consider if Disproportionately elevated in AST

- Hemolysis
- Myopathic process
- Acute rhabdomyolysis
- Recent vigorous physical activity
- Macro-AST → up to 30% of children with isolated high AST

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

AST:ALT Ratio > 2:1

- Alcoholism: Deficient pyridoxal-5 phosphate (cofactor in ALT production)
- Cirrhosis: Decreased portal blood flow → decreased sinusoidal AST uptake
- Fulminant Wilson Disease (AST>ALT 4:1)
- Enterovirus infection

If AST or ALT > 500

Repeat LFTs within 24-48 Hours & check PT/INR

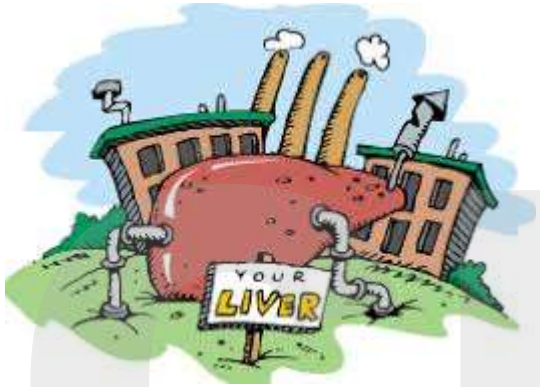
Test	Reason
Creatine kinase (CK)	Muscle injury, muscular dystrophy, other disorders
Serum albumin	Liver function
Serum bilirubin (total and direct)	
Prothrombin time (INR)	
Alkaline phosphatase (ALP)	Cholestasis, disease of the biliary system
Gamma-glutamyl transpeptidase (GGT)	
Ultrasound (ideally with 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 / Refer for Hepatitis

- 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
    - PT$\geq$ 15 or INR $\geq$ 1.5 with encephalopathy
    - PT $\geq$ 20 or INR $\geq$ 2
  - Admit for observation at a liver transplant center

Questions?



OHSU CPD

Biochemical Markers of Impaired bile flow or transport

Bilirubin

Alkaline Phosphatase

GGT

Elevated Direct Bilirubin in Neonatal Cholestasis

- 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

Bilirubin and Jaundice Tidbits

- Percentage of neonates with bilirubin >5mg/dL
  - Term – 60%
  - Pre-term – 80%
- ~6% of term neonates will have bilirubin >15mg/dL
- Around 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

Inherited Disorders of Bilirubin Metabolism

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

Alkaline Phosphatase

- Primary source are bile canaliculi and osteoblasts
  - Other sources include proximal renal tubules, small intestine, WBC, and placenta
- Elevated alkaline phosphatase in cholestatic infant could be from biliary obstruction or bone
  - Check alkaline phosphatase isoenzymes to distinguish between these two causes

Etiologies of Isolated Elevated Alkaline Phosphatase

- An 18 month old
  - Transient Hyperphosphatemia of childhood
    - Lasts 8-12 weeks
    - AP is up to 10x normal
- A 12 year old boy
  - Normal elevations from bone/growth
- A 24 year old woman
  - Pregnancy
  - Blood type B or O → see influx of intestinal alkaline phosphatase after fatty meal

Causes of Low Alkaline Phosphatase

- Zinc deficiency
  - Zinc is a cofactor in AP synthesis
  - Can see in acrodermatitis enteropathica, Crohn's disease
- Fulminant Wilson Disease

Gamma Glutamyl Transferase (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 Values

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 Summary

- 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
  - Valproate cannot induce GGT
- GGT may increase with recovery from bile duct injury
  - Decrease in GGT may lag behind bilirubin decrease

Questions?