OneGI

SECOND ANNUAL GI & LIVER *Summit*

Work Up for Abnormal Liver Functions

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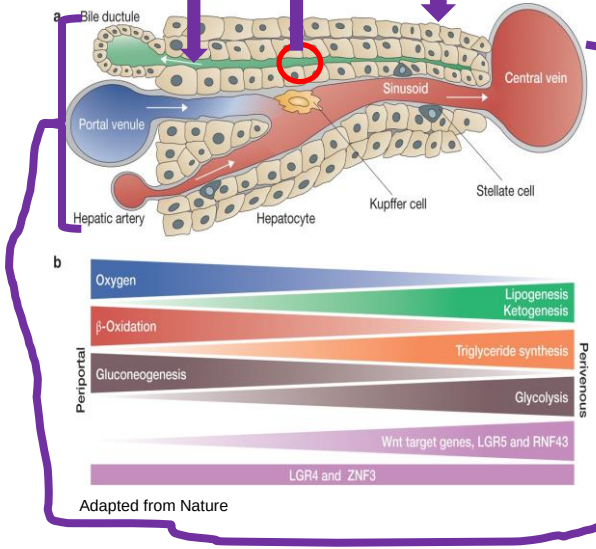
Liver Function Tests in Relation to Anatomy

Multiple Proteins
Pediatric Cholestatic disease

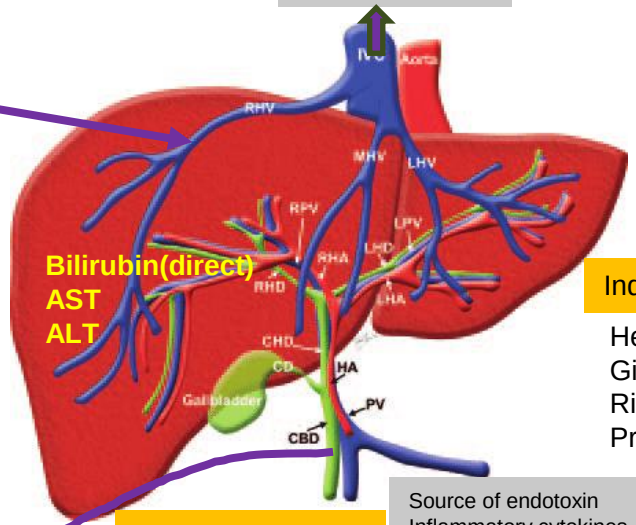
ALP/Bilirubin

AST and ALT



Adapted from Nature

Right Atrium



Bilirubin(direct)
AST
ALT

Indirect bilirubin

Hemolysis,
Gilbert syndrome
Rifampin
Probenecid

Source of endotoxin
Inflammatory cytokines

ALP
(Direct)Bilirubin

ALP (alkaline phosphatase) – liver and bone disorders
ALP and Bilirubin – impaired bile production or flow inside or outside Bile ducts
Gall Bladder disease should not cause ALP of Bilirubin Increase
Some disease affects both extrahepatic and intrahepatic bile duct (PSC Overlap)

Liver “Function” Tests for Prognosis/Staging

- Bilirubin, Albumin, and INR = Liver “Synthetic” Function = Liver Failure
- Platelet count” < 150 suggests Portal Hypertension
- Serum Creatinine and Serum Sodium: Prognostic markers in severe portal Hypertension and Ascites

Initial Determination: Hepatocellular Injury vs Cholestatic Process

- The R value (also known as the R factor)
- **R value = (ALT ÷ ULN ALT) / (Alk Phos ÷ ULN Alk Phos)**

- ≥5: Hepatocellular injury: Viral Hepatitis, AIH, Ischemia
- >2 to <5: Mixed pattern –AIH with Overlap or DILI or ACR
- ≤2: Cholestatic injury

ALT Normal values 29 to 33 units/L for males and 19 to 25 units/L for female

Alk PO4 Normal values Male: 45 to 115 units/L Female: 30 to 100 units/L

AIH Autoimmune Hepatitis DILI = Drug Induced Liver Injury ACR Acute Cellular Rejection of transplanted Liver.

Abnormal Transaminases
Inflammatory and/or Necrosis Process in the Liver

1. Random Fluctuations are not uncommon
2. Do Not Ignore but Repeat before further testing
3. Advanced Liver Disease can be seen even with normal ALT and AST
4. “Unexplained” increase in ALT and AST can be seen – follow fibrosis score
5. Macro AST High AST normal ALT No Liver Disease or Muscle disease

Aspartate aminotransferase (AST) can exist as a macroenzyme by forming a complex with an immunoglobulin

Abnormal Transaminases Clinical Pearls

AST/ALT RATIO

AST > ALT (AST > 2 times ALT, but < 500): Alcoholic Hepatitis

AST > ALT (AST < 1 times but under 100) Cirrhosis- Low Platelets

AST > ALT (AST > 2 times but low Alk PO4 = Acute Liver Failures due to Wilson/s disease

AST >>> ALT (AST > 1000) Normal Bilirubin = Muscle injury (heat stroke) get CPK

Very high ALT

ALT > 1000 ; Acute hepatitis (Bilirubin is elevated)

ALT 5000 Acetaminophen Overdosage “Very High INR” and Bilirubin,

Ischemia with shock liver Bilirubin and INR elevated

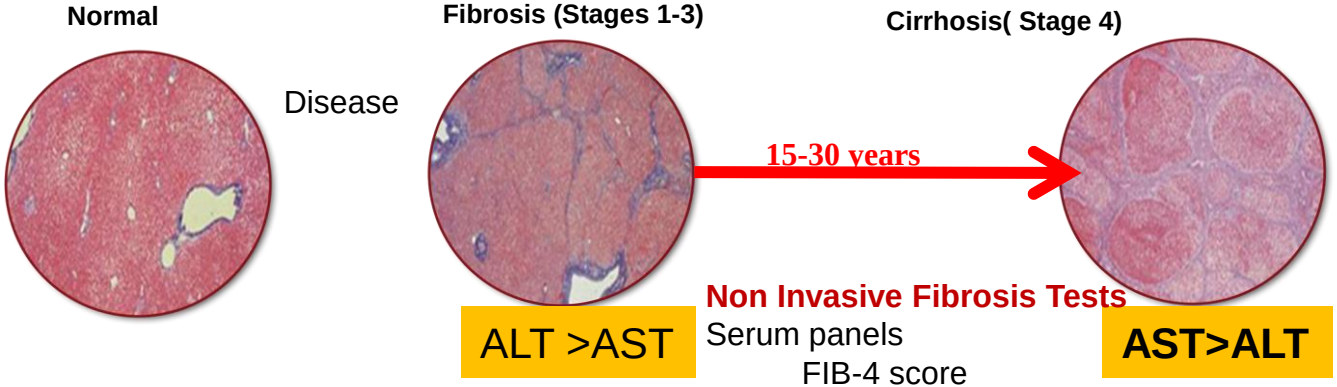
Chronic “Hepatitis” Elevated ALT w/u

- Viral (HBsAg, HCV Antibody)
- Autoimmune (ANA , ASMA, IgG levels)
- Metabolic associated Steatotic Liver (Lipid Panel, HOMA Score)
- Alcohol associated Steatotic Liver (History and PEth test)
- Drug Induced (History)
- Inherited Liver Disease (ceruloplasmin, Ferritin , Iron levels, Alpha 1AAT)

Ultrasound and US doppler is also required in all patients

Progression of Chronic Hepatitis

Duration of ALT Elevation > 6 Months: Levels are under 300



Non Invasive Fibrosis Tests

Serum panels
- FIB-4 score
- APRI score
- Fibrosis panels

Transient Elastography

Imaging
- MR Elastography

Liver biopsy rarely needed for staging

Cirrhosis: Diagnosis

CT

Signs of Porta Hypertension
(low PLT Spleen)

EGD with varices

Liver Biopsy may be needed
To find etiology
r/o infiltrative conditions

Thinking Outside the Box

- Dehydration/Heat Stroke (CPK) Inflammatory Muscle disease (CPK, Aldolase)
- Congestive heart failure (pro BNP)
- Hepatic venous Occlusion (US doppler) –Budd Chiari
- Any intrabdominal process (mesenteric vein occlusion, UTI, PID)
- Liver Tumors/Infiltrative tumors Leukemia, Amyloid (high ALP) – US or CT Bx
- Sarcoidosis (ACE level)
- Celiac disease
- Mononucleosis

Alcohol History

- Standard drink 14 g alcohol
  - 12 oz. beer
  - 5 oz. table wine
  - 8 oz. malt liquor
  - 1.5 oz. distilled spirits

- Alcohol intake
  - Mild up to 20 g women and 30 g men per day
  - Heavy ≥40 g women and ≥ 60 g men per day
- Binge drinking
  - Pattern of drinking that brings blood alcohol concentration levels to 0.08 g/dL

People generally underestimate the amount of Alcohol they consume

PhospahtidylEthanol (PEth)

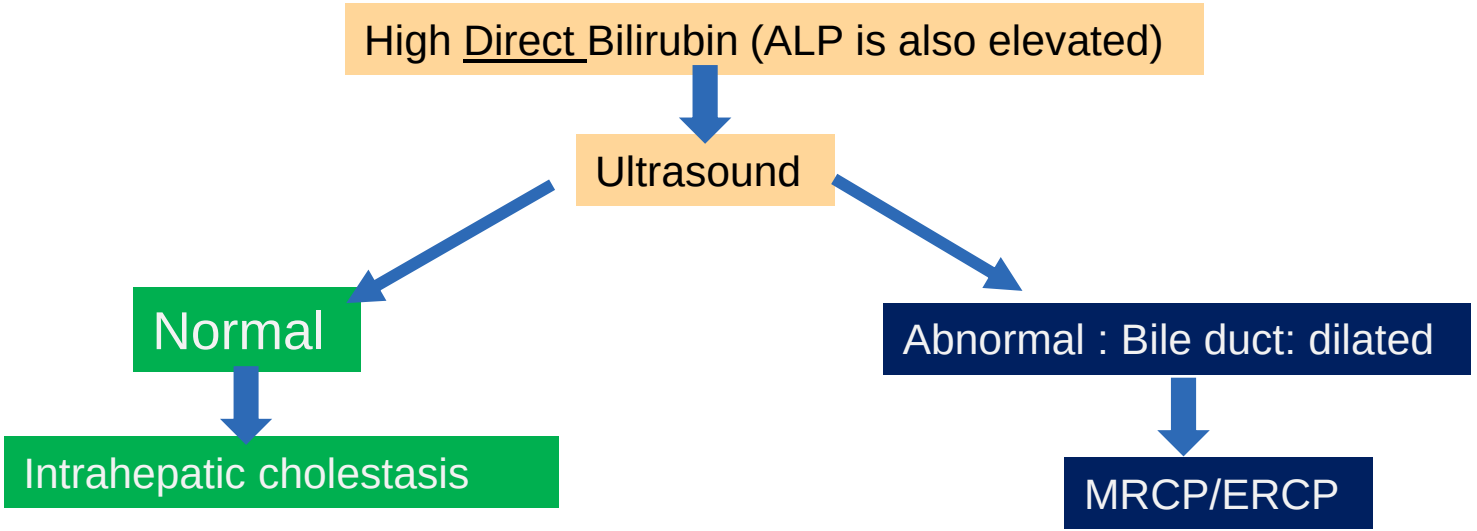
- The Peth test is designed to detect heavy drinking up to approximately **2-4 weeks prior to collection.**
- This is because PEth has an average half-life is 4.5 days.
  - Serial PETHs useful if patient claim that they stopped drinking

- A single bout of alcohol drinking will not produce detectable amounts of PEth; this would require continuous drinking of approximately **1000 g of alcohol over about 2 weeks**.

The sensitivity of PEth for the screening of alcohol use is greater than for traditional biomarkers

Elevated Direct Bilirubin (>50% of Total)

Normal Bilirubin 90% is indirect 5–10% is Direct: Fractionate Bilirubin



Primary sclerosing cholangitis: (ALP >> ALT)

- Primary biliary cholangitis: (ALP >> AST
- Inflammation: Viral Hepatitis , Autoimmune, Drugs (ALT > ALP)
- Intrahepatic cholestasis of pregnancy:
- **Cholestatic drug; Anabolic steroids**

Alkaline phosphatase(ALP)-Liver

Any Abnormal Value may suggest chronic Cholestatic process (BIULIRUBIN MAY BE NORMAL)

Everyone needs an Ultrasound or MRCP if insurance allows it

Elevated ALP and + Antimitochondrial Antibody = Primary Biliary Cholangitis; Liver Biopsy Not needed

Elevated ALP negative AMA normal Bile ducts on Ultrasound

- Cholestasis – drugs
- Primary Sclerosing cholangitis US can be normal MRCP diagnostic
- AMA negative PBC (rare –need Biopsy)
- Non Liver (Bone)
- Induction by Phenytoin, Rifampin , Carbamazepine

Primary Biliary Cholangitis

1. Antimitochondrial antibody AMA (>1:20) is positive in 95% of patients
2. Isolated + AMA should be followed with serial ALP testing
3. Degree of ALP Elevation- imply prognosis
4. Ursodiol 13–15 mg /kg body weight prevents progression
5. If ALP is NOT normalized in 6–12 months of Ursodiol use Obeitcholic acid (OCA)
6. Any degree of ALP elevation should be screened for PBC
7. Ursodiol is disease modifying drug: Early initiation is important

Primary Sclerosing Cholangitis

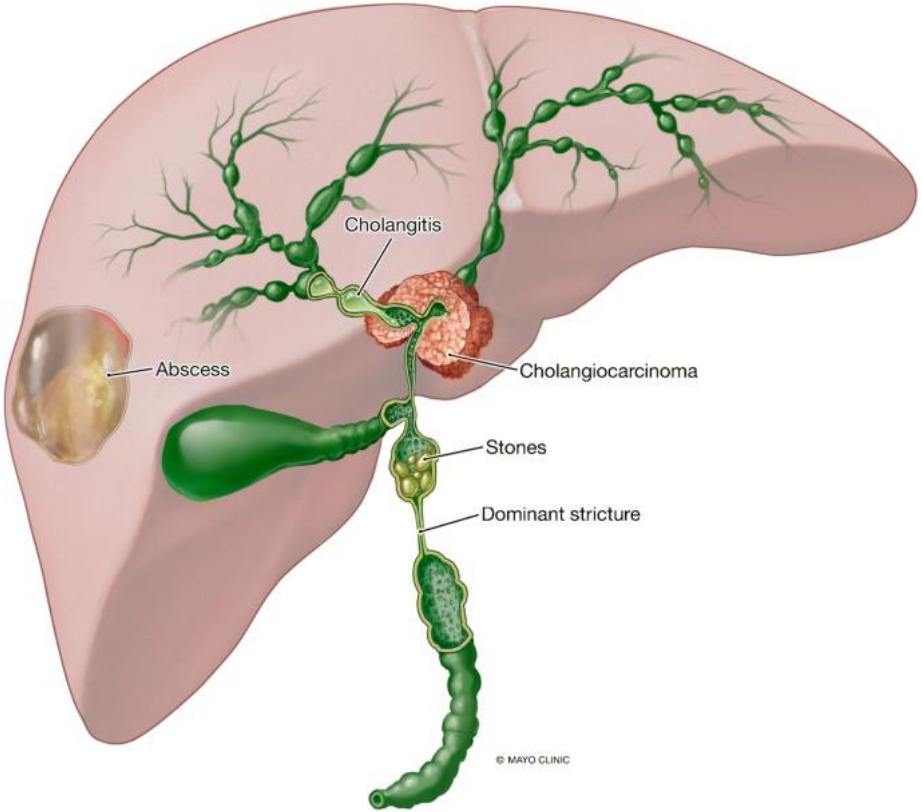
95% have Ulcerative Colitis (UC)

Elevated ALP in UC patient needs MRCP

MRCP is diagnostic

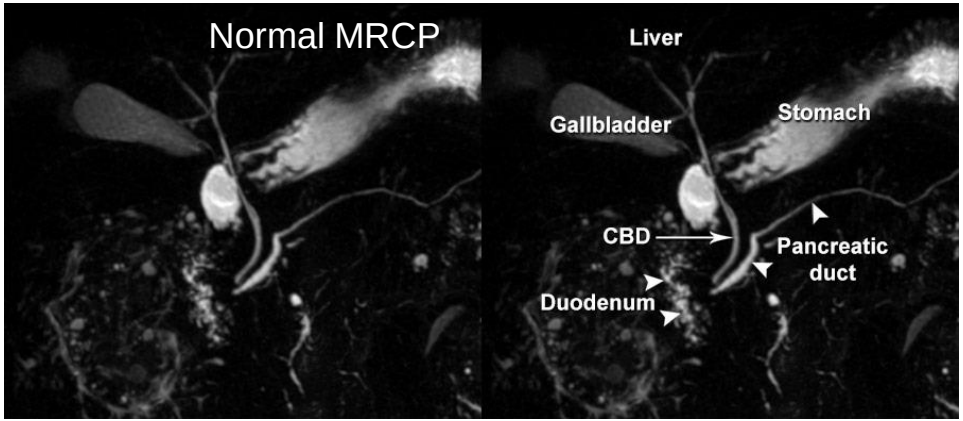
No serum markers are reliable

Ultrasound can be normal in PSC



MRI w/wo MRCP and MRE

MRI Is Very Useful Test in Any Patient With Abnormal LFTS

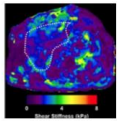


Assessment of Disease Severity

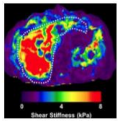
Magnetic Resonance Imaging Technology

MR-Elastography (MRE) for Fibrosis

- 2D and 3D MRE have AUROC >0.92
- Multiple single center trials show MRE>VCTE



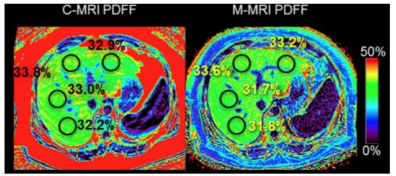
No fibrosis



Advanced fibrosis

MR-Proton density fat fraction for steatosis (MR-PDFF)

- MR-PDFF>CAP for fat quantification



Autoimmune Hepatitis

- + ANA , +ASMA
- ALT >AST 200-500
- Liver Biopsy is needed before initiating Treatment
- Drugs Induced Liver Disease (Nitrofurantoin.Minocycline)

Positive ANA is common on general population: So does not mean Autoimmune Hepatitis
Do Not treat unless confirmatory tests are done

Autoimmune Hepatitis vs Drug Induced Liver Disease

- Mixed Pattern of LFTs / Biopsy cannot differentiate
- Trial of steroids
- If disease recurs after steroid are stopped most likely AIH
- Wilson’s disease may mimic AIH

Drugs and Liver (DILI) (https://www-ncbi-nlm-nih-gov.ezproxy.uthsc.edu; livertox.nih.gov)

Chronic DILI
amoxicillin-clavulanic acid,
Atorvastatin,
Methotrexate,
hypervitaminosis A,
Heroin,
herbal products, and
dietary supplements

Cirrhosis
Methotrexate,
Isoniazid,
amiodarone,
enalapril, and
valproic acid [

Acute hepatitis
Phenytoin, Methyldopa, Isoniazid, and **Diclofenac**
Immune Check Point Inhibitors

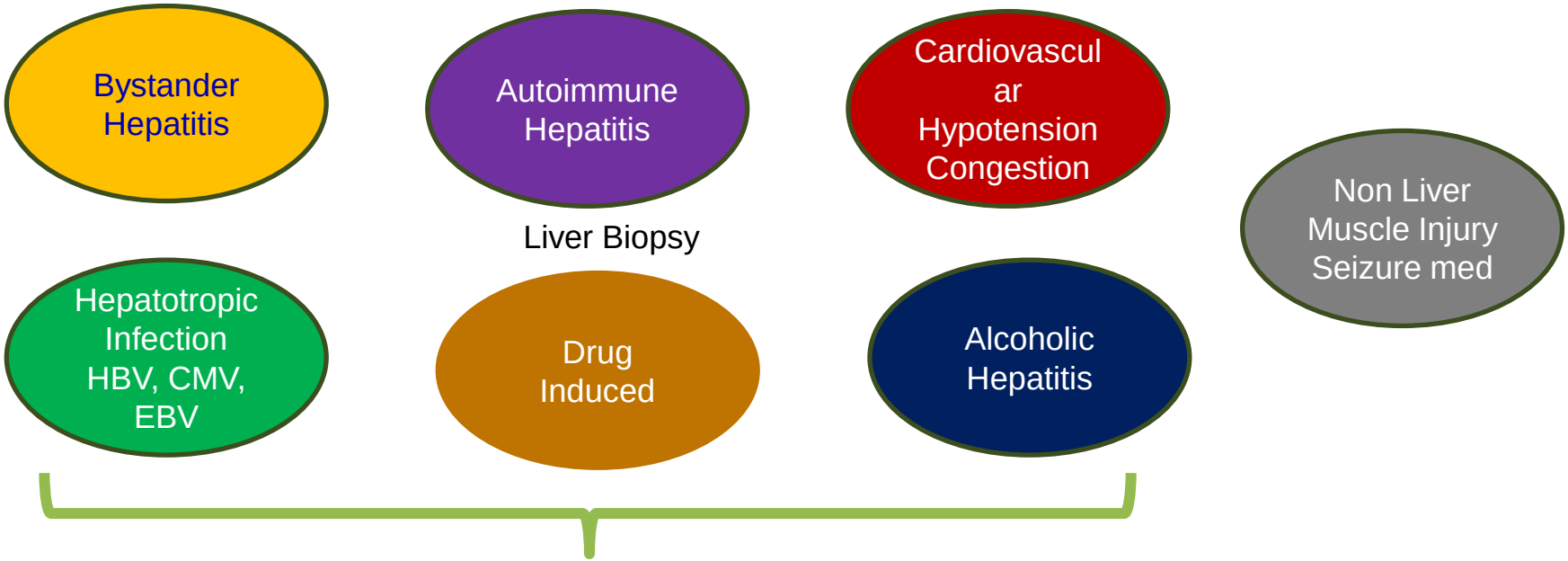
Acute Cholestasis
anabolic steroids or oral contraceptives

Chronic Cholestasis
erythromycin, **amoxicillin-clavulanate,** herbal products, and (ACE) inhibitors

Steatosis
valproic acid, acetylsalicylic acid (Reye syndrome), and **Amiodarone**

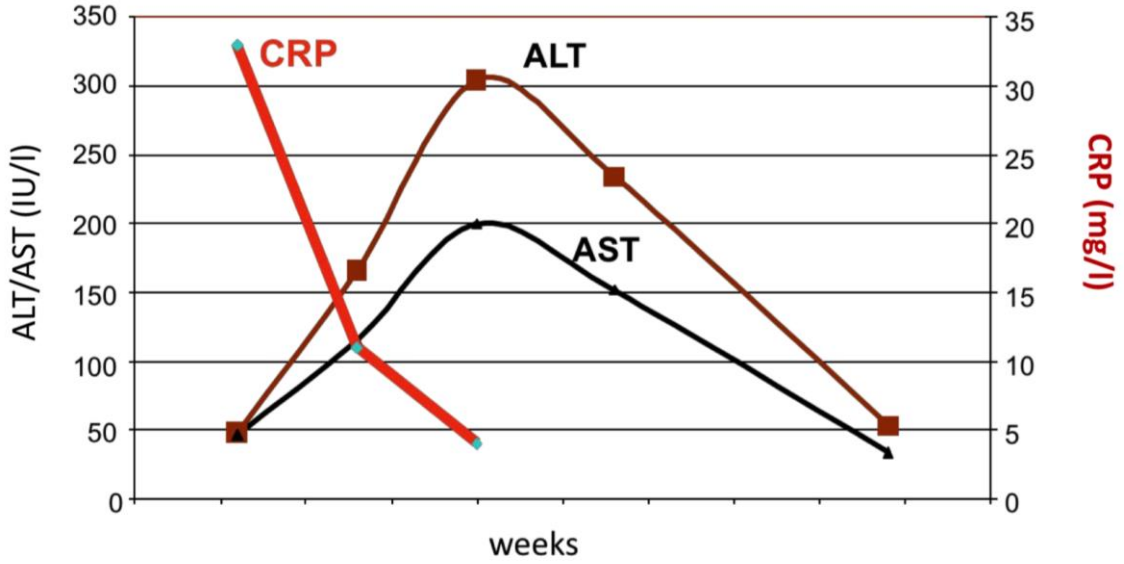
Autoimmune Hepatitis
infliximab, and other tumor necrosis factor-alpha blocking agents,
methyldopa, **minocycline, nitrofurantoin**.

Abnormal Transaminases in Hospitalized Patients



Acute Liver Failure in previously healthy
Acute on Chronic Liver Failure in patients with CLD, Cirrhosis

Bystander Hepatitis: A Typical Course of Liver Enzymes



Inflammatory Cytokine release – No Primary Liver disease
Severe Sepsis High ferritin > 20000, Hemophagocytic Syndrome)

Acute Liver Failure

- AST/ALT >10x ULN = Acute hepatitis
- Watch for progression into ALF
- Rapid acute deterioration of liver function Increasing Bilirubin and INR
- Altered mental Status = ALF Emergent Transplant valuation
- Most common causes
  - Drug-induced liver injury
  - Acute viral hepatitis HBV HAV Herpes
  - Autoimmune conditions Subacute
  - Hypoperfusion –not Tx candidates
  - Rare : Wilson's Disease (low ALP < 40)
  - Infiltrating Rapidly progressing Tumor (Acute Liver Failure with high ALP)

Elevated Bilirubin in Hospitalized Patients

- Sepsis
- Bile duct Obstruction (ALP is also elevated)
- Acute hepatitis
- Congestive Hepatopathy from CHF
- Ischemic Liver Injury (Bilirubin peaks after ALT peaks)

Liver Function and Prognosis Bilirubin, Albumin, PT INR, Creatinine

Normal Bilirubin : question the diagnosis of Liver Failure

No surgery should be done in acute hepatitis (can be mistaken for acute cholecystitis)

“Bilirubin is high in acute Hepatitis and does not mean obstruction”

Clearance of for Non Liver Surgery Outcome

CPT score and MELD score

Chronic Liver Disease Assessment – Child-Pugh Score

Parameters		Score		
		1	2	3
Albumin		> 35 g/L	28 – 35 g/L	< 28 g/L
Ascites		Absent	Slight	Moderate
Bilirubin		< 34.2 µmol/L	34.2 – 51.3 µmol/L	> 51.3 µmol/L
Encephalopathy		None	Grade 1 – 2	Grade 3 – 4
PTT	Seconds over control	< 4	4 – 6	> 6
	INR	< 1.7	1.7 – 2.3	> 2.3

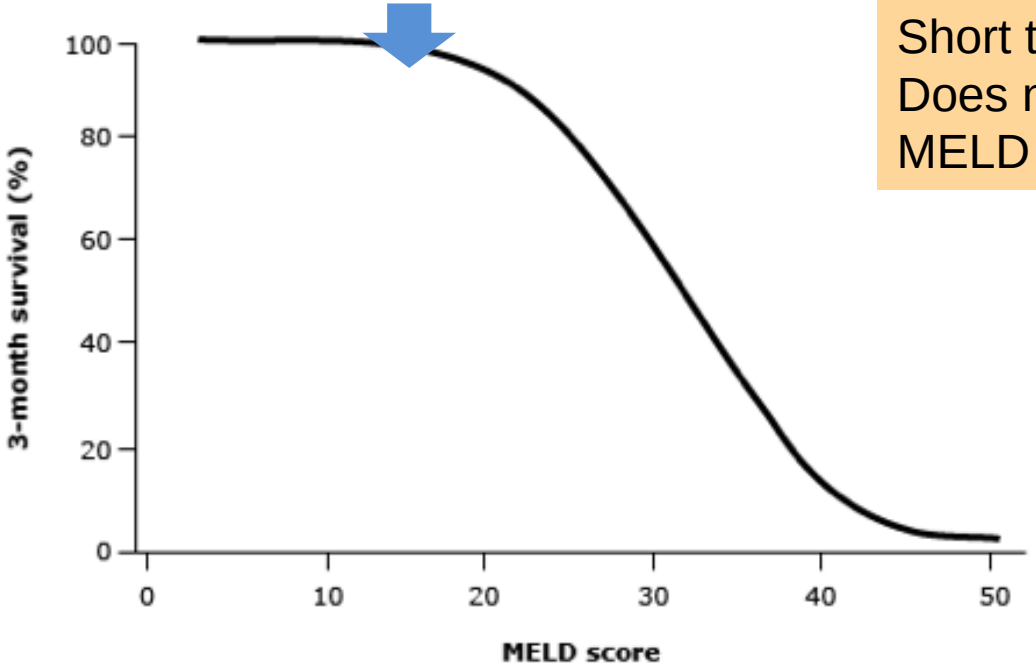
Score	Class	Description	1-Year Survival (%)	2-Year Survival (%)
5 – 6	A	Well-compensated disease	100	85
7 – 9	B	Significant functional compromise	80	60
10 – 15	C	Decompensated disease	45	35

Reference:

1. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646.
2. Child CG, Turcotte JG. The Liver and Portal Hypertension, WB Saunders Co, Philadelphia 1964.
3. Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. NEJM 1966; 274:473.

MELD Score: Bilirubin INR Creatinine

Patients may have higher mortality risk than what MELD score suggest



Short term Mortality
Does not account for Complications
MELD of > 18 equivalent to CPT of 10

Summary

1. ABNORMAL LFTS: DO NOT MISS TREATABLE CAUSES
2. AIH diagnosis should not be made by serology or Positive Autoimmune markers alone
3. ABNOMRAL LFTS In Hospitalized patients are most likely related to a systemic process
4. LIVER BIOPSY IS RESERVED FOR DIAGNOSIS NOT STAGING: WHEN IN DOUBT Biopsy
5. Ultrasound and doppler ultrasound are needed in all patients
6. MRI/MRCP/MRE is full package and is a useful test in many patients