

Elevated LFTs: Fatty Liver & Beyond

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OBJECTIVES

- ▶ 1. Define and identify acute liver failure, acute liver injury and chronic liver disease
- ▶ 2. Review the differential diagnoses for elevated liver enzymes in a cholestatic pattern
- ▶ 3. Review the differential diagnoses for elevated liver enzymes in a hepatocellular pattern

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ACUTE LIVER INJURY

- ▶ Acute liver injury (ALI): "acute derangement in liver function tests associated with liver-related coagulopathy, in the absence of underlying chronic liver disease (CLD)"¹

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ACUTE LIVER FAILURE

- ▶ Acute Liver Failure: Acute liver injury **PLUS** hepatic encephalopathy (HE), **AND** an elevated prothrombin time/international normalized ratio (PT/INR).

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CHRONIC LIVER DISEASE

- ▶ "progressive deterioration of liver functions"
- ▶ "This is a continuous process of inflammation, destruction, and regeneration of liver parenchyma leading to fibrosis and cirrhosis"
- ▶ Generally considered 6+ months

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DIFFERENTIAL DIAGNOSES FOR HYPERBILIRUBINEMIA

Mechanism of Action	Examples
Decreased hepatocellular uptake	Drugs (rifampin, cyclosporine, etc.)
Decreased conjugation	Gilbert syndrome, Crigler-Najjar syndrome, physiologic jaundice of the newborn, drugs (indinavir, atazanavir etc)
Isolated conjugated or mixed hyperbilirubinemia	Dubin-Johnson syndrome, Rotor syndrome

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R Value

- ▶ The R value (also known as the R factor) can be used to help determine the likely type of liver injury (hepatocellular versus cholestatic) in patients with elevated aminotransferases and alkaline phosphatase.
- ▶ $R\ value = \frac{(ALT \div ULN\ ALT)}{(alkaline\ phosphatase \div ULN\ alkaline\ phosphatase)}$
- ▶ The R value is interpreted as follows:
 - ▶ ≥ 5 : Hepatocellular injury
 - ▶ >2 to <5 : Mixed pattern
 - ▶ ≤ 2 : Cholestatic injury

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DIFFERENTIAL DIAGNOSES FOR ELEVATED LFTS IN A CHOLESTATIC PATTERN

- ▶ Disproportionate elevation in the alkaline phosphatase (ALP) compared with the serum aminotransferases (AST and ALT)
 - ▶ Serum bilirubin may be elevated

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Mechanism of Action	Examples
Infiltrative diseases	Granulomatous diseases such as mycobacterial infections, sarcoidosis, lymphoma, granulomatosis with polyangiitis (Wegner's), amyloidosis, malignancy
Cholangiocyte injury	Primary biliary cholangitis, graft-versus host disease, cystic fibrosis, drugs (erythromycin, Bactrim)
Bile Duct Diseases	primary sclerosing cholangitis, AIDS cholangiopathy, Chemotherapy/chemoembolization, strictures (surgical or malignant)
Extrinsic compression	Neoplasms (pancreatic, cholangiocarcinoma, HCC, etc)
Vascular	Aneurysm, cavernous transformation of the portal vein
Miscellaneous conditions	Benign recurrent intrahepatic cholestasis, drugs (estrogens, anabolic steroids), TPN, bacterial or viral (EBV, CMV) infections, paraneoplastic syndromes, intrahepatic cholestasis of pregnancy

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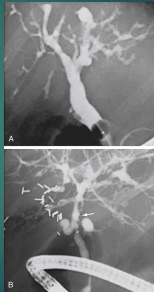
Primary Biliary Cholangitis

- ▶ Autoimmune disease
- ▶ Predominantly middle-aged women with around 50 years old
 - ▶ 5-10% men
- ▶ Symptoms include pruritus, fatigue, jaundice, xanthelasma
- ▶ Elevated ALP > 1.5 UNL and Positive AMA
- ▶ Characterized by intrahepatic bile duct destruction
 - ▶ "ductopenia" and "florid duct lesion"
- ▶ Treatment with ursodial to try to normalize ALP and if unsuccessful obeticholic acid (Ocaliva)
- ▶ Associated with osteopenic bone disease, fat soluble vitamin deficiency, hypercholesterolemia, and steatorrhea

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Primary Sclerosing Cholangitis

- ▶ Autoimmune disease
- ▶ Young men (usually 3rd or 4th decade of life) with wide variety of symptoms
- ▶ Inflammation and fibrosis of the intra- or extrahepatic bile ducts or both
 - ▶ characteristic bile duct lesion is a fibro-obliterative process that may lead to an "onion-skin" appearance of concentric fibrosis surrounding medium-sized bile ducts
- ▶ Associated with IBD
- ▶ Diagnosed with MRCP or ERCP and classically appears as "bead on a string"



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Drug induced liver injury (DILI)

- | | |
|--|---|
| ▶ Anabolic steroids | ▶ Cardiovascular agents: hydralazine, procainamide, quinidine |
| ▶ Estrogens | ▶ Phenylbutazone |
| ▶ Cholestatic hepatitis | ▶ Amoxicillin-clavulanic acid |
| ▶ Angiotensin-converting enzyme inhibitors: captopril, enalapril | ▶ Chlorpromazine |
| ▶ Antimicrobials: amoxicillin-clavulanic acid, ketoconazole | ▶ Dicloxacillin |
| ▶ Azathioprine | ▶ Flucloxacillin |
| ▶ Chlorpromazine | ▶ Macrolides |
| ▶ NSAIDs: sulindac, piroxicam | |
| ▶ Allopurinol | |
| ▶ Antibiotics: sulfonamides | |
| ▶ Antiepileptics: carbamazepine, phenytoin | |

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Intrahepatic cholestasis of pregnancy

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DIFFERENTIAL DIAGNOSES FOR ELEVATED LFTS IN A HEPATOCELLULAR PATTERN

- ▶ Disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase
- ▶ Serum bilirubin may be elevated
- ▶ Tests of synthetic function may be abnormal

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HEPATOCELLULAR PATTERN

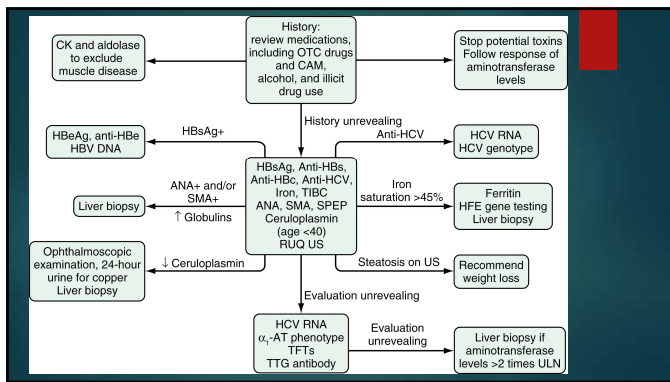
Chronic, Mild Elevations, ALT > AST (<150 U/L OR 5 × Normal)	Severe, Acute Elevations, ALT > AST (>1000 U/L OR > 20-25 × Normal)
α ₁ -Antitrypsin deficiency	Acute bile duct obstruction
Autoimmune hepatitis	Acute Budd-Chiari syndrome
Chronic viral hepatitis (B, C, and D)	Acute viral hepatitis
Hemochromatosis	Autoimmune hepatitis
Medications and toxins	Drugs and Toxins
Steatosis and steatohepatitis	Hepatic artery ligation
Wilson disease	Ischemic hepatitis
Celiac disease	Wilson disease
Hyperthyroidism	

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HEPATOCELLULAR PATTERN

Severe, Acute Elevations, AST > ALT (>1000 U/L OR >20-25 x Normal)	Chronic, mild elevations, AST > ALT (<150 U/L, <5 x normal)
Medications or toxins in a patient with underlying alcohol-associated liver injury	Alcohol-associated liver injury (AST/ALT>2:1, AST nearly always <300 U/L)
Acute rhabdomyolysis	Cirrhosis
	Hypothyroidism
	Myopathy
	Strenuous exercise

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α₁-Antitrypsin deficiency

- ▶ Affects the lungs, liver and skin
- ▶ Alpha 1 antitrypsin is a serine protease inhibitor that is produced in hepatocytes
- ▶ Autosomal co-dominant inheritance of mutations in the A1AT gene
- ▶ Two alleles associated with liver disease Z and M
- ▶ Liver disease is seen in patients with PIZZ homozygotes and PIMZ
- ▶ Transplant is curative

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Autoimmune hepatitis

- ▶ Interface hepatitis (lymphoplasmal cell infiltration and lobular hepatitis with centrilobular necrosis) with clinical laboratory findings
- ▶ Elevated AST, ALT, IgG concentrations commonly seen
- ▶ Two types:
 - ▶ Type 1 positive ANA and/or Smooth Muscle Ab (SMA)
 - ▶ Type 2 positive Liver Kidney Microsome type 1 (anti-LKM1) or Soluble liver antigen (anti-SLA)
- ▶ Treatment includes steroids, azathioprine, mycophenolate mofetil
- ▶ Revised Original Score for Autoimmune Hepatitis (AIH) on MDCalc (score >15)

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Hemochromatosis

- ▶ One of the most common genetic disorders in Caucasians
- ▶ HFE-related
 - ▶ [C282Y/C282Y, C282Y/H63D, or C282Y/S65C]
 - ▶ Screen first degree relatives
- ▶ Non-HFE related
 - ▶ Hemosiderin
 - ▶ Transferrin receptor-2
 - ▶ Ferroporin
 - ▶ Hepsidin
 - ▶ African iron overload
- ▶ Secondary Iron Overload
 - ▶ Iron loading anemias
 - ▶ Parenteral iron overload
 - ▶ Chronic liver disease
 - ▶ Dymetabolic iron overload

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Wilson disease

- ▶ "progressive lenticular degeneration," a familial, lethal neurological disease accompanied by cirrhosis
- ▶ Absent or impaired ATP7B function decreases biliary excretion of copper → toxic hepatocellular copper accumulation → released into the bloodstream → deposits in other organs (brain, kidneys, and cornea)
- ▶ Kayser-Fleischer (KF), sunflower cataracts, hemolysis/non-immune hemolytic anemia, low ALP
- ▶ Serum ceruloplasmin will be low, urine copper will be high
- ▶ Liver biopsy non-specific and can look like MAFLD, can get a copper weight

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NAFLD? MASLD? NASH? MASH?

- ▶ NAFLD → MASLD
 - ▶ NON-ALCOHOLIC FATTY LIVER DISEASE
 - ▶ METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE
- ▶ NASH → MASH
 - ▶ NON-ALCOHOLIC STEATOHEPATITIS
 - ▶ METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS
- ▶ Met-ALD (metabolic and alcohol related associated liver disease)

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MASLD/MASH

Adult Criteria

All meet 1 out of 5:

- BMI ≥ 25 kg/m² (23 kg/m² OR WC ≥ 94 cm (M) 85 cm (F)) OR already diagnosed with obesity
- Fasting serum glucose ≥ 6.0 mmol/L (100 mg/dL) OR 2-hour post-load glucose levels ≥ 7.8 mmol/L (140 mg/dL) OR HbA1c ≥ 6.5% (20 mmol/L) OR type 2 diabetes OR treatment for type 2 diabetes
- Blood pressure ≥ 130/85 mmHg OR specific antihypertensive drug treatment
- Plasma triglycerides ≥ 1.70 mmol/L (150 mg/dL) OR lipid lowering treatment
- Plasma LDL-cholesterol ≥ 1.9 mmol/L (80 mg/dL) OR statin ≥ 1.3 mmol/L (50 mg/dL) OR lipid lowering treatment

Cardiometabolic Criteria

All meet 4 out of 5:

- BMI ≥ 30 kg/m² OR waist circumference ≥ 102 cm (M) 88 cm (F) OR already diagnosed with obesity
- Fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL) OR serum glucose ≥ 11.1 mmol/L (200 mg/dL) OR 2-hour post-load glucose levels ≥ 7.8 mmol/L (140 mg/dL) OR HbA1c ≥ 6.5% (20 mmol/L) OR already diagnosed with type 2 diabetes OR treatment for type 2 diabetes
- Blood pressure ≥ 130/85 mmHg OR specific antihypertensive drug treatment
- Plasma triglycerides ≥ 1.70 mmol/L (150 mg/dL) OR lipid lowering treatment
- Plasma LDL-cholesterol ≥ 1.9 mmol/L (80 mg/dL) OR statin ≥ 1.3 mmol/L (50 mg/dL) OR lipid lowering treatment

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SCORES TO DETERMINE IF YOU SHOULD BIOPSY SUSPECT MASH

- ▶ FIB-4: Age, AST, PLT, ALT
- ▶ APRI: AST and PLT
- ▶ NAFLD Fibrosis Score
- ▶ Fibrotic NASH Index (FNI): AST, HDL, Cholesterol, HbA1c
 - ▶ Fniscore.github.io

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NAFLD (Non-Alcoholic Fatty Liver Disease) Fibrosis Score
 Normative estimate of fibrosis in the liver based on several laboratory tests.

When to Use: Pearls/Tricks: Why Use:

Age: years

BMI: kg/m² (Norm: 20 - 25)

Impaired fasting glucose/diabetes: No Yes <1

AST: U/L (Norm: 15 - 45)

ALT: U/L (Norm: 1 - 35)

Platelet count: x10⁹/L (Norm: 150 - 350)

Albumin: g/dL (Norm: 3.5 - 5.5)

AST to Platelet Ratio Index (APRI)
 Normative estimate of hepatic fibrosis in patients with hepatitis C.

When to Use: Pearls/Tricks: Why Use:

AST: U/L (Norm: 15 - 45)

AST upper limit of normal: U/L (Norm: 40)

Platelet count: x10⁹/L (Norm: 150 - 350)

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Treatments

- ▶ Vitamin E
- ▶ Pioglitazone
- ▶ Weight loss 10% in 6-12 months
- ▶ 2 Cups of Black Coffee daily
- ▶ Future hopes?

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Fibrosis-4 (FIB-4) Index for Liver Fibrosis
 Normative estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

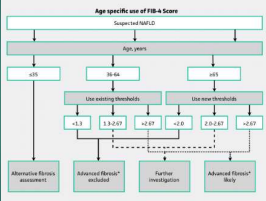
When to Use: Pearls/Tricks: Why Use:

Age: years (Use with caution to patients <15 or >65 years old, as the score has been shown to be less reliable in these patients)

AST Aspartate aminotransferase: U/L (Norm: 15 - 45)

ALT Alanine aminotransferase: U/L (Norm: 1 - 35)

Platelet count: x10⁹/L (Norm: 150 - 350)



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