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

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]

ACUTE LIVER FAILURE

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

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

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

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 = (ALT ÷ ULN ALT) / (alkaline phosphatase ÷ ULN alkaline phosphatase)
- The R value is interpreted as follows:
  - ≥5: Hepatocellular injury
  - >2 to <5: Mixed pattern
  - ≤2: Cholestatic injury

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

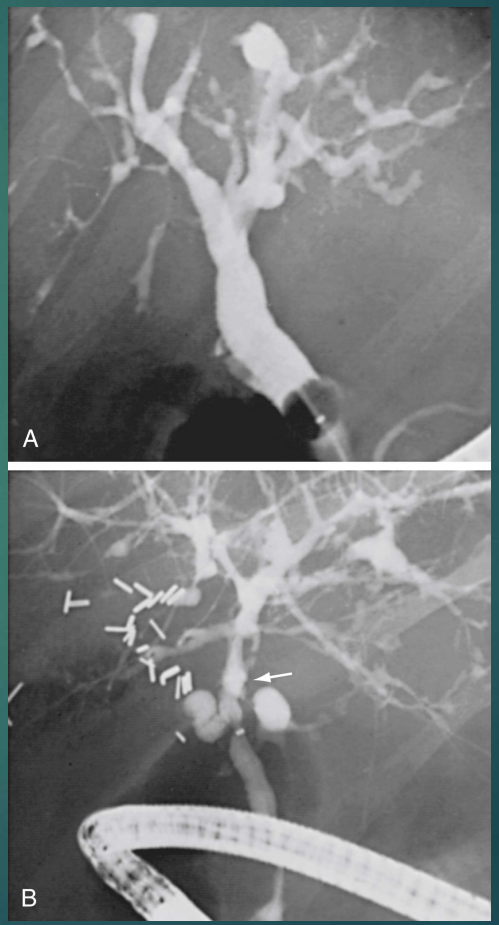
Mechanism of Action	Examples
Infiltrative diseases	Granulomatous diseases such as mycobacterial infections, sarcoidosis, lymphoma, granulomatosis with polyangiitis (Wegner's), amyloidosis, malignancy
Cholangiocyte injury	Primary biliary cholangitis, graft-versus host disease, cystic fibrosis, drugs (erythromycin, 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

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 ursodiol to try to normalize ALP and if unsuccessful obeticholic acid (Ocaliva)
- Associated with osteopenic bone disease, fat soluble vitamin deficiency, hypercholesterolemia, and steatorrhea

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"



Drug induced liver injury (DILI)

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

Intrahepatic cholestasis of pregnancy

DIFFERENTIAL DIAGNOSES FOR ELEVATED LFTS IN A HEPATOCELLULAR PATTERN

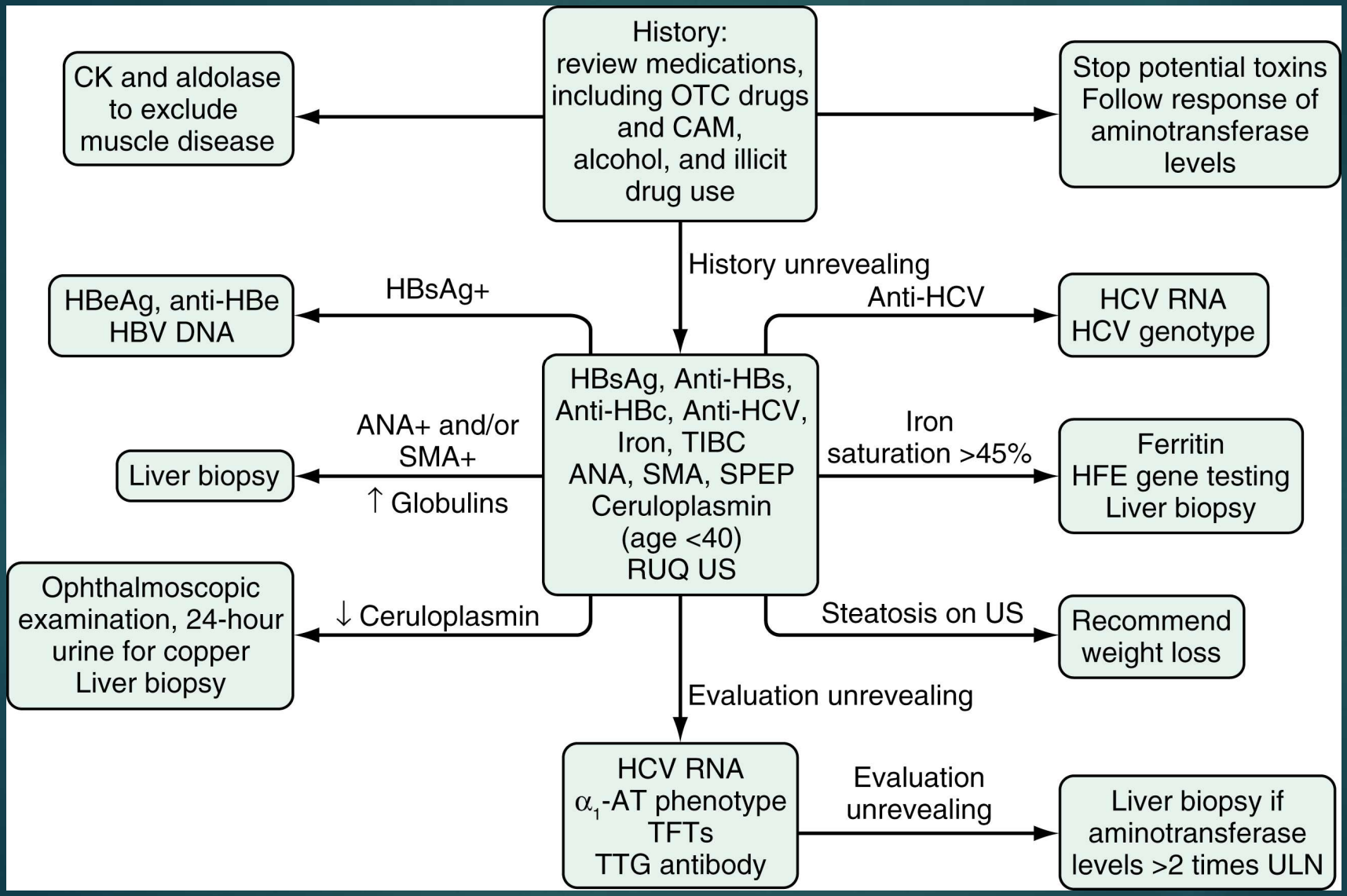
- Disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase
- Serum bilirubin may be elevated
- Tests of synthetic function may be abnormal

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	

HEPATOCELLULAR PATTERN

Severe, Acute Elevations, AST > ALT (>1000 U/L OR >20-25 × Normal)	**Chronic, mild elevations, AST > ALT (<150 U/L, <5 × 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

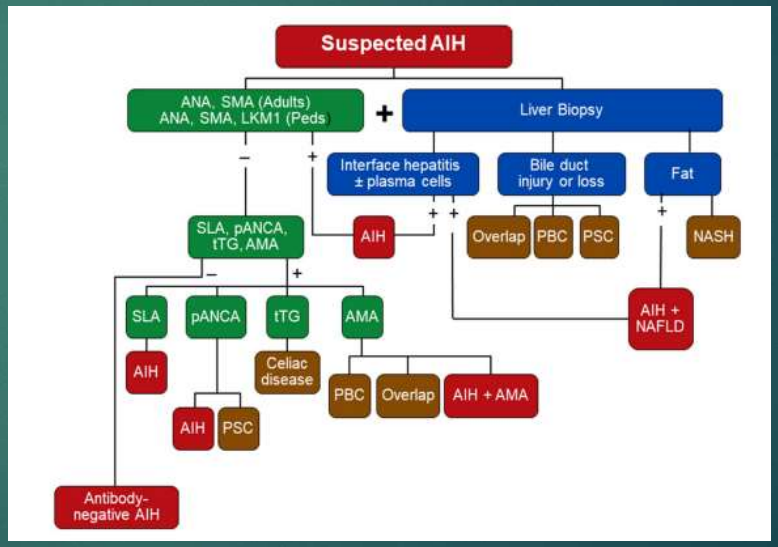

History:
review medications, including OTC drugs and CAM, alcohol, and illicit drug use
CK and aldolase to exclude muscle disease
Stop potential toxins
Follow response of aminotransferase levels
History unrevealing
HBsAg+
HBeAg, anti-HBe
HBV DNA
Anti-HCV
HCV RNA
HCV genotype
HBsAg, Anti-HBs, Anti-HBc, Anti-HCV, Iron, TIBC
ANA, SMA, SPEP
Ceruloplasmin
(age <40)
RUQ US
ANA+ and/or SMA+
↑ Globulins
Liver biopsy
Iron saturation >45%
Ferritin
HFE gene testing
Liver biopsy
Ophthalmoscopic examination, 24-hour urine for copper
Liver biopsy
↓ Ceruloplasmin
Steatosis on US
Recommend weight loss
Evaluation unrevealing
HCV RNA
α_1-AT phenotype
TFTs
TTG antibody
Evaluation unrevealing
Liver biopsy if aminotransferase levels >2 times ULN

α_1-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

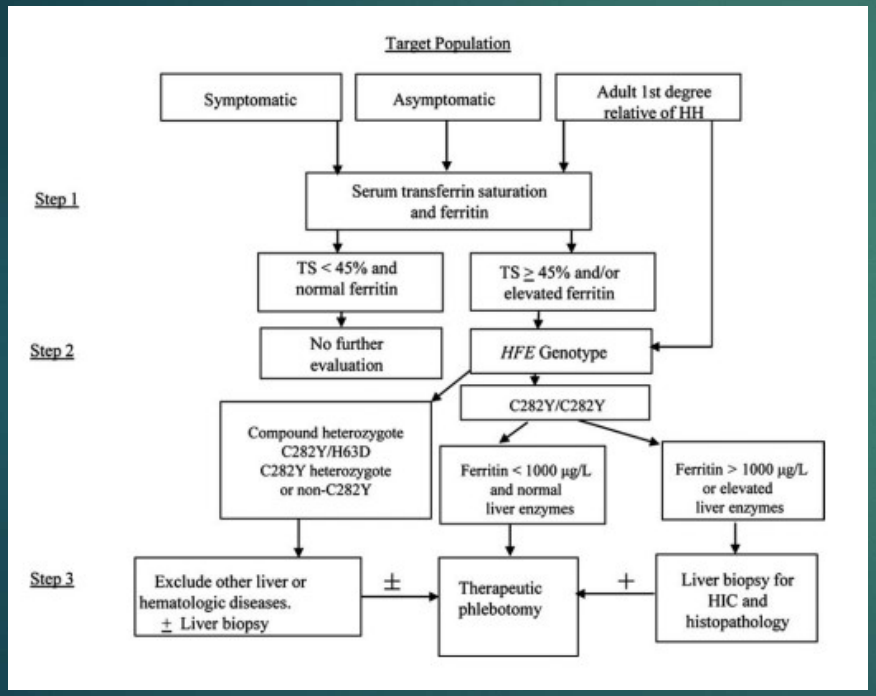
Autoimmune hepatitis

- Interface hepatitis (lymphoplasma cell infiltration and lobar 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)



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
  - Hemojuvelin
  - Transferrin receptor-2
  - Ferroportin
  - Hepcidin
  - African iron overload
- Secondary Iron Overload
  - Iron loading anemias
  - Parental iron overload
  - Chronic liver disease
  - Dysmetabolic iron overload

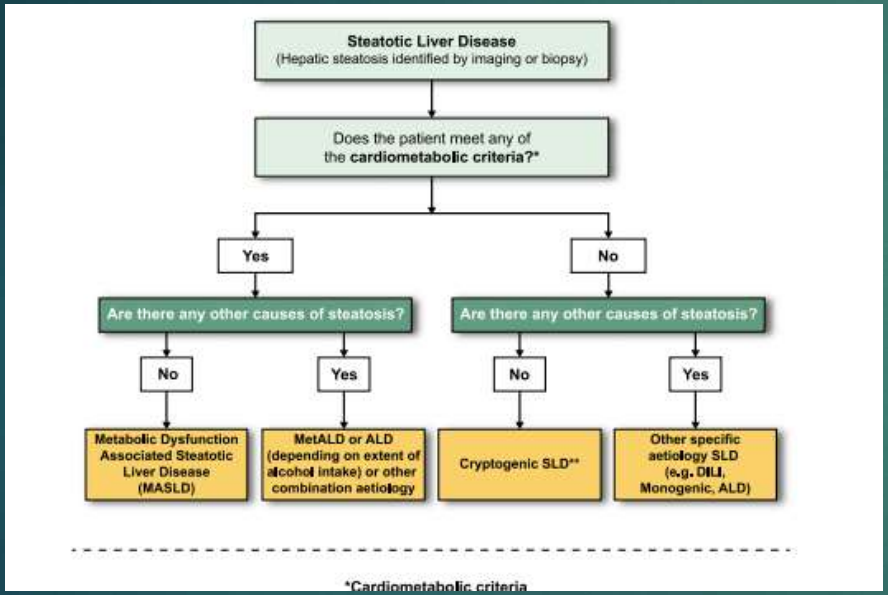
Wilson disease

- "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

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)

MASLD/MASH



Adult Criteria	Paediatric Criteria
At least 1 out of 5:	**At least 1 out of 5:**
☐ BMI ≥ 25 kg/m² [23 Asia] OR WC > 94 cm (M) 80 cm (F) OR ethnicity adjusted equivalent	☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] OR WC > 95th percentile OR ethnicity adjusted equivalent
☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes	☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] OR serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] OR 2-hour postload glucose levels ≥ 7.8 mmol [140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes
☐ Blood pressure ≥ 130/85 mmHg OR specific antihypertensive drug treatment	☐ Blood pressure age < 13y, BP ≥ 95th percentile OR ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg OR specific antihypertensive drug treatment
☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] OR lipid lowering treatment	☐ Plasma triglycerides age < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] OR lipid lowering treatment
☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) OR lipid lowering treatment	☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] OR lipid lowering treatment

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

NAFLD (Non-Alcoholic Fatty Liver Disease) Fibrosis Score ☆

Estimates amount of scarring in the liver based on several laboratory tests.

When to Use | Pearls/Pitfalls | Why Use

Age		years
BMI	Norm: 20 - 25	kg/m²
Impaired fasting glucose/diabetes	No 0 / Yes +1	
AST	Norm: 15 - 41	U/L
ALT	Norm: 1 - 35	U/L
Platelet count	Norm: 150 - 350	× 10³/µL
Albumin	Norm: 3.5 - 5.5	g/dL

AST to Platelet Ratio Index (APRI) ☆

Determines the likelihood of hepatic fibrosis and cirrhosis in patients with hepatitis C.

When to Use | Pearls/Pitfalls | Why Use

AST	Norm: 15 - 41	U/L
AST upper limit of normal	40	U/L
Platelet count	Norm: 150 - 350	× 10³/µL

Treatments

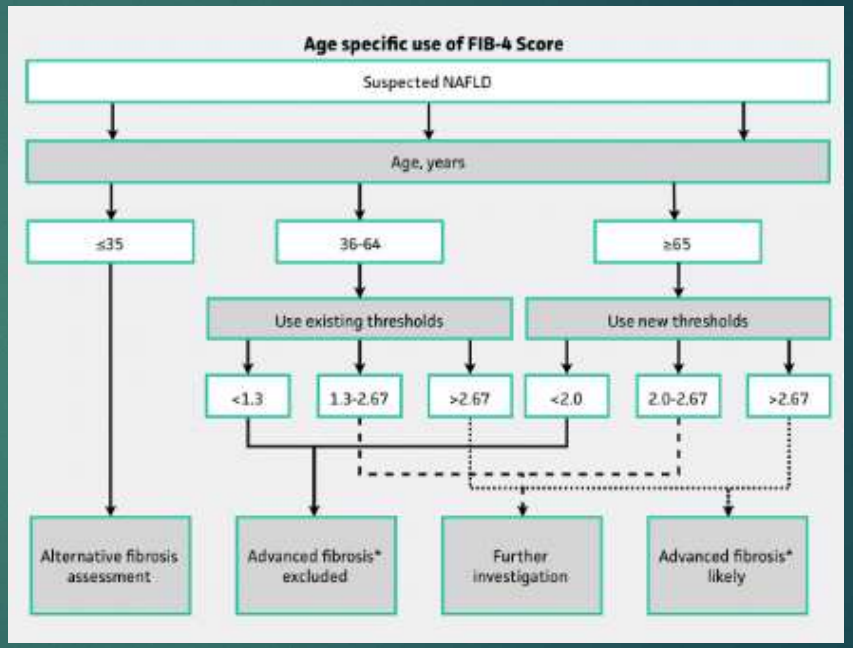
- Vitamin E
- Pioglitazone
- Weight loss 10% in 6-12 months
- 2 Cups of Black Coffee daily
- Future hopes?

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

When to Use | Pearls/Pitfalls | Why Use

Age Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients		years
AST Aspartate aminotransferase	Norm: 15 - 41	U/L
ALT Alanine aminotransferase	Norm: 1 - 35	U/L
Platelet count	Norm: 150 - 350	$\times 10^3/\mu L$



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